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Ricardo Delgado Date

Development of a Novel Cascade Cyclization Reaction and its Application Towards the Total Synthesis of Malagashanine: A Chloroquine Efflux Inhibitor

By

Ricardo Delgado
Doctor of Philosophy

Chemistry

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Lisa A. Tedesco, Ph. D.
Dean of the James T. Laney School of Graduate Studies

_____

Date

# Development of a Novel Cascade Cyclization Reaction and its Application Towards the Total Synthesis of Malagashanine: A Chloroquine Efflux Inhibitor

By

Ricardo Delgado
B.S., Barry University, 2004

Advisor: Simon B. Blakey, Ph.D.

An abstract of
A dissertation submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University
in partial fulfillment of the requirements for the degree of
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2010

Abstract

Development of a Novel Cascade Cyclization Reaction and its Application Towards the Total Synthesis of Malagashanine: A Chloroquine Efflux Inhibitor

By

Ricardo Delgado

A cascade cyclization reaction was developed to access the core of the malagashanine alkaloids with the necessary stereochemistry at C(2), C(3), C(7). The transformation employed stable *N*-tosyl-*O*-TMS-aminols to generate highly reactive $\beta,\gamma$-unsaturated iminium ion intermediates, and the method was amenable to both electron rich and electron poor tryptamine substituents, as well as furans and tryptophol nucleophiles. Additionally, the sequence was successfully employed with intermolecular indole nucleophiles. For the synthesis of malagashanine, the use of a tri-substituted $\beta,\gamma$-unsaturated acid permitted the installation of the fourth requisite stereocenter at C(16). Additionally, the E ring was constructed *via* a formal olefin hydroacylation reaction, and C(19)-C(20)-dehydro-malagashanine was subsequently synthesized.

# Development of a Novel Cascade Cyclization Reaction and its Application Towards the Total Synthesis of Malagashanine: A Chloroquine Efflux Inhibitor

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# Table of Contents

# Table of Schemes

# Table of Figures

# Table of Tables

# Abbreviations

| | |
|---|---|
| Ac | acetyl |
| AcOH | acetic acid |
| 9-BBN | 9-borabicyclo[3.3.1]nonene |
| Boc | *tert*-butoxycarbonyl |
| Bn | benzyl |
| br | broad |
| *n*-BuLi | *n*-butyllithium |
| *t*-BuOOH | *tert*-butylhydroperoxide |
| Cbz | benzyloxycarbonyl |
| d | doublet |
| dba | dibenzylideneacetone |
| DCE | 1, 2-dichloroethane |
| DCM | dichloromethane |
| DIBAL-H | diisobutylaluminum hydride |
| DMAP | *N*, *N*-dimethylaminopyridine |
| DME | 1, 2-dimethoxyethane |
| DMF | *N*, *N*-dimethylformamide |
| DMP | Dess-Martin periodinane |
| DMPU | *N*, *N*'-dimethyl-*N*, *N*'-propylene urea |
| DMS | dimethylsulfide |
| DMSO | dimethylsulfoxide |

| | |
|---|---|
| EDCI | 1-ethyl-3-(3-dimethylaminopropylcarbodiimide) |
| equiv. | equivalent |
| ESI | electrospray ionization |
| EtOAc | ethyl acetate |
| HMPA | hexamethylphosphoric triamide |
| HOBt | 1-hydroxybenzotriazole |
| HRMS | high resolution mass spectroscopy |
| IBX | 2-iodoxybenzoic acid |
| KHMDS | potassium *bis*(trimethylsilyl)amide |
| LA | Lewis acid |
| LAH | lithium aluminum hydride |
| LDA | lithium diisopropylamide |
| LiHMDS | lithium *bis*(trimethylsilyl)amide |
| LiTMP | lithium 2,2,6,6-tetramethylpiperidide |
| m | multiplet |
| mmol | millimole |
| NaHMDS | sodium *bis*(trimethylsilyl)amide |
| Naph | naphtyl |
| NIS | *N*-iodosuccinimide |
| NMO | *N*-methylmorpholine *N*-oxide |
| NMR | nuclear magnetic resonance |
| Ns | 4-nitrobenzenesulfonyl |
| Ph | phenyl |

| | |
|---|---|
| PMP | *para*-methoxyphenyl |
| ppm | parts per million |
| PTSA | *para*-toluenesulfonic acid |
| q | quartet |
| quint | quintet |
| rt | room temperature |
| s | singlet |
| t | triplet |
| TBAHS | tetrabutylammonium hydrogen sulfate |
| TBME | *tert*-butyl methyl ether |
| TBDMS | *tert*-butyldimethylsilyl |
| TBDPS | *tert*-butyldiphenylsilyl |
| TCBoc | 2,2,2-trichloro-*tert*-butyloxycarbonyl |
| Tf | trifluoromethanesulfonyl |
| TFA | trifluoroacetic acid |
| TFAA | trifluoroacetic anhydride |
| TFP | tris(2-furyl)phosphine |
| THF | tetrahydrofuran |
| THP | tetrahydropyran |
| TMS | trimethylsilyl |
| TPAP | tetrapropylammonium perruthenate |
| Ts | *para*-toluenesulfonyl |
| w | weak |

# 1. Chapter One: Introduction to the Monoterpene Indole Alkaloids

## 1.1. Total Synthesis of Strychnos Alkaloids and Related Natural Products

More than 60 years after the first total synthesis of strychnine (**1**) was reported by R. B. Woodward,[1] the synthetic community continues to show great interest in strychnine and other related monoterpene indole alkaloids (Figure 1.1).[2] With the discovery of new compounds over the last decades, the ranks of the strychnos alkaloids have provided a myriad of new synthetic targets.[3] Along with their biosynthetic relatives, including aspidosperma alkaloids such as aspidospermidine (**2**) and vindoline (**3**), they remain an inspiration to the minds of chemists. As intriguing structural features are identified in newly isolated compounds, synthetic chemists continue to push the limits of the field and as a result develop new transformations.

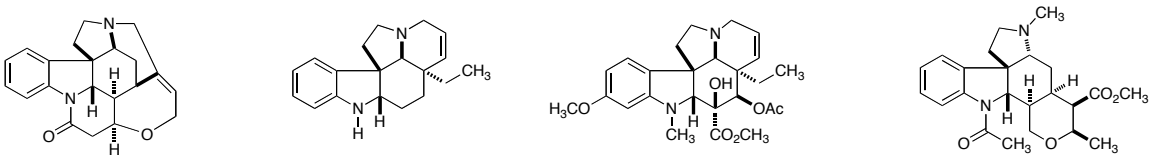



**Figure 1.1** Strychnine and other related monoterpene indole alkaloids.

Many strychnos alkaloids display potent biological activity against a wide array of illnesses.[4] For example, malagashanine (**4**) holds great promise as an adjuvant in the treatment of malaria.[5] The need to procure useful quantities of this compound for

biological testing is of utmost importance, as this and other alkaloids are usually found in nature in minute amounts. Equally important is the need to develop efficient methods for the synthesis of analogs, which not only are useful tools in the elucidation of the biological mode of action, but in many instances may surpass the parent compound in potency.

## 1.2. The Malagashanine Alkaloids: Isolation, Structure and Stereochemistry

In 1991 Rasoanaivo and coworkers reported the isolation of malagashanine (**4**) from the stem bark of *Strychnos mostueoides* in the eastern forest of Madagascar (Figure 1.2).[5a] Malagashanine was isolated using countercurrent distribution (CCD) that afforded 8.0 x $10^{-4}$% yield based on dry weight. Subsequently it has also been isolated from the bark of *Strychnos myrtoides*[5c] and *Strychnos diplotricha*,[6] as well as from the leaves of *Strychnos myrtoides*.[6] Other related compounds isolated from the same plant extract include 12-hydroxymalagashanine (**5**), myrtoidine (**6**) and 11-demethoxymyrtoidine (**7**).[7] Additionally, minor C(3) epimers of myrtoidine have also been isolated.[6]

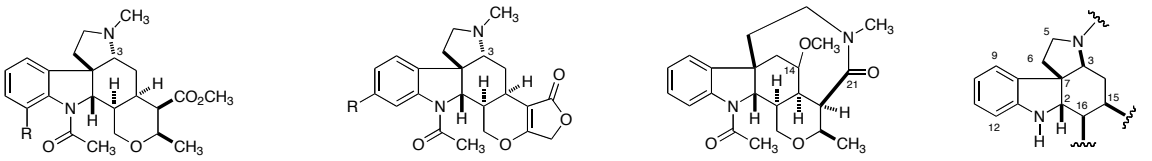



**Figure 1.2** The malagashanine alkaloids and related compounds.

The molecular formula of malagashanine was established to be $C_{23}H_{30}N_2O_4$ by EI-MS.[5a] The structure was originally assigned as $N_b$,C(3) secocuran alkaloid **8** having a $N_b$-methyl, 14-methoxy and C(21) carbonyl substituents. The assignment was based on $^1$H-$^1$H selective decoupling and $^1$H-$^1$H COSY experiments, as well as comparisons to other secocuran alkaloids. However shortly after this original disclosure, the authors subsequently revised their assignment using X-ray crystallographic data and unequivocally assigned the structure as **4**.[8] Malagashanine presents an interesting pentacyclic structure with seven contiguous stereocenters in a stereochemically unique arrangement. In contrast to all other known strychnos and aspidosperma alkaloids, which display the C(2)-H, C(7)-C(6), and C(3)-$N_b$ bonds all in *syn* relationship to each other as shown in Figure 2 (aspidosperma core **9**), malagashanine possesses inverted relative stereochemistry at C(3). NOESY studies also support the revised structure and show cross peaks between H-5a and H-9 that are only explainable if the C(3) stereocenter is inverted (Figure 1.3).[7] Additionally, 3-*epi*-myrtoidine (**10),** which possesses the usual aspidosperma stereochemistry, shows cross peaks between H-3 and H-9 that are not observed in malagashanine.

Interestingly, only one conformer of malagashanine is detectable by NMR at 300 K despite the presence of an *N*-methylacetamide moiety. This is in contrast to the usual mixture of rotamers observed with most members of the malagashanine family. NOE between H-2 and $CH_3$(24) indicate that the *Z*-isomer is the predominant conformer in malagashanine.

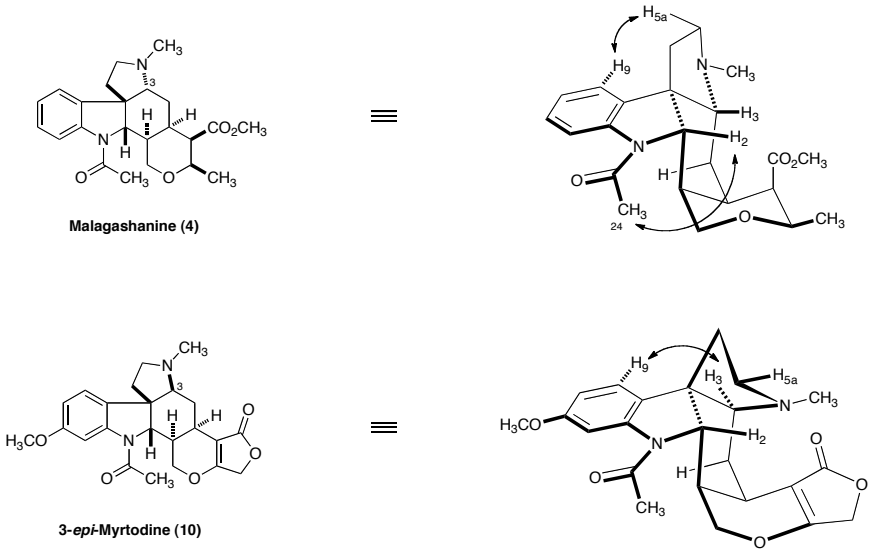



**Figure 1.3** NOE studies on the malagashanine alkaloids.

## 1.3. Biological Activity

Malaria is the major parasitic infection in many tropical and subtropical regions, leading to over one million deaths out of 400-500 million cases each year.[9] The spread of drug resistant strains of *Plasmodium falciparum* is one of the leading causes of the rising rate of malarial infections.

The Malagasy population usually treats malaria *via* self-medication with chloroquine (CQ) taken along with a tonic made from local plants, including *Strychnos myrtoides and Strychnos mostueoides*.[5a] This herbal decoction is claimed to work as an adjuvant to treat malaria, and is used with seeming success even with low doses of CQ (100-200 mg). A series of studies conducted by Rasoanaivo and coworkers beginning in 1991 identified malagashanine **4** as one of the main components of the extract of *Strychnos myrtoides* and *Strychnos mostueoides*. *In vitro* studies using a chloroquine resistant (CQR) strain of *Plasmodium falciparum* FCM 29/Cameroon revealed that

malagashanine exhibited marked CQ enhancement activity (Table 1.1).[5c] Subsequent *in vitro* biological testing showed that malagashanine acted by preventing CQ efflux in drug resistant *Plasmodium falciparum* strains.[5b] There is evidence suggesting that it stimulates CQ influx as well.

| **Malagashanine Dose (μg/ml)** | **Chloroquine Activity (nM)** | | |
|---|---|---|---|
| | **$IC_{50}$** | **$IC_{90}$** | **AEI[a]** |
| 0[b] | 226.0 +/- 4.7 | 522.7 +/- 9.4 | |
| 5 | 90.6 +/- 5.5 | 207.0 +/- 6.7 | 2.5 |
| 10 | 52.9 +/- 4.6 | 142.8 +/- 6.3 | 3.7 |
| 15 | 38.5 +/- 3.6 | 116.9 +/- 5.1 | 4.5 |
| 20 | 33.2 +/- 3.2 | 95.6 +/- 5.4 | 5.5 |
| 25 | 25.5 +/- 2.7 | 76.6 +/- 5.2 | 6.3 |

[a] AEI or activity enhancement index is calculated by dividing the $IC_{90}$ of CQ by the $IC_{90}$ of CQ combined with malagashanine.
[b] Control plate with CQ alone.

**Table 1.1** Chloroquine potentiating activity of malagashanine on CQR strain of *Plasmodium falciparum* FCM 29/Cameroon.

*In vivo* studies using the crude alkaloid extracts from *S. myrtoides* were carried out on Swiss mice infected with a line of *Plasmodium yoelii* subsp. *nigeriensis* N67 resistant to CQ and supsceptible to pyrimethamine and mepacrine. These studies revealed an 81.10% suppression of parasitaemia by the fifth day of the experiment in mice receiving 0.75 mg/Kg dosages of CQ and 100 mg/Kg of crude alkaloid extract. No toxicity was detected against the extract at oral dosages of 100 mg/Kg.

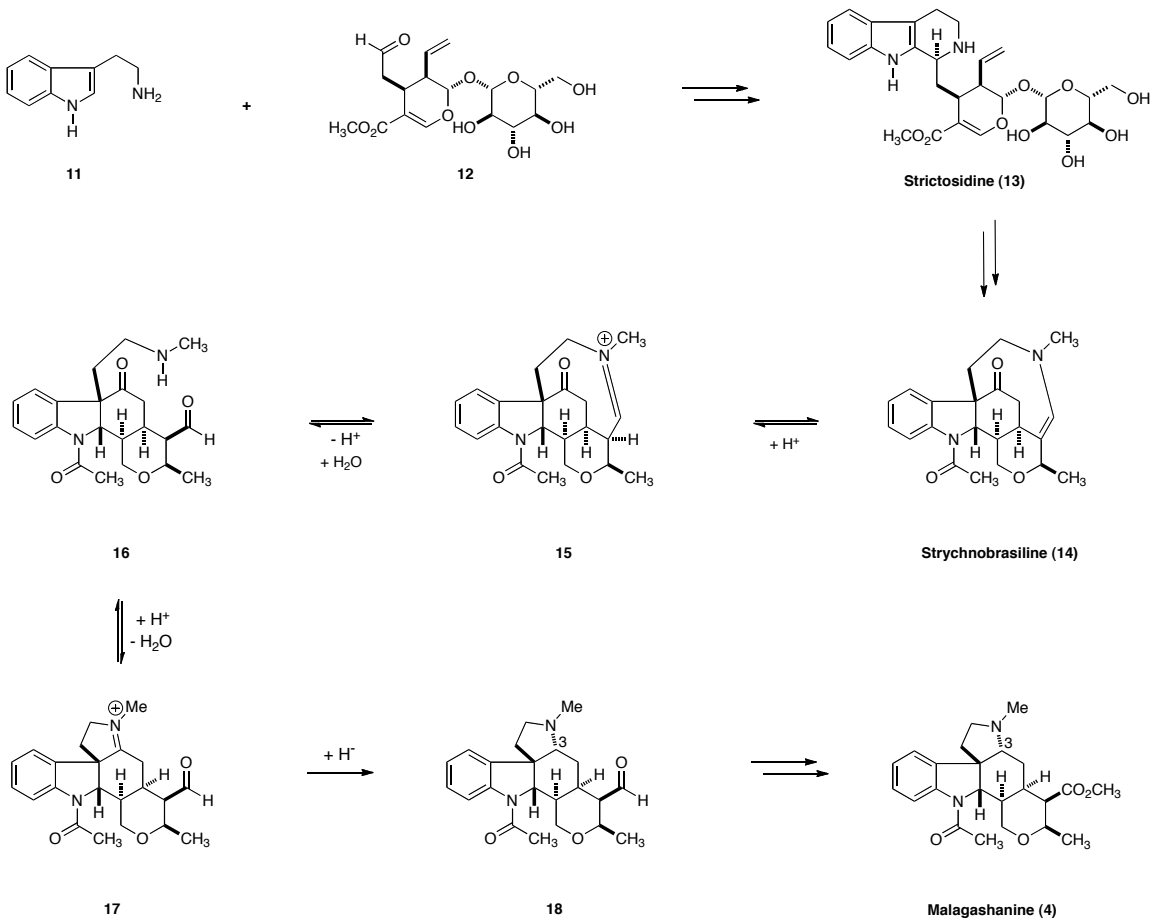
The mechanism through which chloroquine resistance operates still is a topic of debate.[10] There is some evidence suggesting that it is caused by Pgh-1, an ortholog of one of the P-glycoproteins expressed in multi-drug resistant human cancer cells (ABC transporter).[11] Additionally, some research suggests that a *Pf*CRT protein might be responsible for the increased resistance either by changing the vacuolar pH (which would result in reduced CQ uptake or lower binding affinity for ferriprotoporphyrin IX) or by

facilitating the efflux of CQ itself.[12] The ability of malagashanine to negate drug resistance in CQR *Pf* strains provides an excellent opportunity to probe the biological mechanisms controlling these processes. Moreover, such studies could well impact the field of cancer research provided that the parallels of chloroquine resistance and multi-drug resistance in human cancer cells proved accurate. Consequently, useful quantities of malagashanine and synthetic analogs are required. This dissertation describes our efforts to develop a reliable and efficient synthesis of malagashanine, which will allow us to generate a useful amount of material for these biological evaluations.

## 1.4. Biosynthesis and Related Natural Products

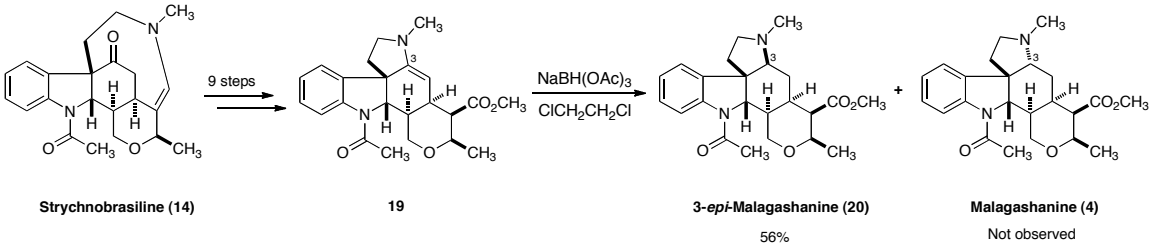
The monoterpene indole alkaloids are a family of several hundred compounds all sharing a common set of building blocks comprised of tryptamine (**11**) and secologanin (**12**), as well as a common biosynthetic intermediate, strictosidine (**13**) (Scheme 1.1).[2-3] Malagashanine is a recent addition to this growing family.

The proposed biosynthetic pathway suggests that malagashanine arises from strychnosbrasiline (**14**), which is biosynthetically related to strychnine (**1**) and is found in large quantities in the bark of *S. myrtoides*.[7] Starting with compound **14**, the process could involve scission of the $N_b$-C(21) bond through protic acid activation *via* iminium ion **15** to afford secondary amine **16**, followed by condensation with the C(3) carbonyl. Hydride reduction of the resulting iminium ion **17** would generate malagashanine precursor **18** with the novel β-configuration at C(3).




**Scheme 1.1** Proposed biosynthetic pathway for malagashanine.

There is one reported biomimetic approach to malagashanine as illustrated in Scheme 1.2.[13] Strychnobrasiline (**14**) was converted to compound **19** in nine steps, and then the reduction of the enamine moeity was attempted in order to install the C(3) stereocenter with the requisite configuration. However, only 3-*epi*-malagashanine (**20**) was obtained. This result is in line with the nucleophile attacking preferentially from the bottom face of enamine **19** to avoid the highly concave upper face.



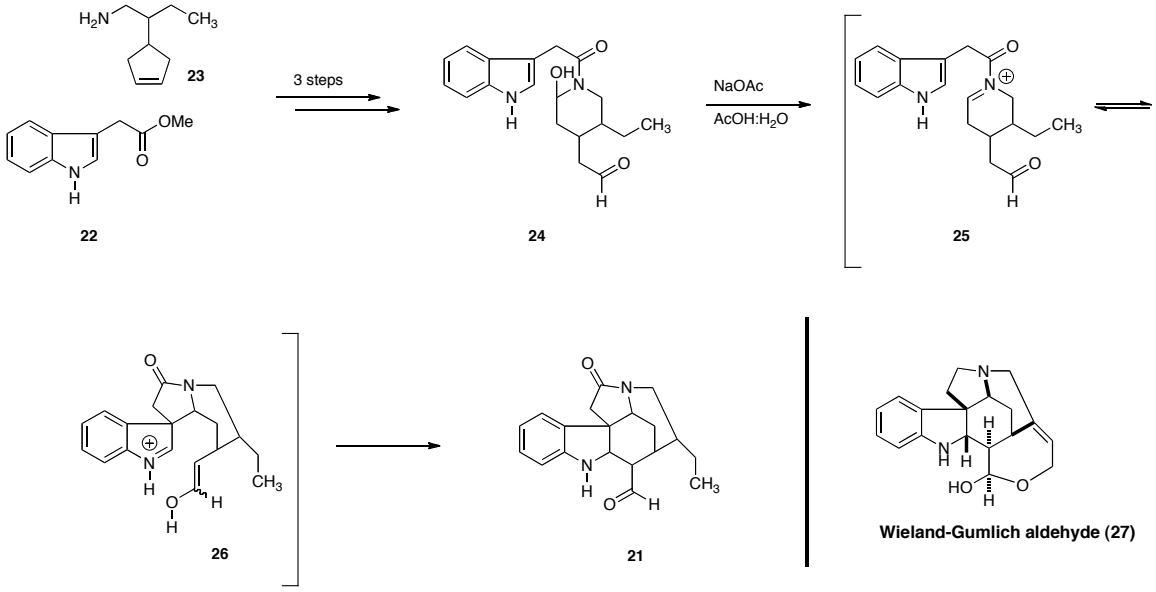

**Scheme 1.2** Synthetic attempt to access malagashanine in a biomimetic fashion.

At the onset of our study, there were no reported synthetic methods that addressed the construction of the C(2), C(7) and C(3) stereocenters with the *syn-anti* stereochemical pattern found in the malagashanine alkaloids. In contrast, a number of approaches have been developed for the generation of the core of the aspidosperma alkaloids with high diastereoselectivity. In considering a synthetic approach for malagashanine, it is first important to review the evolution of successful strategies that employ cascade cyclization reactions to set three or more of these key stereocenters in a single chemical step. By understanding the factors that control the stereoselectivity of these transformations, a successful strategy for the stereoselective synthesis of the core of the malagashanine can be developed.

## 1.5. Van Tamelen, Harley-Mason, and Waterfield: An Ingenious Approach to the Strychnos and Aspidosperma Alkaloids

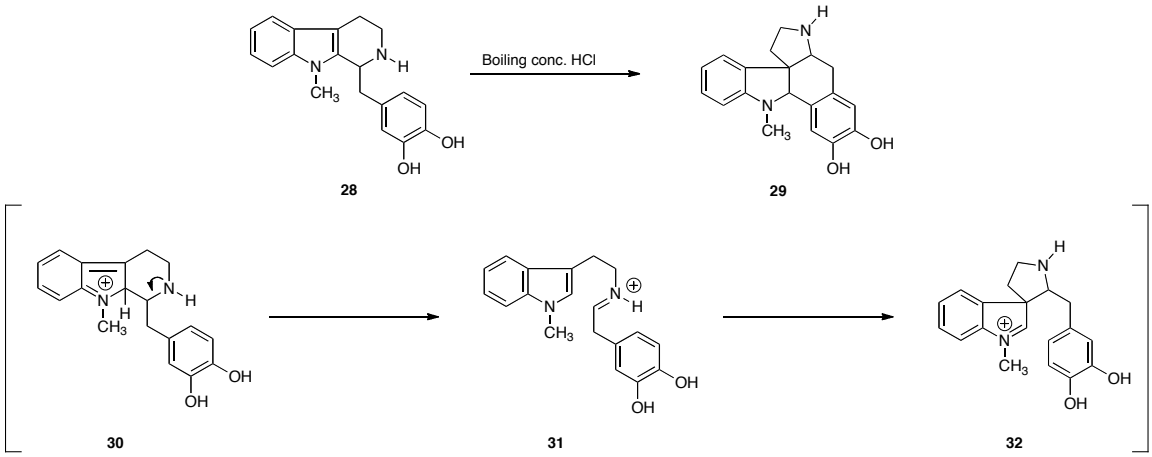
In 1960, Van Tamelen and coworkers published a paper detailing the rapid construction of strychnine-like derivative **21** from basic starting materials **22** and **23** in three chemical steps (Scheme 1.3).[14] This constituted the first laboratory example that applied the principles put forth by Woodward for the biosynthesis of the strychnos

alkaloids. The authors stirred the sensitive amido aminol **24** in aqueous acetate buffer, which presumably generated acyl iminium ion **25**, followed by C(3) nucleophilic attack to form spiroindolium ion **26**, and nucleophilic attack at C(2) by the enol tautomer of the tethered aldehyde, to generate two new rings and four new stereocenters. However, the yield for this transformation was not reported.




**Scheme 1.3** Van Tamelen's approach to the core of strychnine.

The product structure was determined by elemental analysis and by comparison of the ultraviolet spectrum of Wieland-Gumlich aldehyde (**27**) with a derivative of **21** in which the formyl carbonyl was reduced to the corresponding primary alcohol. However, no stereochemical assignments were made.



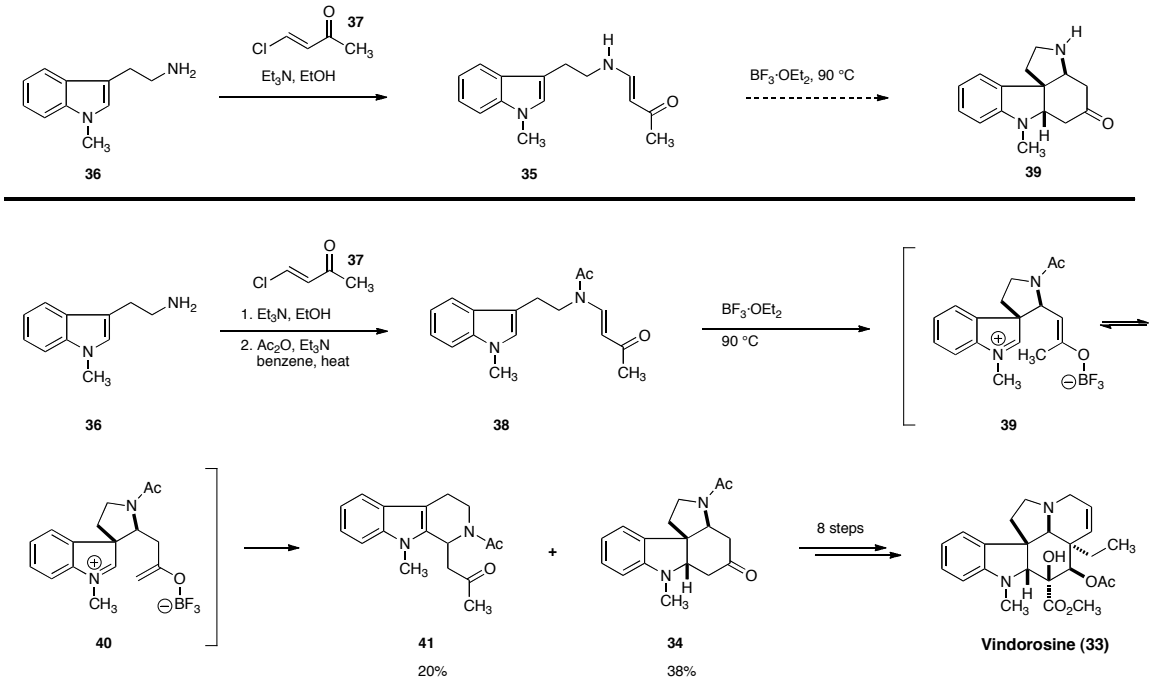

**Scheme 1.4** Novel rearrangement of tetrahydrocarbolines to indoline compounds.

In the same year, Harley-Mason and Waterfield reported a novel skeletal rearrangement of tetrahydrocarboline **28**, which upon treatment with boiling concentrated hydrochloric acid generated indoline **29** (Scheme 1.4).[15] The authors proposed that under the highly acidic reaction conditions, protonation at C(2) afforded compound **30** which rearomatized to the indole moeity *via* carbon-carbon bond scission and generated iminium ion **31**. At this stage, C(3) nucleophilic attack produced a new indolium ion **32** which was subsequently trapped through an intramolecular Friedel-Crafts reaction to afford indoline **29**. The product was characterized by NMR and ultraviolet spectroscopy, but no stereochemical information was provided. Although the authors commented on the high efficiency of the transformation, the yield was not reported.

These experimental contributions along with the valuable synthetic and mechanistic studies provided by other groups helped advance the understanding of the factors controlling C(2) and C(3) attack in the context of tryptamine chemistry.

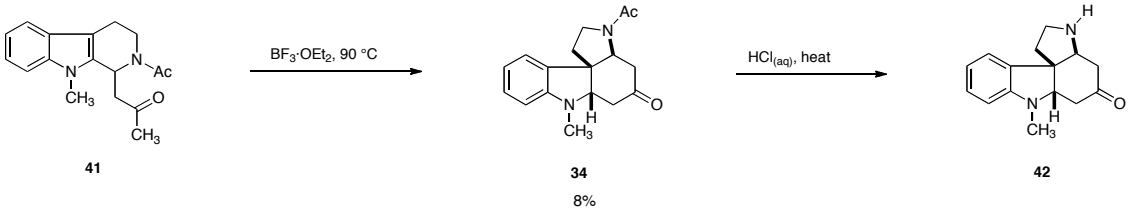
## 1.6. Application of Büchi's Approach to Vindorisone, Vindoline and Other Targets.

In 1971, Büchi and coworkers achieved the first total synthesis of the aspidosperma alkaloid vindorosine (**33**) (Scheme 1.5).[16] The synthetic strategy to access tetracyclic core **34** relied on a tandem double cyclization reaction to set the necessary C(2), C(3) and C(7) stereocenters, as well as generate a carbonyl moeity at C(15) to serve as a functional handle for later transformations. Preliminary attempts to cyclize vinylogous amide **35,** available from the condensation of $N_a$-methyl tryptamine **36** with $\alpha,\beta$-unsaturated ketone **37**, were not fruitful. However, installing an electron withdrawing group at $N_b$ and treating **38** with boron trifluoride etherate at 90 °C afforded the desired cascade cylization product **34** in 38% yield.




**Scheme 1.5** Büchi's approach to Vindorosine (**33**).

The mechanism of this transformation presumably involved activation of the vinylogous amide carbonyl by boron trifluoride followed by conjugate addition *via* C(3) nucleophilic attack to afford spiroindolium **39**. Fluoride mediated tautomerizations ultimately generated ketone enolate **40**, which cyclized to afford spiroindoline **34**. The minor carboline side product **41** in this reaction was also isolated in 20% yield. Re-subjecting **41** to the same reaction conditions afforded 8% of compound **34** and suggested that a similar mechanism to that described by Mason and Waterfield was involved (Scheme 1.6).

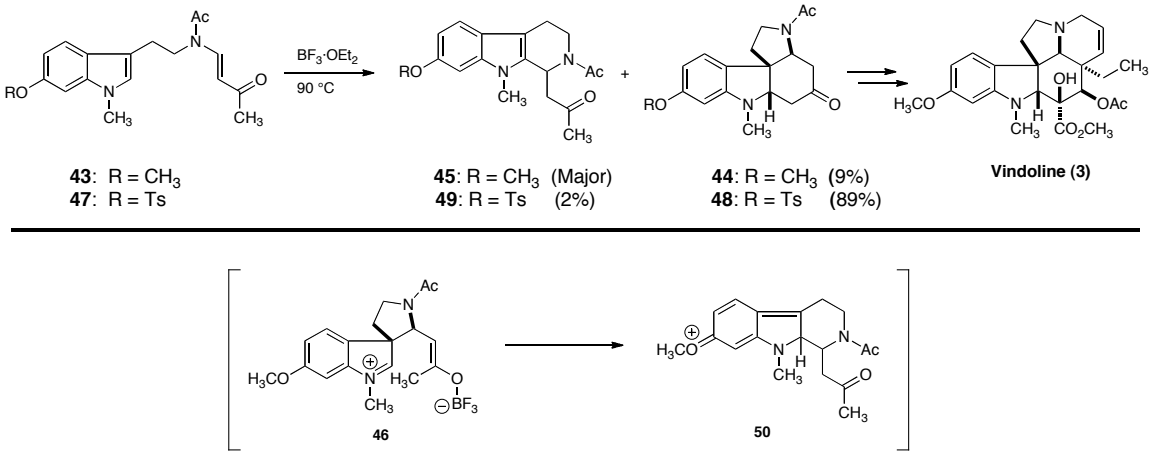



**Scheme 1.6** The Büchi ketone (**34**) is the thermodynamic product.

The authors hydrolyzed the $N_b$-acetyl group using hot aqueous 10% hydrochloric acid without observing any isomerization of the product **42**, despite the presence of the highly labile $\beta,\beta$'-diamino ketone functionality (Scheme 1.6). This observation, as well as the conclusions drawn from molecular modeling studies both suggested that the Büchi ketone (**34**) was the thermodynamic product of the cascade cylization reaction.

Büchi and co-workers were also interested in vindoline (**3**), another aspidosperma alkaloid with a similar structure to that of vindorisine (Scheme 1.7).[17] The synthesis required the installation of a 6-methoxy substituent in the indole starting material **43**.

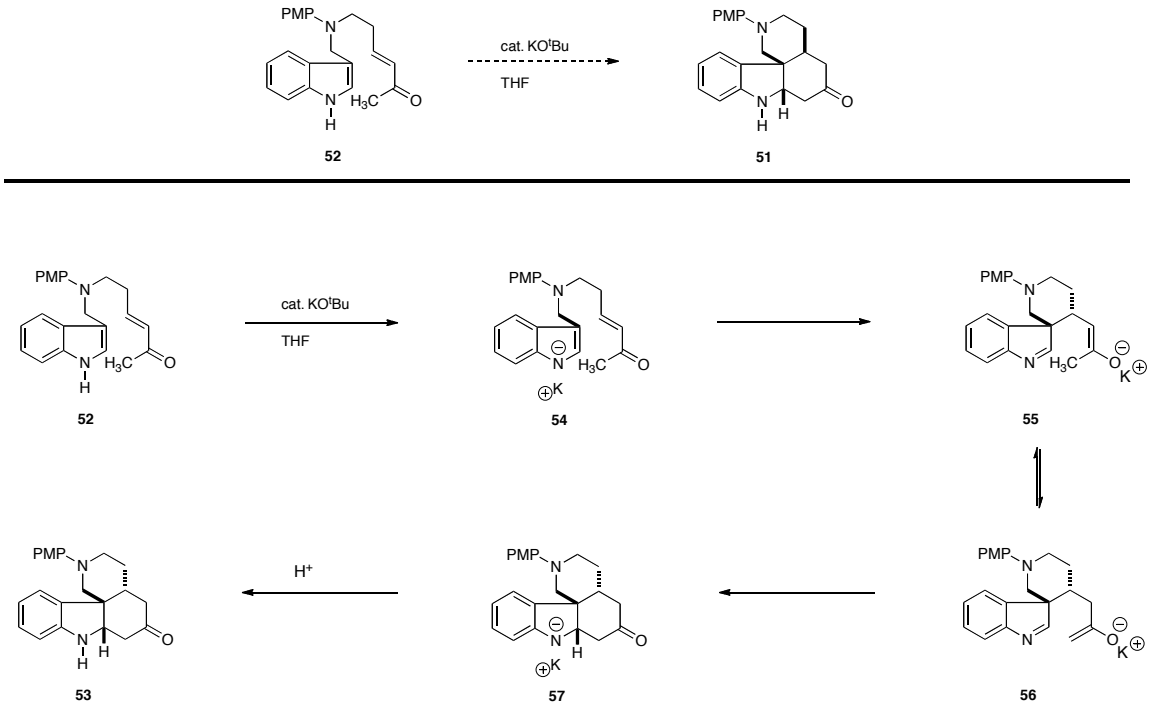
However, treatment of **43** with boron trifluoride etherate at 90 °C produced only 9% of the desired compound **44** and large amounts of tetrahydrocarboline **45**. Resubjecting **45** to the reaction conditions did not afford any **44** either. The authors hypothesized that the high electron density of the indole ring conferred by the methoxy substituent was facilitating the Wagner-Meerwein rearrangement of the initially formed spiroindolium ion **46**, favoring the formation of **45**. Consequently, replacing the methyl substituent with an electron withdrawing tosyl group at the 6-hydroxyl position tuned the selectivity in favor of tetracycle **48** and almost completely suppressed the formation of side product **49**. Vindoline was accessed in nine steps from compound **48**.




**Scheme 1.7** Effect of indole substituents on product ratios.

Throughout the years the Büchi ketone (**34**) has proven to be a very versatile intermediate for the synthesis of a wide range of aspidosperma alkaloids. It has also served as a source of inspiration for the development of methods to access analogous synthons. For example, in their efforts to access the core of the manzamine alkaloids, the Marko group planned to generate a six-membered analog of the Büchi ketone, compound

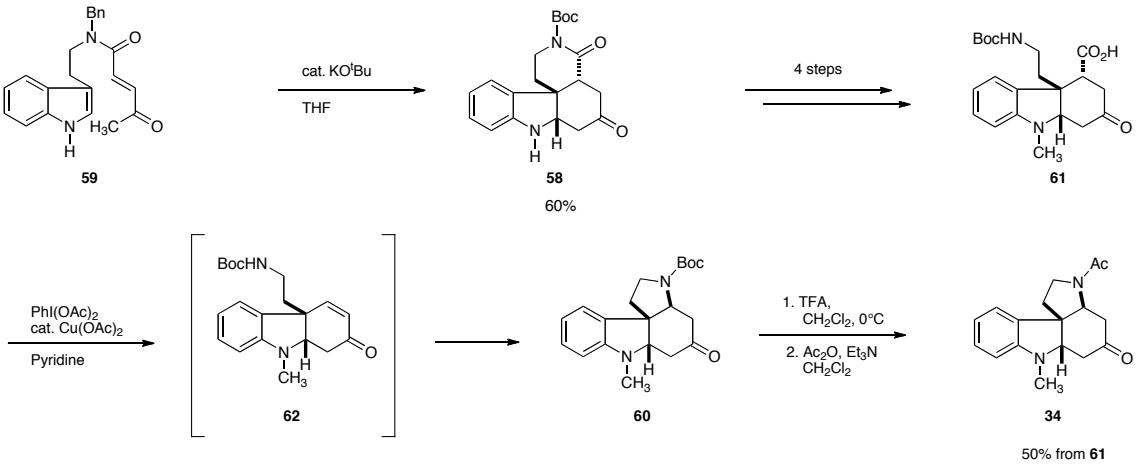
**51**, through an anionic polycyclization cascade reaction from $\alpha,\beta$-unsaturated ketone **52** (Scheme 1.8).[18] However, treatment of **52** with catalytic amounts of potassium *tert*-butoxide in THF did not generate the desired product. Instead, product compound **53**, which displayed a stereochemical pattern reminiscent to that found in the malagashanine alkaloids was isolated as a single diastereomer, presumably through the mechanism shown in Scheme 1.8.




**Scheme 1.8** Marko's approach to the core of the manzamine alkaloids.

In 2005, the Marko group accessed compound **58** using a similar base catalyzed polycyclization reaction, this time using a tryptamine derivative starting material (**59**) (Scheme 1.9).[19] Compound **58** was later converted to the Büchi ketone (**34**) through a seven step sequence, that involved the construction of pyrrolidine **60** through an

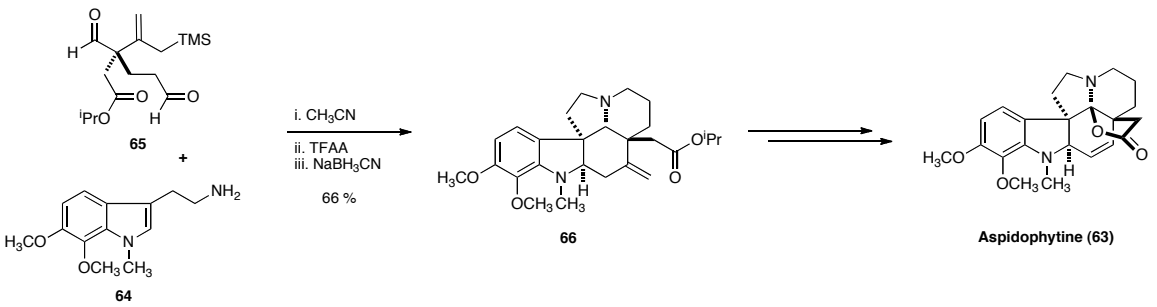
oxidative decarboxylation of compound **61**, followed by Michael addition of the tethered carbamate into the resulting $\alpha,\beta$-unsaturated ketone **62** under basic conditions. Pyrrolidine **60** displayed the same stereochemical pattern found in the aspidosperma alkaloids. This observation is in line with Büchi's hypothesis that the higher stability of the *cis*-fused C-D ring junction ultimately favors the formation of C(2), C(7), and C(3) with all *syn* relative stereochemistry.




**Scheme 1.9** Marko's approach to the Büchi ketone (**34**).

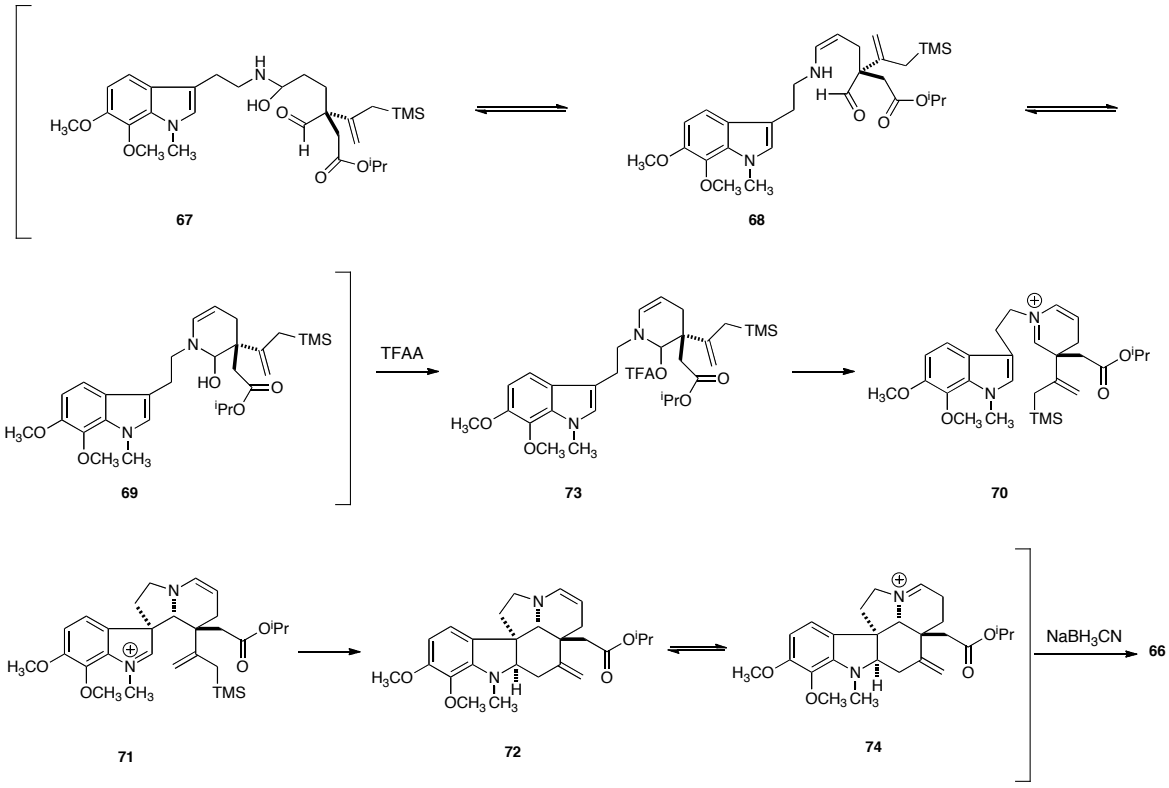
## 1.7. The Corey Approach to Aspidophytine

In 1999, Corey and coworkers achieved the first enantioselective total synthesis of the aspidosperma alkaloid aspidophytine (**63**) (Scheme 1.10).[20] Their strategy revolved around an elegant condensation/cascade reaction between tryptamine **64** and chiral non-racemic aldehyde **65** to generate pentacycle **66** in one step. Aspidophytine was obtained from compound **66** in six steps.




**Scheme 1.10** Corey's approach to aspidophytine (**63**).

A plausible mechanism involves condensation of tryptamine **64** and the less hindered aldehyde at **65** to generate aminol **67**, which can subsequently undergo elimination to *Z*-enamine **68**, followed by intramolecular nucleophilic attack at the tethered tertiary aldehyde to generate the corresponding aminol **69** (Scheme 1.11).

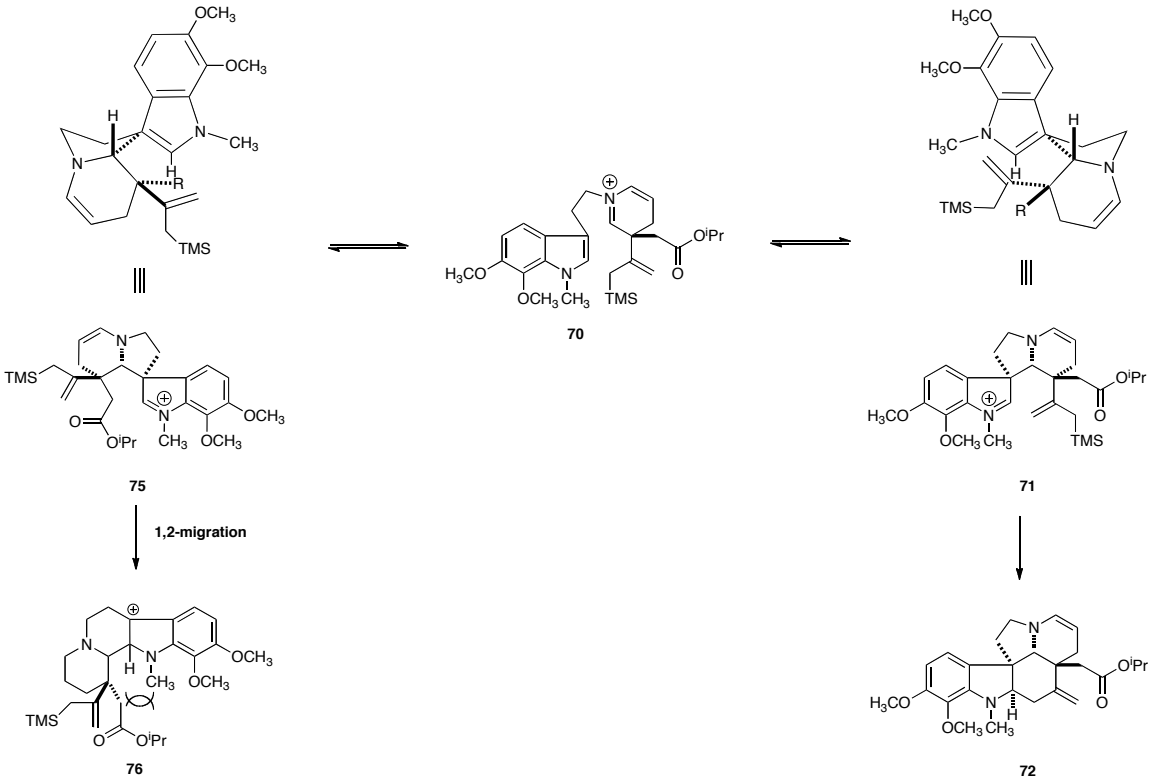



**Scheme 1.11** Plausible machanism for the formation of pentacycle **66.**

Dehydration of the aminol with trifluoroacetic anhydride affords a highly reactive *N*-vinyl iminium ion intermediate **70**, which undergoes a spirocyclization to generate indolium ion **71**. Intramolecular allylation affords pentacycle **72**, followed by *in situ* reduction of the enamine moiety with sodium cyanoborohydride to produce compound **66** in 66% yield.

Regarding the first steps of this mechanism, it is plausible that the diastereomeric spiroindolium ion **75** is initially formed along with **71** (Scheme 1.12). Due to the similarities in size between the $\alpha$-carbon substituents on iminium **70**, the nucleophilic trapping by the tethered indole would be expected to take place with low facial selectivity. At this stage, the allysilane pendant on intermediate **71** is perfectly aligned with the indolium ion and effects the requisite carbon-carbon bond formation to generate the desired tetracycle **72**. On the other hand, the allylsilane pendant on diastereomeric spiroindolium **75** is located on the inaccessible face of the iminium ion (that which is opposite to the indolium ion) and thus is unable to react and complete the cascade sequence. At this stage, spiroindolium **75** can either undergo a 1,2-alkyl migration to produce cation **76** and ultimately produce Pictet-Spengler byproducts (not reported), or it can regenerate iminium ion **70**. It is reasonable to assume that the 1,2-migration would be disfavored because of the non-bonding repulsions that would result between the $\alpha$-carbon substituents and the methyl group at $N_b$ in intermediate **76**. Consequently, the formation of **72** would consume the available amount of **71**, thus driving the conversion of **75** to intermediate **70**. Central to this argument is the structure of cyclic iminium ion **70**. As a consequence of being internal to a six membered ring, iminium ion **70** is configurationally locked into a single geometric isomer, which prevents rotation around

the $N_b$-C bond that would otherwise result in the formation of undesired diastereomers. Ultimately, the configurational rigidity of **70** is responsible for the observed facial selectivity.




**Scheme 1.12** Possible explanation for the observed facial selectivity of the cascade cyclization.

The inflexible nature of iminium ion **70** also simplifies the issue of diastereoselectivity, which is now solely determined by sterics (Figure 1.4). A comparison of transitions states **77** and **78** shows that the former maximizes to a higher degree the distance between the allyl silane moeity and the bulky indole ring, leading to the formation of the only reported diastereomer **72**.

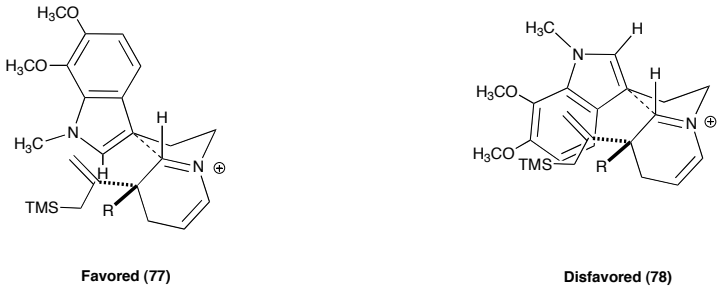


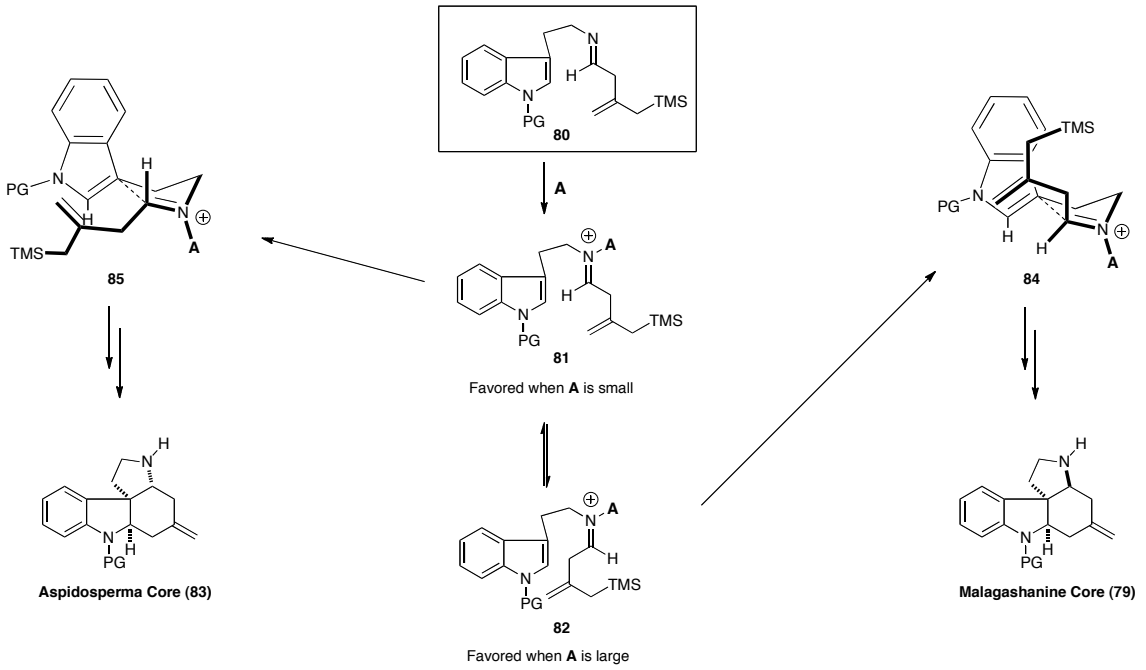

**Figure 1.4** Explanation for the observed diastereoselectivity.

## 1.8. Our Strategy to Access the Core of the Malagashanine Alkaloids

Throughout the last decades the synthetic community has witnessed numerous ingenious approaches to the total synthesis of several aspidosperma and strychnos alkaloids. These methods continue to offer valuable inspiration as well as insight to the synthetic challenges surrounding these molecules. Generally, these approaches rely on the inherent preference of these systems to form the C(2)-C(7) *syn* and C(7)-C(3) *syn* relative stereochemistries with almost exclusive selectivity. On the other hand, as illustrated by the synthesis of aspidophytine by Corey and coworkers, effective stereocontrol can also be achieved when a conformationally restricted iminium ion is utilized.

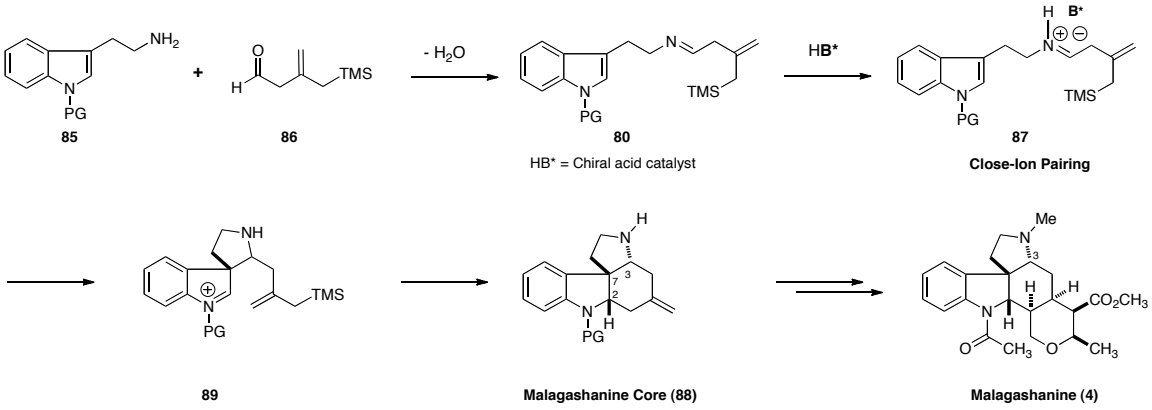
We recognized that the latter case was particularly relevant to the development of a general strategy for the construction of malagashanine. The key to selectively access the requisite core **79** would be to employ an acyclic imine **80** and a suitable acid **A** (Scheme 1.13). The size of the acid **A** could determine the relative ratio of iminium ion/acid complexes **81**/**82**, thus allowing for the selective formation of either alkaloid core **83** or **79**, respectively. A bulky acid would coordinate to imine **80** *via* complex **82** in order to

maximize its distance from the allylsilane moeity. On the other hand, small acids would coordinate *via* complex **81**, in which the larger allylsilane and *N*-alkyl substituents would be positioned *trans* to each other.




**Scheme 1.13** The size of the acid **A** could determine the product distribution.

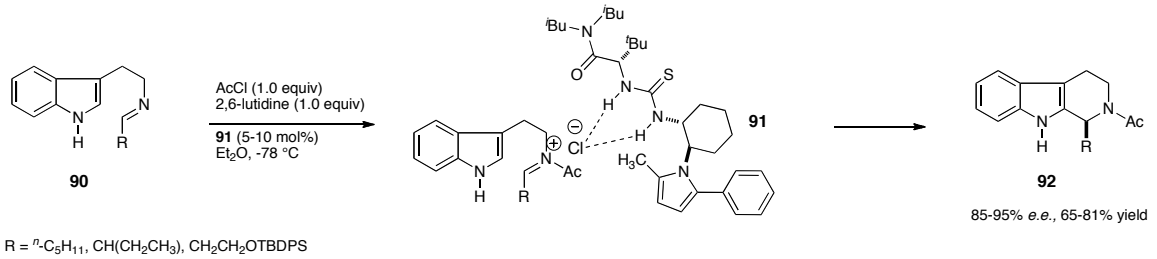
Imine **80** could be accessed easily from tryptamine **85** and aldehyde **86** (Scheme 1.14). Additionally, working with imine **80** would also present the opportunity to eventually carry out the transformation under chiral protic acid catalysis. The stereoinduction of the initial spirocyclization could be controlled by a chiral protic acid *via* close ion pairing between iminium ion **87** and chiral counterion $\mathbf{B}^*$, to afford tetracycle **88** in an enantio- and diastereoselective fashion.




**Scheme 1.14** Our general approach to the malagashanine core.

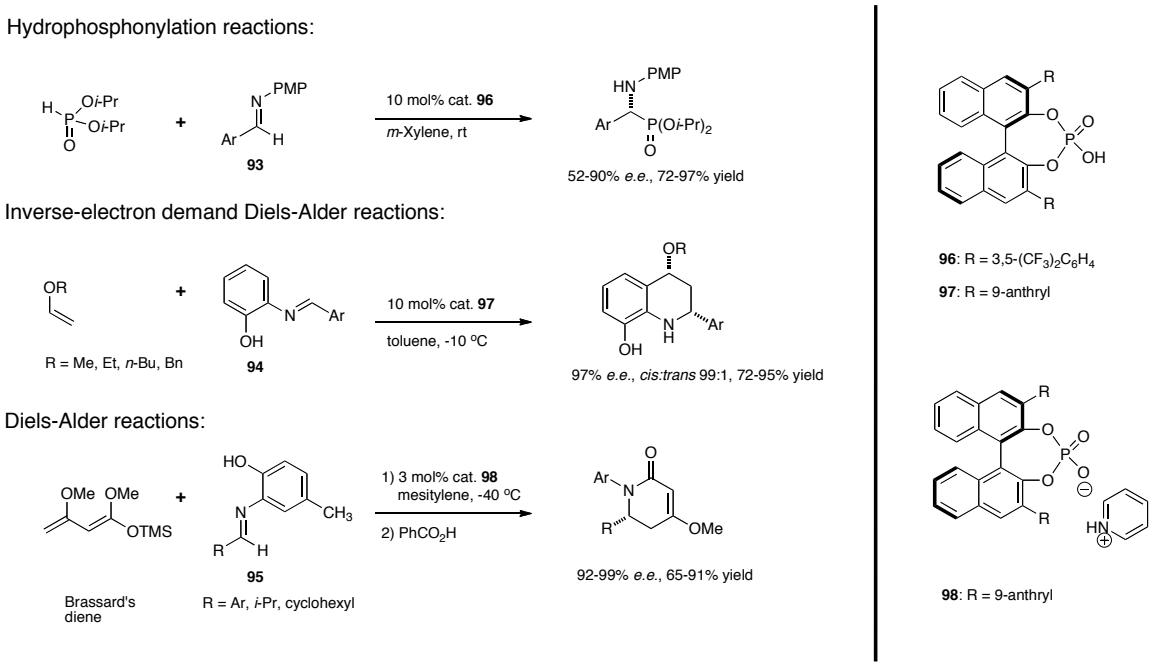
Although our immediate objectives were to develop an efficient method to access the core of malagashanine, and elaborate this into a viable synthetic route to malagashanine itself, the long-range goal of accessing the molecule in an enantioselective fashion played a major role in our investigation. Whenever possible, our model systems were designed to be amenable to the use of chiral thioureas and/or chiral Binol phosphoric acids.

We were especially interested in the precedent established by the Jacobsen group concerning the use of thiourea-based chiral hydrogen-bond donors to promote the reaction of simple alkyl imines **90** with tethered indole nucleophiles (Scheme 1.15).[21] In contrast to the relatively acidic Binol phosphoric acids (which react *via* protonation of the substrate to afford ion-pairs), thioureas are relatively weak acids that operate solely through hydrogen bonding interactions. Consequently, the imine substrates are first activated *in-situ via* acylation. The role of catalyst **91** is then to interact with the chloride ion to form a chiral complex that affords the corresponding Pictet-Spengler product **92** in good yields and high to excellent enantioselectivities.




**Scheme 1.15** Chiral thiourea catalayzed enantioselective Pictet-Spengler reaction.

We were also interested in the work of Akiyama, who had showed that *N*-aromatic aldimines **93-95** could be activated by catalysts **96-98** to undergo a variety of transformations, including hydrophosphonylation reactions as well as normal and inverse-electron demand Diels-Alder reactions, respectively (Scheme 1.16).[22] The yields for these reactions were usually high and the enantioselectivities were excellent.




**Scheme 1.16** Chiral Binol phosphoric acids are versatile Brönsted acid catalysts.

The following chapters detail our efforts to develop a diastereoselective double cyclization cascade reaction to access the core of the malagashanine alkaloids, and its application to the total synthesis of malagashanine.

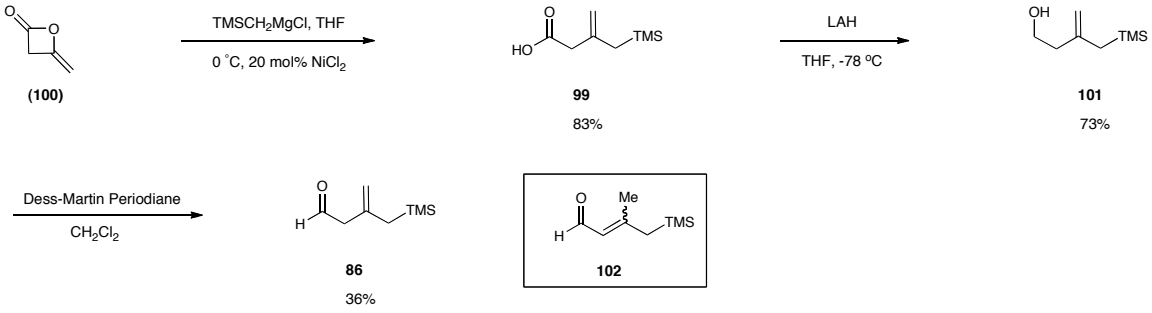
# 2. Chapter Two: Development of a Cascade Cyclization Reaction to Access the Core of the Malagashanine Alkaloids

## 2.1. Early Attempts: Synthesis of $\beta,\gamma$-Unsaturated Imine 80 *via* Condensation of Aldehyde 86 and Tryptamine 36

### 2.1.1. Synthesis of $\beta,\gamma$ -Unsaturated Aldehyde 86

We envisioned the construction of $\beta,\gamma$-unsaturated imine **80** through the condensation of tryptamine **36** and known aldehyde **86** (Scheme 2.1).[23] Although the sensitivity of $\beta,\gamma$-unsaturated aldehyde **86** was a concern to us, we reasoned that the possibility of creating high molecular complexity from such a simple starting material merited the effort. Acid **99** was synthesized using a Kumada cross-coupling of commercially available diketene (**100**) and (trimethylsilyl)-methylmagnesium chloride in the presence of catalytic amounts of $NiCl_2$, using conditions developed by Itoh and coworkers (Scheme 2.1).[23c, 24] However, early attempts to reproduce the authors' reported 95% yield were met with disappointing results, with our highest yields never surpassing 40%. Using freshly prepared (trimethylsilyl)-methylmagnesium chloride did not improve the yields.[25] Moreover, changing the order of addition from that reported (which originally called for treating the Grignard reagent with $NiCl_2$ prior to the slow addition of diketene) was equally unsuccessful. However, during the course of our studies we noticed a steady decrease in reaction performance over time, despite using our best conditions. Given the known susceptibility of diketene (**100**) to undergo polymerization side reactions, we suspected that our starting material was slowly decomposing despite being

stored at 0 °C over $CuSO_4$ stabilizer. Ultimately, purifying diketene (**100**) by sublimation increased the average reaction yield to 80%. Pure diketene **(100**) was stored under argon at -20 °C for 16 months without any noticeable decomposition.




**Scheme 2.1** Synthesis of *β,γ*-unsaturated aldehyde **86.**

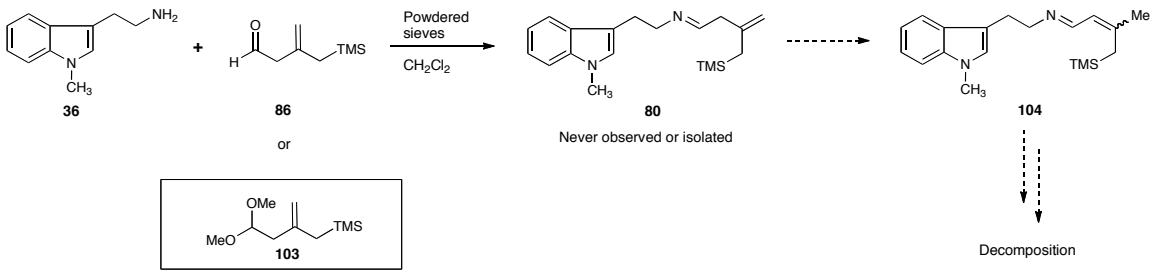
With acid **99** in hand, treatment with LAH at -78 °C afforded known homoallylic alcohol **101**. The oxidation of compound **101** using bipyridyl chromium chlorochromate (BPCC)[26] as indicated by Taylor and coworkers did not generate any of the desired *β,γ*-unsaturated aldehyde **86** in our hands. No starting material was recovered either. Other milder oxidation methods were also employed, including TPAP,[27] which afforded various unidentified side products and trace quantity of the desired aldehyde. Using IBX[28] generated compound **86** as the only product (as assessed by crude $^1$H NMR), but only in trace amounts. Dess-Martin periodinane (DMP)[29] was the most successful oxidation method employed and produced aldehyde **86** without generating significant amounts of side products. The highest yield attained for this reaction was 36%, but the average yields were well below this number. Compound **86** was inherently difficult to isolate because of its high volatility and tendency to decompose on silica. Moreover,

upon standing for two hours it underwent isomerization to the more stable $\alpha,\beta$-unsaturated aldehyde **102**.

### 2.1.2. Attempted Condensation of $\beta,\gamma$-Unsaturated Aldehyde 86 with Tryptamine 36

Our attempts to synthesize imine **80** were mostly carried out under neutral conditions in order to minimize the decomposition of the delicate $\beta,\gamma$-unsaturated aldehyde **86**. However, subjecting the crude compound **86** to tryptamine **36** in the presence of 4Å molecular sieves only generated large amounts of unidentified side products (Scheme 2.2). Unfortunately, the decomposition of **86** was fairly general under neutral (and acidic) conditions. It seemed that the high lability of aldehyde **86** was inherently incompatible with the basicity of the tryptamine reaction partner. We could also envision the observed decomposition as arising from side reactions *via* imine/enamine tautomerizations of compound **80**. We employed the known methoxyacetal[30] **103** as an aldehyde equivalent, but the results were equally disappointing.

Taking into account all of the difficulties we experienced generating and isolating compound **86**, we recognized that the current method would not provide a practical route to the desired tetracyclic core of malagashanine. A better approach would be to *in-situ* generate a $\beta,\gamma$-unsaturated iminium ion, but avoid altogether the use of labile precursors such as $\beta,\gamma$-unsaturated imine **80**.

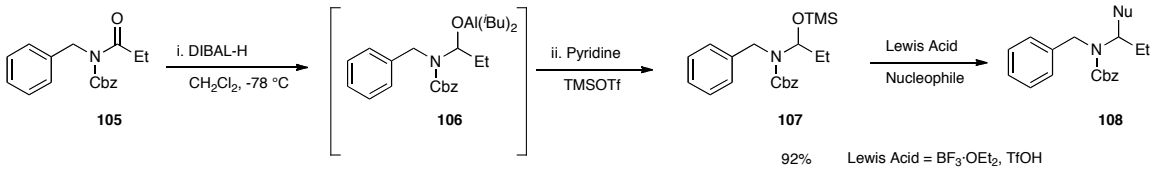



**Scheme 2.2** Synthetic approach to $\beta,\gamma$-unsaturated imine **80.**

## 2.2. Accessing the Key Iminium Ion Intermediate by Reduction of a Stable Amide Precursor

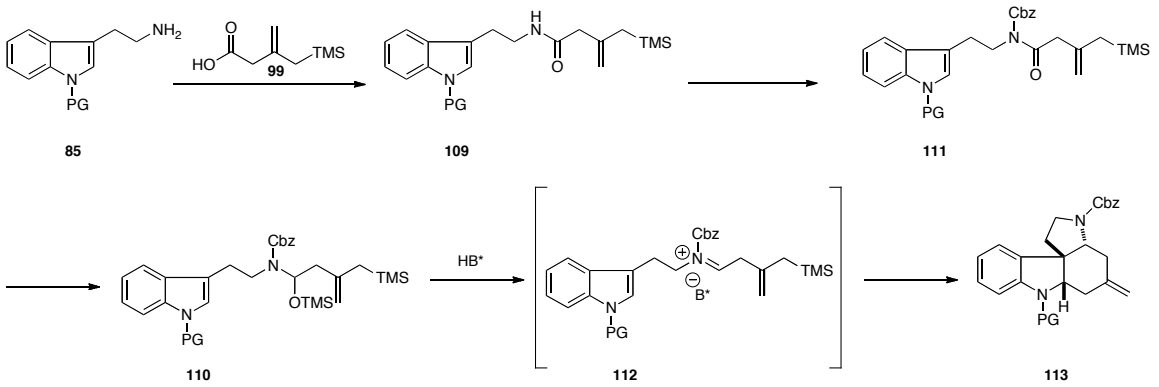
### 2.2.1. *N*-Cbz-*O*-TMS-Aminols are Iminium Ion Precursors

Inspired by Rychnovsky's elegant entry into oxonium ion chemistry initiated by DIBAL-H reduction of esters,[31] we envisioned an analogous amide reduction could deliver our key iminium ion intermediate. A literature search revealed that the Suh group had recently established that *N*-acylamide **105** could be reduced by DIBAL-H, generating the corresponding aluminium hemiacetal **106** (Scheme 2.3).[32] Subsequent addition of pyridine facilitated the decomplexation of the aminol oxygen from the dialkyl aluminum species, and allowed trapping with trimethylsilyl triflate to afford the corresponding *N*-acyl-*O*-TMS-aminol **107**. These species could then be activated with Lewis and protic acids to afford highly reactive *N*-acyliminium ions capable of undergoing additions with a range of nucleophiles.




**Scheme 2.3** *N*-acyl-*O*-TMS-aminols are versatile *N*-acyliminium ion precursors.

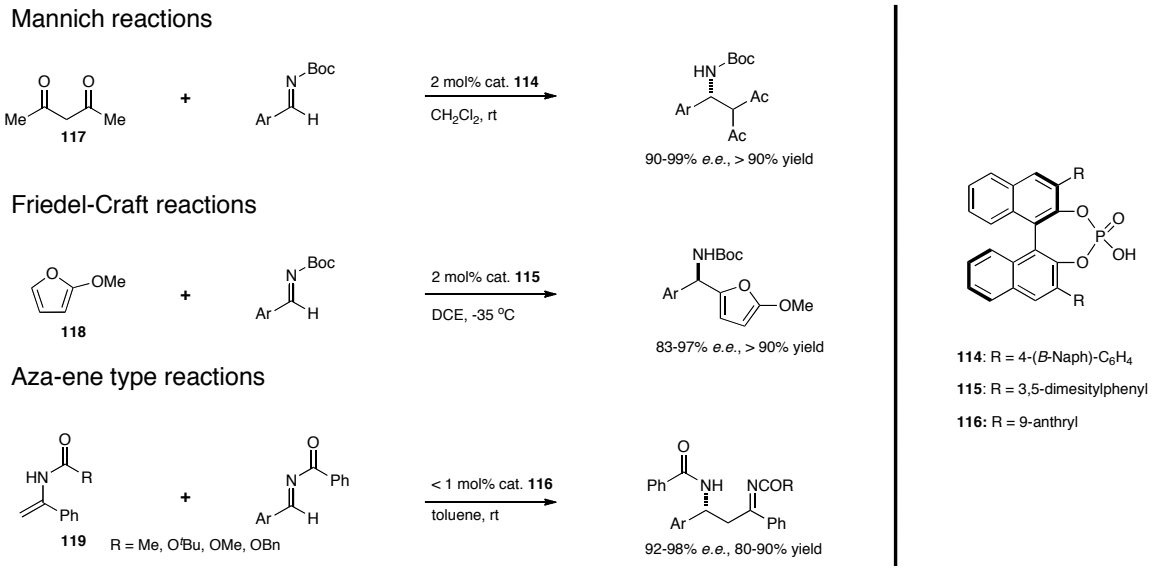
We reasoned that the incorporation of *N*-acyl-*O*-TMS-aminols to our method would circumvent the use of sensitive iminium ion precursors. Moreover, this new approach would require only minor modifications to our original route. The coupling of tryptamine **85** with acid **99** would generate a stable amide **109** that would then be functionalized with a suitable acyl group and converted to *N*-acyl-*O*-TMS-aminol **110** (Scheme 2.4).




**Scheme 2.4** New synthetic approach for the synthesis of core **113.**

This improved approach also remains amenable to protic acid catalysis. Both general classes of chiral protic acids discussed in chapter one can catalyze transformations involving *N*-acyliminium ion intermediates. For example, Terada has utilized *N*-Boc and *N*-acyl aromatic aldimines in the presence of catalysts **114-116** to

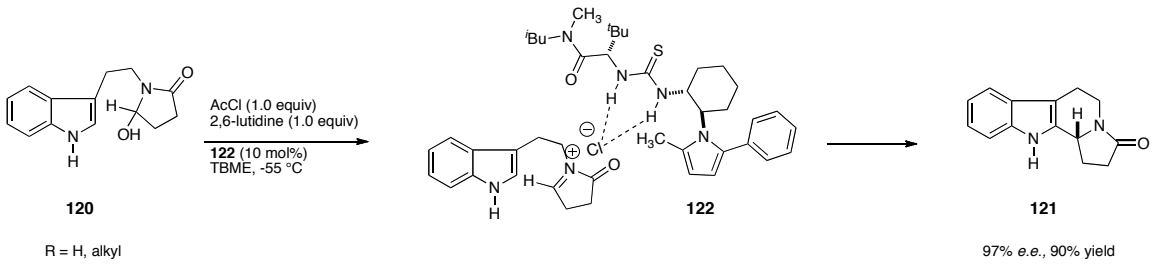
effect various carbon nucleophiles additions, including Mannich reactions with 2,4–pentandione (**117**),[33] Friedel-Crafts reactions with electron rich furans such as 2-methylfuran **118**,[34] and aza-ene reactions with *N*-acyl enamine **119** (Scheme 2.5).[35] The yields and selectivity are also comparable to those reported by Akiyama. A similar process could be envisioned using acyl-iminium ion **112**.




**Scheme 2.5** Terada's work with chiral Binol phosphoric acids.

During the course of our research, the Jacobsen group reported a variant of their original protocol for the enantioselective Pictet-Spengler reaction (Scheme 2.6).[36] This new method allows for the conversion of *β*-indolyl ethyl hydroxylactams (*e.g.* **120)** to the corresponding indolizidinones (*e.g.* **121**) in good yields and excellent enantioselectivities. Activation of hydroxylactam with trimethylsilyl choride (or with combination of HCl and 3 Å sieves) generates an acyliminium ion intermediate, in which the chloride ion presumably interacts with the catalyst **122** through hydrogen-bonding interactions to form

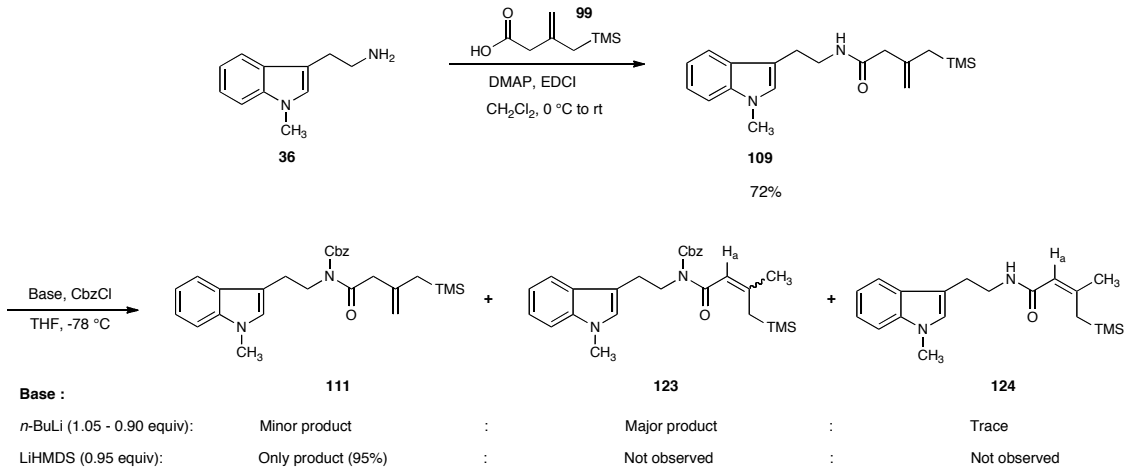
a chiral complex capable of inducing high levels of stereocontrol. This protocol was also investigated in the context of our chemistry (*vide infra*).




**Scheme 2.6** Jacobsen's chiral thiourea catalyst **122** promotes the enatioselective Pictet-Spengler cyclization of hydroxylactams.

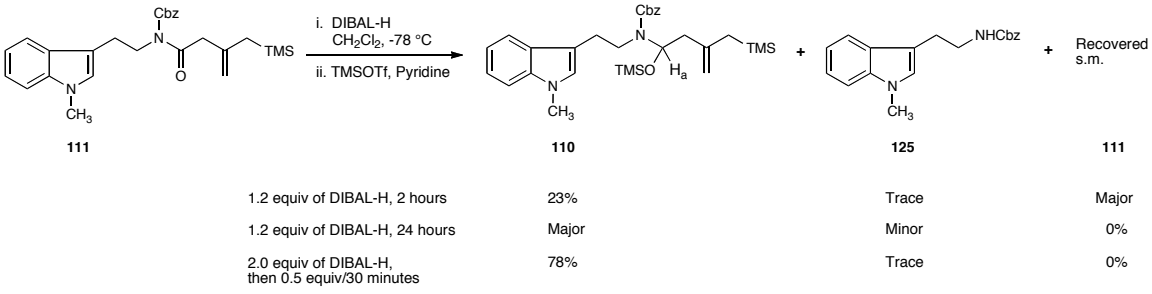
### 2.2.2. Synthesis of *N*-Cbz-*O*-TMS-Aminol 110

The synthesis of *N*-Cbz-*O*-TMS-aminol **110** began with the construction of amide **109** (Scheme 2.7). Tryptamine **36** and acid **99** were coupled using EDCI in the presence of DMAP to afford compound **109** in 61% yield. Our initial efforts to install the Cbz group at $N_b$ entailed low temperature deprotonations with 1.05 equivalents of *n*-BuLi in THF followed by addition of CbzCl to the resulting anion. This led to the isolation of the desired compound **111** and its $\alpha,\beta$-unsaturated isomer **123** (single isomer of undetermined geometry) as an inseparable mixture in a 1:2 ratio. Additionally, trace amounts of the $\alpha,\beta$-unsaturated isomer **124** (single isomer of undetermined geometry) were also isolated. The $^1$H NMR of compound **124** displayed a vinyl proton signal $H_a$ at 4.72 ppm, while that of compound **123** displayed a vinyl proton signal $H_a$ at 6.41 ppm due to the presence of a more electron deficient carbonyl.




**Scheme 2.7** Synthesis of *N*-Cbz-amide **111.**

To prevent isomerization the reaction was carried out using LiHMDS,[37] which conferred higher chemoselectivity in the deprotonation step (presumably by virtue of its lower basicity in comparison to *n*-BuLi). The reaction was also carried out using substoichiometric amounts of base (0.95 equivalents) as a precaution to avoid the formation of the corresponding dianion, which could also lead to isomerization. After optimization, the desired *N*-Cbz-amide **111** was obtained in quantitative yield (based on equivalents of base).



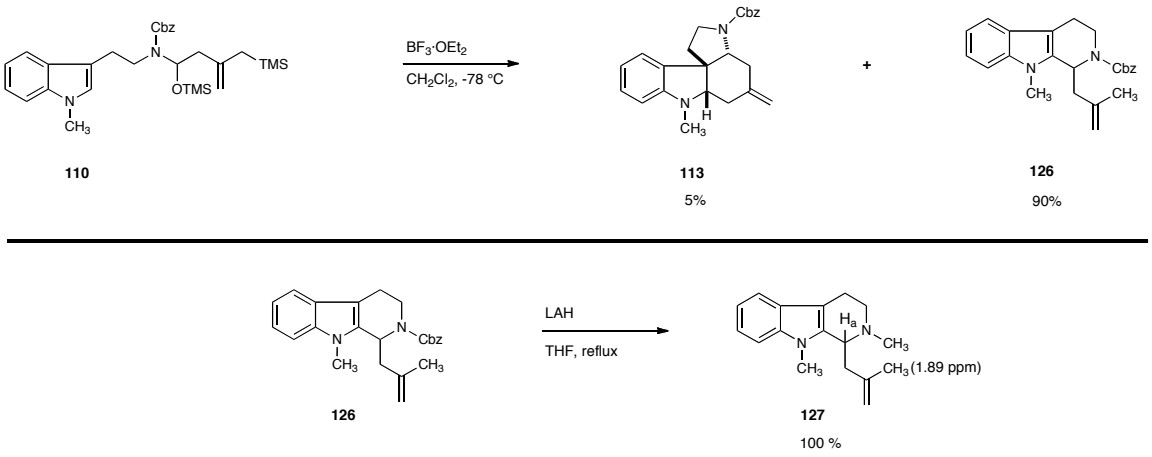

**Scheme 2.8** Synthesis of *N*-Cbz-*O*-TMS-aminol **110.**

With *N*-Cbz-amide **111** in hand, we turned our attention to the synthesis of *N*-Cbz-*O*-TMS-aminol **110** (Scheme 2.8). The reduction of compound **111** was first carried out under identical conditions to those reported by Suh *et al.* (1.2 equivalents of DIBAL-H at -78°C for one hour followed by addition of pyridine and TMSOTf), which afforded **110** in 23% yield, along with significant amounts of recovered starting material and trace amounts of carbamate **125** (obtained through the hydrolysis of the intermediate aluminum acetal). *N*-Cbz-*O*-TMS-aminol **110** was isolated as a 1:0.6 mixture of rotamers with aminol methine $H_a$ signals at 5.95 and 5.79 by $^1$H NMR, respectively. The isolation of starting material suggested that the initial reduction to the intermediate aluminum hemiacetal was not reaching completion, but any attempts to improve the yield by prolonging the reaction time generated large amounts of carbamate **125**. In an effort to minimize the amount of **125** produced, the number of equivalents of DIBAL-H was increased to 2.0. In the event that compound **111** was not consumed after one hour, 0.5 equivalents were added every 30 minutes until the reduction reached completion as assessed by TLC (reagent freshness might be partly responsible for the variation in reaction time). This improved protocol afforded compound **110** in 78% yield.

### 2.2.3. Cyclization of *N*-Cbz-*O*-TMS-Aminol 110: Preliminary Results

With *N*-Cbz-*O*-TMS-aminol **110** in hand, an initial investigation of the double cyclization reaction was undertaken. Treatment of compound **110** with $BF_3{\cdot}OEt_2$ in $CH_2Cl_2$ at -78°C afforded the desired tetracyclic amine **113** in trace amounts as a 2:1 mixture of rotamers (Scheme 2.9). The general structure of compound **113** was tentatively assigned as an indoline derivative based on the upfield shift of two aromatic

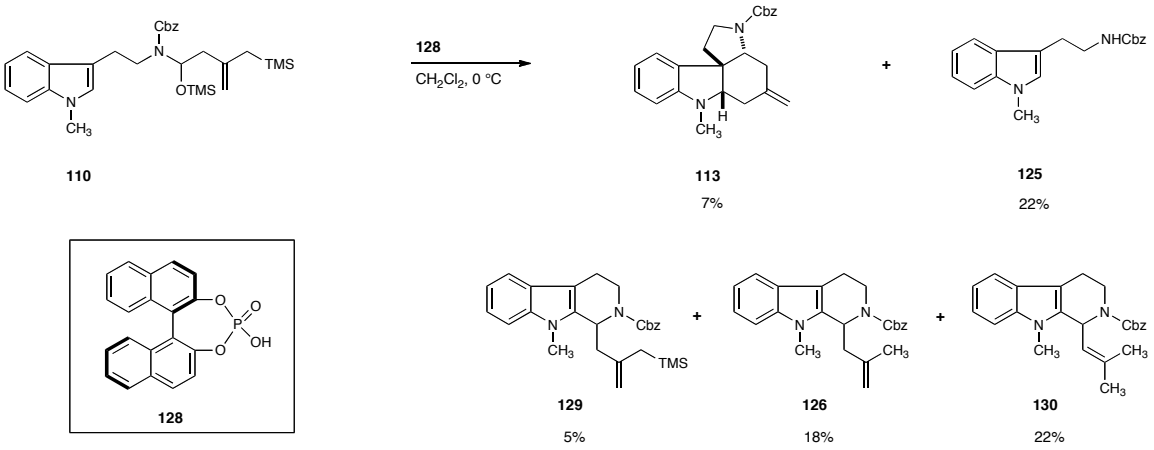
proton signals to 6.62 and 6.36 ppm. This is indicative of an increase in electron density provided by the $sp^3$ hybridized nitrogen substituent through donation of its lone pairs into the aromatic ring. Subsequently, the structure of **113** was also supported by comparison of its $^1$H NMR spectrum to that of compound its $N_a$-benzyl analog, whose structure was corroborated by variable temperature 2D NMR experiments and 1D NOE experiments (*vide infra*). While **113** was only obtained in 5% yield, the majority of the starting material underwent the common Pictet-Spengler reaction to afford tetrahydrocarboline **126** in 90% yield as a 1:0.9 mixture of rotamers. The structural assignment of compound **126** was simplified by reduction of the Cbz group with LAH in refluxing THF to afford the corresponding *N*-methylamine **127**. The $^1$H NMR analysis showed an allylic methyl signal at 1.89 ppm and a methine $H_a$ proton at 3.86 ppm coupled to the neighboring allylic methylene protons ($J$ = 9.8 Hz, 3.8 Hz).




**Scheme 2.9** Cyclization of *N*-Cbz-*O*-TMS-aminol 110 with $BF_3{\cdot}OEt_2$.

Having identified the desired product, we then proceeded to carry out the reaction under protic acid conditions using racemic Binol phosphoric acid **128** (Scheme 2.10).

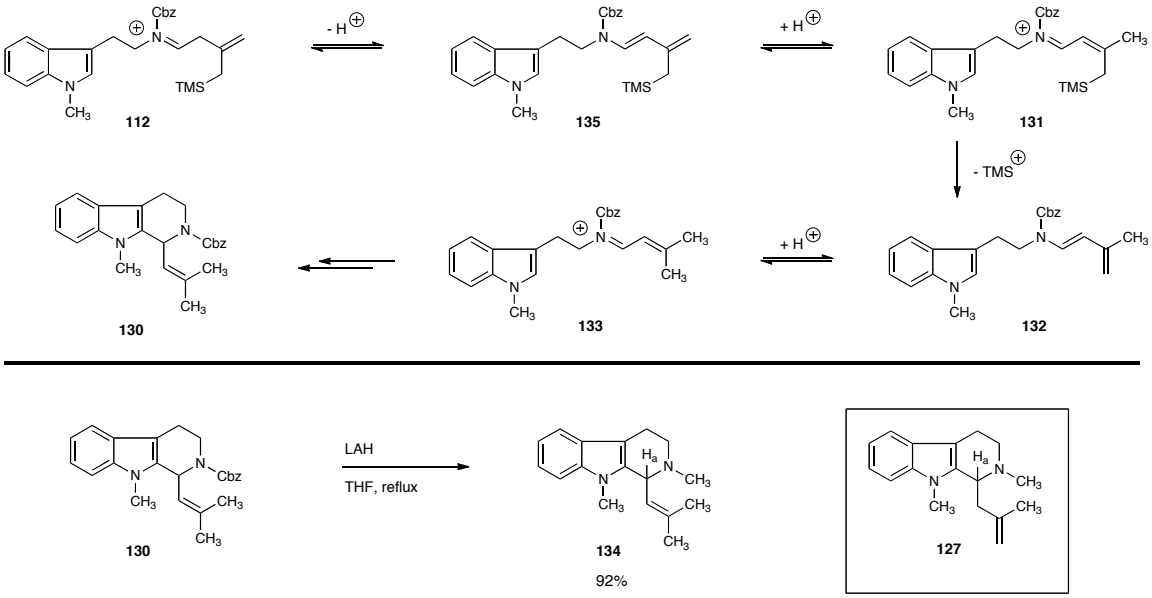
Treating *N*-Cbz-*O*-TMS-aminol **110** with 1 equivalent of **128** at 0 °C generated 7% of tetracyclic amine **113** and a mixture of tetrahydrocarboline side products **126**, **129** and **130** in 18%, 5%, and 22% yield respectively. Compound **125**, the product of hydrolysis of the *N*-Cbz-*O*-TMS-aminol **110**, was also isolated in 22% yield. The structure of compound **129** was assigned by comparison of its $^{1}$H NMR data to that of tetrahydrocarboline **126**, in which the rotameric allylic methyl signals observed in **126** were replaced in **129** by rotameric allylic methylene signals and the corresponding rotameric trimethylsilyl singlets.




**Scheme 2.10** Cyclization of *N*-Cbz-*O*-TMS aminol **110** with protic acid.

Compound **130** is most likely produced through the isomerization of the intermediate iminium ion **112**, which presumably undergoes protodesilylation *via* $\alpha,\beta$-unsaturated iminium ion **131** (Scheme 2.11). Protonation at the $\beta$-carbon of $\alpha,\beta$-unsaturated enamine **132** generates **133**, which is the trapped by the tethered indole to ultimately afford **130**. This is supported by control experiments that indicate that tetrahydrocarboline **126** does not produce **130** under the reaction conditions. Compound

**130** was converted to the corresponding $N_b$-methyl derivative **134** using LAH in refluxing THF, and its structure was assigned by comparison of its $^1$H NMR data to that of compound **127**. The analysis showed that the $H_a$ methine proton signal in **127** had shifted downfield by 0.5 ppm from that observed for the equivalent proton in **134** at 3.86 ppm, which indicated that the allyl group had been replaced by a vinyl substituent.




**Scheme 2.11** Mechanistic rationale for the isomerization of *N*-acyliminium ion **112.**

Lowering the temperature to -78 °C favored formation of the iminium ion hydrolysis product **125** almost exclusively, while reactions at room temperature produced no discernible differences from those carried out at 0 °C. We also investigated the effect of solvent on the product ratio and found that all those examined (DMF, acetonitrile THF, toluene, and $CH_2Cl_2$) led to the formation of Pictet-Spengler products **126**, **129**, and **130**, as well carbamate **125**. We also noticed that compound **125** was the major product when high polarity solvents like DMF and acetonitrile were used. Lastly, the use of stronger

acids such as trifluoroacetic acid (TFA) increased slightly the ratio of cascade product/Pictet-Spengler products (1:4), but not sufficiently enough to merit further investigation.

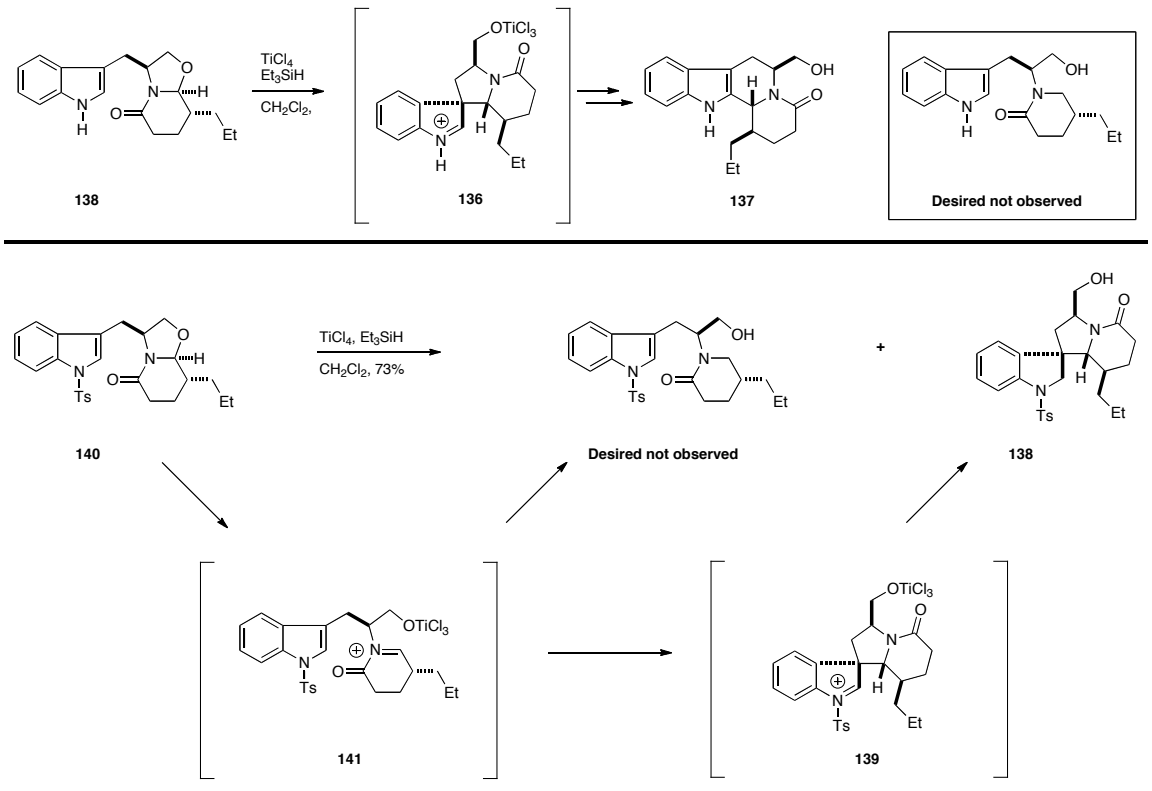
## 2.3. Effect of $N_a$ and $N_b$ Susbtituents on the Key Cyclization Reaction

### 2.3.1. The Substituents on the Nitrogen Atoms Can Have Significant Effects on Product Distribution

The prevalence of Pictet-Spengler side products in the cascade cyclization reaction suggested that subsequent to the C(3) nucleophilic attack at iminium ion **112**, the classical 1,2-migration was occurring faster than the intended intramolecular trapping by the tethered allysilane moiety. This prompted us to carry out an in-depth study to determine what structural features in our system had the most significant effect on the product distribution.

First, we wanted to examine how the steric and electronic nature of the indole nitrogen substituent affected the transformation. To investigate the role of sterics, a large benzyl substituent would be introduced, which should have a similar electronic effect to that of methyl on $N_a$. Additionally, we wanted to assess whether free indole nitrogens were tolerated in the transformation because this could potentially simplify the functionalization of $N_a$ post cyclization. Lastly, given our interest in suppressing the formation of tetrahydrocarboline products, we were interested in an experiment reported by Bosch and coworkers in which they observed a decrease in the rate of C(3) to C(2)

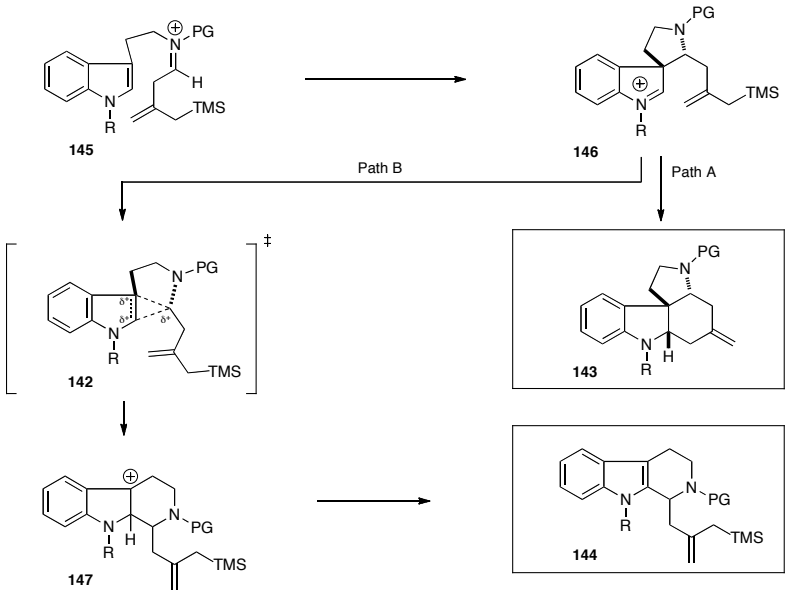
migration of spiroindolium ion **136** when the $N_a$ was substituted with an electron withdrawing group (Scheme 2.12).[38] The original intention of the authors had been to suppress the formation of tetrahydrocarboline **137** during the reductive cleavage of the oxazolidine ring of lactam **138** with $TiCl_4$ and $Et_3SiH$. It seemed that intermediate **136** was forming and rapidly rearranging to tetrahydrocarboline **137** through a classical 1,2-alkyl migration followed by rearomatization. By installing a tosyl group at $N_a$ the authors hoped to deactivate the indole moiety towards nucleophilic attack. However, this did not prevent the initial C(3) attack from taking place, but instead produced **138** in 74% yield. The authors reasoned that the tosyl group was retarding the rate of 1,2-alkyl migration of spiroindolium ion **139**, to allow trapping with $Et_3SiH$ instead.




**Scheme 2.12** Bosch's observations concerning 1,2-migrations in $N_a$-tosyl substituted spiroindoliums**.**

Bosch and coworkers had shown that *N*-acyl-iminium ions were reactive enough to engage even electron deficient indoles. By analogy, our system should also react *via* initial C(3) attack to afford the corresponding spiroindolium ion. At this stage, a decrease in the rate of 1,2-alkyl migration should favor trapping by the tethered allylsilane to afford the desired product.

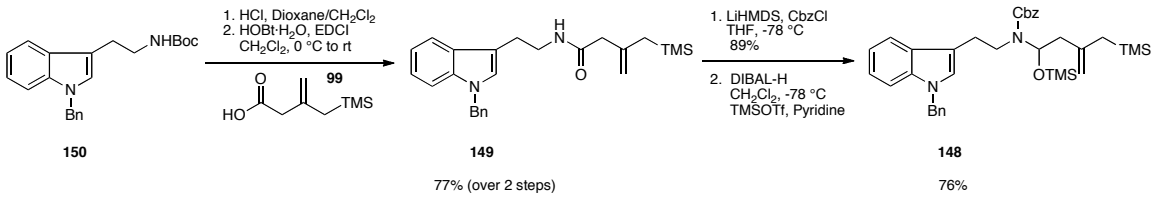
Once an optimal $N_a$ substituent was found, we also wanted to determine how the product distribution was affected by the nature of the $N_b$ substituent. To examine the effect of sterics, we planned to vary the size of the acyl moiety by replacing the Cbz substituent with the bulkier Boc group, as well as the smaller carbomethoxy substituent. On the other hand, the electronic effect of the $N_b$ substituent would be studied by employing auxiliaries with different electron densities. In this respect, we argued that the undesired rearrangement pathway (B) could be disfavored *via* use of highly electron deficient substituents (PG) at the iminium ion nitrogen (Scheme 2.13). This should destabilize the three-membered transition state **142**, which in turn would decrease the rate of 1,2-migration and favor the intramolecular trapping by the pendant allylsilane (Path A). To this end, we planned to install amide and tosyl substituents at $N_b$.




**Scheme 2.13** Mechanistic hypothesis for the formation of compounds **143** and **144.**

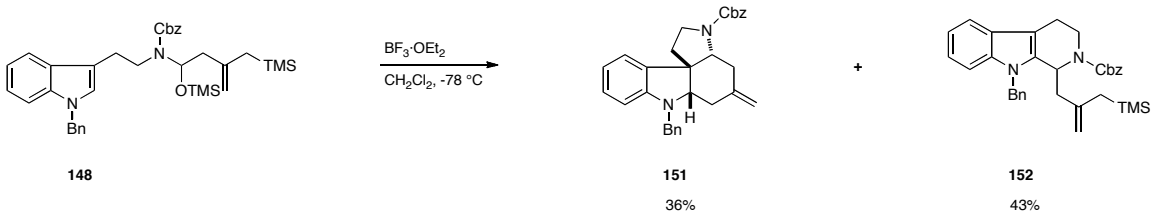
### 2.3.2. Exploring the Effect of $N_a$ Substitution: Synthesis and Cyclization of *$N_a$*-Benzyl-*$N_b$*-Cbz-*O*-TMS-Aminol 148

The synthesis of *N*-Cbz-*O*-TMS-aminol **148** was carried out in an analogous manner to that of compound **110** (Scheme 1.14). Amide **149** was obtained by subjecting tryptamine[39] **150** to 4 M HCl in dioxane to afford the corresponding crude primary amine, followed by treatment with acid **99** and EDCI in the presence of HOBt.[40] We found that HOBt was superior to DMAP both at producing higher overall yields and suppressing minor isomerization side reactions that had previously been observed. Amide **149** was acylated with LiHMDS and CbzCl in 89% yield, and converted to the corresponding *N*-Cbz-*O*-TMS-aminol **148** under standard conditions.




**Scheme 2.14** Synthesis of *N*-Cbz-*O*-TMS-aminol **148.**

Treatment of compound **148** with $BF_3{\cdot}OEt_2$ in $CH_2Cl_2$ at -78°C afforded the desired tetracyclic amine **151** in 36% yield and compound **152** 43% yield respectively (Scheme 1.15). Although not optimal, the results were superior to those obtained during the cyclization *N*-Cbz-*O*-TMS-aminol **110**.




**Scheme 2.15** Cyclization *N*-Cbz-*O*-TMS-aminol **110** with $BF_3{\cdot}OEt_2$.

The structure of compound **151** was established through 1D and 2D NMR techniques (CYCLENOE, COSY and HMQC). Given that compound **151** existed as a 3:2 mixture of rotamers at room temperature, all experiments were conducted at 70 °C in $d_6$-DMSO, conditions under which the two sets of proton NMR signals coalesced into one. The stereochemical assignment was based on the irradiation of $H_i$, which produced key NOE's with $H_a$ (6.1%) and $H_b$ (6.8%), thus indicating that $H_a$ and $H_b$ were located on the same face of the D ring (Figure 2.1).

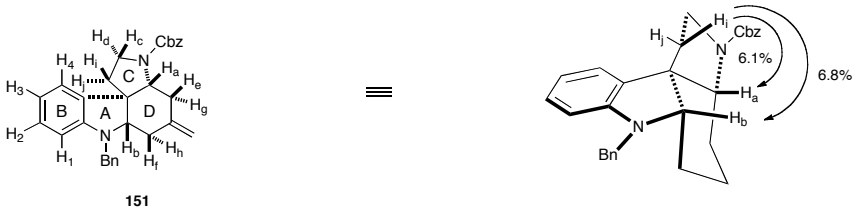
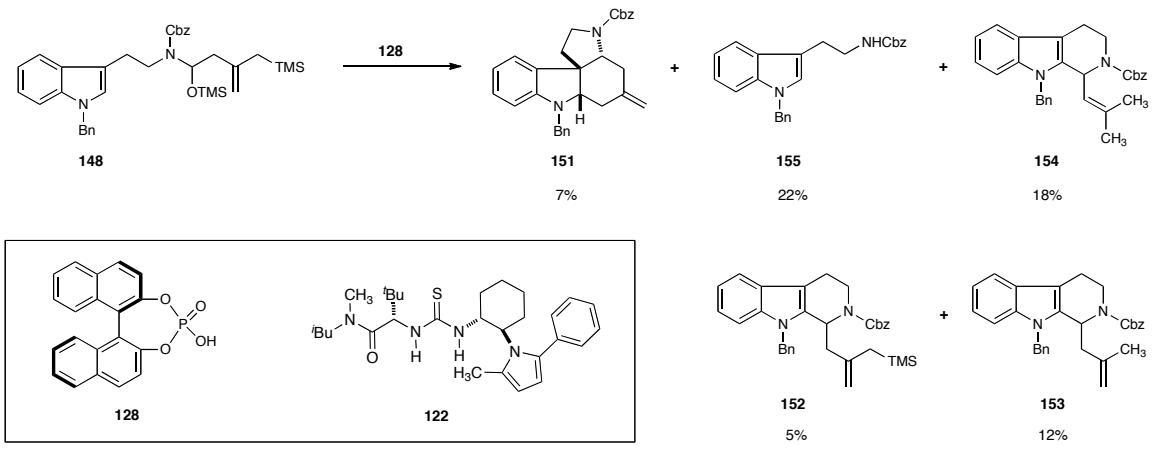



**Figure 2.1** Structural assignment of tetracyclic amine **151**.

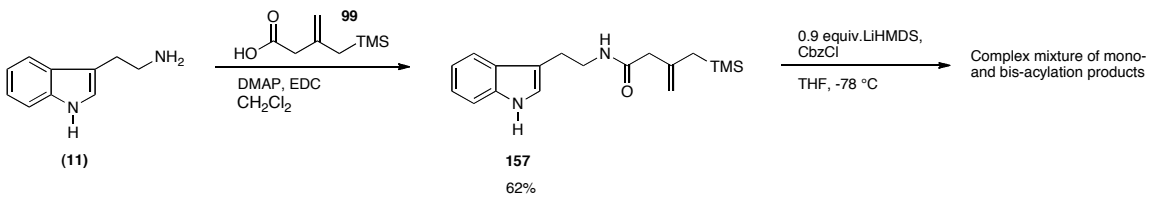
The transformation was also carried out under protic acid conditions using **128**, but the combined amount of isolated Pictet-Spengler products **152**, **153**, and **154** far surpassed that of the desired tetracylic amine **151** (the usual ratios were between 7:1 and 5:1), regardless of the temperature of the reaction or the polarity of the solvent (Scheme 2.16). We also examined other organic acids of higher and lower acidity to that of Binol phosphoric acid (pka ~ 2 in $H_2O$), including trifluoroacetic acid (pka: -0.25 in $H_2O$) and acetic acid (pka: 4.76 in $H_2O$), but no improvement was observed. Additionally, *N*-Cbz-*O*-TMS-aminol **148** was treated with chiral thiourea catalysts **122** in *tert*-butyl methyl ether at -60 °C with either TMSCl or HCl and 3Å sieves.[36a] However, Pictet-Spengler side products were predominant under both sets of conditions. Carbamate **155** was also isolated, but the desired tetracycle **151** was never observed. Carrying out the reaction in $CH_2Cl_2$ produced similar results.




**Scheme 2.16** Cyclization *N*-Cbz-*O*-TMS-aminol **148** with protic acids.

### 2.3.3. Exploring the Effect of $N_a$ Substitution: Synthesis and Cyclization of $N_a$-H-$N_b$-Cbz-*O*-TMS-Aminol 156

Tryptamine (**11**) was treated with DCC and catalytic DMAP in the presence of acid **99** to afford amide **157** in 63% yield (Scheme 2.17). At this stage we carried out a quick study to determine the inherent selectivity of the system towards acylation at the amide nitrogen in the presence of the free indole nitrogen. We wanted to exploit the subtle difference in acidity between the $N_a$ proton and the $N_b$ proton (pka's of 20.95 and ~ 25.0 in DMSO, respectively). However, attempts to install the acyl group with 1.0 equivalent of CbzCl after treatment with LiHMDS generated a complex mixture of mono- and bis-acylation products.

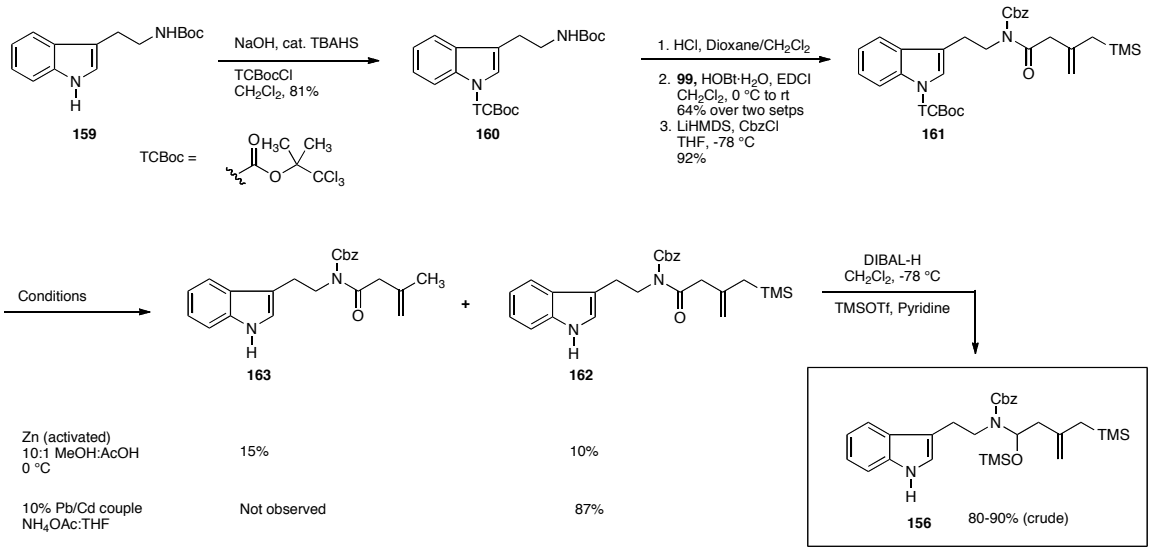



**Scheme 2.17** Early attempts to synthesize *N*-Cbz-amide **158**.

Given this, a more traditional approach was taken toward the synthesis of *N*-Cbz-*O*-TMS-aminol **156** by first protecting the indole nitrogen of known tryptamine **159** with 2,2,2-trichloro-*tert*-butyloxychloroformate (TCBoc)[41] under standard phase transfer conditions to afford compound **160** in 81% yield (Scheme 2.18). The TCBoc group was deliberately chosen because it would endure the subsequent acidic hydrolysis of the Boc group at $N_b$, as well as provide a convenient set of neutral conditions to chose from once we needed to remove it. Removal of the Boc group from **160** with 4 M HCl and amide formation with EDCI generated the corresponding amide in 64% yield over two steps. Acylation of $N_b$ with CbzCl afforded **161** in almost quantitative yield. With **161** in hand, our initial attempts to remove the TCBoc group under standard reducing conditions with activated zinc dust in 10:1 methanol/acetic acid at 0 °C generated the desired compound **162** in only 10% yield, along with 15% of the desilylated product **163** and large amounts of recovered starting material. The $^1$H NMR spectrum of compound **162** displayed a broad singlet signal at 8.01 ppm corresponding to the indole nitrogen proton.

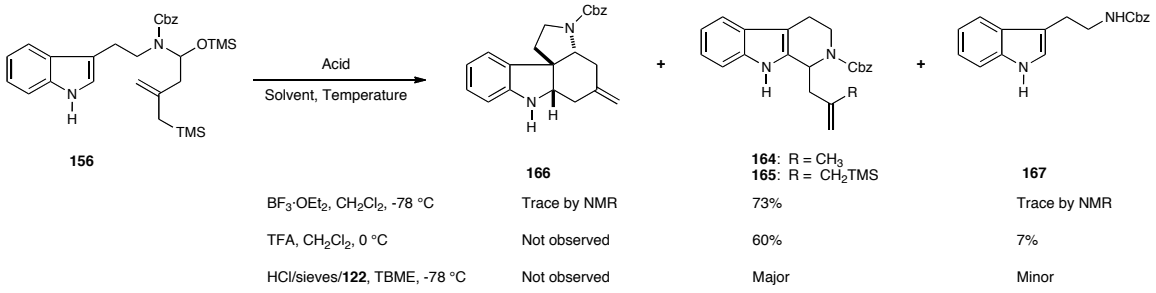
Given the propensity of compound **162** to undergo protodesilylation under acidic conditions, a milder system was required. The problem was solved using conditions developed by Ciufolini[41a] for the removal of TCBoc groups at pH = 7 by buffering with

aqueous $NH_4OAc$ in THF in the presence of a 10% Pb/Cd couple. The reaction proceeded smoothly to afford compound **162** in 87% yield. Reduction with DIBAL-H under standard conditions afforded the sensitive *N*-Cbz-*O*-TMS-aminol **156** that was used without further purification given its propensity to hydrolyze on silica.




**Scheme 2.18** Synthesis of *N*-Cbz-*O*-TMS-aminol **156**.

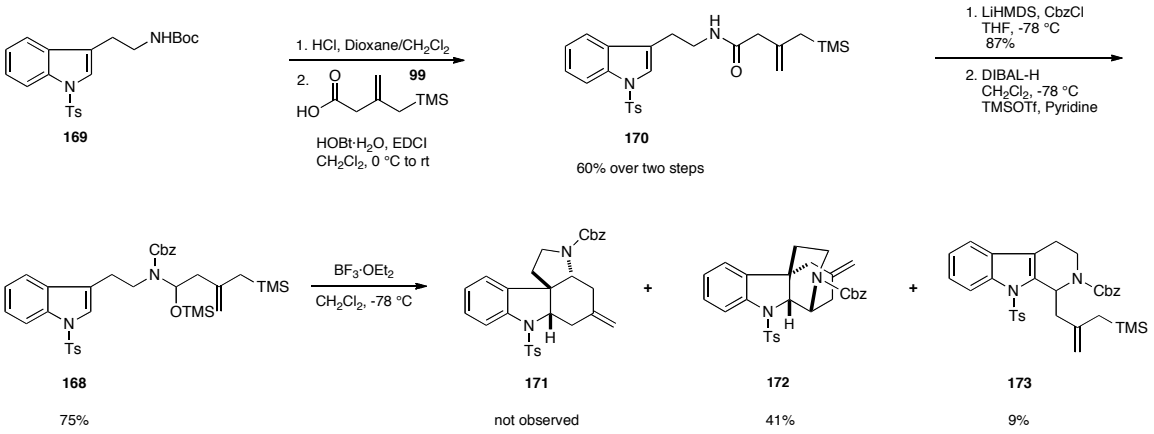
Subjecting *N*-Cbz-*O*-TMS-aminol **156** to standard reaction conditions using $BF_3 \cdot OEt_2$ at -78 °C generated a combined 73% of Pictet-Spengler products **164** and **165**, with only traces of tetracyclic amine **166** isolated (Scheme 2.19). Carrying out the reaction under protic conditions, either using trifluoroacetic acid or HCl and catalyst **122** produced only large amounts of tetrahydrocarboline **164** and carbamate **167**.




**Scheme 2.19** Cyclization of *N*-Cbz-*O*-TMS-aminol **156**.

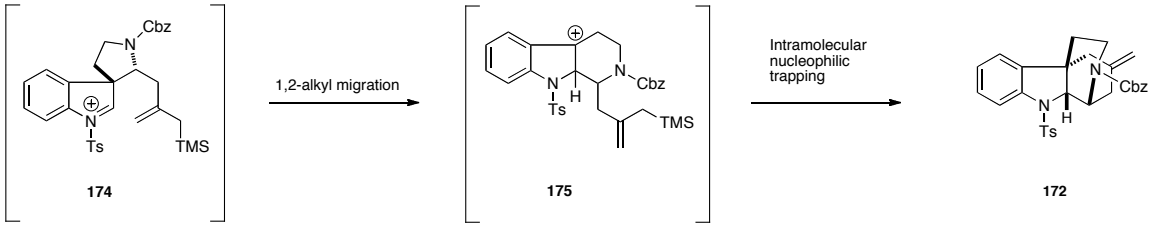
### 2.3.4. Exploring the Effect of $N_a$ Substitution: Synthesis and Cyclization of $N_a$-Tosyl-$N_b$-Cbz-*O*-TMS-Aminol 168

The synthesis of *N*-Cbz-*O*-TMS-aminol **168** started with Boc deprotection of known tryptamine[42] **169** under acidic conditions followed by EDCI coupling with acid **99** and HOBt to generate amide **170** in 60% over two steps (Scheme 2.20). Compound **176** was deprotonated with LiHMDS and treated with Cbz-Cl to afford the corresponding *N*-Cbz-amide, which then was subjected to DIBAL-H and trimethylsilyltriflate to generate *N*-Cbz-*O*-TMS-aminol **168** in 75% yield. However, upon treatment with $BF_3{\cdot}OEt_2$, compound **168** did not afford the desired tetracyclic tosylamine **171** and instead produced an interesting caged-tetracyclic compound **172** and small amounts of tetrahydrocarboline **173** in a 4:1 ratio. The structure of compound **172** was established based on comparisons of its $^1$H NMR spectrum to that of compound **257,** the structure of which was unequivocally established by 2D NMR and X-ray crystallography (*vide infra*, section 2.6.1). A large number of unidentified minor sideproducts were also observed.



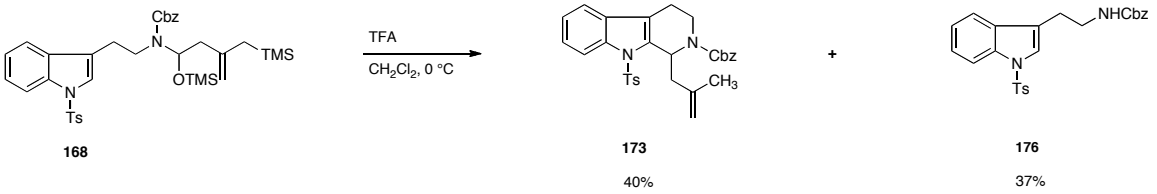

**Scheme 2.20** Synthesis and cyclization of *N*-Cbz-*O*-TMS-aminol **168**.

The formation of compound **172** can be explained by a mechanism involving 1,2-alkyl migration of spirodindolium ion **174** to generate a benzylic cation intermediate **175** (Scheme 2.21). It is reasonable to assume that the inductive effect of the neighboring *N*-tosyl group might enhance the electrophilicity at C(3), thus facilitating nucleophilic trapping by the tethered allylsilane moeity to generate **172**. In sharp contrast to the observations of Bosch and coworkers that indicate that tosyl substituted indole nitrogens retard the rate of 1,2-alkyl migration of spiroindolium intermediates, installing a tosyl group at $N_a$ in our system seems to have favored the migration. This is also supported by the isolation of Pictet-Spengler byproduct **173** and the absence of the desired tetracycle **171** from the reaction mixture.



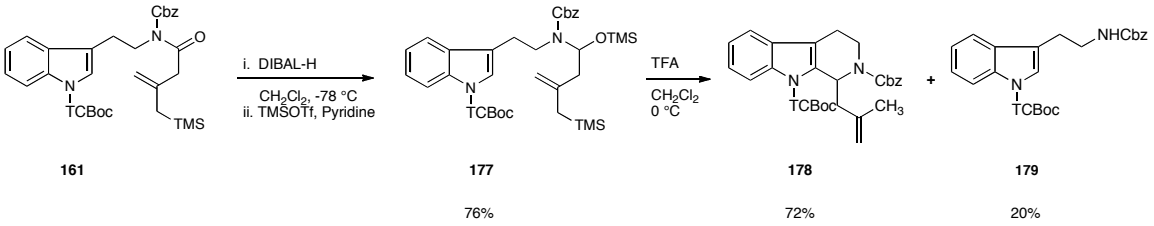

**Scheme 2.21** Mechanistic rationale for the formation of compound **172**.

Treating *N*-Cbz-*O*-TMS-aminol **168** with trifuoroacetic acid at 0 °C afforded tetrahydrocarboline **173** in 40% and substantial amounts of carbamate **176** (Scheme 2.22). On the other hand, when Jacobsen conditions were utilized only iminium ion hydrolysis product **176** was isolated. The data suggests that under protic conditions less electron rich systems are susceptible to hydrolysis pathways that compete with the initial formation of the spiroindolium ion **174**.




**Scheme 2.22** Cyclization of *N*-Cbz-*O*-TMS-aminol **168** with protic acid.

In order to confirm that our observations with the tosyl group were representative of other electron-withdrawing groups as well, we repeated our experiment with compound **177** (Scheme 2.23). Subjecting *N*-Cbz-*O*-TMS-aminol **177** (synthesized from *N*-Cbz-amide **161** in one step using standard procedures) to trifluoroacetic acid at 0 °C only produced significant amounts of tetrahydrocarboline **178** and carbamate **179**, and did not afford any of the cascade annulation product.




**161** **177** **178** **179**

76% 72% 20%

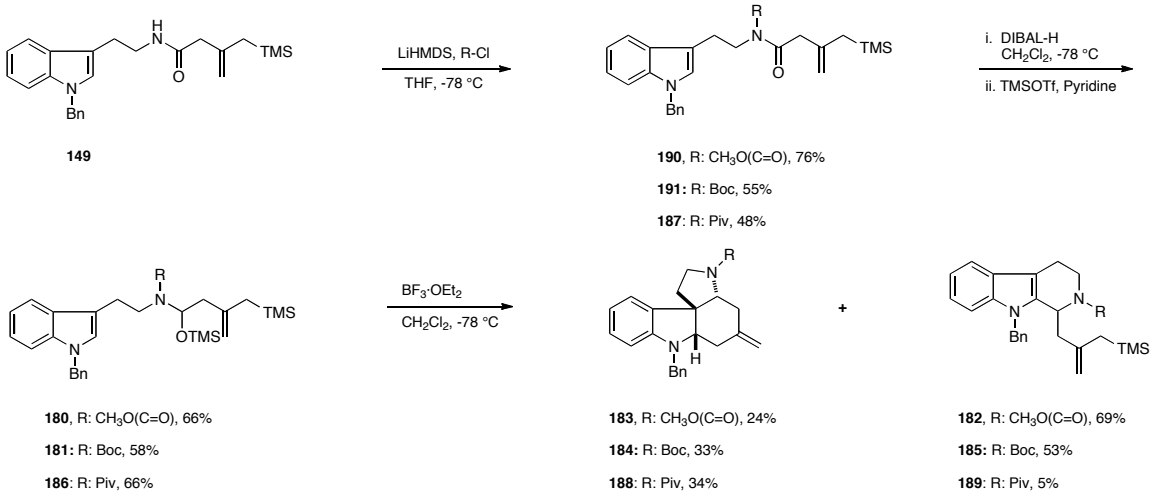
**Scheme 2.23** Cyclization of *N*-Cbz-*O*-TMS-aminol **161** with protic acid.

Overall, our investigations showed that using a benzyl substituent at $N_a$ afforded the best yields and relative ratios of the cascade annulation product. On the other hand, the unprotected indole nitrogen afforded mainly Pictet Spengler products. Additionally, electron-withdrawing groups also favored the formation of tetrehydorcarbolines, as well as regioisomeric tetracyclic products when the substituent was a tosyl group. Consequently, we employed the benzyl group at $N_a$ in all the remaining optimization studies.

### 2.3.5. Exploring the Effect of $N_b$ Substitution: Synthesis and Cyclization of *N*$_a$-Benzyl-*N*$_b$-Carbomethoxy- and *N*$_a$-Benzyl-*N*$_b$-Boc-*O*-TMS-Aminols 180 and 181

*N*-Acyl-*O*-TMS-aminols **180** and **181** were generated as outlined in Scheme 2.24 using our standard conditions. Subjecting **180** to $BF_3{\cdot}OEt_2$ at -78 °C afforded tetrahydrocarboline **182** in 69% yield along with 24% yield of the desired tetracycle **183**. The ratio of **183** to **182** was slightly lower than that observed in the cyclization of *N*-Cbz-*O*-TMS-aminol **148**. On the other hand, treating *N*-Boc-*O*-TMS-aminol **181** with $BF_3{\cdot}OEt_2$ produced compounds **184** and **185** in 33% and 53% yield, respectively. This

result was comparable but not superior to that obtained with *N*-Cbz-*O*-TMS-aminol **148**. Overall, the large Cbz and Boc auxiliaries performed marginally better than the methoxycarbonyl group. These results indicated that sterics had a measurable but minor effect on the transformation.




**Scheme 2.24** Synthesis and cyclization of *N*-Cbz-*O*-TMS-aminols **180**,**181** and **186**.

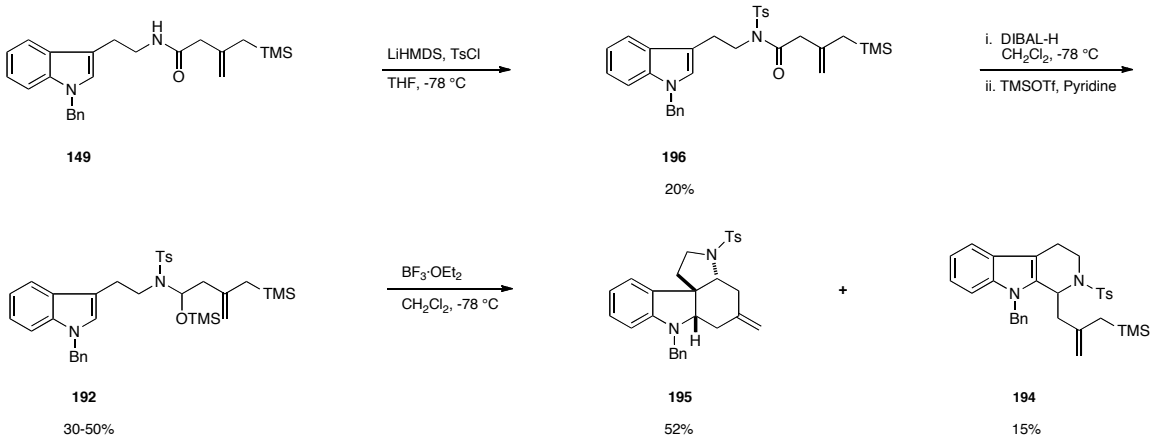
### 2.3.6. Exploring the Effect of $N_b$ Substitution: Synthesis and Cyclization of $N_a$-Benzyl-$N_b$-Piv-*O*-TMS-Aminol 186

At this stage we proceeded to install the more electron withdrawing pivaloate functionality. Imide **187** was synthesized using our standard acylation conditions, followed by regioselective reduction of the least hindered amide carbonyl with DIBAL-H and trapping with trimethylsilyl triflate to generate *N*-Piv-*O*-TMS-aminol **186** in 66% yield (Scheme 2.24). Subjecting compound **186** to $BF_3{\cdot}OEt_2$ at -78 °C afforded the desired tetracycle **188** in 34% and minor amounts of tetrahydrocarboline **189** (5%). Although the yield was modest, the ratio of cascade product/Pictet Spengler product was

promising (~ 6:1). Compound **186** was also treated with thiourea catalysts **122** in combination with HCl and molecular sieves at -78 °C, but these conditions led mainly to the hydrolysis of the starting material.

### 2.3.7. Exploring the Effect of $N_b$ Substitution: Synthesis and Cyclization of *N*$_a$-Benzyl-*N*$_b$-Tosyl- and *N*$_a$-Benzyl-*N*$_b$-Nosyl-*O*-TMS-Aminols 192 and 193

At this stage, we expected the more electron-withdrawing tosyl group to improve further the ratio of tetracyclic amine/tetrahydrocarboline. To synthesize **192**, we turned to our standard acylation conditions and treated amide **149** with LiHMDS at -78 °C and tosyl chloride (Scheme 2.25). To our surprise, the yields for this reaction were low (around 20% on average), but we were able to synthesize sufficient material to continue our study. The subsequent reduction with DIBAL-H at -78 °C was also problematic and afforded *N*-Tosyl-*O*-TMS-aminol **192** in modest yields (30-50%). More specifically, we noticed that the trapping of the aluminum hemiacetal intermediate with trimethylsilyl triflate caused partial *in situ* cyclization to afford tetrahydrocarboline **194**. Despite difficulties in suppressing this side reaction, we managed to synthesize enough material to investigate the key cyclization step. Subjecting compound **192** to $BF_3{\cdot}OEt_2$ at -78 °C afforded 52% of tetracyclic amine **195** and only 15% of Pictet-Spengler side product **194**.




**Scheme 2.25** Synthesis and cyclization of *N*-tosyl-*O*-TMS-aminol **192**.

The structure of compound **195** was established through 1D and 2D NMR experiments (CYCLENOE, DEPT, COSY and HMQC). Irradiation of $H_j$ produced NOE's with $H_c$ (7.0%) and $H_e$ (6.9%), which indicated that $H_c$ and $H_e$ were located on the same face of the D ring (Figure 2.2). This was also supported by the irradiation of $H_c$, which produced a 3.5% NOE on $H_e$. Moreover, an enhancement of the aromatic proton $H_4$ signal (11.0%) was observed upon irradiation of $H_a$, just as reported for malagashanine by Rasoanaivo and coworkers. Nevertheless, as a measure of extra precaution, the structure of the methoxy-substituted analog **247** (*vide infra*, section 2.6.1) was secured by X-ray crystallography. Compound **247** displayed similar NOEs to those indicated for **195**.

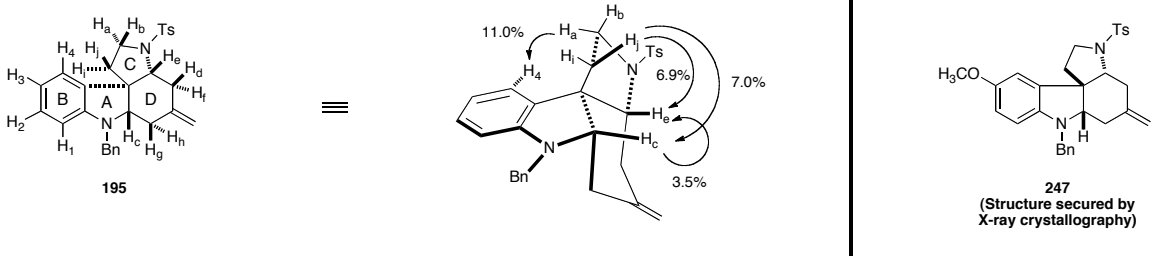
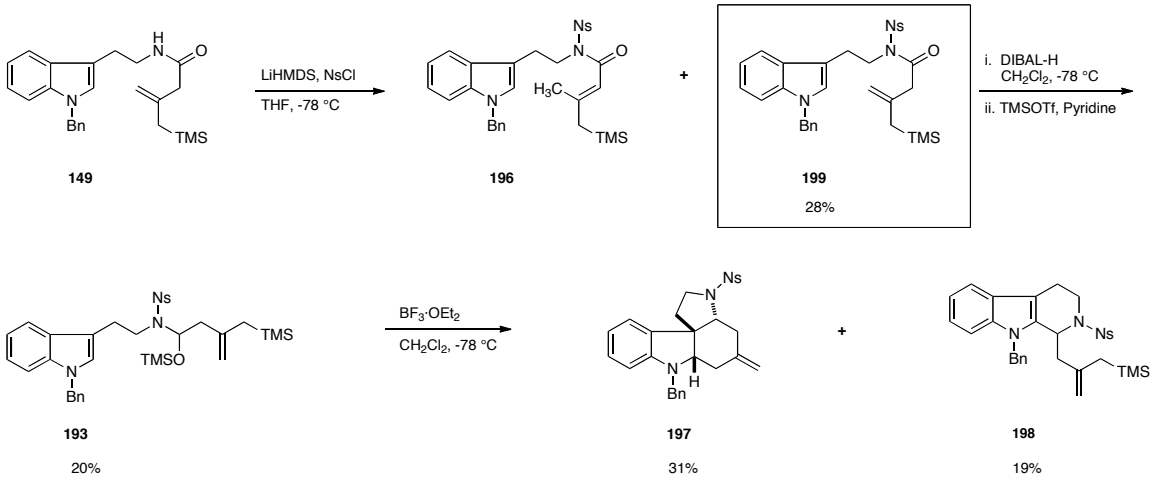



**Figure 2.2** Structural assignment of tetracyclic amine **195**.

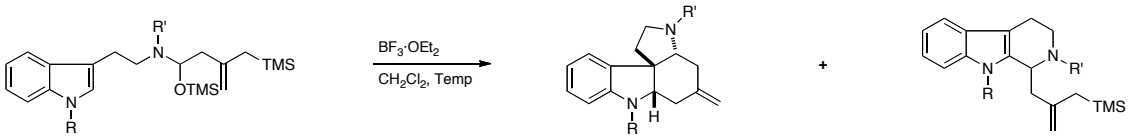
The cyclization of *N*-tosyl-*O*-TMS-aminol **192** produced synthetically useful yields of compound **195**, which encouraged us to further remove electron density from $N_b$ in an effort to completely suppress the formation of tetrahydrocarboline side products. For this task, the nosyl auxiliary seemed like an obvious choice.

The synthesis of *N*-nosyl-*O*-TMS-aminol **193** was slightly more problematic than that of compound **192** (Scheme 2.26). In both the tosylation step and the subsequent reduction/trapping step, only low yields of the desired product were obtained and a number of side products were generated. Additionally, the isolation of isomerized compound **196** suggested that that the high electron-withdrawing ability of the nosyl group lowered the pka of the amide $\alpha$-protons sufficiently to promote side reactions. However, useful quantities of *N*-nosyl-*O*-TMS-aminol **193** were synthesized which allowed us to explore the key transformation. Treating compound **193** with $BF_3{\cdot}OEt_2$ afforded a disappointing ratio of ~ 1.5:1 of compounds **197** and **198**, which did not fulfill our expectations.




**Scheme 2.26** Synthesis and cyclization of *N*-nosyl-*O*-TMS-aminol **193**.

Despite the failure of system **193** to produce higher yields and selectivity towards the desired product, the overall results of this study were very positive (Table 2.1). Installing a tosyl substituent at $N_b$ decreased the formation of tetrahydrocarboline side product **200** while increasing the overall yield of the transformation. Additionally, after some optimization we found that carrying the cyclization of *N*-tsoyl-*O*-TMS-aminol **201** at 0 °C with 5 equivalents of $BF_3{\cdot}OEt_2$ (entry 9) increased the yield of compound **202** to 82% and nearly completely suppressed the formation of Pictet-Spengler side products.

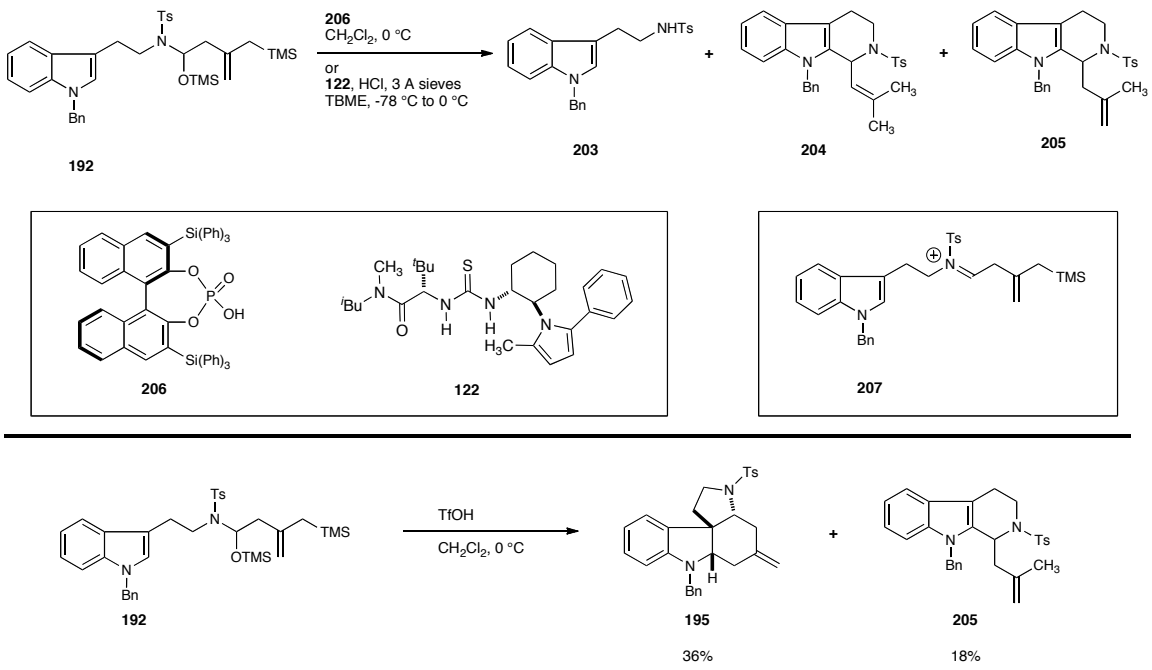



**201** **202** **200**

| entry | R | R' | Temp (°C) | Time (h) | % yield **202** | % yield **200** |
|---|---|---|---|---|---|---|
| 1 | Bn | Cbz | -78 | 0.25 | 36 | 43 |
| 2 | H | Cbz | -78 | 0.25 | <5 | 51 |
| 3 | Ts | Cbz | -78 | 43 | 0 | 5 |
| 4 | Bn | Boc | -78 | 0.25 | 33 | 53 |
| 5 | Bn | C(O)OMe | -78 | 0.25 | 32 | 48 |
| 6 | Bn | C(O)$^t$Bu | -78 | 6 | 34 | <5 |
| 7 | Bn | Ts | -78 | 1 | 52 | 15 |
| 8 | Bn | Ns | -78 | 1 | 31 | 19 |
| 9 | Bn | Ts | 0 | 1 | 82 | <5 |

**Table 2.1** Summary of the cascade annulation optimization.

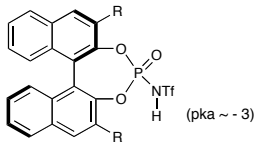
We also treated *N*-tosyl-*O*-TMS-aminol **192** with chiral thiourea catalyst **122** in combination with HCl/sieves at various temperatures (Scheme 2.27). After 36 hours at -78 °C, only recovered starting material and iminium ion hydrolysis product **203** were isolated, while at 0 °C the starting material was consumed within 3 hours to afford the usual mixtures of Pictet-Spengler side products **204** and **205**. The desired tetracycle **195** was never observed. Additionally, using chiral Binol phosphoric acid **206** produced only trace amounts of **195** and large amounts of previously mentioned side products.




**Scheme 2.27** Cyclization of *N*-tosyl-*O*-TMS-aminol **192** with protic acid.

The isolation of compound **204** was indicative that the isomerization of iminium ion **207** was competing with the formation of the spiroindolium intermediate (Scheme 2.27). One possibility could be that the acidity of the $\alpha$-protons was high enough as to facilitate deprotonation by even weak conjugate bases like chloride. We argued that using an acid such as triflic acid, which has an even weaker conjugate base, might disfavor the deprotonation/isomerization pathway. Treating *N*-tosyl-*O*-TMS-aminol **192** with triflic acid in the presence of 4 Å molecular sieves in $CH_2Cl_2$ at 0 °C indeed produced 36% of the desired tetracyclic amine **195**, and 18% of tetrahydrocarboline **205**. As expected, compound **204** was not observed, indicating that very weak conjugate bases like triflate were suitable to use in our chemistry. This promising result suggests that our future research in this area should focus on the use of more acidic species, like the chiral Binol

*N*-triflylphosphoramides (*e.g.* **208**) developed by Yamamoto and co-workers (Figure 2.3).[43]



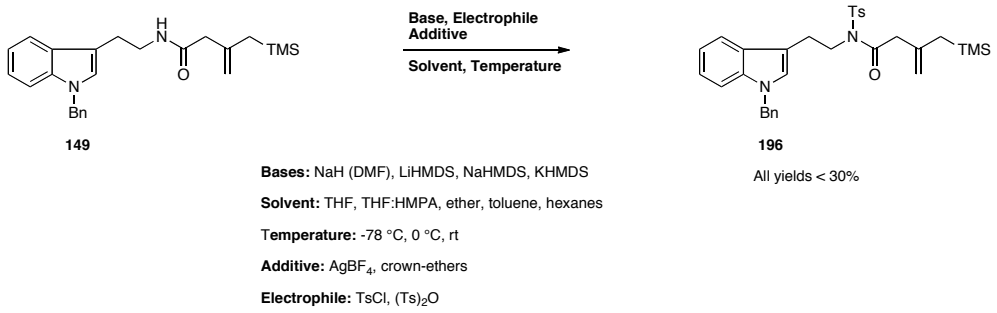

**208**

R = 1,3,5-(*i*-Pr)$_3$C$_6$H$_2$)

**Figure 2.3** Yamamoto's chiral Binol *N*-triflylphosphoramide catalyst.

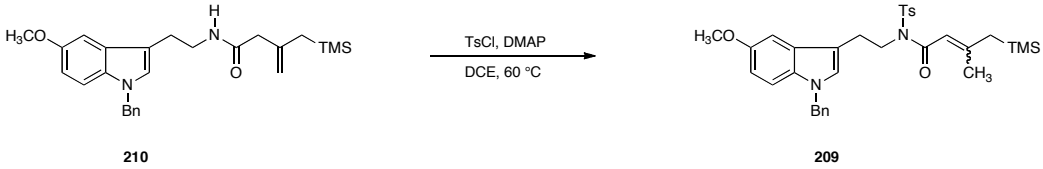
## 2.4. Optimization of the Synthesis of *N*-Tosyl-*O*-TMS-Aminol 192

With our success in developing a cascade annulation sequence to access core **195**, we needed to optimize the synthesis of *N*-Tosyl-*O*-TMS-aminol **192** in order to make this method truly synthetically useful. Our first priority was to find an efficient way of introducing the tosyl group at $N_b$, however, all attempts to do so *via* deprotonation of amide **149** with LiHMDS failed to produce high yields of **196**. The results were surprising given that the same general approach had worked well for the construction of *N*-acyl-amides. We started by investigating a wide range of conditions including solvent, base, counterion, additive, temperature, and electrophile (Scheme 2.28). Unfortunately, the best yield obtained for compound **196** did not surpass 30%. Additionally, the starting material was usually recovered along with small amounts of isomerized starting material.




**Scheme 2.28** Early attempts to install a tosyl group at the amide nitrogen.

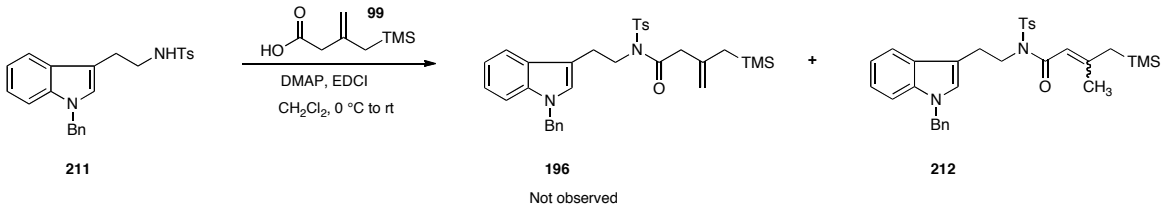
Additionally, phase transfer conditions were employed using tetrabutylammonium hydrosulfate (TBAHS) with NaOH in 1,2-dichloroethane, but only decomposition of the starting material was observed.[44] On the other hand, when weaker bases ($Et_3N$ and DBU) were employed in the presence of tosyl chloride activated by DMAP, only starting material was recovered. At higher temperatures (60 °C) the sole product was $\alpha,\beta$-unsaturated isomer **209** (for information on the synthesis of compound **210** refer to experimental section) (Scheme 2.29).




**Scheme 2.29** Attempts to install a tosyl group at the amide nitrogen**.**

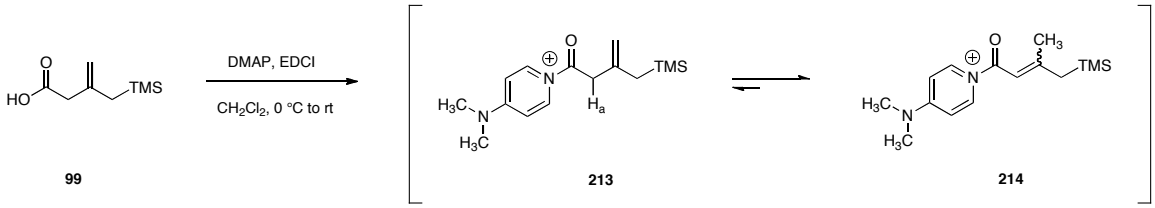
At this stage we also envisioned an alternate disconnection by way of tosylamine **211** and acid **99** (Scheme 2.30). However, we were concerned that the relatively low nucleophilicity of tosylamine **211** might render it unreactive to common amide coupling

reagents such as EDCI. While this was initially the case when HOBt was used as an additive, using DMAP[45] afforded the amide coupling product **212**.




**Scheme 2.30** Attempts to synthesize **196** *via* amide coupling methods.

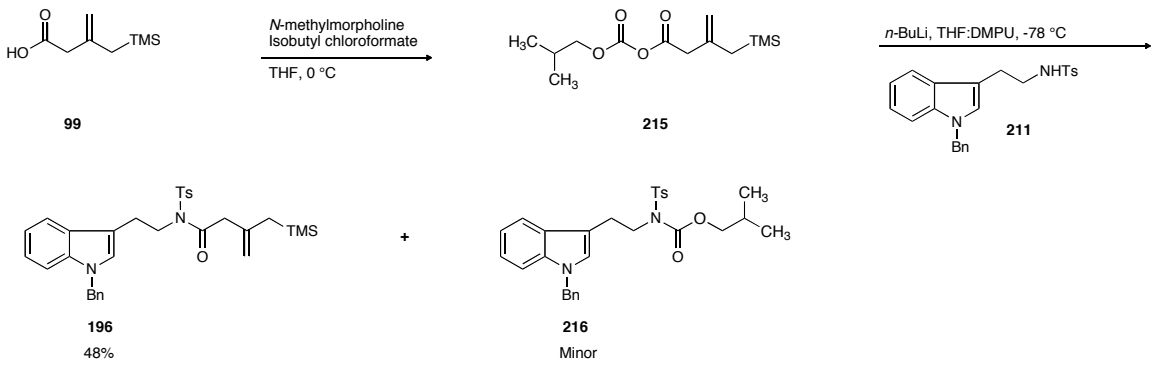
The isolation of isomerized product was not a surprise given that we had observed similar outcomes when EDCI was employed in the presence of DMAP to couple acid **99** and tryptamine **36**. The assumption was that the intermediate **213** (Scheme 2.31) was prone to isomerization by virtue of its highly acidic $\alpha$-protons (due to the inductive effect of the 4-dimethylamine pyridinium group).[46]




**Scheme 2.31** Possible mechanism for the isomerization of acid segment **213**.

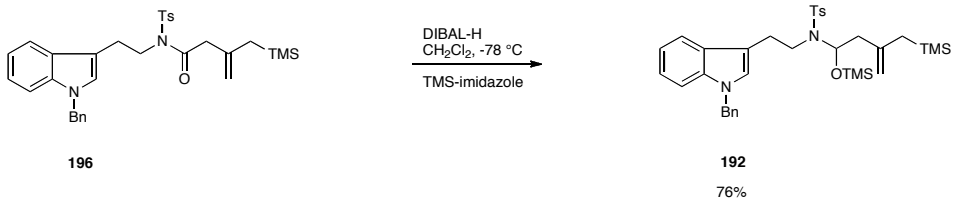
In order to avoid the isomerization of the activated complex and still promote the reaction, we realized that we had to use a less reactive electrophile. We decided to use mixed anhydride **215** because its $\alpha$-protons were not nearly as acidic as those of intermediate **213**, and thus should afford the desired product **196** without promoting

isomerization (Scheme 2.32). Additionally, the tosylamine nucleophile **211** could be activated *via* its anion by deprotonation with strong base. Treatment of acid **99** with isobutyl chloroformate in the presence of *N*-methylmorpholine afforded the corresponding mixed anhydride **215**, which was followed by addition of the lithium anion of tosylamine **211**.[47] Gratifyingly, the protocol produced 48% of *N*-tosyl-amine **196**. We also isolated compound **216** generated by nucleophilic attack at the carbonate carbonyl. Although the yields were modest, this new procedure represented a significant improvement over the previous method and afforded useful quantities of **196** in a reproducible manner.




**Scheme 2.32** Improved synthesis of *N*-tosyl-amide **196** from **211**.

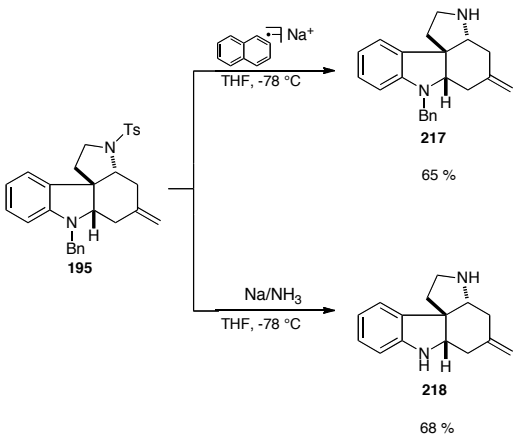
Our next objective was to optimize the transformation of compound **196** into *N*-Tosyl-*O*-TMS-aminol **192**, which as noted earlier, was difficult to control because the trapping reagent (trimethylsilyltriflate) was promoting the *in situ* cyclization of **192** to Pictet-Spengler products. The issue was addressed by switching to a less reactive trapping reagent such as trimethylsilylimidazole,[48] which after some optimization afforded the desired product in yields as high as 80% (Scheme 2.33).




**Scheme 2.33** Improved synthesis of *N*-tosyl-*O*-TMS-aminol **192** from **196**.

## 2.5. Removal of Benzyl and Tosyl Protecting Groups From Tetracyclic Core 195

To demonstrate the synthetic utility of core **195**, it was first necessary to find efficient conditions to deprotect the nitrogen indole and to remove the tosyl auxiliary. Our main concern was the chemoselective deprotection of $N_b$, given that tosylamines are robust functionalities that in some instances prove difficult to cleave under mild conditions. However, we were pleasantly surprised to find that the tosyl functionality was easily removed at -60 °C with sodium naphthalide in 1,2-dimethoxyethane (DME) to afford monoamine **217** in 65% (Scheme 2.34).[49] Additionally, both the benzyl and the tosyl could be removed by treatment of **195** with sodium in liquid ammonia to provide diamine **218** in 68% yield.

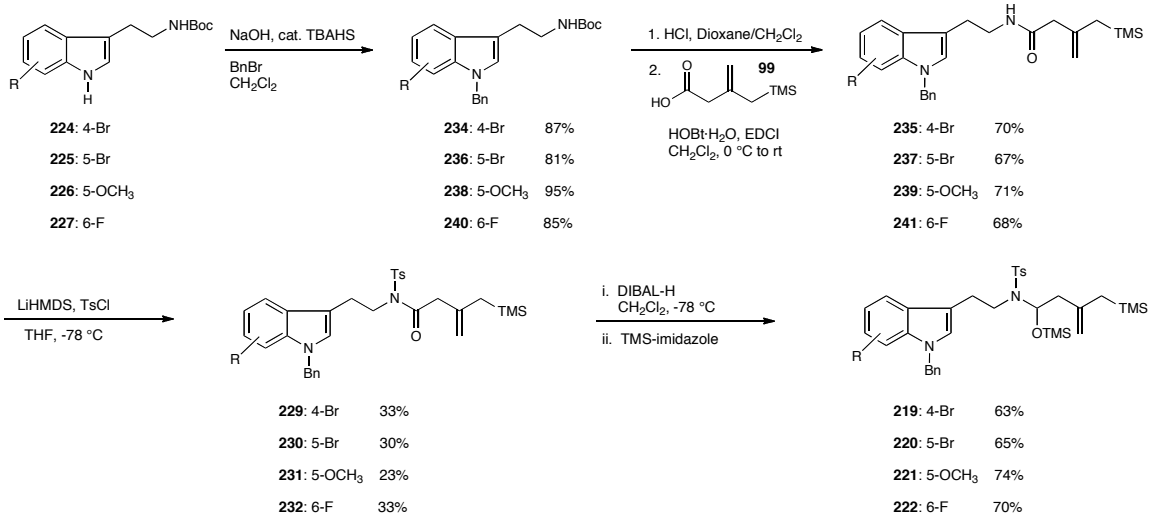



**Scheme 2.34** Protecting group removal following cascade annulation reaction.

## 2.6. Extending the Substrate Scope of the Cascade Annulation Reaction

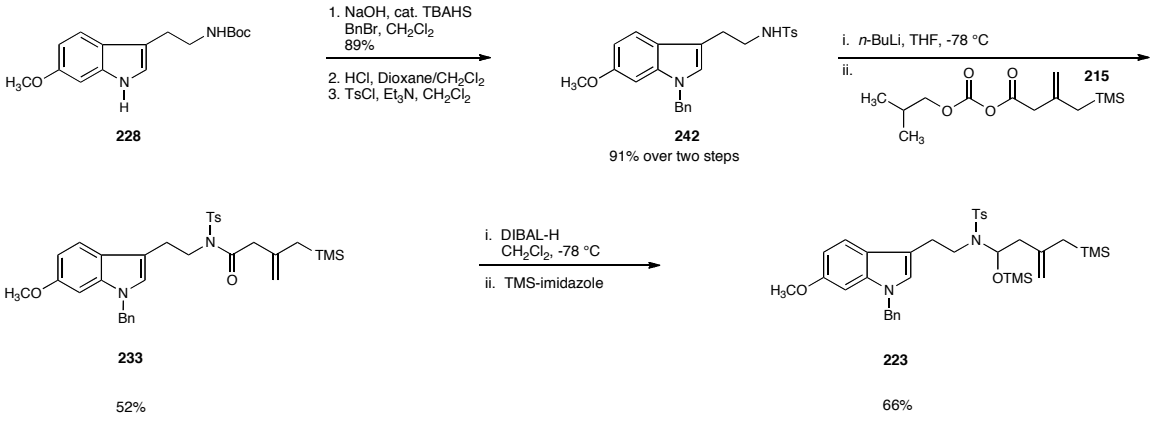
### 2.6.1. Synthesis and Cyclization of Substrates with Substituted Indoles

With an efficient and reliable protocol in hand, it was possible to explore the substrate scope of the transformation. More specifically, we were interested in utilizing indoles with either electron donating or electron withdrawing substituents (4-Br, 5-Br, 6-F, 5-$OCH_3$, 6-$OCH_3$). To this end, the syntheses of *N*-Tosyl-*O*-TMS-aminols **219**-**223** were accomplished using standard conditions as indicated in Schemes 2.35 and 2.36, starting from compounds **224**-**228**.



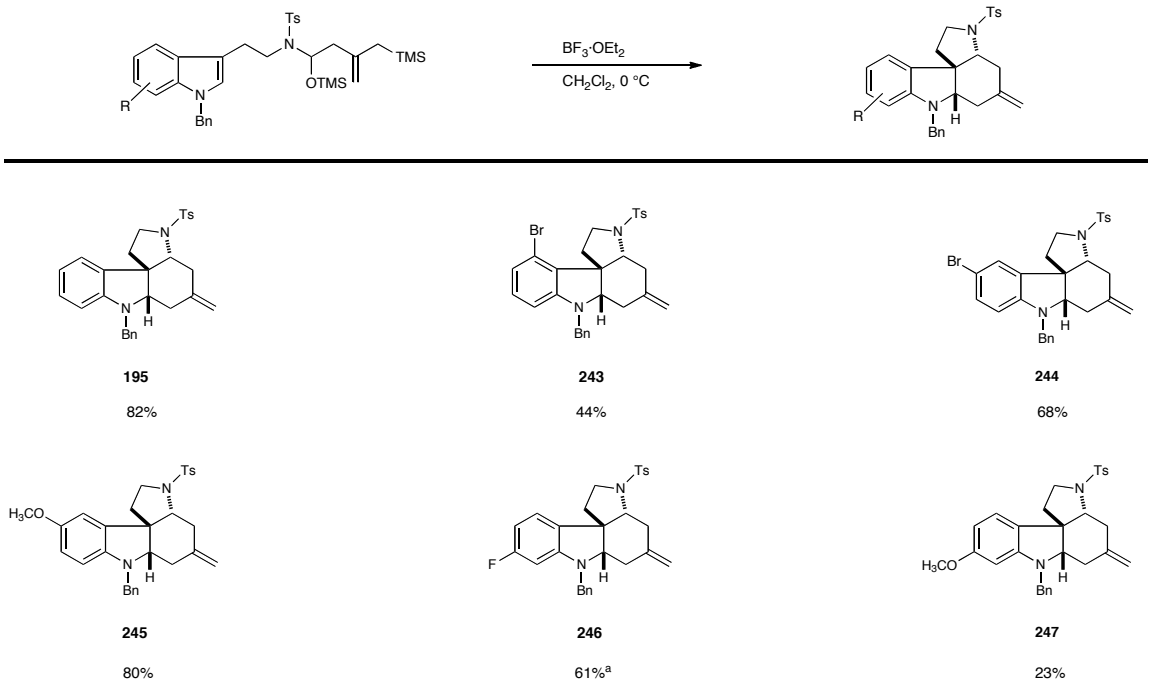

**Scheme 2.35** Synthesis of *N*-tosyl-*O*-TMS-aminols **219-222.**

It is important to mention that the syntheses of *N*-tosyl-amides **229-232** were carried out before the optimized conditions described in the previous section had been developed, therefore the yields are not optimized. However, the synthesis of compound **233** incorporates the improved protocol (Scheme 2.36**)**.




**Scheme 2.36** Synthesis of *N*-tosyl-*O*-TMS-aminol **223**.

*N*-Tosyl-*O*-TMS-aminols **219-223** were subjected to the standard cyclization condition with 5.0 equivalents of $BF_3{\cdot}OEt_2$ in $CH_2Cl_2$ at 0 °C to afford the corresponding tetracyclic products **243-247** as shown in Table 2.2 (6-fluoro-substituted *N*-Tosyl-*O*-TMS-aminol **222** was cyclized with $BF_3{\cdot}OEt_2$ in refluxing 1,2-dichloroethane because the yield was generally higher under these conditions).



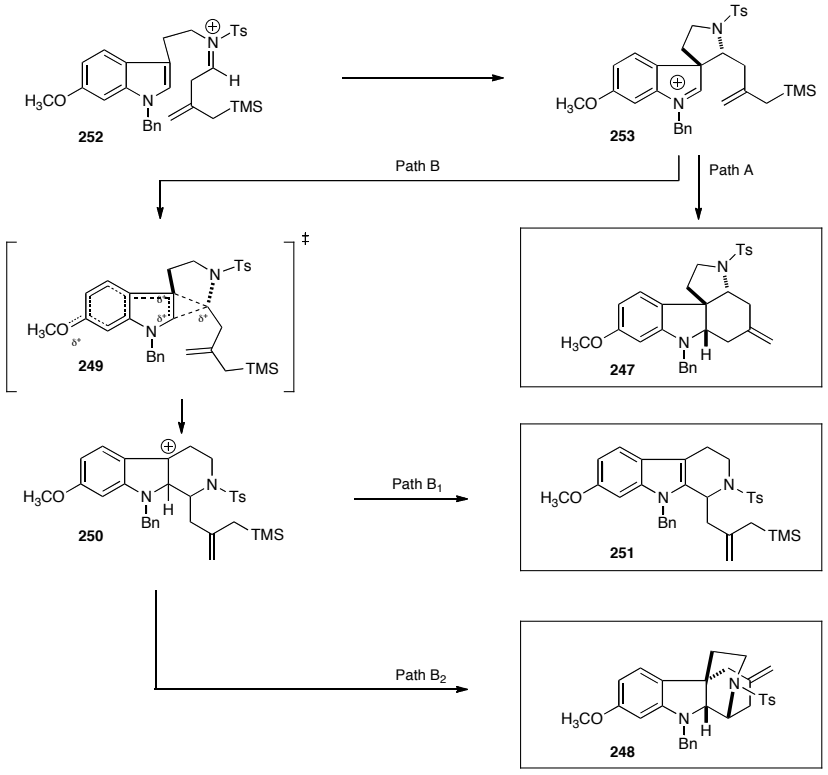

[a]Cyclized at 85 °C in 1,2-dichlororethane.

**Table 2.2** Cascade cyclization of substituted indoles.

The transformation is amenable to electron-withdrawing substituents at the 4-, 5- and 6-positions as well as electron donating groups at the 5-position and 6-position. In most cases the use of a tosyl auxiliary on the iminium ion nitrogen and a benzyl group on the indole nitrogen provided exquisite selectivity for the desired cascade product. However, for the 6-methoxyindole substrate **223**, this auxiliary pattern resulted in only

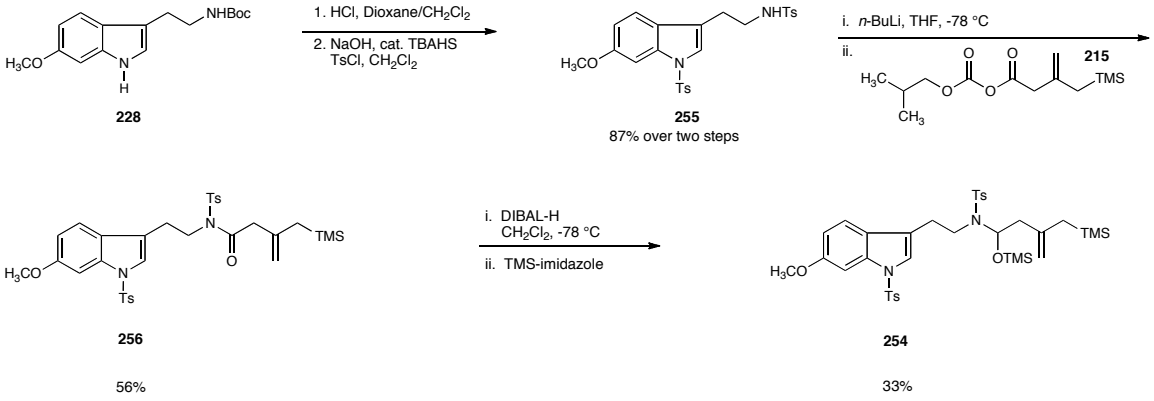
23% of the desired product **247**, with competitive Pictet-Spengler rearrangement dominating the reaction profile (38% yield). The regioisomeric tetracyclic amine **248** was also isolated in 23% yield (Scheme 2.37), and its structure was assigned by comparison of its $^{1}$H NMR data to that of compound **257** (*vide infra*, section 2.6.1).

This observation can be accounted for in our mechanistic hypothesis, with the electron-donating 6-methoxy group stabilizing the three-membered transition state **249** leading to the undesired rearrangement intermediate **250** (Path B). Additionally, the high electron-density of the aromatic system could also extend the lifetime of the resulting benzylic carbocation sufficiently enough to be intercepted by the internal nucleophile (path $B_2$).



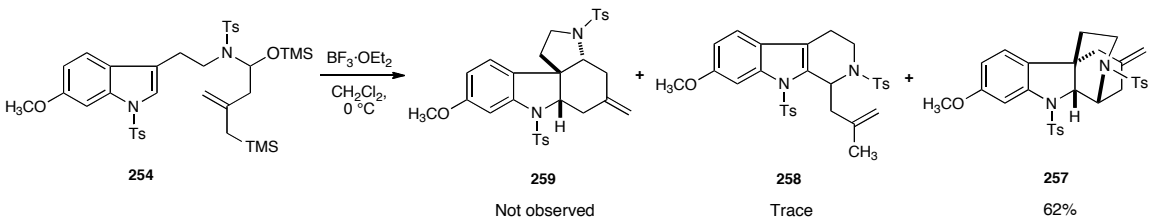

**Scheme 2.37** Mechanistic rationale for the formation of compounds **247**, **248** and **251**.

In order to overcome this side reaction, we attempted to tune the electronics of the substrate by placing an electron withdrawing tosyl group on the indole nitrogen atom. Although this latter functional group strategy had led to the formation of regioisomeric tetracyclic product **172** when it was employed in electron deficient compound **168**, we reasoned that the combined effect of the $N_a$-tosyl group and a 6-methoxy indole substituent might tune the reactivity of **254** to resemble that of $N_a$-benzyl-$N_b$-tosyl-*O*-TMS-aminol **148** (Scheme 2.38). Therefore, compound **254** was synthesized using standard conditions.




**Scheme 2.38** Synthesis of *N*-tosyl-*O*-TMS-aminol **254**.

This simple change however resulted in a dramatic shift in the reaction profile, with the isomeric tetracyclic amine **257** (Scheme 2.39) now being the major component of the mixture (62% yield). Minor amounts of Pictet-Spengler product **258** were isolated, but the desired cascade product **259** was not observed.




**Scheme 2.39** Cyclization of *N*-tosyl-*O*-TMS-aminol **254**.

The structure of compound **257** was initially assigned based on by $^{1}$H COSY and HMQC NMR experiments, which indicated the presence of two adjacent methine protons $H_a$ and $H_d$ ($J$ = 3.0Hz) (Figure 2.4). Moreover, the COSY data suggested an 8-proton spin system consisting of a relatively isolated 2-proton- ($H_f$-C-$H_g$) and 4-proton spin system ($H_d$-C-C[$H_a$]-C[$H_e$,$H_h$]) which shared common correlations with the exocyclic olefin protons ($H_A$-C-$H_B$). Additionally, irradiation of $H_j$ produced signal enhancements on $H_d$ and $H_3$ as would be expected in a compound of such structure. Subsequently, X-ray crystallography data supported our assignment.

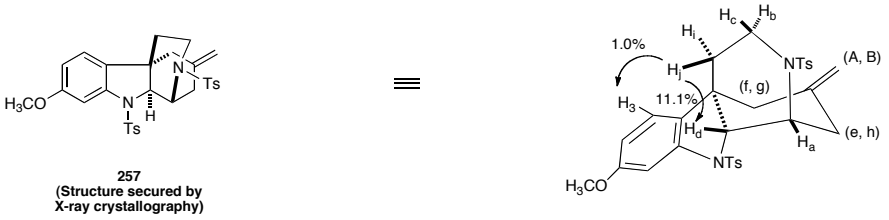
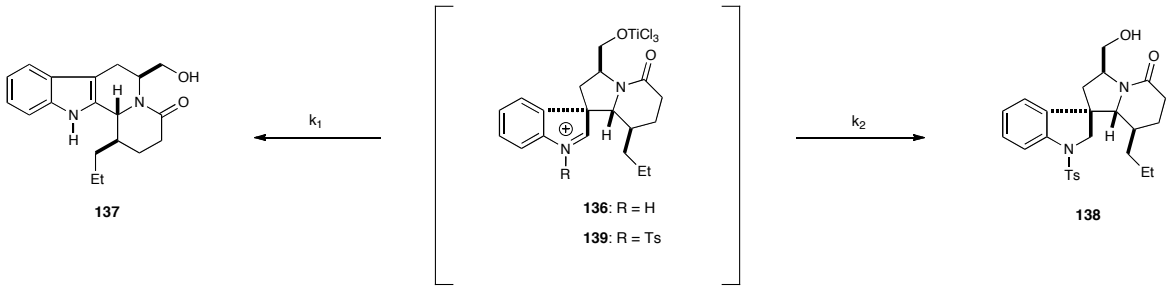



**Figure 2.4** Structural assignment of isomeric tetracyclic tosylamine **257**.

The outcome of this experiment in conjunction with our earlier observations strongly suggested that the 1,2-alkyl migration was indeed reinforced by electron-withdrawing groups at $N_a$. In considering the experiment by Bosch and co-workers that reported a retardation of the rate of 1,2-alkyl migration in $N_a$-tosyl substituted

spiroindolium intermediates, we recognized that an alternate explanation to the apparent decrease in migration rate was also possible (Scheme 2.40). We hypothesized that the increased electrophilicity of $N_a$-tosyl-spiroindolium **139** promotes a rapid reaction with $Et_3SiH/TiCl_4$ and thus precludes the classical 1,2-rearrangement ($k_2 >> k_1$), overall leading to the preferential formation of **138** as reported by Bosch. On the other hand, by virtue of its lower electrophilicity $N_a$-H-spiroindolium **136** undergoes 1,2-alkyl migration faster than intermolecular trapping by $Et_3SiH$ and generates the classical Pictet-Spengler product **137** ($k_1 >> k_2$).




**Scheme 2.40** Alternate explanation to Bosch's observations.

While the failure of *N*-tosyl-*O*-TMS-aminol **223** to produce tetracyclic compound **247** in high yield outlines the current limitation of our methodology, we have not exhausted all the potential solutions to this problem. The most obvious strategy would be to exchange the methyl substituent at the 6-hydroxylindole position for a tosyl group (**260**, Figure 2.5) in similar manner to that employed by Buchi and co-workers to solve an analogous issue.[17] Additionally, the problem could be circumvented by using an electron-withdrawing group at the 6-position (**261**), which could then be converted to the corresponding hydroxyl group post-cyclization.

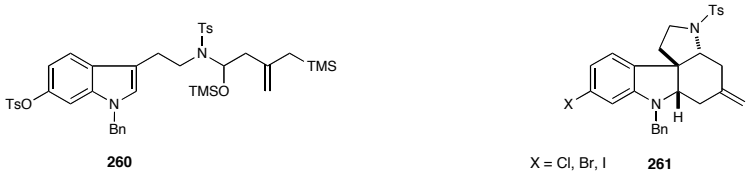
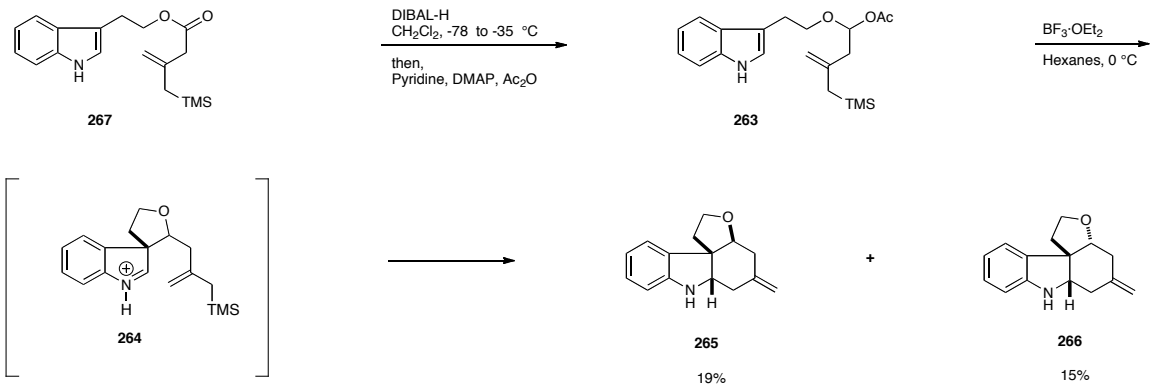



**Figure 2.5** Possible solutions to address the limitations of our method concerning the cyclization of 6-methoxy- *N*-tosyl-*O*-TMS-aminol **223**.

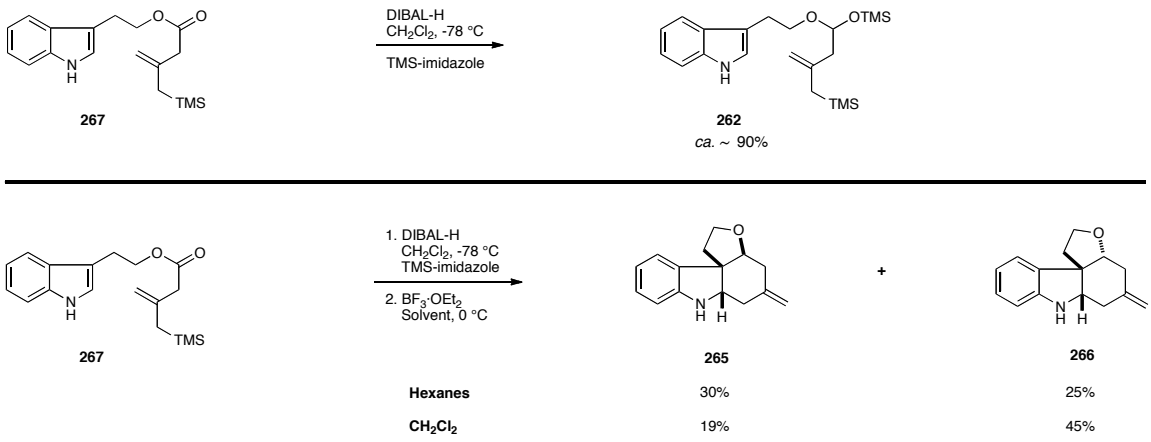
### 2.6.2. Application of Our Cascade Annulation Strategy to Tryptophol-Based System 262

Our interest in the synthesis of indoline base natural products led us to apply the cascade annulation sequence to tryptophol-based system **263**. This initial investigation, carried out by Dr. Hussaini in our lab (Scheme 2.41), had revealed that upon treating acetoxy-acetal **263** with $BF_3{\cdot}OEt_2$ in hexanes at 0 °C, the resulting oxonium ion **264** cyclized to a 1.2:1 mixture of C(3)-epimeric tetracyclic ethers **265** and **266** in 34% overall yield. Despite these promising results, the transformation had not been fully realized due to the significant technical challenge associated with the synthesis and handling of the highly sensitive acetoxy-acetal **263**.




**Scheme 2.41** Preliminary results with acetoxy-acetal **263**.

Encouraged by our recent success in developing an efficient cascade annulation sequence for tryptamine-based systems, we revisited the analogous transformation of tryptophol-based system **263**. Our goal was to circumvent the synthesis of acetoxy-acetal **263** altogether, by utilizing instead a more stable oxonium ion precursor **262**. Additionally, we wanted to improve the yield of the overall transformation and unambiguously assign the relative stereochemistry of the tetracylic ether products **265** and **266**.




**Scheme 2.42** Improved procedure for the formation of tetracyclic ethers **265** and **266**.

Ester **267** was subjected to DIBAL-H reduction at -78 °C and then treated with the mild trapping reagent trimethysilylimidazole. The reaction proceeded smoothly and the carbinol signal at 4.89 ppm observed in the $^{1}$H NMR spectrum of the crude reaction mixture, clearly indicated that trimethylsilyloxy-acetal **262** was the main product. However, compound **262** was never isolated in higher than 30% yield after purification by column chromatography using silica gel (treated with 1% $Et_3N$) or neutral alumina. Nevertheless, we found that washing the crude reaction mixture with saturated aqueous

$CuSO_4$ removed the imidazole impurity and afforded compound **262** in almost quantitative yield. The crude product was then treated with $BF_3{\cdot}OEt_2$ in hexanes at 0 °C to generate a 1.2:1 mixture of **265** and **266** in 55% yield over two steps. This result was a considerable improvement over the yields previously reported (overall 23% for the conversion of **267** to compounds **265** and **266**). When $CH_2Cl_2$ was used as the solvent the reaction sequence proceeded in 64% overall yield, and the ratio of C(3)-epimers switched in favor of compound **266** (1:2.3).

The structure of compound **266** was established by 1D and 2D NMR experiments, in which the assignment of methine protons $H_b$ and $H_c$ was based on chemical shift analysis (3.90 and 3.74 ppm, respectively) and COSY data (Figure 2.6). Additionally, NOE between the methylene proton $H_f$ and the aromatic proton $H_4$ permitted the indirect assignment of $H_b$ as the neighboring ethereal methine signal. Irradiation of $H_g$ produced enhancements of 5.5% and 5.0% for $H_b$ and $H_c$, respectively, thus indicating that both protons were located on the same face of the D ring.

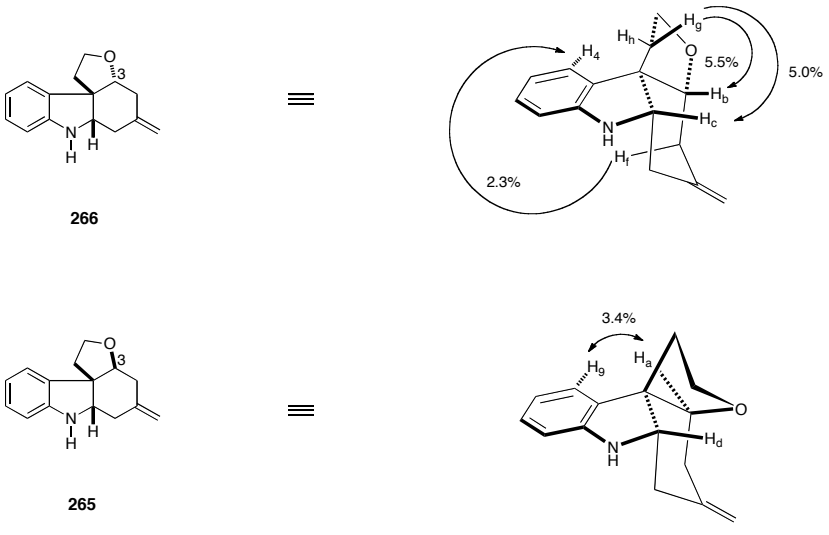
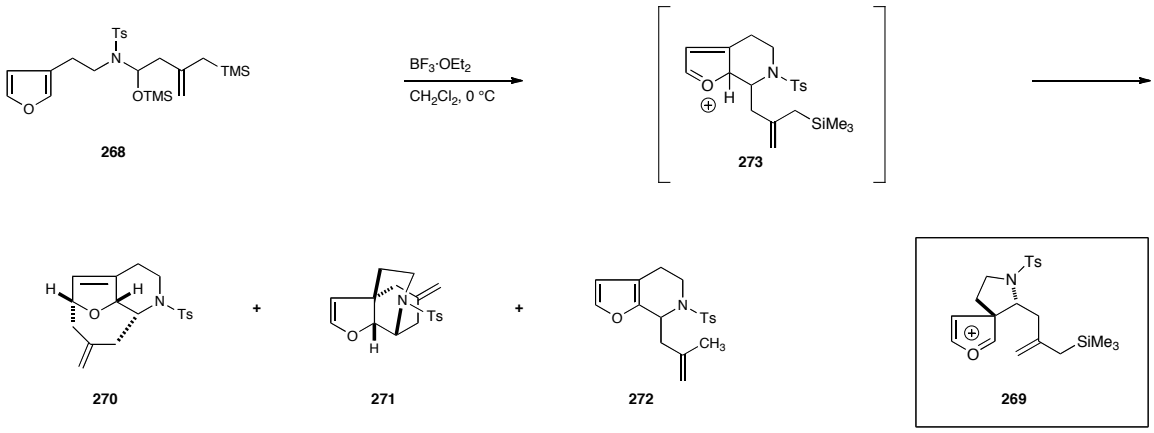



**Figure 2.6** Structural assignment of ethers **265** and **266**.

The initial assignment of compound **265** was difficult because of signal overlap in its $^{1}$H NMR spectrum. However, the insight gained from the structural characterization of the C(3)-epimer **266** was helpful in the assignment of key protons signals at 3.89 and 3.26 ppm in **265** as $H_a$ and $H_d$, respectively. At this stage, irradiation of $H_a$ produced a 3.4% enhancement in the signal of the aromatic $H_4$, which was indicative of the aspidosperma-like stereochemistry as described in section 1.2.

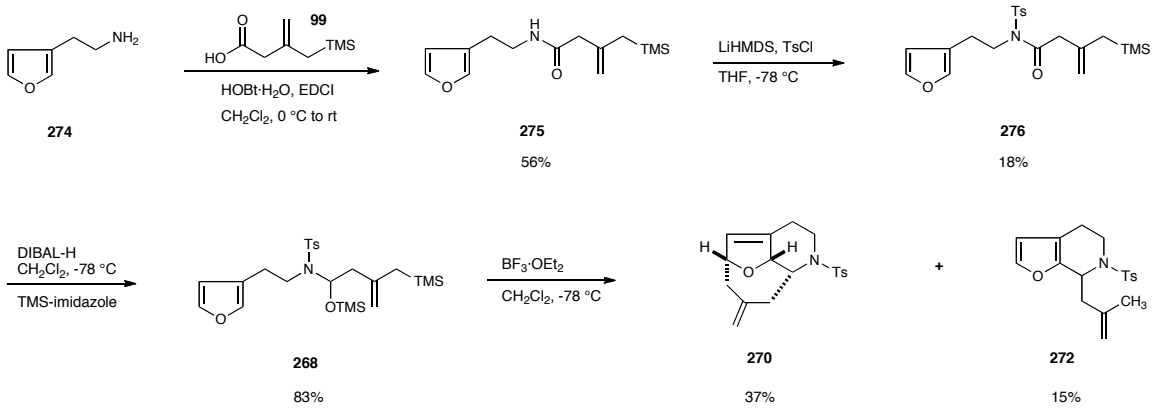
### 2.6.3. Application of Our Cascade Annulation Strategy to Furan-Based System 268

We were also interested in extending our methodology beyond the construction of indoline-based heterocycles. By exchanging the indole moeity in our starting material for another aromatic group such as furan, we could develop a variant of our cascade annulation reaction to construct new interesting and highly complex structures. Although we did not expect for the system to display the same reactivity profile of compound **192** (as it is well known that 3-substituted furans react preferentially at the 2-position thus precluding the intermediacy of a spirocylic intermediate **269**),[50] the cyclization of compound **192** could generate one of three possible products **270**, **271** and **272** (Scheme 2.43).



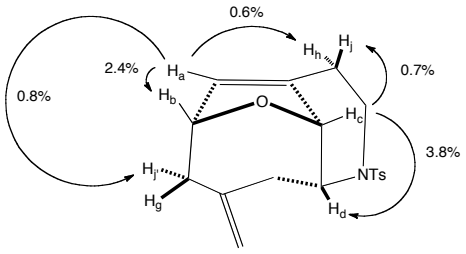

**Scheme 2.43** Possible products from the cyclization of *N*-tosyl-*O*-TMS-aminol **268**.

After the initial formation of intermediate **273**, compound **270** could arise *via* 1,2-nucleophilic attack of the tethered allylsilane onto the least hindered carbon of the oxonium ion moeity, to afford a new seven membered ring in the process. On the other hand, the formation of compound **271** would entail 1,4-addition onto the more hindered electrophilic carbon of oxonium ion **273**, but would afford the kinetically preferred six membered ring. Lastly, compound **272** could be generated if rearomatization to the furan ocurred more rapidly than the desired intramolecular nucleophilic attack. In order to answer these questions regarding the reactivity profile of furans in the context of our cascade annulation reaction, we undertook the synthesis of compound **268** as shown in Scheme 2.44.




**Scheme 2.44** Synthesis and cyclization of *N*-tosyl-*O*-TMS-aminol **268**.

The known furan **274**[50] was condensed with acid **99** in the presence of EDCI and HOBt to afford amide **275** in 56% yield, which under standard tosylation conditions only generated 18% yield of the desired *N*-tosylamide **276**. Reduction with DIBAL-H and trimethylsilylimidazole produced compound **268** in 83% yield. Subjecting *N*-tosyl-*O*-TMS-aminol **268** to our optimized cyclization conditions afforded 37% yield of caged-ether **270** along with 15% of furan **272**.

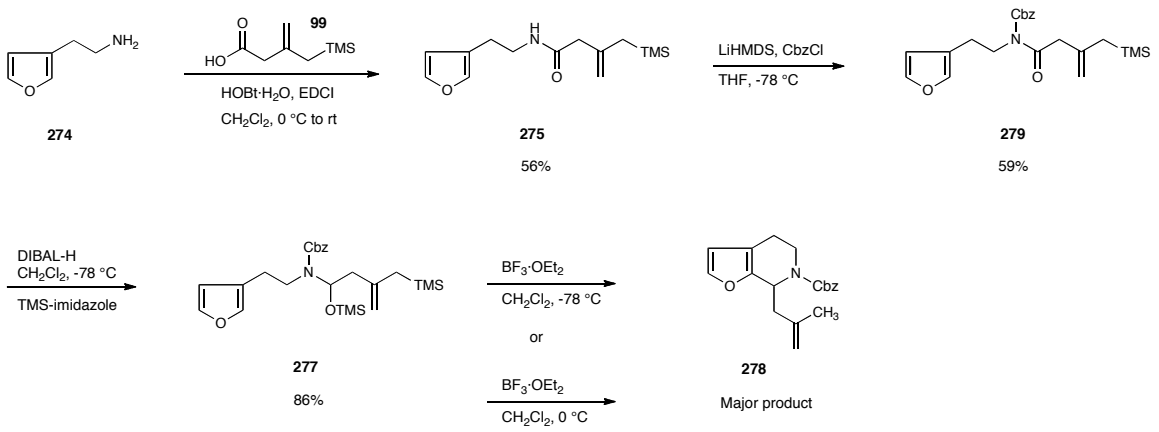



**270**

**Figure 2.7** Structural assignment of ether **270**.

The number of vinyl proton signals in **270** ($H_a$ at 5.49 ppm and the exocyclic methylene protons at 5.02 and 4.78 ppm) allowed us to identify its general structure from among the three possible product structures listed in Scheme 2.43. Subsquent COSY and HMQC experiments supported our initial assignment, but the lack of a measurable $^3J$ value between protons $H_a$ and $H_b$ prompted us to carry out CYCLENOE experiments to confirm their supposed proximity (Figure 2.7). Irradiation of $H_a$ produced signal enhancements of 2.4%, 0.8%, and 0.6% on $H_b$, $H_j$, and $H_h$ respectively, which indicated that $H_a$ and $H_b$ were indeed attached to neighboring carbons. The NMR data gathered in combination with the study of molecular models suggested that the dihedral angle between $H_a$ and $H_b$ was close to 90° (the Karplus equation predicts an insignificant coupling constant value at 90°), which would explain our observations. Additionally, conformational analysis *via* molecular models also explains the lack of NOE at $H_c$ upon irradiation of $H_b$, which predict that the ethereal protons $H_b$ and $H_c$ are arranged in an almost orthogonal manner to each other. Our structural assignment was subsequently corroborated *via* X-ray crystallography.

*N*-Cbz-*O*-TMS-aminol **277** was also synthesized in order to assess the effect of the acyl auxiliary on product distribution (Scheme 2.45). Compound **277** was constructed using our standard conditions. However, treating *N*-Cbz-*O*-TMS-aminol **277** with $BF_3{\cdot}OEt_2$ either at -78 or 0 °C produced furan **278** as the major product.



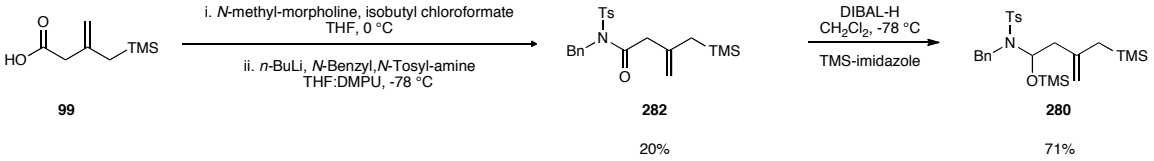

**Scheme 2.45** Synthesis and cyclization of *N*-tosyl-*O*-TMS-aminol **277**.

Although the transformation was not fully optimized at this stage, we recognized that we had successfully shown that furans could be implemented in our cascade annulation sequence. Given that our main focus remained on the synthesis of malagashanine, no further attempts were made to improve the yield of compound **270**.

### 2.6.4. Development of an Intermolecular Cascade Annulation Reaction

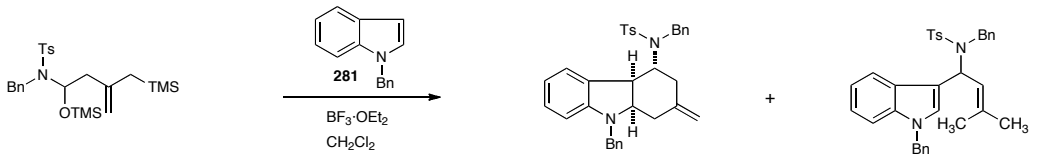
Having established the utility of our intramolecular cascade annulation reaction for the construction of the core of the malagashanine alkaloids, we embarked on the development of an intramolecular variant, which would expand the range of synthetic targets attainable through our methodology. As a model system, we chose the reaction of *N*-tosyl-*O*-TMS-aminol **280** (Scheme 2.46) with *N*-benzyl indole (**281**) because it closely resembled the intramolecular parent system **148**. Compound **280** was constructed by treating acid **99** with isobutylchloroformate and *N*-methylmorpholine to generate the corresponding mixed anhydride, followed by treatment with the lithium anion of

*N*-benzyl,*N*-tosyalmine at -78 °C, which generated *N*-tosylamide **282** in 20%. The low yield of compound **282** was surprising given how well the same protocol had worked for our tryptamine derived systems. Compound **282** was then converted to **280** under standard conditions in 71% yield.




**Scheme 2.46** Synthesis of *N*-tosyl-*O*-TMS-aminol **280**.

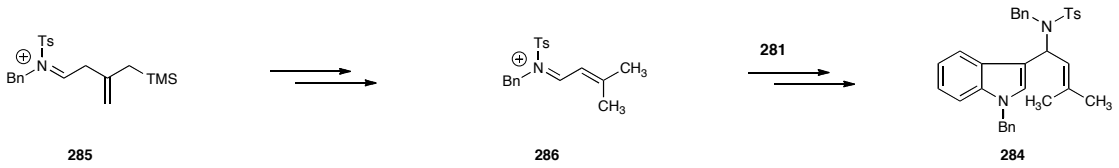
Treatment of three equivalents of **280** and one equivalent of *N*-benzylindole (**281**) with $BF_3{\cdot}OEt_2$ at 0 °C afforded the desired intramolecular product **283** in 52% yield (Table 2.3, entry 1) along with minor amounts of uncyclized byproduct **284**. The structure of **283** was unambiguously established by X-ray crystallography.




| Entry | **280** (equiv) | **281** (equiv) | Temp (°C) | Conc. (M) | % yield **283** | % yield **284** |
|---|---|---|---|---|---|---|
| 1 | 3 | 1 | 0 | 0.1 | 62 | Minor |
| 2 | 1 | 3 | 0 | 0.1 | 31 | 29 |
| 3 | 1 | 1.05 | 0 | 0.6 | 46 | Minor |
| 4 | 1 | 4 | -78 | 0.1 | 53 | Trace |
| 5 | 1 | 1.05 | -78 | 0.2 | 85 | Trace |

**Table 2.3** Optimization of the intermolecular cascade cyclization reaction.

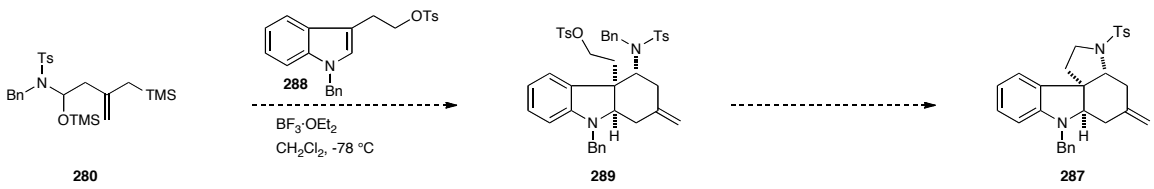
Compound **284** was most likely generated by the protodesilylation of the intermediate iminium ion **285** as shown in Scheme 2.47.




**Scheme 2.47** Possible mechanism regarding the formation of compound **284**.

Reversing the proportion of the starting materials (entry 2) produced a ~ 1:1 ratio of cyclization product **283** and byproduct **284**. Recognizing that low concentrations of *N*-tosyl-*O*-TMS-aminol **280** led to the formation of compound **284**, the effective concentrations of both starting materials were increased by carrying out the reaction at 0.6 M. This suppressed the formation of **284** but lowered the overall yield to 46% (entry 3). In an effort to minimize the decomposition of iminium ion **285** while keeping the concentration of starting material below 0.6 M, the reaction was carried out at -78 °C (entries 4). After some optimization we found that at this temperature and a concentration of 0.2 M the reaction could be carried out using nearly equimolar amounts of the starting materials to afford 85% yield of compound **283 (**entry 5).

Compound **283** displays complementary stereochemistry to that obtained *via* our intramolecular cascade annulation reaction and therefore represents a potential entry into the core of the aspidosperma alkaloids (**287**) (Scheme 2.48). A direct extension of our newly developed intermolecular annulation sequence would be to employ *O*-tosyltryptophol **288** and *N*-tosyl-*O*-TMS-aminol **280** to access tricyclic amine **289**, which could then be easily converted to **287**.




**Scheme 2.48** Possible application of the intermolecular annulation sequence to access the core of the aspidosperma alkaloids **287**.

## 2.7. Conclusions

During this phase of our studies towards the total synthesis of malagashanine, we have developed an efficient cascade annulation sequence to build the core of the molecule and install the C(2), C(3) and C(7) stereocenters with the necessary relative stereochemistry. We have shown that the use of *N*-acyl- and *N*-tosyl-*O*-TMS-aminols as iminium ion precursors circumvents the problems associated with the condensation of primary amine **36** with sensitive $\beta,\gamma$-unsaturated aldehyde **86**. Additionally, the use of a tosyl auxiliary on the iminium ion nitrogen and a benzyl group on the indole nitrogen provides exquisite selectivity for the desired cascade product **195**. The efficiency of this transformation is nothing short of remarkable considering the large number of side products that are accessible *via* the highly reactive $\beta,\gamma$ unsaturated iminium ion intermediate **207**.

The cascade annulation sequence is amenable to both electron-withdrawing and electron-donating substituents on the indole moiety. However, the failure of 6-methoxy-substituted *N*-tosyl-*O*-TMS-aminol **223** to cyclize in high yield outlines a

minor current limitation to our methodology. We also demonstrated that furans are useful substrates for the annulation sequence and can produce interesting caged structures such as **270**. Additionally, our methodology can be extended to tryptophol-based system **262**, which reacts *via* an oxonium ion (**264**) to afford oxygen analogs of the aspidoesperma and malagashanine cores **265** and **266**, respectively. Moreover, an intermolecular cascade annulation sequence has been developed that affords tricyclic amine product **283,** which possess aspidosperma-like stereochemistry and might allow entry to this class of molecules in the future. Lastly, preliminary attempts to cyclize *N*-tosyl-*O*-TMS-aminols in the presence of protic acid catalysts suggest that the use of acids with particularly weak conjugate bases is essential in order to suppress the isomerization of the key iminium ion intermediates.

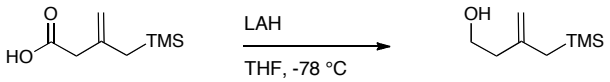
## 2.8. Experimentals

**General Information.** $^{1}H$ and $^{13}C$ NMR spectra were recorded on a Varian Inova 600 spectrometer (600 MHz $^{1}H$, 150 MHz $^{13}C$), a Varian Unity plus 600 spectrometer (600 MHz $^{1}H$, 150 MHz $^{13}C$), and a Varian Inova 400 spectrometer (400 MHz $^{1}H$, 100 MHz $^{13}C$) at room temperature in $CDCl_3$ with internal $CHCl_3$ as the reference (7.27 ppm for $^{1}H$ and 77.23 ppm for $^{13}C$), unless otherwise stated. Chemical shifts (δ values) were reported in parts per million (ppm) and coupling constants (*J* values) in Hz. Infrared (IR) spectra were recorded using Thermo Electron Corporation Nicolet 380 FT-IR spectrometer. High resolution mass spectra were obtained using a Thermo Electron Corporation Finigan LTQFTMS (at the Mass Spectrometry Facility, Emory University). We acknowledge the use of shared instrumentation provided by grants from the NIH and the NSF. Melting points (m.p.) were measured using a Fisher-Johns melting point apparatus and are not corrected. Analytical thin layer chromatography (TLC) was performed on precoated glass backed EMD 0.25 mm silica gel 60 plates. Visualization was accomplished with UV light or ethanolic anisaldehyde. Flash column chromatography was carried out using EMD Geduran® silica gel 60 (40-63 μm) or Fluka basic alumina (0.05-0.15 mm, pH 9.5).

All reactions were conducted with anhydrous solvents in oven dried or flame-dried and argon-charged glassware. Anhydrous solvents were purified by passage through activated alumina using a *Glass Contours* solvent purification system unless otherwise noted. Solvents used in workup, extraction and column chromatography were used as received

from commercial suppliers without prior purification. All reagents were purchased from Sigma-Aldrich and used as received unless otherwise noted. Hexamethyldisilazane, triethylamine, *N*-methylmorpholine, pyridine, and boron trifluoride diethyletherate were purified by distillation from calcium hydride.

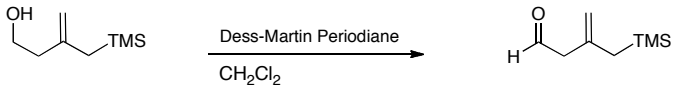
**Synthesis of 3-((trimethylsilyl)methyl)but-3-en-1-ol (101):**




**99** **101**

A solution of acid **99** (5.84 g, 33.9 mmol) in $Et_2O$ (94.0 mL) was cooled to -78 °C. LAH (2.0 M in THF, 19.0 mL, 38.0 mmol) was added over 15 minutes, and the resulting solution was stirred at -78 °C for 12 h. The mixture was warmed to 0 °C and quenched by slow addition of saturated Rochelle's salt solution (100 mL). The mixture was stirred vigorously at r.t. for 8 h. The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (3 x 50 mL). The organic extracts were combined, washed with brine (100 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (4:1 hexanes/EtOAc) afforded homoallylic alcohol **101** as a yellow oil (3.92 g, 73%); $\mathbf{R_f}$ 0.27 (4:1 hexanes/EtOAc); $^1$**H NMR** ($CDCl_3$, 400 MHz) δ 4.70 (s, 1H), 4.68 (s, 1H), 3.72 (t, 2H, *J* = 7.0 Hz), 2.24 (t, 2H, *J* = 7.0 Hz), 1.56 (s, 2H), 0.04 (s, 9H); **IR** (thin film, $cm^{-1}$) 3344.10 (br m), 3075.3 (w), 2953.8 (s), 1633.0 (w), 1417.8 (w), 1249.1 (m), 1156.8 (w), 1047.5 (m), 852.0 (s).

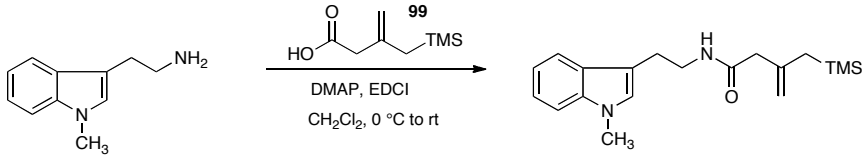
**Synthesis of 3-((trimethylsilyl)methyl)but-3-enal (86):**




**101** **86**

A solution of Dess-Martin periodinane (0.528 g, 1.25 mmol) in $CH_2Cl_2$ (14.0 mL) was added to a stirring solution of homoallylic **101** (0.066 g, 0.42 mmol) in $CH_2Cl_2$ (14.0 mL), and the resulting suspension was stirred for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$ / 20% aqueous $Na_2SO_3$ (1:1, 30 mL). The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (3 x 20 mL). The organic extracts were combined, washed with brine (30 mL), dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo* to afford crude aldehyde **86** as a brown oil (0.024 g, 37%); $\mathbf{R_f}$ 0.65 (in $CH_2Cl_2$); $^1$**H NMR** ($CDCl_3$, 400 MHz) δ 9.64 (t, 1H, *J* = 2.6 Hz), 4.84 (s, 1H), 4.78 (s, 1H), 3.02 (t, 2H, *J* = 2.6 Hz), 1.59 (s, 2H), 0.05 (s, 9H); **IR** (thin film, $cm^{-1}$) 2954.7 (w), 1725.5 (s), 1632.1 (w), 1248.5 (s), 839.4 (s).

**Synthesis of amide 109:**

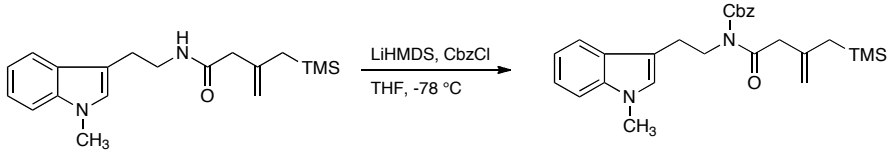



**36** **109**

A solution of tryptamine **36** (0.986 g, 5.66 mmol) and DMAP (0.206 g, 1.68 mmol) in $CH_2Cl_2$ (53.0 mL) was cooled to 0 °C. Carboxylic acid **99** (0.967 g, 5.61 mmol) was added, followed by dropwise addition of EDCI (1.49 mL, 8.42 mmol) over 20 minutes. The reaction was stirred at 0 °C for 1 h, warmed to r.t. and stirred for 24 h. $Et_2O$ (100

mL) was added, and the reaction was stirred for 15 minutes. The mixture was washed with 0.1 M aqueous HCl (2 x 100 mL), saturated aqueous $NaHCO_3$ (2 x 100 mL), and brine (100 mL). The organic layer was dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (1:1 hexanes/EtOAc) afforded amide **109** as a crystalline white solid (1.34 g, 72%); $\mathbf{R_f}$ 0.40 (1:1 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 400 MHz) δ 7.61 (d, 1H, *J* = 8.0 Hz), 7.51 (d, 1H, *J* = 8.4 Hz), 7.25 (dt, 1H, *J* = 8.4, 1.2 Hz), 7.12 (dt, 1H, *J* = 7.4, 1.2 Hz), 6.88 (s, 1H), 5.94 (br s), 4.68 (s, 1H), 4.67 (s, 1H), 3.76 (s, 3H), 3.57 (q, 2H, *J* = 6.4 Hz), 2.96 (t, 2H, *J* = 6.4 Hz), 2.88 (s, 2H), 1.58 (s, 2H), 0.09 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 170.4, 142.5, 137.2, 127.9, 127.0, 121.9, 119.1, 119.0, 112.7, 111.6, 109.4, 47.1, 40.1, 32.8, 26.9, 25.3, -1.35.

**Synthesis of *N*-Cbz-amide 111:**

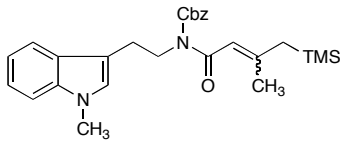



**109** **111**

A solution of amide **109** (1.13 g, 3.43 mmol) in THF (10.4 mL) was cooled to -78 °C. A freshly prepared LiHMDS solution (0.31 M in THF, 10.4 mL, 3.23 mmol) was cooled to -78 °C and added to the staring material solution *via* cannula. The reaction was stirred for 1 h at -78 °C. Benzyl chloroformate (0.68 mL, 4.8 mmol) was added and the mixture was stirred for 12 h for -78 °C. The reaction was quenched with saturated aqueous $NH_4Cl$ (5 mL) and warmed to 0 °C. $H_2O$ (5 mL) was added and the mixture was stirred for 5 minutes. The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (2 x 15 mL). The organic extracts were combined, washed with brine (20 mL), dried over

anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (17:1 hexanes/EtOAc) afforded *N*-Cbz amide **111** as a colorless oil (1.44 g, 95%); **$R_f$** 0.41 (4:1 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 400 MHz) δ 7.53 (d, 1H, *J* = 8.0 Hz), 7.51-7.28 (m, 6H), 7.24 (t, 1H, *J* = 7.8 Hz), 7.05 (d, 1H, *J* = 7.4 Hz), 6.86 (s, 1H), 5.20 (s, 2H), 4.78 (s, 1H), 4.73 (s, 1H), 4.10-4.01 (m, 2H), 3.73 (s, 3H), 3.67 (s, 2H), 3.07-2.99 (m, 2H), 1.70 (s, 2H), 0.10 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 173.8, 154.5, 141.7, 137.0, 135.2, 128.9, 128.9, 128.7, 127.9, 127.1, 121.7, 119.2, 119.0, 111.3, 111.1, 109.3, 68.7, 47.3, 45.6, 32.7, 27.5, 24.7, -1.20.

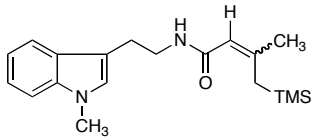
***N*-Cbz-amide 123** was obtained during our initial attempts to install the Cbz group in compound **111** using 1.05 equivalents of *n*-BuLi in place of KHMDS as described in the previous procedure.




**123**

$R_f$ 0.41 (4:1 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 400 MHz) δ 7.53 (d, 1H, *J* = 8.0 Hz), 7.51-7.28 (m, 6H), 7.24 (t, 1H, *J* = 7.8 Hz), 7.05 (d, 1H, *J* = 7.4 Hz), 6.86 (s, 1H), 6.41 (s, 1H), 5.19-5.16 (m, 2H), 4.15-4.05 (m, 2H), 3.73 (s, 3H), 3.07-2.99 (m, 2H), 2.19 (d, 3H, *J* = 3.0 Hz), 1.81 (s, 2H), 0.10 (s, 9H)

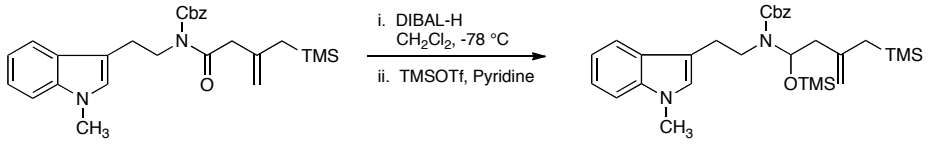
**Amide 124** was obtained during our initial attempts to install the Cbz group in compound **111** using 1.05 equivalents of *n*-BuLi in place of KHMDS as described in the previous procedure.




**124**

**$R_f$** 0.45 (1:1 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 400 MHz) δ 7.61 (d, 1H, *J* = 7.8 Hz), 7.31 (d, 1H, *J* = 8.4 Hz), 7.43 (t, 1H, *J* = 7.2 Hz), 7.11 (t, 1H, *J* = 7.5 Hz), 6.90 (s, 1H), 5.29 (br s, 1H), 4.72 (d, 1H, *J* = 4.8 Hz), 3.77 (s, 3H), 3.61 (q, 2H, *J* = 7.2 Hz), 2.96 (t, 2H, *J* = 5.4 Hz), 2.48 (s, 2H), 1.79 (d, 3H, *J* = 4.8 Hz), 0.07 (s, 9H).

**Synthesis of *N*-Cbz-*O*-TMS-aminol 110:**

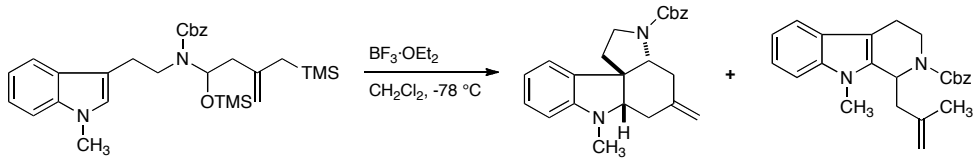



**111** **110**

A solution of *N*-Cbz amide **111** (0.681 g, 1.55 mmol) in $CH_2Cl_2$ (6.7 mL) was cooled to -78 °C. DIBAL-H (1.0 M in $CH_2Cl_2$, 3.1 mL, 3.1 mmol) was added dropwise over 10 minutes. The reaction mixture was stirred for 2 h, then pyridine (0.38 mL, 4.6 mmol) was added dropwise and the reaction was stirred for 20 minutes. Trimethylsilyl triflate (0.70 mL, 3.9 mmol) was added dropwise and the mixture was stirred for 20 minutes at -78 °C. The reaction was warmed to 0 °C and was quenched by slow addition of aqueous 15% Rochelle's salt solution (5 mL). The biphasic mixture was transferred to a 25 mL

Erlenmeyer flask, and $Et_2O$ (12 mL) was added. The mixture was stirred vigorously at r.t. until both layers were clear. The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (2 x 5 mL). The organic extracts were combined, washed with brine (20 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (9:1 hexanes/EtOAc, silica gel deactivated with 1% $Et_3N$) afforded *N*-Cbz-*O*-TMS-aminol **110** as a colorless oil (0.633 g, 76%); $\mathbf{R_f}$ 0.50 (4:1 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) (1.0: 0.6 mixture of rotamers) δ 7.79 (d, 0.6H, *J* = 8.4 Hz), 7.47-7.19 (m, 12.2H), 7.14 (t, 0.6H, *J* = 7.5 Hz), 6.98 (t, 1.0H, *J* = 7.5 Hz), 6.92 (s, 0.6H), 6.79 (s, 1.0H) 5.95 (t, 1.0H, *J* = 6.3 Hz), 5.79 (t, 0.6H, *J* = 6.3 Hz), 5.29-5.16 (m, 3.2H), 3.78 (s, 1.8H), 3.73 (s, 3H), 3.59-3.33 (m, 3.2H), 3.12-3.07 (m, 2.2H), 2.95 (dt, 1.0H, *J* = 12.6, 5.4 Hz), 2.35-2.23 (m, 3.2H), 1.64 (d, 1.0H, *J* = 13.2 Hz), 1.54 (d, 1.0H, *J* = 13.2 Hz), 1.50 (d, 0.6H, *J* = 13.5 Hz), 1.39 (d, 0.6H, 13.5 Hz), 0.13 (s, 9.0H), 0.08 (s, 5.4H), 0.04 (s, 9.0H), -0.03 (s, 5.4H); **HRMS** (+ESI) calculated for $C_{30}H_{45}N_2O_3Si_2$ 537.2969, found 537.2960 $[M+H]^+$.

**Synthesis of tetracyclic amine 113:**

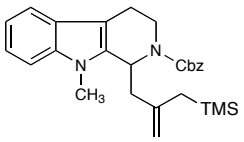



**110** **113** **126**

A solution of *N*-Cbz-*O*-TMS-aminol **110** (0.081 g, 0.15 mmol) in $CH_2Cl_2$ (3.0 mL) was cooled to -78 °C. $BF_3{\cdot}OEt_2$ (21 μL, 0.17 mmol) was added dropwise and the mixture was stirred at -78 °C for 1 h, warmed to room temperature and stirred for 12 hours. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ solution (2 mL). The

resulting biphasic mixture was stirred vigorously for 15 minutes. The organic layer was separated, and the aqueous layer was extracted with $CH_2Cl_2$ (2 x 3 mL). The organic extracts were combined, washed with brine (3 mL), dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (9:1 hexanes/EtOAc) afforded tetracyclic amine **113** as a colorless oil (2.8 mg, 5%); $\mathbf{R_f}$ 0.23 (4:1 hexanes/EtOAc); **$^1$H NMR** (CDCl3, 300 MHz) (0.7:0.3 mixture of rotamers) δ 7.45-7.32 (m, 5H), 7.11 (dt, 1H, *J* = 7.8, 1.0 Hz), 6.98 (d, 1H, *J* = 7.2 Hz), 6.62 (t, 1H, *J* = 7.2 Hz), 6.36 (d, 1H, *J* = 7.8 Hz), 5.30-5.06 (m, 2H), 4.71-4.47 (m 2H), 3.79 (dd, 1H, *J* = 12.3, 5.4 Hz), 3.75-3.56 (m, 3H), 3.46-3.24 (m, 0.7H), 3.24-3.01 (m, 0.3H), 2.81 (s, 3H), 2.39-2.21 (m, 2H), 2.15 (dd, 1H, *J* = 14.1, 3.9 Hz), 1.98-1.86 (m, 2H); **HRMS** (+ESI) calculated for $C_{24}H_{27}N_2O_2$ 375.2073, found 375.2061 $[M+H]^+$; and tetrahydro-*β*-carboline **126** as a colorless oil (0.051 g, 90%); $\mathbf{R_f}$ 0.40 (4:1 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 400 MHz) (1.0:0.9 mixture of rotamers) δ 7.51 (d, 0.9H, *J* = 8.0 Hz), 7.48 (d, 1.0H, *J* = 8.0 Hz), 7.43-7.28 (m, 11.4H), 7.26-7.20 (m, 1.9H), 7.17-7.09 (m, 1.9H), 5.65 (dd, 1.0H, *J* = 10.6, 3.4 Hz), 5.41 (dd, 0.9H, *J* = 10.6, 3.0 Hz), 5.20 (d, 0.9H, *J* = 12.4 Hz), 5.18 (s, 2H), 5.09 (d, 0.9H, *J* = 12.4 Hz), 4.89 (s, 1H), 4.84-4.67 (m, 1.9H), 4.76 (s, 0.9H), 4.67 (dd, 0.9H, *J* = 13.6, 6.0 Hz), 4.42 (dd, 1.0H, *J* = 13.4, 5.4 Hz), 3.71 (s, 3H), 3.67 (s, 2.7H), 3.33 (dt, 1.9H, *J* = 12.0, 4.8 Hz), 2.99-2.83 (m, 1.9H), 2.76 (dt, 1.9H, *J* = 16.0, 4.4 Hz), 2.62-2.53 (m, 1.9H), 2.48 (dd, 1.0H, *J* = 14.2, 3.0 Hz), 2.36 (dd, 0.9H, *J* = 14.2, 2.6 Hz); **HRMS** (+ESI) calculated for $C_{24}H_{27}N_2O_2$ 375.2073, found 375.2062 $[M+H]^+$.

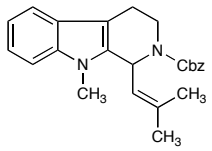
**Tetrahydro-*β*-carboline 129** was obtained during our attempts to cyclize compound **110** using Binol phosphoric acid (**128**) at 0 °C in place of $BF_3 \cdot OEt_2$ at -78 °C as described in the previous procedure.




**129**

**$R_f$** 0.60 (4:1 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) (01.0:0.8 mixture of rotamers) δ 7.50 (d, 0.8H, *J* = 7.8 Hz), 7.47 (d, 1.0H, *J* = 7.8 Hz), 7.41-7.26 (m, 10.8), 7.24-7.19 (m, 1.8), 7.14-7.09 (m, 1.8), 5.64 (dd, 1.0H, *J* = 10.5, 3.9 Hz), 5.42 (dd, 0.8H, *J* = 10.8, 3.0 Hz), 5.21 (d, 1H, *J* = 12.0 Hz), 5.18 (s, 2H), 5.07 (d, 1H, *J* = 12.0 Hz), 4.73 (s, 1.0H), 4.66 (s, 0.8H), 4.64 (s, 1.0H), 4.60-4.55 (m, 1.6H), 4.41 (dd, 1.0H, *J* = 13.8, 6.0 Hz), 3.70 (s, 3H), 3.66 (s, 2.4H), 3.37-3.27 (m, 1.8H), 2.98-2.83 (m, 1.8H), 2.78 (dd, 0.8H, *J* = 15.6, 4.2 Hz), 2.74 (dd, 1.0H, *J* = 15.6, 4.2 Hz), 2.52-2.45 (m, 1.8H), 2.43 (dd, 1.0H, *J* = 14.7, 3.9 Hz), 2.32 (dd, 0.8H, *J* = 14.1, 3.3 Hz), 1.76 (d, 1H, *J* = 13.8 Hz), 1.72 (d, 1H, *J* = 13.8 Hz), 1.46 (d, 1.0H, *J* = 13.8 Hz), 1.41 (d, 1H, *J* = 13.8 Hz), 0.07 (s, 9H), 0 (s, 7.2H); **HRMS** (+ESI) calculated for $C_{24}H_{35}N_2O_2Si$ 447.2468, found 447.2461 $[M+H]^+$.

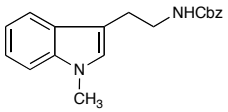
**Tetrahydro-*β*-carboline 130** was obtained during our attempts to cyclize compound **110** using Binol phosphoric acid (**128**) at 0 °C in place of $BF_3 \cdot OEt_2$ at -78 °C as described in the previous procedure.




**130**

**$R_f$** 0.45 (4:1 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 400 MHz) (01.0:0.8 mixture of rotamers) δ 7.55-7.46 (m, 1.8H), 7.43-7.27 (m, 9.2H), 7.21 (dt, 1.8H, *J* = 7.6, 0.8 Hz), 7.11 (t, 1.8H, *J* = 7.2 Hz), 6.10 (d, 1.0H, *J* = 9.5 Hz), 5.87 (d, 0.8H, *J* = 9.4 Hz), 5.45-5.34 (m, 1.8H), 5.25 (d, 1.0H, *J* = 12.1 Hz), 5.16 (d, 1.0H, *J* = 12.1 Hz), 4.55 (d, 0.8H, *J* = 7.9 Hz), 4.41 (d, 1.0H, *J* = 8.3 Hz), 3.61-3.47 (m, 5.4H), 3.24 (m, 2.6H), 2.96-2.72 (m, 4.6H), 2.07 (s, 3H), 1.85-1.63 (m, 7.8H); **HRMS** (+ESI) calculated for $C_{24}H_{27}N_2O_2$ 375.2073, found 375.2082 $[M+H]^+$.

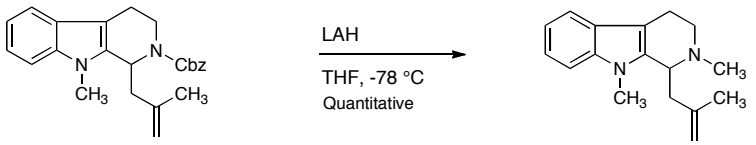
**Carbamate 125** was obtained during our attempts to cyclize compound **110** using Binol phosphoric acid (**128**) at 0 °C in place of $BF_3 \cdot OEt_2$ at -78 °C as described in the previous procedure.




**125**

**$^1$H NMR** ($CDCl_3$, 400 MHz) δ 7.60 (d, 1H, *J* = 8.0 Hz), 7.42-7.29 (m, 6H), 7.25 (t, 1H, *J* = 8.0Hz), 7.12 (t, 1H, *J* = 7.4 Hz), 6.88 (s, 1H), 5.12 (s, 2H), 4.85 (br s, 1H), 3.75 (s, 3H), 3.54 (q, 2H, *J* = 6.4 Hz), 2.98 (t, 2H, *J* = 6.4 Hz).

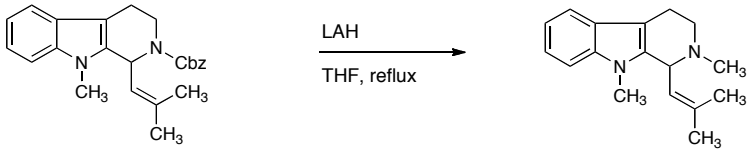
**Synthesis of tetrahydro-$\beta$-carboline 127:**




**126** **127**

A solution of **126** (0.014 g, 0.037 mmol) in THF (1.0 mL) was cooled to 0 °C. LAH (1.0 M in $Et_2O$, 0.20 mL, 0.20 mmol) was added over 15 minutes and the resulting solution was heated to 70 °C and stirred for 1 h. The mixture was cooled to 0 °C and quenched by slow addition of saturated Rochelle's salt solution (1 mL). The resulting biphasic mixture was stirred vigorously at r.t. until both layers were clear. The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (3 x 2 mL). The organic extracts were combined, washed with brine (2 mL), dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (1:1 hexanes/EtOAc) afforded amine **127** as a crystalline white solid (8.9 mg, 99%); **$^1$H NMR** ($CDCl_3$, 400 MHz) δ 7.52 (d, 1H, *J* = 7.6 Hz), 7.30 (d, 1H, *J* = 8.4 Hz), 7.21 (dt, 1H, *J* = 7.6, 1.2 Hz), 7.11 (dt, 1H *J* = 7.4, 0.8 Hz), 4.93 (s), 4.86 (s), 3.86 (dd, 1H *J* = 9.8, 3.8 Hz), 3.65 (s, 3H), 3.33-3.26 (m, 1H), 3.04-2.89 (m, 2H), 2.60-2.45 (m, 5H), 2.39 (dd, 1H, *J* = 15.4, 3.8 Hz), 1.89 (s, 3H).

**Synthesis of tetrahydro-$\beta$-carboline 134:**

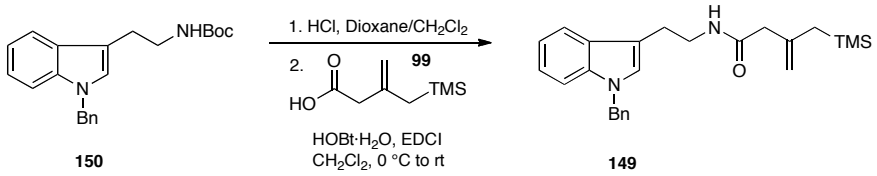



**130** **134**

A solution of **130** (0.010 g, 0.026 mmol) in THF (1.0 mL) was cooled to 0 °C. LAH (1.0 M in $Et_2O$, 0.13 mL, 0.13 mmol) was added over 15 minutes and the resulting solution

was heated to 70 °C and stirred for 1 h. The mixture was cooled to 0 °C and quenched by slow addition of saturated Rochelle's salt solution (1 mL). The resulting biphasic mixture was stirred vigorously at r.t. until both layers were clear. The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (3 x 2 mL). The organic extracts were combined, washed with brine (2 mL), dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (1:1 hexanes/EtOAc) afforded amine **134** as crystalline yellow solid (6.2 mg, 92%); **$^1$H NMR** ($CDCl_3$, 400 MHz) δ 7.51 (d, 1H, *J* = 8.0 Hz), 7.26 (d, 1H, *J* = 8.0 Hz), 7.18 (dt, 1H, *J* = 7.6, 1.2 Hz), 7.09 (dt, 1H, *J* = 7.6, 1.0), 5.23 (dt, 1H, *J* = 10.0, 1.4 Hz), 4.33 (d, 1H, *J* = 10.0 Hz), 3.52 (s, 3H), 3.15-3.07 (m, 1H), 2.89-2.82 (m, 2H), 2.79-2.72 (m, 1H), 2.50 (s, 3H), 1.91 (d, 3H, *J* = 1.2 Hz), 1.82 (d, 3H, *J* = 1.6 Hz).

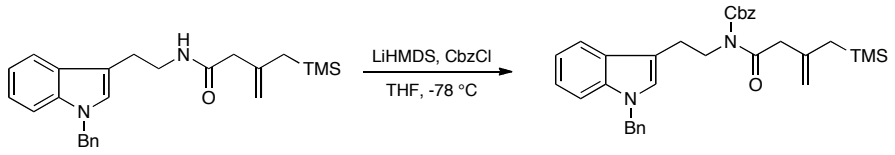
**Synthesis of amide 149:**




A solution of tryptamine **150** (1.72 g, 4.90 mmol) in $CH_2Cl_2$ (25.0 mL) was cooled to 0 °C. Hydrochloric acid (4.0 M in dioxane, 25.0 mL) was added dropwise, and the resulting mixture was stirred at 0 °C for 30 minutes, warmed to r.t. and stirred for 6 hours. The mixture was concentrated *in vacuo*. The crude hydrochloride salt was added to a stirring solution of HOBt·$H_2O$ (0.662 g, 4.90 mmol) in $CH_2Cl_2$ (49.0 mL). The resulting mixture was stirred at r.t. for 5 minutes and then cooled to 0 °C. Carboxylic acid **99** (0.83 mL, 4.66 mmol) was added dropwise, followed by dropwise addition of EDCI (0.87 mL, 4.90

mmol) over 20 minutes. The reaction was stirred at 0 °C for 1 h, warmed to r.t. and stirred for 24 h. $Et_2O$ (100 mL) was added, and the reaction was stirred for 15 minutes. The mixture was washed with 0.1 M aqueous HCl (2 x 100 mL), saturated aqueous $NaHCO_3$ (2 x 100 mL), and brine (100 mL). The organic layer was dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (9:1 → 3:1 hexanes/EtOAc) afforded amide **149** as a crystalline white solid (1.53 g, 77% over two steps); $\mathbf{R_f}$ 0.44 (1:1 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 400 MHz) δ 7.63 (d, 1H, *J* = 8.0 Hz), 7.34-7.27 (m, 4H), 7.21 (dt, 1H, *J* = 7.6, 5.2 Hz), 7.15-7.11 (m, 3H), 6.95 (s, 1H), 5.97 (s, 1H), 5.29 (s, 2H), 4.64 (s, 1H), 4.61 (s, 1H), 3.59 (q, 2H, *J* = 6.4 Hz), 2.98 (t, 2H, *J* = 6.4 Hz), 2.87 (s, 2H), 1.44 (s, 2H), 0.04 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 170.4, 142.6, 137.7, 137.0, 129.0, 128.2, 127.9, 127.0, 126.3, 122.2, 119.4, 119.2, 112.8, 112.4, 109.9, 50.1, 47.2, 40.0, 26.9, 25.4, -1.3; **IR** (thin film, $cm^{-1}$) 3294.2 (br, w), 3065.6 (br, w), 2950.8 (w), 1645.3 (m), 1540.5 (w), 1246.4 (m), 1172.7 (w), 839.1 (s), 736.3 (s), 697.0 (s); **m.p.** 68-69 °C; **HRMS** (+APCI) calculated for $C_{25}H_{33}O_1N_2Si_1$ 405.2362, found 405.2357 $[M+H]^+$.

**Synthesis of *N*-Cbz amide 404:**

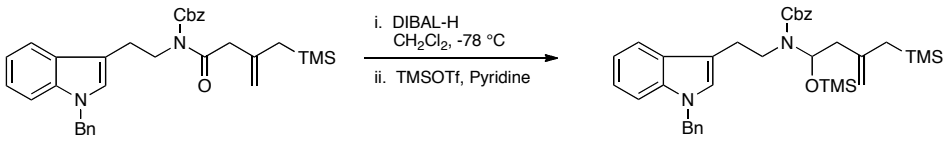



**149** **404**

A solution of amide **149** (0.509 g, 1.26 mmol) in THF (5.0 mL) was cooled to -78 °C. A freshly prepared LiHMDS solution (0.33 M in THF, 3.7 mL, 1.2 mmol) was cooled to -78 °C and added to the staring material solution *via* cannula. The reaction was stirred for

1 h at -78 °C. Benzyl chloroformate (0.21 mL, 1.5 mmol) was added and the mixture was stirred for 12 h for -78 °C. The reaction was quenched with saturated aqueous $NH_4Cl$ (1.0 mL) and warmed to 0 °C. $H_2O$ (3 mL) was added and the mixture was stirred for 5 minutes. The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (2 x 4 mL). The organic extracts were combined, washed with brine (12 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (4:1 hexanes/EtOAc) afforded *N*-Cbz amide **404** as a colorless oil (0.605 g, 89%); $\mathbf{R_f}$ 0.52 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) δ 7.49 (dd, 1H, *J* = 7.8, 0.6 Hz), 7.41-7.35 (m, 5H), 7.32-7.22 (m, 4H), 7.15 (dt, 1H, *J* = 7.8, 1.2 Hz), 7.11 (dd, 2H, *J* = 7.8, 1.2 Hz), 7.00 (td, 1H, *J* = 7.2, 0.6 Hz), 6.90 (s, 1H), 5.24 (s, 2H), 5.13 (s, 2H), 4.72 (s, 1H), 4.67 (s, 1H), 4.01-3.98 (m, 2H), 3.59 (s, 2H), 2.97-2.95 (m, 2H), 1.62 (s, 2H), 0.04 (m, 9H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 173.6, 154.3, 141.6, 137.6, 136.6, 135.1, 128.8, 128.8, 128.7, 128.6, 128.2, 127.6, 126.9, 126.4, 121.8, 119.2, 119.2, 111.9, 111.0, 109.7, 68.6, 49.9, 47.2, 45.4, 27.4, 24.7, -1.2; **IR** (thin film, $cm^{-1}$) 3031.5 (w), 2952.8 (w), 1732.2 (s), 1692.6 (m), 1351.4 (m), 1331.9 (w), 1278.6 (m), 1247.0 (m), 1152.8 (s), 839.6 (s), 731.1 (s), 694.9m (s); **HRMS** (+ESI) calculated for $C_{33}H_{39}N_2O_3Si$ 539.2730, found 539.2715 $[M+H]^+$.

**Synthesis of *N*-Cbz-*O*-TMS-aminol 148:**



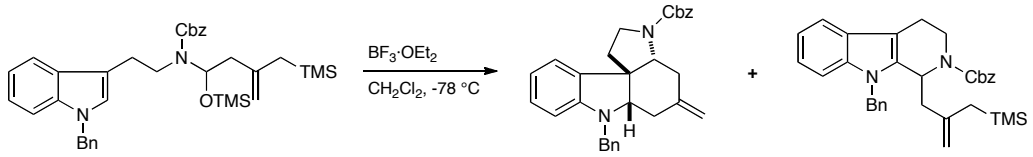

**404** **148**

A solution of *N*-Cbz amide **404** (0.605 g, 1.12 mmol) in $CH_2Cl_2$ (5.6 mL) was cooled to -78 °C. DIBAL-H (1.0 M in $CH_2Cl_2$, 2.3 mL, 2.3 mmol) was added dropwise over 10

minutes. The reaction mixture was stirred for 20 minutes, then pyridine (0.27 mL, 3.4 mmol) was added dropwise and the reaction was stirred for 10 minutes. Trimethylsilyl triflate (0.51 mL, 2.8 mmole) was added dropwise and the mixture was stirred for 45 minutes at -78 °C. The reaction was warmed to 0 °C and was quenched by slow addition of aqueous 15% Rochelle's salt solution (5 mL). The biphasic mixture was transferred to a 25 mL Erlenmeyer flask, and $Et_2O$ (12 mL) was added. The mixture was stirred vigorously at r.t. until both layers were clear. The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (2 x 5 mL). The organic extracts were combined, washed with brine (15 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (15:1 hexanes/EtOAc, silica gel deactivated with 1% $Et_3N$) afforded *N*-Cbz-*O*-TMS-aminol **148** as a colorless oil (0.524 g, 76%); $\mathbf{R_f}$ 0.57 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) (1.0: 0.6 mixture of rotamers) δ 7.83 (d, 0.6H, *J* = 7.8 Hz), 7.48-7.25 (m, 14.0H), 7.23-7.11 (m, 5.0H), 7.05-6.98 (m, 1.6H), 6.89 (s, 1.0H), 5.98 (t, 1.0H, *J* = 6.6 Hz), 5.82 (t, 0.6H, *J* = 6.6 Hz), 5.24 (m, 6.4H), 4.69 (s, 1.0H), 4.62 (m, 1.6H), 4.58 (s, 0.6H), 3.61-3.38 (m, 3.2), 3.10 (m, 2.2H), 2.99 (m, 1.0H), 2.33 (m, 3.2H), 1.67 (d, 1.0H, *J* = 13.8 Hz), 1.57 (d, 1.0H, *J* = 13.8 Hz), 1.52 (d, 0.6H, *J* = 13.2 Hz), 1.41 (d, 0.6H, *J* = 13.2 Hz), 0.15 (s, 9.0H), 0.10 (s, 5.4 H), 0.06 (s, 9.0H), -0.00 (s, 5.4H); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) δ 155.8, 154.9, 142.9, 141.9, 137.8, 137.8, 136.9, 136.8, 136.8, 136.7, 128.9, 128.7, 128.7, 128.5, 128.3, 128.3, 127.8, 127.7, 127.1, 127.0, 126.2, 126.1, 121.9, 119.7, 119.5, 119.4, 119.3, 119.2, 113.4, 113.2, 111.0, 110.9, 109.8, 109.8, 79.4, 79.3, 67.4, 67.4, 50.1, 50.1, 45.4, 45.1, 42.9, 42.5, 27.2, 27.1, 26.8, 25.7, 0, 0, -1.1, -1.2; **IR** (thin film, $cm^{-1}$) 2955.8 (w), 1689.9 (m), 1466.6

(w), 1454.1 (w), 1416.9 (w), 1250.5 (w), 905.3 (s), 841.7 (s), 725.3 (s), 696.3 (m), 647.8 (m); **HRMS** (+ESI) calculated for $C_{36}H_{49}N_2O_3Si_2$ 613.3282, found 613.3284 $[M+H]^+$.

**Synthesis of tetracyclic amine 151:**



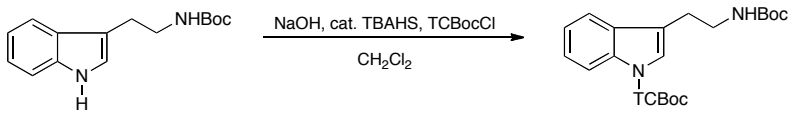

**148** **151** **152**

A solution of *N*-Cbz-*O*-TMS-aminol **148** (0.089 g, 0.146 mmol) in $CH_2Cl_2$ (3.0 mL) was cooled to -78 °C. $BF_3{\cdot}OEt_2$ (27 μL, 0.22 mmol) was added dropwise and the mixture was stirred at -78 °C for 15 minutes. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ solution (1 mL). The resulting biphasic mixture was warmed to 0 °C and stirred vigorously for 15 minutes. The organic layer was separated, and the aqueous layer was extracted with $CH_2Cl_2$ (2 x 1 mL). The organic extracts were combined, washed with brine (3 mL), dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (4:1 hexanes/EtOAc) afforded tetracyclic amine **151** as a colorless oil (0.024 g, 36%); $\mathbf{R_f}$ 0.68 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) (0.3:0.2 mixture of rotamers) δ 7.46-7.32 (m, 9H), 7.31-7.28 (m, 1H), 7.06 (dt, 1H, *J* = 7.8, 1.2 Hz), 7.03 (d, 1H, *J* = 7.2 Hz), 6.64 (t, 1H, *J* = 7.2 Hz), 6.34 (d, 1H, *J* = 7.8 Hz), 5.26-5.13 (m, 2H), 4.71-4.55 (m, 2H), 4.48 (d, 1H, *J* = 15.0 Hz), 4.23 (d, 1H, *J* = 15.0 Hz), 3.76 (dd, 1H, *J* = 12.6, 5.4 Hz), 3.69 (br s, 2H), 3.65 (t, 1H. *J* = 5.4 Hz), 3.43-3.35 (m, 0.6H), 3.17-3.10 (m, 0.4H), 2.38-2.27 (m, 2H), 2.16 (dd, 1H, *J* = 14.4, 4.2 Hz), 2.03-1.99 (m, 1H), 1.91-1.86 (q, 1H, *J* = 10.8 Hz); **$^1$H NMR** (*$d_6$*-DMSO, 70 °C, 600 MHz) 7.42-7.31 (m, 9H), 7.26 (t, 1H, *J* = 7.2 Hz), 6.93 (dt, 1H, *J* = 7.2, 1.2 Hz), 6.83

(d, 1H, *J* = 7.2 Hz), 6.51 (dt, 1H, *J* = 7.8, 0.6 Hz), 6.30 (d, 1H, *J* = 7.8 Hz), 5.15 (q, 2H, *J* = 12.0 Hz), 4.62 (s, 1H), 4.50 (s, 1H), 4.45 (d, 1H, *J* = 15.6 Hz), 4.31 (d, 1H, *J* = 15.6), 3.86 (dd, 1H, *J* = 12.0, 6.0 Hz), 3.74 (dd, 1H, *J* = 6.0, 3.0 Hz), 3.64 (t, 1H, *J* = 9.0 Hz), 3.55 (dt, 1H, *J* = 10.8, 7.2 Hz), 3.15 (br s, 1H), 2.36 (dd, 1H, *J* = 14.4, 5.4 Hz), 2.18 (dd, 1H, *J* = 14.4, 13.2 Hz), 2.12 (dd, 1H, *J* = 14.4, 3.0 Hz), 1.98 (dt, 1H, *J* = 11.4, 9.6 Hz), 1.80 (dd, 1H, *J* = 12.0, 7.2 Hz); **$^{13}$C NMR** (*$d_6$*-DMSO, 70 °C, 150 MHz) δ 154.8, 150.4, 142.0, 138.4, 136.8, 130.8, 128.0, 128.0, 127.6, 127.4, 127.2, 126.9, 126.5, 123.2, 116.1, 111.5, 105.6, 65.8, 65.6, 57.8, 54.3, 47.6, 45.7, 35.3, 33.6, 33.0; **IR** (thin film, $cm^{-1}$) 3030.4 (w), 2946 (w), 2894.5 (w), 1701.1 (s), 1600.5 (m), 1414.9 (m), 1348.3 (m), 1327.3 (m), 1119.5 (m), 737.4 (m), 697.7 (m); **HRMS** (+APCI) calculated for $C_{30}H_{31}N_2O_2$ 451.2386, found 451.2380 $[M+H]^+$; and tetrahydro-*β*-carboline **152** as a crystalline white solid (0.033 g, 43%); **$R_f$** 0.78 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) (1.0:0.9 mixture of rotamers) δ 7.53 (dd, 1.0H, *J* = 7.2, 1.2 Hz), 7.50-7.48 (m, 0.9H), 7.38-7.33 (m, 3H), 7.32-7.18 (m, 11H), 7.15-7.07 (m, 5.5H), 6.99 (d, 1.9H, *J* = 7.8 Hz), 6.90 (d, 1.9H, *J* = 7.2 Hz), 5.63 (dd, 0.9H, *J* = 10.8, 3.0 Hz), 5.36 (d, 1.0H, *J* = 17.4 Hz), 5.34-5.29 (s, 2.8H), 5.22 (d, 1H, *J* = 17.4 Hz), 5.18 (d, 0.9H, *J* = 10.2 Hz), 5.13 (d, 0.9H, *J* = 10.2 Hz), 5.08 (d, 1.0H, *J* = 12.0 Hz), 4.96 (d, 1.0H, *J* = 12.0 Hz), 4.62 (s, 0.9H), 4.58-4.54 (m, 2.7H), 4.48 (s, 1.0H), 4.41 (dd, 0.9H, *J* = 13.8 Hz, 6.0 Hz), 3.37-3.29 (m, 1.9H), 3.01-2.89 (m, 1.9H), 2.84-2.74 (m, 1.9H), 2.47-2.41 (q, 1.9H, *J* = 12.0 Hz), 2.20 (ddd, 1.9 Hz, *J* = 22.2, 14.4, 3.0 Hz), 1.63 (d, 0.9H, *J* = 13.8 Hz), 1.56 (d, 0.9H, *J* = 13.8 Hz), 1.27 (q, 2.0H, *J* = 13.2 Hz), -0.14 (s, 8.1H), -0.16 (s, 9.0H); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) (1.0:0.9 mixture of rotamers) δ 155.9, 155.7, 143.3, 142.8, 137.3, 137.2, 136.6, 136.1, 135.5, 129.0, 128.6, 128.5, 128.4, 128.1, 128.1, 127.8, 127.7, 127.6,

127.1, 127.0, 126.0, 125.9, 122.1, 121.9, 119.8, 119.7, 118.5, 118.3, 111.4, 110.8, 110.2, 109.9, 108.9, 108.0, 67.4, 67.3, 49.4, 49.2, 47.2, 47.0, 43.2, 43.0, 37.6, 37.1, 26.4, 21.8, 21.2, -1.4, -1.5; **IR** (thin film, $cm^{-1}$) 3030.6 (w), 2950.4 (w), 1696.8 (s), 1419.2 (m), 1306.8 (w), 1247.2 (w), 1223.7 (w), 1194.0 (m), 1100.4 (m), 842.2 (m), 736.1 (s), 696.7 (m); **m.p.** 86-87 °C; **HRMS** (+APCI) calculated for $C_{33}H_{39}N_2O_2Si$ 523.2781, found 523.2774 $[M+H]^+$.

**Synthesis of carbamate 160:**

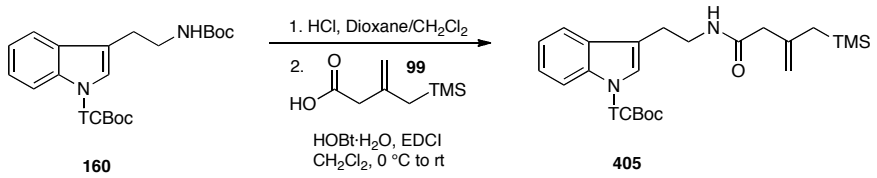



**159** **160**

Powdered NaOH (0.039 g, 0.96 mmol) and TBAHS (0.007 g, 0.019 mmol) were added to a solution of tryptamine **159** (0.100 g, 0.384 mmol) in $CH_2Cl_2$ (3.9 mL), and the resulting suspension was stirred for 10 minutes. A solution of *β,β,β*-trichloro-*tert*-butyl chloroformate (0.276 g, 1.15 mmol) in $CH_2Cl_2$ (1.0 mL) was added *via* cannula, and the mixture was stirred for 3 h. $H_2O$ (3 mL) was added, and the reaction was stirred for 10 minutes. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 x 4 mL). The organic extracts were combined, washed with brine (10 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (10:1 → 4:1 hexanes/EtOAc) afforded carbamate **160** as an amorphous white solid (0.145 g, 81%); **$^1$H NMR** ($CDCl_3$, 400 MHz) δ 8.25 (d, 1H, *J* = 8.0 Hz), 7.57 (d, 1H, *J* = 7.6 Hz), 7.42 (s, 1H), 7.37 (dt, 1H, *J* = 8.0, 1.2 Hz), 7.28 (dt, 1H, *J* = 7.6, 1.2 Hz), 4.69 (s, 1H), 3.45 (q, 2H, *J* = 6.8 Hz), 2.91 (t, 2H, *J* = 6.8 Hz), 2.11 (s, 6H), 1.42 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 156.0, 145.2, 135.9, 130.6, 125.1, 123.3, 123.0,

119.3, 119.3, 115.5, 105.9, 91.0, 79.5, 40.4, 28.6, 25.8, 21.8; **IR** (thin film, $cm^{-1}$) 3358.8 (br, w), 2976.5 (w), 1737.8 (m), 1699.2 (m), 1506.9 (w), 1454.4 (m), 1381.0 (s), 1363.5 (m), 1252.7 (m), 1151.5 (s), 799.0 (m), 735.4 (s); **HRMS** (+APCI) calculated for $C_{20}H_{25}Cl_3N_2O_4$ 462.0880, found 462.0881 $[M]^+$.

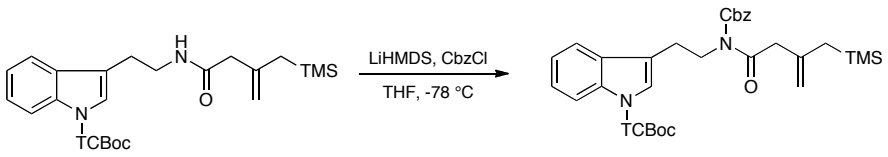
**Synthesis of amide 405:**




A solution of carbamate **160** (2.32 g, 5.00 mmol) in $CH_2Cl_2$ (25.0 mL) was cooled to 0 °C. Hydrochloric acid (4.0 M in dioxane, 25.0 mL) was added dropwise, and the resulting mixture was stirred at 0 °C for 30 minutes, warmed to r.t. and stirred for 6 h. The mixture was concentrated *in vacuo*. The crude hydrochloride salt was added to a stirring solution of HOBt·$H_2O$ (0.676 g, 5.00 mmol). The resulting mixture was stirred at r.t. for 5 minutes and then cooled to 0 °C. Carboxylic acid **7** (0.81 mL, 4.55 mmol) was added dropwise, followed by dropwise addition of EDCI (0.89 mL, 5.00 mmol) over 20 minutes. The reaction was stirred at 0 °C for 1 h, warmed to r.t. and stirred for 16 h. $Et_2O$ (100 mL) was added, and the reaction was stirred for 15 minutes. The mixture was washed with 0.1 M aqueous HCl (2 x 100 mL), saturated aqueous $NaHCO_3$ (2 x 100 mL), and brine (100 mL). The organic layer was dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (9:1 → 7:3 hexanes/EtOAc) afforded amide **405** as a yellow oil (1.67 g, 64%, over two steps); $\mathbf{R_f}$ 0.35 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 400 MHz) δ 8.25 (d, 1H, $J$ = 8.0 Hz),

7.58 (d, 1H, *J* = 7.6 Hz), 7.44-7.37 (br s, 1H), 7.37 (t, 1H, *J* = 7.6 Hz), 7.30 (d, 1H, *J* = 8.0 Hz), 6.15 (t, 1H, *J* = 5.6 Hz), 4.70 (s, 2H), 3.58 (q, 2H, *J* = 6.8 Hz), 2.93 (t, 2H, *J* = 6.8 Hz), 2.90 (s, 2H), 2.11 (s, 6H), 1.49 (s, 2H), -0.01 (s, 9H); **$^{13}$C NMR** ($d_6$-DMSO, 100 MHz) δ 169.5, 147.4, 142.1, 134.8, 130.3, 124.7, 123.0, 122.4, 119.4, 119.4, 114.7, 110.1, 105.3, 90.4, 45.4, 38.3, 26.1, 24.6, 21.2, -1.4; **IR** (thin film, cm$^{-1}$) 3290.3 (br, w), 3074.9 (w), 2952.7 (w), 1740.9 (s), 1646.6 (m), 1546.7 (w), 1455.4 (m), 1382.2 (s), 1360.4 (m), 1255.1 (s), 1209.0 (w), 1155.9 (s), 1090.9 (m), 848.0 (m), 800.7 (m), 754.9 (m); **HRMS** (+APCI) calculated for $C_{23}H_{32}Cl_3N_2O_3Si$ 517.1248, found 517.1246 $[M+H]^+$.

**Synthesis of *N*-Cbz-amide 161:**

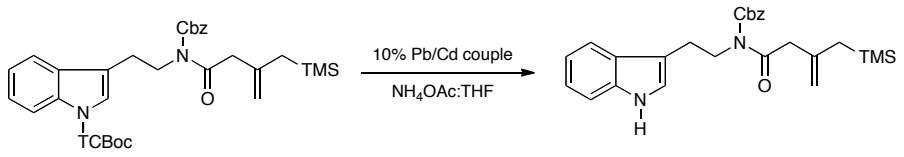



**405** **161**

A solution of amide **405** (3.02 g, 5.84 mmol) in THF (18.0 mL) was cooled to -78 °C. A freshly prepared LiHMDS solution (0.33 M in THF, 16.8 mL, 5.55 mmol) was cooled to -78 °C and added to the starting material solution *via* cannula. The reaction was stirred for 1 h at -78 °C. Benzyl chloroformate (1.09 mL, 7.76 mmol) was added, and the mixture was stirred at -78 °C for 6 h. The reaction was quenched with saturated aqueous $NH_4Cl$ (4 mL) and warmed to 0 °C. $H_2O$ (10 mL) was added, and the mixture was stirred for 5 minutes. The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (2 x 14 mL). The organic extracts were combined, washed with brine (20 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on

silica gel (10:1 hexanes/EtOAc) afforded *N*-Cbz-amide **161** as a crystalline white solid (3.52 g, 92%); $\mathbf{R_f}$ 0.70 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 400 MHz) δ 8.23 (d, 1H, *J* = 8.0 Hz), 7.50 (d, 1H, *J* = 8.0 Hz), 7.44-7.38 (m, 6H), 7.34 (dt, 1H, *J* = 8.0, 0.8 Hz), 7.18 (dt, 1H, *J* = 8.0, 0.8 Hz), 5.22 (s, 2H), 4.76 (s, 1H), 4.70 (s, 1H), 4.06-4.02 (m, 2H), 3.65 (s, 2H), 2.97-291 (m, 2H), 2.11 (s, 6H), 1.67 (s, 2H), 0.07 (s, 9H); **$^{13}$C NMR** ($d_6$-DMSO, 100 MHz) δ 172.5, 153.5, 147.3, 141.2, 135.1, 134.9, 130.0, 128.5, 128.5, 128.3, 124.8, 123.1, 122.6, 119.2, 118.4, 114.7, 110.4, 105.3, 90.4, 68.2, 46.3, 43.5, 26.8, 23.7, 21.2, -1.5; **IR** (thin film, $cm^{-1}$) 2953.4 (w), 1733.9 (s), 1697.3 (m), 1454.7 (m), 1380.5 (m), 1355.0 (m), 1276.9 (w), 1248.3 (m), 1148.1 (s), 1084.5 (m), 1043.1 (m), 844.6 (m), 800.0 (m), 752.8 (m), 696.7 (m); **m.p.** 62.5-63.5 °C; **HRMS** (+ESI) calculated for $C_{31}H_{38}Cl_3N_2O_5Si$ 651.1616, found 651.1620 $[M+H]^+$.

**Synthesis *Na*-H-*Nb*-Cbz-amide 162:**

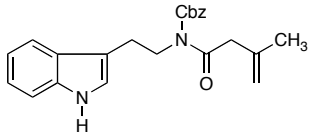



**161** **162**

$NH_4OAc$ (1.0 M in $H_2O$, 6.2 mL) was added to a solution of *N*-Cbz-amide **161** (1.00 g, 1.53 mmol) in THF (6.2 mL). 10% Pb/Cd couple[2] (0.861 g, 7.66 mmol) was added slowly, and the resulting suspension was stirred vigorously for 4 h. The mixture was filtered through celite. The filtered cake was washed with THF (3 x 6 mL). The filtrate was washed with brine (15 mL), dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (4:1 hexanes/$Et_2O$) afforded compound **162** as a crystalline white solid (0.598 g, 87%); $\mathbf{R_f}$ 0.48 (7:3 hexanes/EtOAc);

**$^1$H NMR** ($CDCl_3$, 600 MHz) δ 8.01 (br s, 1H), 7.51 (d, 1H, *J* = 7.8 Hz), 7.42-7.38 (m, 5H), 7.34 (d, 1H, *J* = 7.8 Hz), 7.19 (t, 1H, *J* = 7.2 Hz), 7.03 (t, 1H, *J* = 7.2 Hz), 6.98 (s, 1H), 5.16 (s, 2H), 4.75 (s, 1H), 4.70 (s, 1H), 4.05 (t, 2H, *J* = 7.8 Hz), 3.64 (s, 2H), 3.01 (t, 2H, *J* = 7.8 Hz), 1.67 (s, 2H), 0.11 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) 173.9, 154.6, 141.7, 136.4, 135.2, 128.9, 128.9, 128.8, 127.6, 122.4, 122.2, 119.6, 119.1, 112.9, 111.2, 111.1, 68.8, 47.3, 45.5, 27.5, 24.8, -1.17; **IR** (thin film, $cm^{-1}$) 3403.1 (br, w), 2953.1 (w), 1736.1 (m), 1686.2 (w), 1456.5 (w), 1389.2 (w), 1353.7 (w), 1280.1 (w), 1247.5 (w), 1170.4 (s), 849.7 (m), 741.7 (m); **m.p.** 92-93.5 °C; **HRMS** (+ESI) calculated for $C_{26}H_{32}N_2NaO_3Si$ 471.2080, found 471.2071 $[M+Na]^+$.

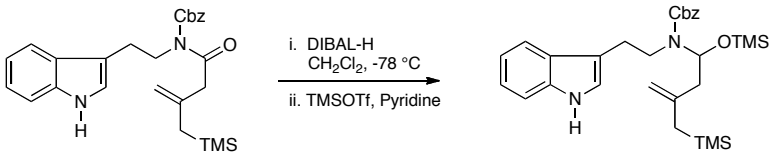
**Protodesilylation byproduct 163** was obtained during our initial attempts to remove the TCBoc group in compound **161** using activated zinc in methanol:acetic acid (10:1).




**163**

**$^1$H NMR** ($CDCl_3$, 400 MHz) δ 7.96 (s, 1H), 7.49 (d, 1H, *J* = 7.8 Hz), 7.43-7.32 (m, 6H), 7.18 (t, 1H, *J* = 7.4 Hz), 7.02 (t, 1H, *J* = 7.2 Hz), 6.98 (d, 1H, *J* = 2.4 Hz), 5.12 (s, 2H), 4.93 (s, 1H), 4.77 (s, 1H), 4.06-3.97 (m, 2H), 3.64 (s, 2H), 3.13-2.96 (m, 2H,), 1.80 (s, 3H); **HRMS** (+ESI) calculated for $C_{23}H_{24}N_2NaO_3$ 399.1685, found 399.1674 $[M+Na]^+$.

**Synthesis of *N*-Cbz-*O*-TMS-aminol 166:**

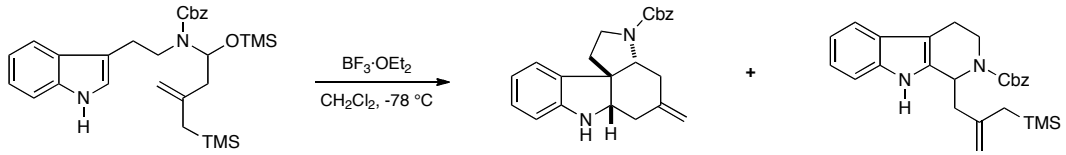



**162** **156**

A solution of compound **162** (0.150 g, 0.335 mmol) in $CH_2Cl_2$ (1.5 mL) was cooled to -78 °C. DIBAL-H (1.0 M in $CH_2Cl_2$, 0.67 mL, 0.67 mmol) was added dropwise over 10 minutes. The reaction mixture was stirred for 40 minutes, then pyridine (0.11 mL, 1.34 mmol) was added dropwise and the reaction was stirred for 10 minutes. Trimethylsilyl triflate (0.21 mL, 1.2 mmol) was added dropwise and the mixture was stirred for 75 minutes at -78 °C. The reaction was warmed to 0 °C and was quenched by slow addition of aqueous 15% Rochelle's salt solution (1 mL). The biphasic mixture was transferred to a 25 mL Erlenmeyer flask, and $Et_2O$ (6 mL) was added. The mixture was stirred vigorously at r.t. until both layers were clear. The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (2 x 3 mL). The organic extracts were combined, washed with saturated aqueous $Cu_2SO_4$ (2 x 5 mL), $H_2O$ (2 x 5 mL), brine (10 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude *N*-Cbz-*O*-TMS-aminol **156** was obtained as a colorless oil (0.171 g, 98%) and was used without further purification; $\mathbf{R_f}$ 0.71 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) (1:0.6 mixture of rotamers) δ 8.16-8.06 (m, 1.6H), 7.84 (d, 0.6H, *J* = 7.8 Hz) 7.55-7.34 (m, 10.6H), 7.26-7.14 (m, 2.2H), 7.07-7.01 (m, 1.6H), 6.97 (s, 1H), 6.01 (t, 1H, *J* = 6.6 Hz), 5.85 (t, 0.6H, *J* = 6.0 Hz), 5.35-5.21 (m, 3.2H), 4.7 (s, 1H), 4.65 (s, 0.6H), 4.63 (s, 1H), 4.59 (s, 0.6H), 3.67-3.39 (m, 3.2H), 3.20-2.97 (m, 3.2H), 2.44-2.29 (m, 3.2H), 1.68 (d, 1H, *J* = 13.2 Hz), 1.58 (d, 1H, *J* = 13.2 Hz), 1.54 (d, 0.6H, *J* = 13.2 Hz), 1.43 (d, 0.6H, *J* = 13.2

Hz), 0.17 (s, 9H), 0.12 (s, 5.4 Hz), 0.07 (s, 9H), 0.01 (s, 5.4 Hz); **HRMS** (+ESI) calculated for $C_{29}H_{42}N_2NaO_3Si_2$ 545.2632, found 545.2631 $[M+Na]^+$.

**Synthesis of tetracyclic amine 166:**

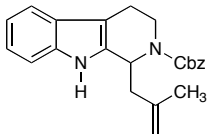



**156** **166** **165**

*N*-Cbz-*O*-TMS-aminol **156** (0.171 g, 0.327 mmol) was dissolved in $CH_2Cl_2$ (6.5 mL), and the resulting clear solution was cooled to -78 °C. $BF_3{\cdot}OEt_2$ (61 μL, 0.490 mmol) was added dropwise and the mixture was stirred at -78 °C for 15 minutes. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ solution (2 mL). The resulting biphasic mixture was warmed to 0 °C and stirred vigorously for 15 minutes. The organic layer was separated, and the aqueous layer was extracted with $CH_2Cl_2$ (2 x 2 mL). The organic extracts were combined, washed with brine (8 mL), dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (9:1 → 7:3 hexanes/EtOAc) afforded tetracyclic amine **166** as a crystalline white solid (1.8 g, 2%); $\mathbf{R_f}$ 0.43 (7:3 hexanes/EtOAc); $^1$**H NMR** ($CDCl_3$, 600 MHz) (2:1 mixture of rotamers) δ 7.48-7.29 (m, 5H), 7.06 (t, 1H, $J$ = 7.5 Hz), 7.02 (d, 1H, $J$ = 7.5 Hz), 6.70 (t, 1H, $J$ = 7.2 Hz), 6.62 (d, 1H, $J$ = 7.8 Hz), 5.28-5.13 (m, 2H), 4.69-4.56 (m, 2H), 3.85 (dd, 1H, $J$ = 12.0, 5.4 Hz), 3.79-3.63 (m, 3H), 3.43-3.32 (m, 0.6H), 3.17-3.06 (m, 0.3H), 2.64-2.55 (m, 1H), 2.38-2.30 (m, 1H), 2.00-1.86 (m, 2H); and tetrahydro-*β*-carboline **165** as an amorphous white solid (0.103 g, 73%); $\mathbf{R_f}$ 0.43 (7:3 hexanes/EtOAc); $^1$**H NMR** ($CDCl_3$, 600 MHz) (1:1 mixture of rotamers) δ 8.05 (s, 1H), 7.96 (s, 1H), 7.53-7.46 (m, 4H), 7.40-

7.30 (m, 10H), 7.19-7.15 (m, 2H), 7.15-7.08 (m, 2H), 5.51-5.48 (m, 1H), 5.37-5.35 (m, 1H), 5.24-5.18 (m, 4H), 4.85 (s, 1H), 4.82 (s, 1H), 4.77 (s, 1H), 4.77 (s, 1H), 4.60 (dd, 1H, *J* = 12.9, 5.1 Hz), 4.46 (dd, 1H, *J* = 13.2, 4.8 Hz), 3.26-3.19 (m, 2H), 2.92-2.73 (m, 4H), 2.57 (dd, 1H, *J* = 12.3, 4.5 Hz), 2.52 (dd, 1H, *J* = 12.3, 4.5 Hz), 2.47 (d, 1H, *J* = 9.0), 2.44 (d, 1H, *J* = 9.6), 1.83 (d, 1H, *J* = 13.3 Hz), 1.67 (d, 1H, *J* = 13.3), 1.60 (d, 1H, *J* = 13.2 Hz), 1.55 (d, 1H, *J* = 13.2 Hz), 0.06 (s, 69H), -0.03 (s, 9H); **IR** (thin film, $cm^{-1}$) 3319.8 (br, w), 3032.1 (br, w), 2951.6 (br, w), 2847.5 (br, w), 1680.1 (s), 1424.4 (m), 1248.3 (m), 1223.9 (m), 1098.4 (m), 853.4 (m), 740.2 (m), 696.5 (w); **m.p.** 169.0-170.5 °C; **HRMS** (+ESI) calculated for $C_{26}H_{33}N_2O_2Si$ 433.2311, found 433.2303 $[M+H]^+$.

**Tetrahydro-*β*-carboline 164** was obtained during our attempts to cyclize compound **156** using trifluoroacetic acid at 0°C in place of $BF_3{\cdot}OEt_2$ at -78°C as described in the previous procedure.

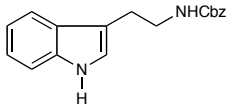



**164**

Amorphous white solid; $\mathbf{R_f}$ 0.38 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) (1:1 mixture of rotamers) δ 8.06 (s, 1H), 7.98 (s, 1H), 7.52 (d, 1H, *J* = 7.8 Hz), 7.51 (d, 1H, *J* = 7.8 Hz), 7.44-7.31 (m, 12H), 7.19 (t, 2H, *J* = 7.8 Hz), 7.17-7.12 (m, 2H), 5.53 (t, 1H, *J* = 6.6 Hz), 5.36 (t, 1H, *J* = 6.6 Hz), 5.28-5.23 (m, 3H), 5.18 (d, 1H, *J* = 12.0 Hz), 4.98 (s, 1H), 4.96 (s, 1H), 4.89 (s, 1H), 4.85 (s, 1H), 4.62 (dd, 1H, *J* = 13.0, 5.0 Hz), 4.47 (dd, 1H, *J* = 13.8, 4.8 Hz), 3.30-3.21 (m, 2H), 2.96-2.83 (m, 2H), 2.80-2.74 (m, 2H), 2.64-2.54 (m, 4H), 1.95 (s, 3H), 1.78 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) (1:1 mixture of rotamers) δ 155.6, 155.5, 142.7, 142.4, 136.9, 136.6, 136.1, 136.0, 134.5, 134.0, 128.7,

128.4, 128.3, 128.2, 127.9, 126.7, 122.1, 121.9, 119.7, 119.6, 118.4, 118.2, 114.7, 114.7, 114.3, 111.1, 110.0, 109.1, 108.5, 67.7, 67.4, 50.0, 49.9, 43.4, 43.0, 38.9, 38.6, 22.8, 22.7, 21.9, 21.4; **IR** (thin film, $cm^{-1}$) 3306.9 (br w), 3032.6 (w), 2914.2 (w), 2846.4 (w), 1670.3 (s), 1421.8 (s), 1265.2 (w), 1218.0 (m), 1191.5 (w), 1097.0 (m), 733.6 (s), 696.3 (s); **HRMS** (+ESI) calculated for $C_{23}H_{25}N_2O_2$ 361.1916, found 361.1910 $[M+H]^+$.

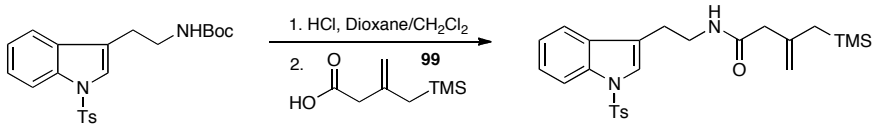
**Carbamate 167** was obtained during our attempts to cyclize compound **156** using trifluoroacetic acid at 0°C in place of $BF_3{\cdot}OEt_2$ at -78°C as described in the previous procedure.




**167**

**$^1$H NMR** ($CDCl_3$, 600 MHz) δ 8.00 (br s, 1H), 7.61 (d, 1H, *J* = 8.4 Hz), 7.42-7.29 (m, 6H), 7.21 (t, 1H, *J* = 7.5 Hz), 7.13 (t, 1H, *J* = 7.5 Hz), 7.03 (s, 1H), 5.11 (s, 2H), 4.82 (br s, 1H), 3.56 (q, 2H, *J* = 6.4 Hz), 3.00 (t, 2H, *J* = 6.6 Hz); **HRMS** (+ESI) calculated for $C_{18}H_{19}N_2O_2$ 295.1447, found 295.1440 $[M+H]^+$.

**Synthesis of amide 170:**

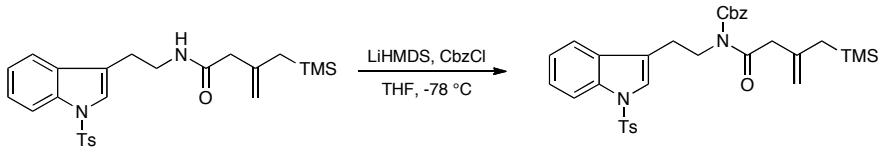



**169** **170**

A solution of trypyamine **169** (0.660 g, 1.59 mmol) in $CH_2Cl_2$ (5.0 mL) was cooled to 0 °C. Hydrochloric acid (4.0 M in dioxane, 5.0 mL) was added dropwise, and the resulting mixture was stirred at 0 °C for 30 minutes, warmed to r.t. and stirred for 5 hours. The

mixture was concentrated in vacuo. The crude hydrochloride salt was added to a stirring solution of HOBT·$H_2O$ (0.236 g, 1.75 mmol) in $CH_2Cl_2$ (16.0 mL). The resulting mixture was stirred at r.t. for 5 minutes and then cooled to 0 °C. Carboxylic acid **99** (0.30 mL, 1.67 mmol) was added dropwise, followed by dropwise addition of EDCI (0.31 mL, 1.75 mmol) over 20 minutes. The reaction was stirred at 0 $^oC$ for 1 h, warmed to r.t. and stirred for 24 h. $Et_2O$ (30 mL) was added, and the reaction was stirred for 15 minutes. The mixture was washed with 0.1 M aqueous HCl (2 x 20 mL), saturated aqueous $NaHCO_3$ (2 x 20 mL), and brine (20 mL). The organic layer was dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (7:3 → 3:2 hexanes/EtOAc) afforded amide **170** as a yellow oil (0.450 g, 60% over two steps); $\mathbf{R_f}$ 0.16 (7:3 hexanes/EtOAc); $^{\mathbf{1}}$**H NMR** ($CDCl_3$, 600 MHz) δ 7.99 (d, 1H, $J$ = 8.4 Hz), 7.76-7.75 (dd, 2H, $J$ = 8.4, 1.2 Hz), 7.53 (d, 1H, $J$ = 7.8 Hz), 7.37 (s, 1H), 7.34 (t, 1H, $J$ = 7.8 Hz), 7.28-7.22 (m, 3H), 5.98 (s, 1H), 4.71 (s, 1H), 4.69 (s, 1H), 3.55 (q, 2H, $J$ = 6.6 Hz), 2.93-2.88 (m, 4H), 2.35 (s, 3H), 1.49 (s, 2H), 0.03 (m, 9H); $^{\mathbf{13}}$**C NMR** ($CDCl_3$, 150 MHz) δ 170.6, 145.0, 142.4, 135.4, 135.3, 130.8, 130.0, 126.9, 125.0, 123.4, 123.3, 119.8, 119.6, 113.8, 112.8, 47.0, 39.1, 26.8, 25.2, 21.7, -1.4; **IR** (thin film, $cm^{-1}$) 3303.2 (br, w), 3074.8 (w), 2952.4 (w), 1646.9 (m), 1528.8 (m), 1447.2 (m), 1366.7 (m), 1170.7 (s), 1131.8 (m), 1120.2 (m), 847.9 (s), 745.2 (m), 668.2 (s); **HRMS** (+APCI) calculated for $C_{25}H_{33}N_2O_3SSi$ 469.1981, found 469.1974 $[M+H]^+$.

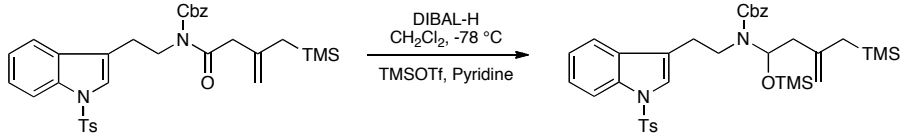
**Synthesis of *N*-Cbz-amide 406:**




**170** **406**

A solution of amide **170** (0.560 g, 1.19 mmol) in THF (3.6 mL) was cooled to -78 °C. A freshly prepared LiHMDS solution (0.33 M in THF, 3.42 mL, 1.13 mmol) was cooled to -78 °C and added to the starting material solution *via* cannula. The reaction was stirred for 1 h at -78 °C. Benzyl chloroformate (0.24 mL, 1.67 mmol) was added and the mixture was stirred for 12 h for -78 °C. The reaction was quenched with saturated aqueous $NH_4Cl$ (0.5 mL) and warmed to 0 °C. $H_2O$ (2 mL) was added and the mixture was stirred for 5 minutes. The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (2 x 5 mL). The organic extracts were combined, washed with brine (12 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (9:1 → 4:1 hexanes/EtOAc) afforded *N*-Cbz amide **406** as a colorless oil (0.623 g, 87%); $\mathbf{R_f}$ 0.48 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) δ 7.96 (d, 1H, *J* = 8.4 Hz), 7.74 (d, 2H, *J* = 8.4 Hz), 7.43-7.39 (m, 4H), 7.35-7.32 (m, 3H), 7.29 (t, 1H, *J* = 7.8 Hz), 7.21 (d, 2H, *J* = 8.4 Hz), 7.13 (t, 1H, *J* = 7.8 Hz), 5.07 (s, 2H), 4.73 (s, 1H), 4.66 (s, 1H), 3.98-3.96 (m, 2H), 3.61 (s, 2H), 2.89 (t, 2H, *J* = 7.8 Hz), 2.33 (s, 3H), 1.64 (s, 2H), 0.05 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) δ 173.6, 154.1, 144.9, 141.5, 135.3, 135.2, 134.9, 130.8, 129.9, 128.9, 128.9, 128.6, 126.9, 124.8, 123.7, 123.3, 119.7, 119.4, 113.7, 110.0, 68.7, 47.2, 44.4, 27.5, 24.4, 21.6, -1.2; **IR** (thin film, $cm^{-1}$) 2953.4 (w), 1735.5 (m), 1692.9 (m), 1634.6 (w), 1597.3 (w), 1447.5 (w), 1353.9 (m), 1168.4 (s), 846.1 (m), 730.5 (m); **HRMS** (+APCI) calculated for $C_{33}H_{39}N_2O_5SSi$ 603.2349, found 603.2344 $[M+H]^+$.

**Synthesis of *N*-Cbz-*O*-TMS aminol 168:**

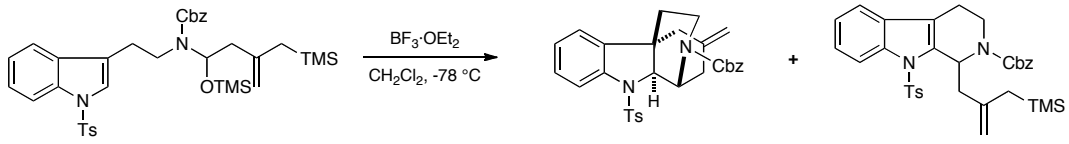



**406** **168**

A solution of *N*-Cbz amide **406** (0.623 g, 1.03 mmol) in $CH_2Cl_2$ (4.5 mL) was cooled to -78 °C. DIBAL-H (1.0 M in $CH_2Cl_2$, 2.07 mL, 2.07 mmol) was added dropwise over 10 minutes. The reaction mixture was stirred for 20 minutes, then pyridine (0.25 mL, 3.10 mmol) was added dropwise and the reaction was stirred for a further 10 minutes. Trimethylsilyl triflate (0.47 mL, 2.6 mmol) was added dropwise and the mixture was stirred for 45 minutes at -78 °C, warmed to 0 °C and stirred for 1 hr. The reaction was quenched by slow addition of aqueous 15% Rochelle's salt solution (4 mL). The biphasic mixture was transferred to a 25 mL Erlenmeyer flask, and $Et_2O$ (12 mL) was added. The mixture was stirred vigorously at r.t. until both layers were clear. The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (2 x 5 mL). The organic extracts were combined, washed with brine (15 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (15:1 hexanes/EtOAc, silica gel deactivated with 1% $Et_3N$) afforded *N*-Cbz-*O*-TMS aminol **168** as a colorless oil (0.526 g, 75%); $\mathbf{R_f}$ 0.57 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) (1.0:0.6 mixture of rotamers) 7.99 (d, 0.6H, $J$ = 8.4 Hz), 7.96 (d, 1.0H, $J$ = 8.4 Hz), 7.81-7.71 (m, 3.8H), 7.47-7.21 (m, 16.0H), 7.08 (t, 1.0H, $J$ = 7.2 Hz), 5.96 (t, 1.0H, $J$ = 6.6 Hz), 5.80 (t, 0.6H, $J$ = 6.6 Hz), 5.26 (d, 0.6H, $J$ = 12.6 Hz), 5.21-5.14 (m, 2.6H), 4.65 (s, 1.0H), 4.61 (s, 1.0H), 4.60 (s, 0.6H), 4.56 (s, 0.6H), 3.58-3.29 (m, 3.2H), 3.08-

2.85 (m, 3.2H), 2.33 (s, 4.8H), 2.32-2.23 (m, 3.2H), 1.64 (d, 1.0H, *J* = 13.8 Hz), 1.54 (d, 1H, *J* = 13.8 Hz), 1.48 (d, 0.6H, *J* = 13.2 Hz), 1.37 (d, 0.6H, *J* = 13.2), 0.14 (s, 9.0H), 0.08 (s, 5.4H), 0.04 (s, 9.0H), -0.02 (s, 5.4H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz) (1.0:0.6 mixture of rotamers) 155.6, 154.8, 145.0, 144.9, 142.7, 142.5, 136.7, 136.5, 135.5, 135.5, 135.4, 135.3, 131.2, 130.9, 130.0, 128.8, 128.7, 128.5, 128.5, 128.4, 127.0, 124.8, 123.3, 123.2, 120.7, 120.4, 120.1, 119.8, 113.8, 111.1, 111.0, 79.3, 79.3, 67.5, 45.3, 45.0, 41.6, 41.3, 29.9, 27.1, 27.1, 26.5, 25.4, 21.8, 0, -1.1, -1.2; **IR** (thin film, $cm^{-1}$) 2954.1 (w), 1698.4 (m), 1446.6 (w), 1414.8 (w), 1371.4 (w), 1249.0 (m), 1171.7 (s), 839.2 (s), 745.7 (m), 667.7 (m), 576.1 (m); **HRMS** (+ESI) calculated for $C_{36}H_{49}N_2O_5SSi_2$ 677.2901, found 677.2908 $[M+H]^+$.

**Synthesis of regioisomeric tetracyclic amine 172:**

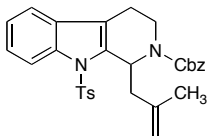



**168** **172** **173**

A solution of *N*-Cbz-*O*-TMS aminol **168** (0.052 g, 0.077 mmol) in $CH_2Cl_2$ (1.5 mL) was cooled to -78 °C. $BF_3{\cdot}OEt_2$ (14 μL, 0.12 mmol) was added dropwise and the mixture was stirred at -78 °C for 43 hours. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (1 mL). The resulting biphasic mixture was warmed to 0 °C and stirred vigorously for 15 minutes. The organic layer was separated, and the aqueous layer was extracted with $CH_2Cl_2$ (2 x 1 mL). The organic extracts were combined, washed with brine (3 mL), dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (7:3 hexanes/EtOAc) afforded regioisomeric tetracyclic

amine **172** as a colorless oil (0.016 g, 41%); $\mathbf{R_f}$ 0.35 (7:3 hexanes/EtOAc); **$^1$H NMR** ($d_6$-DMSO, 70 °C, 600 MHz) δ 7.69-7.59 (m, 2H), 7.64 (d, 1H, *J* = 7.8 Hz), 7.35-7.21 (m, 7H), 7.19 (dt, 1H, *J* = 7.8, 1.2 Hz), 7.10 (dd, 1H, *J* = 7.4, 1.2 Hz), 6.99 (t, 1H, *J* = 7.4 Hz), 5.35 (s, 1H), 5.28-5.10 (m, 2H), 4.76 (d, 1H, *J* = 2.4 Hz), 4.73 (d, 1H, *J* = 2.4 Hz), 3.84 (dd, 1H, *J* = 13.8, 6.6 Hz), 3.72-3.67 (br s, 1H), 2.88 (d, 1H, *J* = 2.4 Hz), 2.77 (dd, 1H, *J* = 12.6, 2.4 Hz), 2.53 (dd, 1H, *J* = 15.0, 1.2 Hz), 2.41 (s, 1H), 2.30-2.24 (m, 4H), 2.03 (d, 1H, *J* = 15.0 Hz), 1.66 (dt, 1H, *J* = 12.0, 7.2 Hz); **$^{13}$C NMR** ($d_6$-DMSO, 22 °C, 150 MHz) (1:1 mixture of rotamers) δ 155.3, 154.5, 145.1, 145.0, 143.7, 141.0, 140.9, 139.4, 139.2, 136.9, 136.8, 130.5, 130.1, 128.6, 128.4, 128.1, 127.9, 127.8, 127.7, 127.5, 124.3, 124.3, 121.7, 114.8, 110.0, 109.9, 68.7, 68.5, 66.7, 50.5, 50.4, 42.4, 42.0, 32.7, 32.4, 32.1, 32.0, 21.0; **IR** (thin film, $cm^{-1}$) 2927.1 (w), 1693.3 (s), 1598.7 (w), 1414.2 (m), 1353.8 (m), 1309.2 (m), 1255.6 (w), 1233.4 (w), 1170.7 (s), 754.5 (m), 581.6 (s); **HRMS** (+ESI) calculated for $C_{30}H_{31}N_2O_4S$ 515.2005, found 515.2006 $[M+H]^+$; and tetrahydro-*β*-carboline **173** as a white crystalline solid ( 4.1 mg, 9%); $\mathbf{R_f}$ 0.48 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 400 MHz) (1:0.7 mixture of rotamers) δ 8.17 (d, 1.7H, *J* = 8.4 Hz), 7.73 (d, 1.7H, *J* = 8.4 Hz), 7.25-7.19 (m, 16H), 7.01 (d, 1H, *J* = 8.4 Hz), 6.82 (d, 1.7H, *J* = 8.4 Hz), 6.26 (d, 0.7H, *J* = 9.6 Hz), 6.02 (d, 1H, *J* = 10.4 Hz), 5.26-5.14 (m, 3.4H), 4.70-4.64 (m, 1.7H), 4.60 (s, 1.7H), 4.50 (dd, 1H, *J* = 14.0, 6.8 Hz), 4.34 (dd, 1H, *J* = 14.0, 6.0 Hz), 3.33-3.20 (m, 1.7H), 2.98 (dd, 0.7H, *J* = 14.0, 2.6 Hz), 2.88 (dd, 1H, *J* = 13.4, 2.6 Hz), 2.81-2.56 (m, 3.4H), 2.44-2.32 (m, 1.7H), 2.28 (s, 2.1H), 2.23 (s, 3H), 1.97 (d, 0.7H, *J* = 13.6 Hz), 1.86 (d, 1H, *J* = 13.2 Hz), 1.65 (d, 0.7H, *J* = 13.6 Hz), 1.47 (d, 1H, *J* = 13.2 Hz), 0.9 (s, 6.3H), 0.06 (s, 9H).

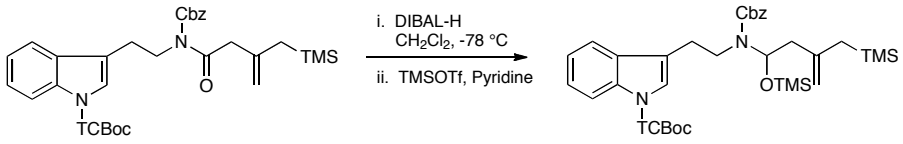
**Tetrahydro-*β*-carboline 173** was obtained during our attempts to cyclize compund **168** using trifluoroacetic acid at 0 °C in place of $BF_3 \cdot OEt_2$ at -78 °C as described in the previous procedure.




**173**

**$R_f$** 0.44 (7:3 hexanes/EtOAc); **$^1$H NMR** (*$d_6$*-DMSO, 22 °C, 600 MHz) (1:1 mixture of rotamers) δ 8.05 (d, 1H, *J* = 8.4 Hz), 8.02 (d, 1H, *J* = 8.4 Hz), 7.66 (d, 2H, *J* = 7.8 Hz), 7.47 (d, 2H, *J* = 7.8 Hz), 7.44-7.23 (m, 16H), 7.21 (d, 2H, *J* = 7.8 Hz), 7.07 (d, 2H, *J* = 7.8 Hz), 6.16 (d, 1H, *J* = 10.8 Hz), 5.93 (d, 1H, *J* = 10.2 Hz), 5.21-5.11 (m, 4H), 4.83-4.74 (m, 4H), 4.26 (dd, 1H, *J* = 13.8, 6.6 Hz), 4.18 (d, 1H, *J* = 14.4, 6.0 Hz), 3.40-3.27 (m, 2H), 2.78-2.56 (m, 8H), 2.25 (m, 3H), 2.22 (s, 3H), 1.86 (s, 3H), 1.79 (s, 3H); **$^{13}$C NMR** (*$d_6$*-DMSO, 22 °C, 150 MHz) (1:1 mixture of rotamers) δ 155.5, 154.6, 145.5, 145.5, 145.4, 141.9, 141.7, 136.9, 136.6, 136.0, 135.8, 135.1, 133.3, 133.1, 130.0, 129.5, 128.5, 128.4, 128.1, 128.0, 127.9, 127.4, 126.3, 125.9, 125.2, 125.1, 124.3, 124.3, 119.1, 119.0, 118.8, 114.9, 114.9, 113.9, 113.4, 66.9, 66.6, 50.2, 50.2, 42.0, 41.7, 35.4, 34.8, 21.5, 20.9, 20.8, 20.3; **IR** (thin film, $cm^{-1}$) 3067.8 (w), 2921.9 (w), 1697.0 (s), 1597.2 (w), 1451.3 (w), 1422.3 (m), 1367.1 (m), 1316.4 (w), 1211.6 (m), 1172.7 (s), 1146.1 (m), 755.1 (m); **m.p.** 158.5-159.5 °C; **HRMS** (+APCI) calculated for $C_{30}H_{31}N_2O_4S$ 515.2005, found 515.2003 $[M+H]^+$.

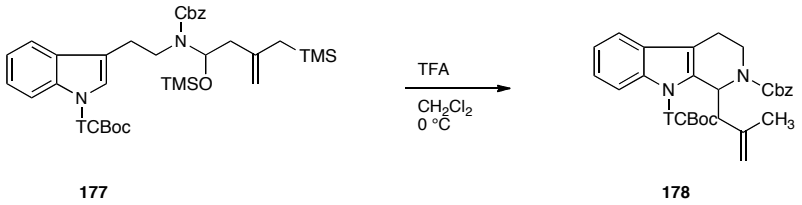
**Synthesis of *N*-Cbz-*O*-TMS-aminol 177:**




**161** **177**

A solution of *N*-Acyl-amide **161** (0.102 g, 0.157 mmol) in $CH_2Cl_2$ (0.7 mL) was cooled to -78 °C. DIBAL-H (1.0 M in $CH_2Cl_2$, 0.31 mL, 0.31 mmol) was added dropwise over 10 minutes. The reaction mixture was stirred for 45 minutes, then pyridine (38 μL, 0.47 mmol) was added dropwise and the reaction was stirred for a further 10 minutes. Trimethylsilyl triflate (71 μL, 0.39 mmole) was added dropwise and the mixture was stirred for 45 minutes at -78 °C. The reaction was warmed to 0 °C and was quenched by slow addition of aqueous 15% Rochelle's salt solution (1 mL). The biphasic mixture was diluted with $Et_2O$ (3 mL) was added. The mixture was stirred vigorously at r.t. until both layers were clear. The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (2 x 1 mL). The organic extracts were combined, washed with brine (5 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (15:1: hexanes/ $Et_2O$, silica gel deactivated with 1% $Et_3N$) afforded aminol **177** as a colorless oil (0.087 g, 76%); $\mathbf{R_f}$ 0.78 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 400 MHz) (1.0: 0.7 mixture of rotamers) δ 8.28-8.20 (m, 1.7H), 7.80 (d, 0.7H, *J* = 8.4 Hz), 7.47-7.28 (m, 13.6H), 7.13 (t, 1H, *J* = 8.0 Hz), 5.97 (t, 1.0H, *J* = 7.6 Hz), 5.81 (t, 0.7H, *J* = 8.0 Hz), 5.30-5.16 (m, 3.4H), 4.66 (s, 1.0H), 4.62 (s, 1.7H), 4.56 (s, 0.7H), 3.64-3.33 (m, 3.4H), 3.14-2.86 (m, 3.4H), 2.36-2.24 (m, 3.4H), 2.12 (s, 10.2H), 1.66 (d, 1.0H, *J* = 16.0 Hz), 1.56 (d, 1.0H, *J* = 16.0 Hz), 1.50 (d, 0.7H, *J* = 16.0 Hz), 1.40 (d, 0.7H, *J* = 16.0 Hz), 0.14 (s, 9.0H), 0.09 (s, 6.3H), 0.04 (s, 9.0H), -0.02 (s, 6.3H).

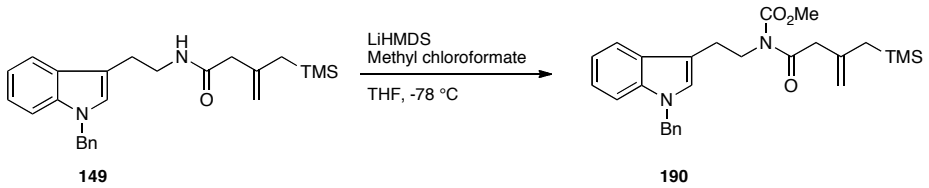
**Synthesis of tetrahydro-*β*-carboline 178:**




**177** **178**

A solution of TFA (9 μL, 0.12 mmol) in $CH_2Cl_2$ (1.0 mL) at 0 °C was added *via* cannula to a solution of *N*-Cbz-*O*-TMS-aminol **177** (0.087 g, 0.119 mmol) in $CH_2Cl_2$ (3.8 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 5 minutes, and was quenched by addition of saturated aqueous $NaHCO_3$ solution (2 mL). The organic layer was separated, and the aqueous layer was extracted with $CH_2Cl_2$ (2 x 2 mL). The organic extracts were combined, washed with brine (3 mL), dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (9:1 → 4:1 hexanes/EtOAc) afforded tetrahydro-*β*-carboline **178** as an amorphous white solid (0.055 g, 72%); $\mathbf{R_f}$ 0.57 (4:1 hexanes/EtOAc).

**Synthesis of *N*-Carbomethoxy-amide 190:**

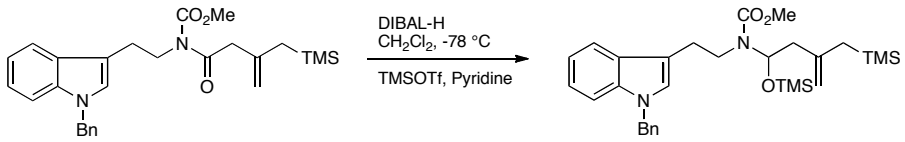



**149** **190**

A solution of amide **149** (0.135 g, 0.334 mmol) in THF (2.0 mL) was cooled to -78 °C. A freshly prepared LiHMDS solution (0.33 M in THF, 1.0 mL, 0.33 mmol) was cooled to -78 °C and added to the staring material solution *via* cannula. The reaction was stirred for 1 h at -78 °C. Methyl chloroformate (77 μL g, 1.0 mmol) was added, and the mixture was

stirred for 12 h at -78 °C. The reaction was quenched with saturated aqueous $NH_4Cl$ (1 mL) and warmed to 0 °C. $H_2O$ (1 mL) was added, and the mixture was stirred for 5 minutes. The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (2 x 2 mL). The organic extracts were combined, washed with brine (6 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (7:3 hexanes/EtOAc) afforded *N*-Cbz-amide **190** as a colorless oil (0.117 g, 76%); $\mathbf{R_f}$ 0.56 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) δ 7.74 (d, 1H, *J* = 7.8 Hz), 7.32-7.29 (m, 2H), 7.28-7.25 (m, 2H), 7.18 (dt, 1H, *J* = 7.8, 1.2 Hz), 7.16-7.11 (m, 3H), 6.96 (s, 1H), 5.27 (s, 2H), 4.73 (s, 1H), 4.67 (s, 1H), 4.03 (dd, 2H, *J* = 9.0, 6.6 Hz), 3.71 (s, 3H), 3.60 (s, 2H), 3.01 (dd, 2H, *J* = 9.0, 6.6 Hz), 1.66 (s, 2H), 0.06 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) δ 173.6, 155.0, 141.7, 137.7, 136.7, 128.8, 128.3, 127.6, 126.9, 126.4, 121.9, 119.3, 119.2, 112.0, 110.9, 109.7, 53.5, 49.9, 47.2, 45.2, 27.5, 24.7, -1.2; **IR** (thin film, $cm^{-1}$) 2954.2 (w), 1736.1 (m), 1689.9 (w), 1467.1 (w), 1451.6 (w), 1356.5 (w), 1165.2 (m), 906.9 (m), 839.7 (m), 726.1 (s); **HRMS** (+ESI) calculated for $C_{27}H_{35}N_2O_3Si$ 463.2417, found 463.2406 $[M+H]^+$.

**Synthesis of *N*-Cbz-*O*-TMS aminol 180:**

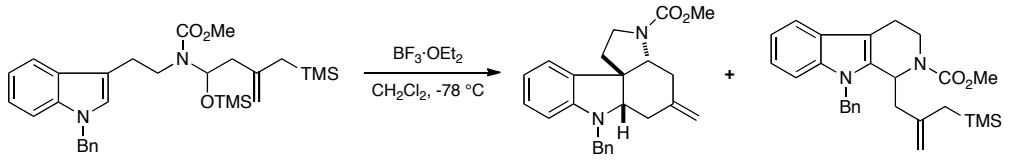



**190** **180**

A solution of *N*-Acyl-amide **190** (0.107 g, 0.230 mmol) in $CH_2Cl_2$ (1.0 mL) was cooled to -78 °C. DIBAL-H (1.0 M in $CH_2Cl_2$, 0.28 mL, 0.28 mmol) was added dropwise over 10 minutes. The reaction mixture was stirred for 1.5 h, then pyridine (56 μL, 0.69 mmol)

was added dropwise and the reaction was stirred for a further 10 minutes. Trimethylsilyl triflate (104 μL, 0.575 mmole) was added dropwise and the mixture was stirred for 45 minutes at -78 °C. The reaction was warmed to 0 °C and was quenched by slow addition of aqueous 15% Rochelle's salt solution (0.5 mL). The biphasic mixture was diluted with $Et_2O$ (3 mL) was added. The mixture was stirred vigorously at r.t. until both layers were clear. The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (2 x 1 mL). The organic extracts were combined, washed with brine (5 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (9:1: hexanes/ $Et_2O$, silica gel deactivated with 1% $Et_3N$) afforded aminol **180** as a colorless oil (0.081 g, 66%); $\mathbf{R_f}$ 0.65 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) (1.0: 0.7 mixture of rotamers) δ 7.81 (d, 0.7H, *J* = 7.2 Hz), 7.71 (m, 1.0H, *J* = 7.8 Hz), 7.35-7.25 (m, 7.0H), 7.21-7.13 (m, 6.6H), 6.99-6.97 (m, 1.7H), 5.94 (t, 1.0H, *J* = 6.0 Hz), 5.74 (t, 0.7H, *J* = 5.4 Hz), 5.30 (m, 3.4H), 4.70-4.63 (m, 1.7H), 4.61 (s, 1.7H), 3.79 (s, 5.1H), 3.56-3.36 (m, 3.4H), 3.12-2.95 (m, 3.4H), 2.35-2.25 (m, 3.4H), 1.66-1.50 (m, 3.4H), 0.18-0.12 (m, 15.3H), 0.04 (s, 15.3H); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) δ 156.3, 155.6, 143.0, 142.9, 137.8, 136.9, 136.8, 128.9, 128.4, 128.3, 127.8, 127.7, 127.0, 126.2, 126.0, 122.0, 121.9, 119.7, 119.4, 119.2, 113.4, 113.3, 110.8, 109.9, 109.8, 79.5, 79.3, 52.7, 52.6, 50.1, 50.0, 45.3, 45.1, 42.9, 42.2, 27.3, 27.2, 26.7, 25.7, -0.04, -1.14; **IR** (thin film, $cm^{-1}$) 2954.0 (w), 1695.6 (m), 1466.4 (w), 1452.6 (w), 1345.3 (w), 1249.0 (m), 1076.9 (w), 1030.6 (w), 837.9 (s), 728.9 (s), 695.2 (m); **HRMS** (+APCI) calculated for $C_{30}H_{45}N_2O_3Si_2$ 537.2969, found 537.2966 $[M+H]^+$.

**Synthesis of tetracyclic amine 183:**

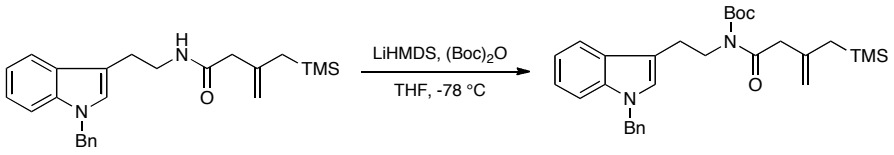



**180** **183** **182**

A solution of aminol **180** (0.048 g, 0.089 mmol) in $CH_2Cl_2$ (1.8 mL) was cooled to -78 °C. $BF_3{\cdot}OEt_2$ (12 μL, 0.13 mmol) was added dropwise and the mixture was stirred at -78 °C for 15 minutes. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ solution (1 mL). The resulting biphasic mixture was warmed to 0 °C and stirred vigorously for 15 minutes. The organic layer was separated, and the aqueous layer was extracted with $CH_2Cl_2$ (2 x 1 mL). The organic extracts were combined, washed with brine (3 mL), dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (4:1 hexanes/EtOAc) afforded tetracyclic amine **183** as a colorless oil (8.2 g, 24%); $\mathbf{R_f}$ 0.40 (4:1 hexanes/EtOAc); **$^1$H NMR** ($d_6$-DMSO, 70 °C, 600 MHz) δ 7.38-7.33 (m, 4H), 7.27-7.25 (m, 1H), 6.94 (dt, 1H, *J* = 7.8, 1.2 Hz), 6.84 (dd, 1H, *J* = 7.2, 1.2 Hz), 6.52 (dt, 1H, *J* = 7.2, 1.2 Hz), 6.30 (d, 1H, *J* = 7.8 Hz), 4.63 (s, 1H), 4.53 (s, 1H), 4.45 (d, 1H, *J* = 15.6 Hz), 4.31 (d, 1H, *J* = 15.6 Hz), 3.83 (dd, 1H, *J* = 12.0, 5.4 Hz), 3.74 (dd, 1H, *J* = 6.0, 3.6 Hz), 3.67 (s, 3H), 3.60 (t, 1H, *J* = 10.2 Hz), 3.51 (dt, 1H, *J* = 10.8, 6.6 Hz), 3.17-3.14 (br s, 1 H), 2.37 (dd, 1H, *J* = 14.4, 6.0 Hz), 2.16 (dt, 1H, *J* = 13.2, 1.2 Hz), 2.13 (dd, 1H, *J* = 14.4, 2.4 Hz), 1.96 (dt, 1H, *J* = 11.4, 9.6 Hz), 1.79 (dd, 1H, *J* = 12.0, 7.2 Hz); **$^{13}$C NMR** ($d_6$-DMSO, 70 °C, 150 MHz) δ 155.5, 150.4, 142.0, 138.4, 130.9, 128.0, 127.6, 126.9, 126.5, 123.3, 116.1, 111.5, 105.6, 65.8, 57.7, 54.2, 51.5, 47.6, 45.7, 35.4, 33.5, 33.0; **IR** (thin film, $cm^{-1}$) 3028.3 (w), 2950.2 (w), 1704.2 (s), 1600.6 (m), 1486.4 (w), 1473.5 (w), 1450.9 (m), 1391.0 (w), 1355.1 (m),

1126.1 (m), 739.1 (m); **HRMS** (+APCI) calculated for $C_{24}H_{27}N_2O_2$ 375.2073, found 375.2070 $[M+H]^+$; and tetrahydro-*β*-carboline **182** as a colorless oil (0.027 g, 69%); $\mathbf{R_f}$ 0.52 (4:1 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 400 MHz) (1:1 mixture of rotamers) δ 7.57-7.49 (m, 2H), 7.33-7.21 (m, 6H), 7.16-7.07 (m, 6H), 7.03-6.94 (m, 4H), 5.61 (dd, 1H, *J* = 11.2, 3.2 Hz), 5.41-5.25 (m, 5H), 4.64 (s, 1H), 4.60-4.57 (m, 3H), 4.54 (dd, 1H, *J* = 11.2, 3.2 Hz), 4.33 (dd, 1H, *J* = 14.0, 6.0 Hz), 3.72 (s, 3H), 3.61 (s, 3H), 3.38-3.28 (m, 2H), 3.04-2.86 (m, 2H), 2.85-2.73 (m, 2H), 2.53-2.38 (m, 2H), 2.29-2.13 (m, 2H), 1.66 (d, 1H, *J* = 14.0 Hz), 1.63-1.54 (m, 2H), 1.44 (d, 1H, *J* = 14.0 Hz), -0.09 (s, 9H), -0.12 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz) (1:1 mixture of rotamers) δ 156.6, 156.5, 143.4, 143.0, 137.3, 137.3, 137.2, 137.1, 136.2, 135.5, 129.1, 129.0, 127.6, 127.6, 127.1, 127.0, 126.1, 126.0, 122.0, 121.9, 119.8, 119.7, 118.5, 118.3, 111.2, 110.7, 110.2, 100.0, 108.7, 108.0, 53.0, 52.5, 49.3, 49.1, 47.2, 47.1, 43.2, 43.0, 37.5, 37.0, 26.3, 26.3, 21.6, 21.2, -1.4, -1.4; **IR** (thin film, $cm^{-1}$) 2951.1 (w), 1697.2 (s), 1451.3 (m), 1406.8 (w), 1308.1 (w), 1245.9 (w), 1195.6 (m), 1110.5 (m), 840.9 (s), 735.2 (s); **HRMS** (+APCI) calculated for $C_{27}H_{35}N_2O_2Si$ 447.2468, found 447.2462 $[M+H]^+$.

**Synthesis of *N*-Boc-amide 191:**

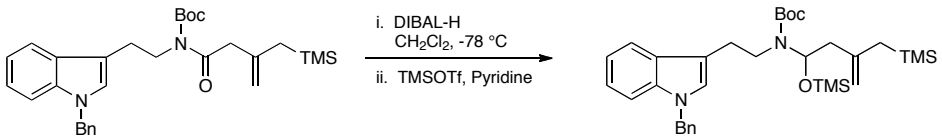



**149** **191**

A solution of amide **149** (0.427 g, 1.06 mmol) in THF (3.2 mL) was cooled to -78 °C. A freshly prepared LiHMDS solution (0.33 M in THF, 3.0 mL, 1.0 mmol) was cooled to -78 °C and added to the staring material solution *via* cannula. The reaction was stirred for

1 h at -78 °C. In a separate flask, a solution of di-*tert*-butyl dicarbonate (0.322 g, 1.48 mmol) in THF (1.0 mL) was cooled to -78 °C and added into the reaction mixture *via* cannula. The mixture was stirred for 12 h at -78 °C, quenched with saturated aqueous $NH_4Cl$ (1 mL) and warmed to 0 °C. $H_2O$ (4 mL) was added and the mixture was stirred for 5 minutes. The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (2 x 5 mL). The organic extracts were combined, washed with brine (12 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (20:1 → 9:1 hexanes/$Et_2O$) afforded *N*-Boc amide **191** as a colorless oil (0.293 g, 55%); $\mathbf{R_f}$ 0.5 (4:1 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 400 MHz) δ 7.77 (d, 1H, $J$ = 7.6 Hz), 7.32-7.08 (m, 8H), 6.97 (s, 1H), 5.24 (s, 2H), 4.75 (s, 1H), 4.74 (s, 1H), 4.00 (dd, 2H, $J$ = 8.4, 6.8 Hz), 3.61 (s, 2H), 3.05 (dd, 2H, $J$ = 8.4, 7.2 Hz), 1.69 (s, 2H), 1.46 (m, 9H), 0.08 (m, 9H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 173.9, 153.2, 141.9, 137.7, 136.7, 128.8, 128.3, 127.6, 127.0, 126.4, 121.9, 119.4, 119.2, 112.3, 111.1, 109.8, 82.9, 50.0, 47.3, 45.7, 28.0, 27.4, 24.6, -1.2; **IR** (thin film, $cm^{-1}$) 2953.8 (w), 1730.9 (m), 1685.3 (m), 1467.4 (w), 1453.4 (w), 1355.5 (m), 1247.8 (m), 1143.6 (s), 850.1 (m), 738.3 (m); **HRMS** (+ESI) calculated for $C_{30}H_{41}N_2O_3Si$ 505.2886, found 505.2881 $[M+H]^+$.

**Synthesis of *N*-Boc-*O*-TMS-aminol 181:**

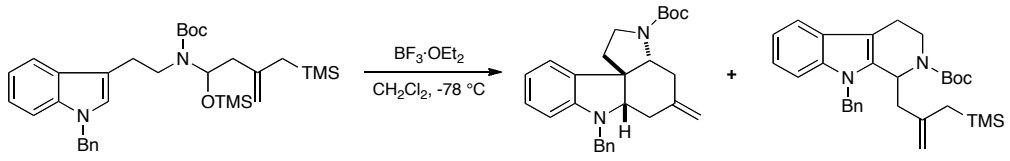



**191** **181**

A solution of *N*-Boc amide **191** (0.293 g, 0.580 mmol) in $CH_2Cl_2$ (2.5 mL) was cooled to -78 °C. DIBAL-H (1.0 M in $CH_2Cl_2$, 1.16 mL, 1.16 mmol) was added dropwise over 10

minutes. The reaction mixture was stirred at -78 °C for 1 h, then pyridine (0.14 mL, 1.74 mmol) was added dropwise and the reaction was stirred for 5 minutes. Trimethylsilyl triflate (0.26 mL, 1.45 mmol) was added dropwise and the mixture was stirred for 20 minutes. The reaction was warmed to 0 °C and was quenched by slow addition of aqueous 15% Rochelle's salt solution (3 mL). The biphasic mixture was transferred to a 25 mL Erlenmeyer flask, and $Et_2O$ (7 mL) was added. The mixture was stirred vigorously at r.t. until both layers were clear. The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (2 x 3 mL). The organic extracts were combined, washed with brine (10 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (7:3 hexanes/$CH_2Cl_2$, silica gel deactivated with 1% $Et_3N$) afforded *N*-Boc-*O*-TMS-aminol **181** as a colorless oil (0.196 g, 58%); $\mathbf{R_f}$ 0.64 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) (1.0: 0.8 mixture of rotamers) δ 7.78 (d, 0.8H, *J* = 7.2 Hz), 7.73 (d, 1.0H, *J* = 7.8 Hz), 7.36-7.24 (m, 7H), 7.23-7.11 (m, 7H), 6.99 (s, 0.8H), 6.96 (s, 1.0H), 5.93 (t, 1.0H, *J* = 6.6 Hz), 5.78 (t, 0.8H, *J* = 6.6 Hz), 5.30 (s, 2.0H), 5.27 (s, 1.6H), 4.67 (s, 1.0H), 4.64 (s, 0.9 H), 4.60 (s, 1.8H), 3.51-3.34 (m, 3.6H), 3.11-3.06 (m, 2.6H), 3.01-2.98 (m, 1.0H), 2.33-2.25 (m, 3.6H), 1.67-1.51 (m, 19.8H), 0.20-0.11 (m, 16.2H), 0.04 (m, 16.2H); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) δ 155.1, 154.0, 143.2, 142.9, 137.9, 136.8, 136.8, 128.9, 128.6, 128.4, 127.7, 127.7, 127.1, 126.9, 126.2, 126.0, 122.0, 121.8, 119.7, 119.5, 119.1, 113.6, 113.6, 110.8, 110.6, 109.9, 109.7, 80.0, 79.9, 79.4, 78.6, 50.1, 50.0, 45.4, 45.1, 42.6, 42.4, 28.8, 27.3, 27.2, 26.7, 25.7, 0.1, 0, -1.1; **IR** (thin film, $cm^{-1}$) 2954.5 (w), 1691.4 (m), 1466.7 (w), 1453.7 (w), 1248.5 (m), 1151.7 (m), 1028.7 (m), 837.6 (s), 736.5 (m), 696.3 (w); **HRMS** (+APCI) calculated for $C_{33}H_{51}N_2O_3Si_2$ 579.3438, found 579.3433 $[M+H]^+$.

**Synthesis of Tetracyclic amine 184:**

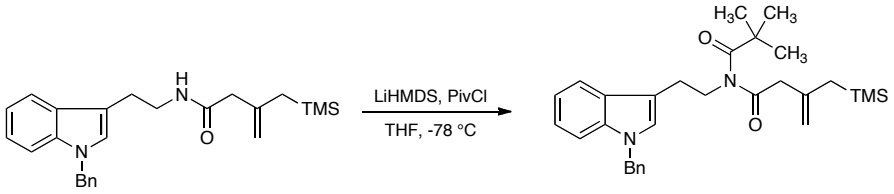



**181** **184** **185**

A solution of *N*-Boc-*O*-TMS-aminol **181** (0.097 g, 0.167 mmol) in $CH_2Cl_2$ (3.4 mL) was cooled to -78 °C. $BF_3{\cdot}OEt_2$ (31 μL, 0.25 mmol) was added dropwise, and the mixture was stirred at -78 °C for 15 minutes. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ solution (1 mL). The resulting biphasic mixture was warmed to 0 °C and stirred vigorously for 15 minutes. The organic layer was separated, and the aqueous layer was extracted with $CH_2Cl_2$ (2 x 1 mL). The organic extracts were combined, washed with brine (3 mL), dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (4:1 hexanes/EtOAc, silica gel deactivated with 1% $Et_3N$) afforded tetracyclic amine **184** as a colorless oil (0.023 g, 33%); $\mathbf{R_f}$ 0.43 (4:1 hexanes/EtOAc); $^{1}$**H NMR** (*d*$_6$-DMSO, 70 °C, 600 MHz) δ 7.38-7.33 (m, 4H), 7.27-7.25 (m, 1H), 6.93 (td, 1H, *J* = 7.8, 1.2 Hz), 6.83 (dd, 1H, *J* = 7.8, 1.2 Hz), 6.53 (td, 1H, *J* = 7.2, 1.2 Hz), 6.29 (d, 1H, *J* = 7.8 Hz), 4.61 (s, 1H), 4.51 (s, 1H), 4.45 (d, 1H, *J* = 15.6 Hz), 4.31 (d, 1H, *J* = 15.6 Hz), 3.78 (dd, 1H, *J* = 12.0, 6.0 Hz), 3.73 (dd, 1H, *J* = 6.0, 3.0 Hz), 3.54 (t, 1H, *J* = 11.4 Hz), 3.45 (td, 1H, *J* = 10.8, 6.6 Hz), 3.17-3.08 (m, 1H), 2.35 (dd, 1H, *J* = 14.4, 6.0 Hz), 2.16 (t, 1H, *J* = 13.8 Hz), 2.12 (dd, 1H, *J* = 15.0, 3.6 Hz), 1.93 (td, 1H, *J* = 14.4, 9.6 Hz), 1.76 (dd, 1H, *J* = 12.0, 6.0 Hz), 1.46 (s, 9H); $^{13}$**C NMR** (*d*$_6$-DMSO, 70 °C, 150 MHz) δ 154.4, 150.5, 142.2, 138.4, 131.0, 128.0, 127.6, 126.9, 126.5, 123.2, 116.0, 111.3, 105.6, 78.4, 65.9, 57.5, 54.4, 47.6, 45.7, 35.2, 33.9, 33.0, 27.9; **IR** (thin film, $cm^{-1}$) 2973.8 (w), 2925.9 (w), 1687.5 (s), 1600.6 (m), 1474.2 (w) 1452.2 (w),

1401.4 (w), 1352.6 (m), 1168.8 (w), 1122.7 (s), 906.4 (m), 731.3 (s), 698.7 (w); **HRMS** (+APCI) calculated for $C_{27}H_{33}N_2O_2$ 417.2542, found 417.2536 $[M+H]^+$; and tetrahydro-*β*-carboline **185** as a crystalline white solid (0.043 g, 53%); $\mathbf{R_f}$ 0.54 (4:1 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) (1.0:0.6 mixture of rotamers) δ 7.56 (d, 1.0H, *J* = 7.2 Hz), 7.55-7.52 (m, 0.6H), 7.30-7.21 (m, 6H), 7.19-7.05 (m, 4H), 7.02 (d, 1.0H, *J* = 7.6 Hz), 6.96 (d, 1.9H, *J* = 7.2 Hz), 5.64 (dd, 0.6H, *J* = 10.8, 2.4 Hz), 5.43 (d, 1H, *J* = 17.4 Hz), 5.34 (s, 1.2H), 5.31-5.26 (m, 1.6H), 5.25 (s, 0.4H), 4.68 (s, 1.0H), 4.63 (s, 0.6H), 4.62 (s, 1.0H), 4.58 (s, 0.6H), 4.53 (dd, 1.0H, *J* = 13.8, 6.0 Hz), 4.33 (dd, 0.6H, *J* = 13.8, 6.0 Hz), 3.32 (dt, 0.6H, *J* = 12.6, 4.2 Hz), 3.26 (td, 1H, *J* = 12.6, 4.2 Hz), 3.02-2.90 (m, 1.6H), 2.80 (d, 1.0H, *J* = 3.6 Hz), 2.77 (d, 0.6H, *J* = 4.0 Hz), 2.50 (dd, 1.0H, *J* = 13.8, 10.8 Hz), 2.43 (dd, 0.6H, *J* = 14.4 Hz, 11.4 Hz), 2.26 (dd, 1H, *J* = 14.4, 2.4 Hz), 2.20 (dd, 0.6H, *J* = 14.4, 2.4 Hz), 1.69 (d, 0.6H, *J* = 13.8 Hz), 1.65 (d, 1.0H, *J* = 13.2 Hz), 1.61 (d, 0.6H, *J* = 13.8 Hz), 1.52 (d, 1.0H, *J* = 13.2 Hz), 1.46 (s, 5.4H), 1.37 (s, 9.0H), -0.01 (s, 9.0H), -0.11 (s, 5.4H); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) (1.0:0.6 mixture of rotamers) δ 155.1, 154.8, 143.6, 142.9, 137.5, 137.4, 137.3, 137.2, 136.7, 136.0, 129.1, 129.0, 127.7, 127.5, 127.2, 127.1, 126.1, 126.0, 122.0, 121.8, 119.8, 119.6, 118.5, 118.2, 111.3, 110.6, 110.2, 109.7, 109.1, 108.1, 79.9, 79.7, 49.5, 48.4, 47.1, 47.0, 43.0, 43.0, 37.8, 36.2, 28.6, 28.4, 27.1, 26.4, 21.7, 21.2, -1.3, -1.4; **IR** (thin film, $cm^{-1}$) 2951.4 (w), 1686.6 (s), 1411.4 (m), 1246.3 (m), 1162.7 (s), 1105.8 (m), 838.4 (s), 729.8 (s), 695.3 (m); **m.p.** 122-123 °C; **HRMS** (+ESI) calculated for $C_{30}H_{41}N_2O_2Si$ 489.2937, found 489.2931 $[M+H]^+$.

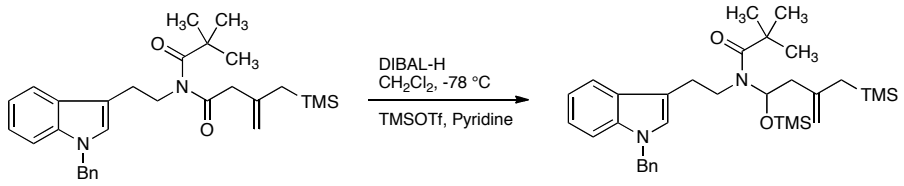
**Synthesis of *N*-pivaloyl-amide 187:**




**149** **187**

A solution of amide **149** (0.229 g, 0.567 mmol) in THF (2.0 mL) was cooled to -78 °C. A freshly prepared LiHMDS solution (0.33 M in THF, 1.6 mL, 0.54 mmol) was cooled to -78 °C and added to the starting material solution *via* cannula. The reaction was stirred for 1 h at -78 °C. Pivaloyl chloride (77 μL, 0.62 mmol) was added, and the mixture was stirred for 12 h. The reaction was quenched with saturated aqueous $NH_4Cl$ (0.5 mL) and warmed to 0 °C. $H_2O$ (1 mL) was added, and the mixture was stirred for 5 minutes. The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (2 x 3 mL). The organic extracts were combined, washed with brine (10 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (20:1 → 9:1 pentane/$Et_2O$) afforded *N*-pivaloyl amide **187** as a colorless oil (0.133 g, 48%); $\mathbf{R_f}$ 0.48 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 400 MHz) δ 7.70 (d, 1H, *J* = 7.6 Hz), 7.33-7.26 (m, 4H), 7.19 (dt, 1H, *J* = 7.6, 1.2 Hz), 7.16-7.11 (m, 3H), 6.96 (s, 1H), 5.28 (s, 2H), 4.74 (d, 1H, *J* = 0.4 Hz), 4.69 (d, 1H, *J* = 1.2 Hz), 3.90-3.86 (m, 2H), 3.19 (s, 2H), 3.05-3.01 (m, 2H), 1.60 (s, 2H), 1.30 (s, 9H), -0.03 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 187.2, 174.0, 141.1, 137.6, 136.7, 128.9, 128.0, 127.7, 127.0, 126.4, 122.1, 119.5, 119.2, 112.2, 111.7, 109.9, 50.0, 46.7, 45.8, 43.0, 28.5, 26.9, 25.4, -1.2; **IR** (thin film, $cm^{-1}$) 2955.1 (w), 1676.6 (m), 1466.6 (w), 1332.8 (w), 1247.5 (m), 1132.9 (w), 1003.9 (w), 838.9 (s), 735.4 (s), 697.0 (m); **HRMS** (+APCI) calculated for $C_{30}H_{41}N_2O_2Si$ 489.2937, found 489.2927 $[M+H]^+$.

**Synthesis of *N*-pivaloyl-*O*-TMS-aminol 186:**

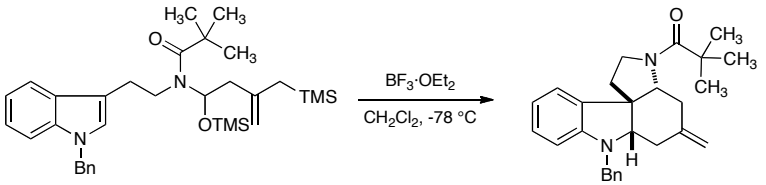



**187** **186**

A solution of *N*-pivaloyl amide **187** (0.106 g, 0.187 mmol) in $CH_2Cl_2$ (0.80 mL) was cooled to -78 °C. DIBAL-H (1.0 M in $CH_2Cl_2$, 0.23 mL, 0.23 mmol) was added dropwise over 10 minutes. The reaction mixture was stirred for 2 h, then pyridine (46 μL, 0.56 mmol) was added dropwise and the reaction was stirred for 5 minutes. Trimethylsilyl triflate (85 μL, 0.47 mmol) was added dropwise and the mixture was stirred for 45 minutes at -78 °C. The reaction was warmed to 0 °C and was quenched by slow addition of aqueous 15% Rochelle's salt solution (0.5 mL). $Et_2O$ (3 mL) was added, and the biphasic mixture was stirred vigorously at r.t. until both layers were clear. The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (2 x 1 mL). The organic extracts were combined, washed with brine (5 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (9:1 pentane/$Et_2O$, silica gel deactivated with 1% $Et_3N$) afforded the *N*-pivaloyl-*O*-TMS-aminol **186** as a colorless oil (0.069 g, 66%); $\mathbf{R_f}$ 0.63 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) δ 7.75 (d, 1H, *J* = 7.8 Hz), 7.32-7.26 (m, 4H), 7.20 (t, 1H, *J* = 7.8 Hz), 7.16-7.13 (m, 3H), 6.98 (s, 1H), 6.07-5.94 (br s, 1H), 5.30 (s, 2H), 4.71 (s, 1H), 4.64 (s, 1H), 3.78-3.69 (m, 1H), 3.64-3.60 (m, 1H), 3.23-3.13 (m, 1H), 3.04 (dt, 1H, *J* = 12.6, 4.8 Hz), 2.40 (dd, 1H, *J* = 13.8, 8.4 Hz), 2.36-2.31 (m, 1H), 1.65 (d, 1H, *J* = 13.2 Hz), 1.58 (d, 1H, *J* = 13.2 Hz), 1.33 (s, 9H), 0.17 (s, 9H), 0.04 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) δ 177.0, 143.3, 137.8, 136.8, 128.9, 128.4, 127.8, 127.0, 125.9, 122.0, 119.6,

119.3, 113.5, 110.8, 109.9, 80.5, 50.1, 45.5, 44.0, 39.9, 29.1, 28.9, 27.3, 0.5, -1.2; **IR** (thin film, $cm^{-1}$) 2956.3 (br, w), 1621.4 (m), 1250.3 (m), 906.1 (m), 840.2 (m), 726.0 (s), 646.8 (w); **HRMS** (+ESI) calculated for $C_{33}H_{51}N_2O_2Si_2$ 563.3489, found 563.3491 $[M+H]^+$.

**Synthesis of tetracyclic amine 188:**

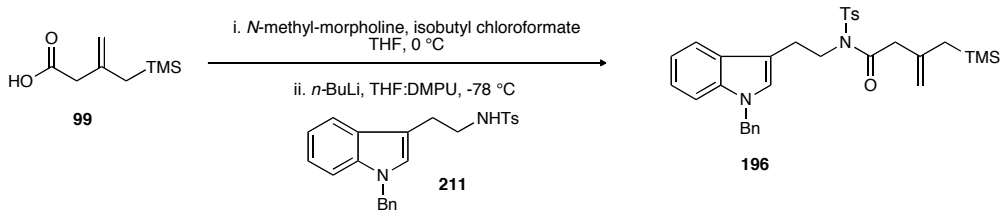



**186** **188**

A solution of *N*-pivaloyl-*O*-TMS-aminol **186** (0.044 g, 0.078 mmol) in $CH_2Cl_2$ (3.0 mL) was cooled to -78 °C. $BF_3{\cdot}OEt_2$ (14 μL, 0.18 mmol) was added dropwise and the mixture was stirred at -78 °C for 6 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (1 mL). The resulting biphasic mixture was warmed to 0 °C and stirred vigorously for 15 minutes. The organic layer was separated, and the aqueous layer was extracted with $CH_2Cl_2$ (2 x 1 mL). The organic extracts were combined, washed with brine (3 mL), dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (7:3 hexanes/EtOAc) afforded tetracyclic amine **188** as a colorless oil (0.011 g, 34%); $\mathbf{R_f}$ 0.48 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) δ 7.41-7.34 (m, 4H), 7.29 (t, 1H, *J* = 7.2 Hz), 7.05 (t, 1H, *J* = 7.2 Hz), 6.97 (d, 1H, *J* = 6.6 Hz), 6.64 (t, 1H, *J* = 7.2 Hz), 6.32 (d, 1H, *J* = 7.2 Hz), 4.59 (s, 1H), 4.58 (s, 1H), 4.47 (d, 1H, *J* = 15.6 Hz), 4.25 (d, 1H, *J* = 15.6 Hz), 3.91-3.83 (m, 3H), 3.67 (dd, 1H, *J* = 6.6, 3.6 Hz), 3.43 (dd, 1H, *J* = 14.4, 4.8 Hz), 2.33 (dd, 1H, *J* = 14.4, 6.6 Hz), 2.19 (dd, 1H, *J* = 14.4, 3.6 Hz), 2.16 (t, 1H, *J* = 13.2 Hz), 2.04 (dd, 1H, *J* = 11.4, 5.4 Hz), 1.90 (dt, 1H, *J* =

11.4, 9.0 Hz), 1.36 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) δ 180.7, 151.3, 143.1, 138.6, 131.9, 128.8, 128.4, 127.6, 127.3, 124.4, 117.1, 112.1, 106.9, 67.4, 61.5, 53.6, 48.9, 47.6, 40.1, 37.2, 35.0, 34.0, 28.1; **IR** (thin film, $cm^{-1}$) 3028.8 (w), 2966.5 (w), 2930.2 (w), 1631.4 (s), 1600.7 (m) 1477.5 (m), 1452.5 (w), 1400.5 (w), 1341.9 (m), 738.1 (m); **HRMS** (+APCI) calculated for $C_{27}H_{33}N_2O$ 401.2593, found 401.2592 $[M+H]^+$.

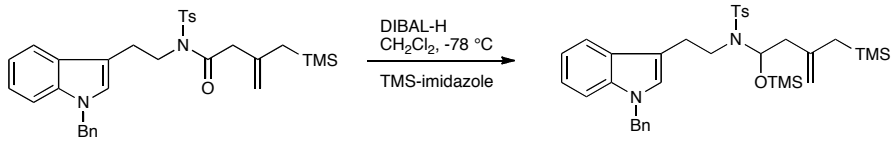
**Synthesis of *N*-Tosylamide 196:**




A solution of tosylamine **211** (0.200 g, 0.494 mmol) in THF:DMPU (12:1, 5.0 mL) was cooled to -78 °C. *n*-BuLi (1.6 M in hexanes, 0.32 mL, 0.519 mmol) was added over 15 minutes, and the resulting solution was stirred at -78 °C for 1 h. In a separate flask, a solution of carboxylic acid **99** (0.10 mL, 0.57 mmol) in THF (5.0 mL) was cooled to 0 °C. *N*-methyl-morpholine (62 μL, 0.57 mmol) was added to the carboxylic acid solution, followed by addition of isobutyl chloroformate (74 μL, 0.57 mmol) over 10 minutes. The resulting mixture was stirred for 30 minutes at 0 °C. Stirring was discontinued, and the suspension was allowed to settle for 30 minutes. The yellow supernatant was separated from the white precipitate, and was filtered through celite into a flask pre-cooled to 0 °C. The filtered cake was washed with dry THF (2 x 2 mL). The mixed anhydride solution was cooled to -40 °C and stirred for 5 minutes. The lithiate solution was added to the mixed anhydride solution *via* cannula, and the resulting orange solution was allowed to reach 0 °C over 2 h. The reaction was quenched with $H_2O$ (4

mL). The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (3 x 4 mL). The organic extracts were combined, washed with brine (15 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (20:1 → 9:1 hexanes/EtOAc) afforded tosylamide **196** as a colorless oil (0.307 g, 49%); $\mathbf{R_f}$ 0.45 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) δ 7.85 (d, 2H, *J* = 8.4 Hz), 7.78 (d, 1H, *J* = 7.8 Hz), 7.34-7.26 (m, 6H), 7.20 (dt, 1H, *J* = 7.8, 1.2 Hz), 7.18 (dt, 1H, *J* = 7.8, 0.6 Hz), 7.13 (d, 2H, *J* = 7.2 Hz), 7.00 (s, 1H), 5.27 (s, 2H), 4.67 (s, 1H), 4.49 (d, 1H, *J* = 1.2 Hz), 4.08-4.04 (m, 2H), 3.25-3.21 (m, 2H), 3.12 (s, 2H), 2.44 (s, 3H), 1.48 (s, 2H), -0.06 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 171.0, 144.8, 140.2, 137.5, 136.9, 136.7, 129.7, 128.8, 128.0, 127.9, 127.7, 126.9, 126.8, 122.1, 119.5, 119.2, 111.9, 111.2, 109.9, 50.0, 48.1, 45.6, 27.1, 26.4, 21.7, -1.4; **IR** (thin film, $cm^{-1}$) 3030.4 (w), 2952.7 (w), 1693.5 (m), 1467.2 (w), 1453.3 (w), 1350.6 (s), 1247.8 (w), 1162.1 (s), 847.0 (s), 739.1 (s); **HRMS** (+ESI) calculated for $C_{32}H_{39}N_2O_3SSi$ 559.2451, found 559.2448 $[M+H]^+$.

**Synthesis of *N*-tosyl-*O*-TMS-aminol 192:**

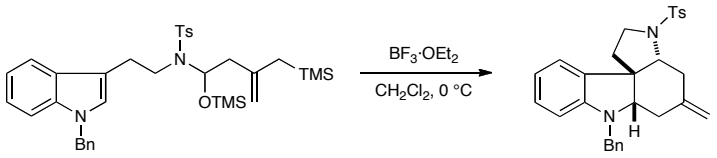



**196** **192**

A solution of *N*-tosylamide **196** (0.072 g, 0.13 mmol) in $CH_2Cl_2$ (1.0 mL) was cooled to -78 °C. DIBAL-H (1.0 M in $CH_2Cl_2$, 0.26 mL, 0.26 mmol) was added dropwise over 30 minutes. The reaction mixture was stirred for 20 minutes, then trimethylsilyl imidazole (60 μL, 0.37 mmol) was added dropwise. The mixture was warmed to -25 °C and stirred

for 20 h. The mixture was warmed to 0 °C and stirred for 2 h. The reaction was quenched by slow addition of aqueous 15% Rochelle's salt solution (1 mL). The biphasic mixture was transferred to a 25 mL Erlenmeyer flask, and $Et_2O$ (4 mL) was added. The mixture was stirred vigorously at r.t. until both layers were clear. The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (2 x 1 mL). The organic extracts were combined, washed with brine (5 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (20:1 → 9:1 hexanes/$Et_2O$, silica gel deactivated with 1% $Et_3N$) afforded *N*-tosyl-*O*-TMS-aminol **192** as a colorless oil (0.062 g, 76%); $\mathbf{R_f}$ 0.50 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) δ 7.75 (d, 2H, *J* = 8.4 Hz), 7.72 (dd, 1H, *J* = 7.8, 0.6 Hz), 7.32-7.26 (m, 6H), 7.19 (dt, 1H, *J* = 7.2, 1.2 Hz), 7.14-7.11 (m, 3H), 6.96 (s, 1H), 5.55 (dd, 1H, *J* = 8.4, 3.6 Hz), 5.28 (s, 2H), 4.64 (s, 1H), 4.60 (s, 1H), 3.54 (ddd, 1H, *J* = 15.0, 12.0, 5.4 Hz), 3.39 (ddd, 1H, *J* = 15.0, 12.0, 4.8 Hz), 3.23 (dt, 1H, *J* = 13.2, 4.8 Hz), 3.10 (dt, 1H, 13.2, 4.8 Hz), 2.40 (s, 3H), 2.31 (dd, 1H, *J* = 13.2, 8.4 Hz), 1.97 (dd, 1H, *J* = 13.2, 3.6 Hz), 1.59 (d, 1H, *J* = 13.8 Hz), 1.40 (d, 1H, *J* = 13.8 Hz), 0.15 (s, 9H), -0.02 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 143.2, 142.5, 138.6, 137.8, 136.8, 129.8, 129.0, 128.2, 127.8, 127.3, 127.0, 126.2, 122.0, 119.5, 119.3, 113.0, 111.3, 109.9, 81.9, 50.1, 45.7, 44.0, 27.8, 27.1, 21.7, 0.3, -1.3; **IR** (thin film, $cm^{-1}$) 2953.5 (w), 1466.8 (w), 1453.3 (w), 1332.0 (m), 1248.6 (m), 1157.8 (m), 838.2 (s), 730.5 (s), 658.0 (m), 548.5 (m); **HRMS** (+APCI) calculated for $C_{32}H_{39}N_2O_2SSi$ 543.2502, found 543.2497 $[M\text{-}OTMS]^+$.

**Synthesis of tetracyclic amine 195:**

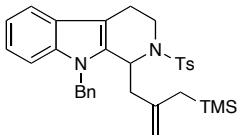



**192** **195**

A solution of *N*-tosyl-*O*-TMS-aminol **192** (0.093 g, 0.147 mmol) in $CH_2Cl_2$ (3.7 mL) was cooled to 0 °C. $BF_3{\cdot}OEt_2$ (91 uL, 0.74 mmol) was added dropwise and the mixture was stirred at 0 °C for 15 minutes. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (2.5 mL). The resulting biphasic mixture was stirred vigorously for 15 minutes. The organic layer was separated, and the aqueous layer was extracted with $CH_2Cl_2$ (2 x 2 mL). The organic extracts were combined, washed with brine (5 mL), dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (7:3 hexanes/$Et_2O$) afforded tetracyclic amine **195** as a crystalline white solid (0.057 g, 82%); $\mathbf{R_f}$ 0.40 (7:3: hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) δ 7.73 (d, 2H, *J* = 8.4 Hz), 7.45 (dd, 1H, *J* = 7.2, 1.2 Hz), 7.37-7.29 (m, 6H), 7.28-7.24 (m, 1H), 7.10 (dt, 1H, *J* = 7.8, 1.2 Hz), 6.73 (dt, 1H, 7.8, 1.2 Hz), 6.40 (d, 1H, 7.8 Hz), 4.77 (s, 1H), 4.68 (s, 1H), 4.44 (d, 1H, *J* = 15.0 Hz), 4.09 (d, 1H, *J* = 15.0 Hz), 3.67 (dt, 1H, *J* = 10.8, 6.6 Hz), 3.43 (t, 1H, *J* = 10.2 Hz), 3.36 (t, 1H, *J* = 6.0 Hz), 3.08 (dd, 1H, *J* = 13.8, 4.8 Hz), 2.99 (dd, 1H, *J* = 12.6, 4.8 Hz), 2.49 (t, 1H, *J* = 13.2 Hz), 2.45 (s, 3H), 2.27 (dd, 1H, *J* = 14.4, 5.4 Hz), 2.04 (dd, 1H, *J* = 14.4, 6.0 Hz), 1.89 (dd, 1H, *J* = 11.4, 6.6 Hz), 1.46 (q, 1H, *J* = 10.8 Hz); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) δ 150.5, 143.9, 142.5, 138.2, 132.5, 131.3, 129.9, 128.7, 128.5, 127.9, 127.7, 127.3, 125.2, 118.0, 112.8, 107.6, 67.1, 62.4, 54.9, 48.8, 47.8, 35.8, 35.6, 33.8, 21.7; **IR** (thin film, $cm^{-1}$) 3029.6 (w), 2922.2 (w), 1599.7 (m), 1492.3 (w), 1473.7 (w), 1452.0 (w), 1349.4 (m), 1161.5 (s),

1097.0 (w), 737.1 (m), 665.3 (s), 603.5 (w), 565.8 (w), 550.1 (m); **m.p.** 65.5-67.0 °C; **HRMS** (+ESI) calculated for $C_{29}H_{31}N_2O_2S$ 471.2106, found 471.2096 $[M+H]^+$.

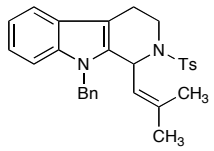
**Tetrahydro-*β*-carboline 194** was obtained during our attempts to cyclize compound **192** using catalyst **122** (in the presence of HCl and 3Å molecular sieves) at -78 °C in place of $BF_3{\cdot}OEt_2$ at 0 °C as described in the previous procedure.




**194**

**$R_f$** 0.42 (7:3: hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) δ 7.42 (d, 2H, *J* = 8.4), 7.35 (d, 1H, *J* = 7.8 Hz), 7.34-7.27 (m, 3H), 7.8 (d, 1H, *J* = 8.4 Hz), 7.13 (t, 1H, *J* = 6.9 Hz), 7.07 (t, 1H, *J* = 6.9. Hz), 7.00 (d, 2H, *J* = 8.4 Hz), 6.97 (d, 2H, *J* = 6.6 Hz), 5.41 (d, *J* = 17.1 Hz, 1H), 5.27-5.24 (m, 2H), 4.72 (s, 1H), 4.67 (s, 1H), 4.09 (dd, 1H, *J* = 15.0, 6.2 Hz), 3.52 (ddd, 1H, *J* = 15.0, 12.0, 4.8 Hz), 2.57 (dd, 1H, *J* = 15.6, 4.8 Hz), 2.51 (dd, 1H, *J* = 12.0, 6.0 Hz), 2.46 (dd, 1H, *J* = 14.1, 9.9 Hz), 2.32 (dd, 1H, *J* = 14.2, 3.4 Hz), 2.27 (s, 3H), 1.67 (d, 1H, *J* = 13.9 Hz), 1.52 (d, 1H, *J* = 13.9 Hz), -0.03 (s, 9H); **HRMS** (+APCI) calculated for $C_{32}H_{39}N_2O_2SSi$ 543.2502, found 543.2496 $[M+H]^+$.

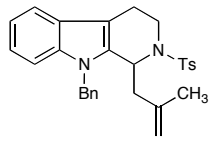
**Tetrahydro-*β*-carboline 204** was obtained during our attempts to cyclize compound **192** using catalyst **122** (in the presence of HCl and 3Å molecular sieves) at -78 °C in place of $BF_3 \cdot OEt_2$ at 0 °C as described in the previous procedure.




**204**

Amorphous white solid; $\mathbf{R_f}$ 0.40 (7:3 hexanes/EtOAc); 7.52 (d, 2H, *J* = 7.8 Hz), 7.45 (d, 1H, *J* = 8.4 Hz), 7.28-7.22 (m, 3H), 7.17-7.08 (m, 5H), 6.87 (d, 2H, *J* = 7.9 Hz), 5.75 (d, 1H, *J* = 9.9 Hz), 5.23-5.14 (m, 3H), 4.18-4.14 (m, 1H), 3.41-3.36 (m, 1H), 2.75-2.71 (m, 2H), 2.34 (s, 3H), 1.80 (s, 3H), 1.45 (s, 3H).

**Tetrahydro-*β*-carboline 205** was obtained during our attempts to cyclize compound **192** using catalyst **122** (in the presence of HCl and 3Å molecular sieves) at -78 °C in place of $BF_3 \cdot OEt_2$ at 0 °C as described in the previous procedure.

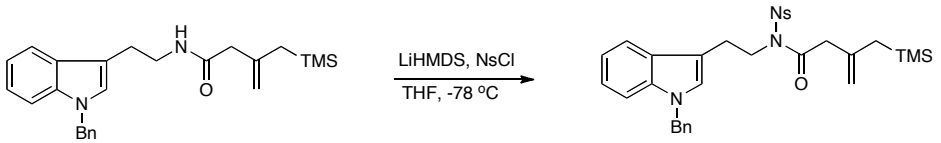



**205**

White amorphous solid; $\mathbf{R_f}$ 0.42 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) δ 7.38 (d, 2H, *J* = 8.4 Hz), 7.34-7.28 (m, 4H), 7.23 (d, 1H, *J* = 7.8 Hz), 7.16 (t, 1H, *J* = 7.8 Hz), 7.07 (t, 1H, *J* = 7.2 Hz), 7.02 (d, 2H, *J* = 7.8 Hz), 6.99 (d, 2H, *J* = 8.4 Hz), 5.42 (d, 1H, *J* = 16.8 Hz), 5.27-5.24 (m, 2H), 4.89 (d, *J* = 1.2 Hz, 1H), 4.79 (s, 1H), 4.09 (dd, 1H, *J* = 15.0, 6.6 Hz), 3.54-3.49 (m, 1H), 2.58-2.49 (m, 2H), 2.47-2.42 (m, 1H), 2.4 (dd, 1H,

*J* = 14.4, 3.0 Hz), 2.28 (s, 3H), 1.84 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) 143.2, 141.2, 138.1, 137.5, 137.3, 134.6, 129.4, 129.2, 128.0, 127.1, 126.9, 126.4, 122.2, 119.6, 118.5, 115.0, 109.8, 107.9, 50.9, 47.1, 43.9, 38.4, 22.2, 21.6, 19.8; **IR** (thin film, $cm^{-1}$) 3029.5 (w), 2922.8 (w), 1463.6 (m), 1453.5 (m), 1343.9 (m), 1157.0 (s), 738.2 (m), 719.2 (m); **HRMS** (+APCI) calculated for $C_{29}H_{31}N_2O_2S$ 471.2106, found 471.2100 $[M+H]^+$.

**Synthesis of *N*-nosyl-amide 199:**

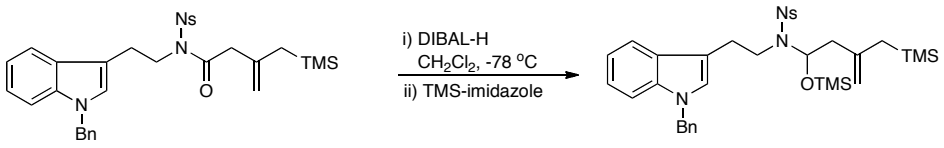



**149** **199**

A solution of amide **149** (0.537 g, 1.33 mmol) in THF (6.0 mL) was cooled to -78 °C. Freshly prepared LiHMDS solution (0.33 M in THF, 3.93 mL, 1.30 mmol) was cooled to -78 °C and added to the staring material solution *via* cannula. The reaction was stirred for 1 h at 78 °C. In a separate flask, a solution of nosyl chloride (0.411 g, 1.86 mmol) in THF (4.0 mL) was cooled to 0 °C and added into the reaction mixture *via* cannula. The mixture was stirred for 16 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (2 mL) and warmed to 0 °C. $H_2O$ (6 mL) was added, and the mixture was stirred for 5 minutes. The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (2 x 6 mL). The organic extracts were combined, washed with brine (20 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (20:1 to 9:1 hexanes:EtOAc) afforded compound **199** as a crystalline yellow oil (0.216 g, 27%); $\mathbf{R_f}$ 0.59 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 400 MHz) δ 8.32 (d, 2H, *J* = 9.2 Hz), 8.15 (d, 2H, *J* = 9.2 Hz), 7.69 (d, 1H, *J* = 8.0, 0.4 Hz), 7.33-7.26 (m,

4H), 7.23-7.09 (m, 4H), 6.99 (s, 1H), 5.27 (s, 2H), 4.62 (s, 1H), 4.34 (s, 1H), 4.10 (t, 2H, $J$ = 7.2 Hz), 3.26 (t, 2H, $J$ = 7.2 Hz), 2.85 (s, 2H), 1.38 (s, 2H), -0.10 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 171.2, 150.6, 145.2, 139.7, 137.4, 136.9, 129.9, 129.0, 128.0, 127.9, 127.1, 127.1, 124.1, 122.5, 119.9, 118.9, 111.8, 110.6, 110.3, 50.3, 48.5, 45.4, 27.3, 26.9, -1.3; **IR** (thin film, $cm^{-1}$) 2953.7 (br, w), 1694.5 (w), 1607.0 (w), 1531.0 (m), 1348.6 (m), 1169.1 (m), 907.0 (m), 850.1 (m), 726.0 (s); **m.p.** 92.5-93.5 °C; **HRMS** (+APCI) calculated for $C_{31}H_{36}N_3O_5SSi$ 590.2145, found 590.2142 $[M+H]^+$.

**Synthesis of *N*-nosyl-*O*-TMS-aminol 193:**

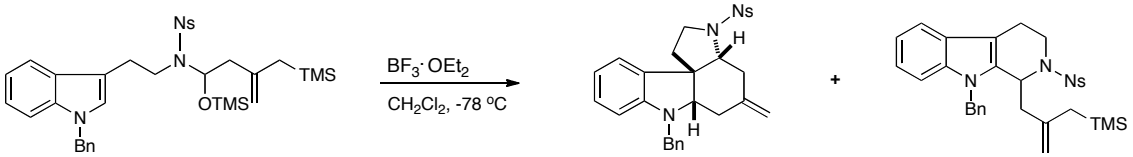



**199** **193**

A solution of tosylamide **199** (0.034 g, 0.058 mmol) in $CH_2Cl_2$ (0.6 mL) was cooled to -78 °C. DIBAL-H (1.0 M in $CH_2Cl_2$, 0.12 mL, 0.12 mmol) was added dropwise over 30 minutes. The reaction mixture was stirred for 20 minutes, then trimethylsilyl imidazole (50 μL, 0.23 mmol) was added dropwise. The mixture was warmed to -25 °C and stirred for 20 h. The mixture was warmed to 0 °C and stirred for 2 h. The reaction was quenched by slow addition of aqueous 15% Rochelle's salt solution (1 mL). The biphasic mixture was transferred to a 25 mL Erlenmeyer flask, and $Et_2O$ (4 mL) was added. The mixture was stirred vigorously at r.t. until both layers were clear. The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (2 x 1 mL). The organic extracts were combined, washed with brine (5 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (4:1 hexanes/EtOAc, silica gel

deactivated with 1% $Et_3N$) afforded *N*-tosyl-*O*-TMS-aminol **193** as a yellow oil (7.7 mg, 20%); $\mathbf{R_f}$ 0.58 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 400 MHz) δ 8.29 (d, *J* = 9.2 Hz, 2H), 8.03 (d, *J* = 9.2 Hz, 2H), 7.69 (d, 1H, *J* = 7.6 Hz), 7.36-7.25 (m, 4H), 7.21 (t, 1H, *J* = 7.6 Hz), 7.18-7.09 (m, 3H), 6.96 (s, 1H), 5.63 (dd, 1H, *J* = 7.2, 5.0 Hz), 5.28 (s, 2H), 4.65 (s, 1H), 4.61 (s, 1H), 3.55 (ddd, 1H, *J* = 14.8, 11.6, 5.2 Hz), 3.42 (ddd, 1H, *J* = 14.8, 11.6, 5.2), 3.25 (dt, 1H, *J* = 12.6, 4.8), 3.12 (dt, 1H, *J* = 12.6, 4.8 Hz), 2.37 (dd, 1H, *J* = 13.6, 7.2 Hz), 2.14 (dd, 1H, *J* = 13.6, 5.0 Hz), 1.59 (d, 1H, *J* = 13.2 Hz), 1.44 (d, 1H, *J* = 13.2 Hz), 0.17 (s, 9H), 0.01 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 149.9, 147.1, 142.1, 137.7, 136.9, 129.0, 128.6, 128.0, 127.9, 127.1, 126.3, 124.3, 122.2, 119.5, 119.2, 112.4, 111.7, 110.1, 82.4, 50.1, 45.8, 44.5, 27.7, 27.4, 0.39, -1.20; **IR** (thin film, $cm^{-1}$) 2954.2 (br, w). 1530.5 (s), 1467.0 (w), 1453.7 (w), 1347.8 (s), 1250.0 (m), 1164.0 (s), 933.4 (m), 846.9 (s), 739.2 (s); **HRMS** (+APCI) calculated for $C_{34}H_{45}N_3O_5SSi_2$ 663.2618, found 663.2616 $[M]^+$.

**Synthesis tetracyclic amine 197:**

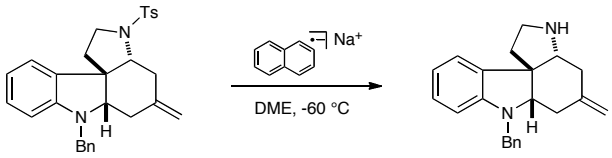



**193** **197** **198**

A solution of *N*-nosyl-*O*-TMS-aminol **193** (0.042 g, 0.064 mmol) in $CH_2Cl_2$ (1.3 mL) was cooled to -78 °C. $BF_3{\cdot}OEt_2$ (39 μL, 0.32 mmol) was added dropwise and the mixture was stirred at -78 °C for 3 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (1 mL). The resulting biphasic mixture was warmed to 0 °C and stirred vigorously for 15 minutes. The organic layer was separated, and the aqueous layer was

extracted with $CH_2Cl_2$ (2 x 1 mL). The organic extracts were combined, washed with brine (3 mL), dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (9:1 hexanes/EtOAc) afforded tetracyclic amine **197** as a yellow oil (0.010 g, 31%); $\mathbf{R_f}$ 0.53 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) δ 8.43 (d, 2H, *J* = 9.0 Hz), 8.04 (d, 2H, *J* = 9.0 Hz), 7.37-7.29 (m, 6H), 7.11 (t, 1H, *J* = 7.5 Hz), 6.73 (t, 1H, *J* = 7.5 Hz), 6.42 (d, 1H, *J* = 7.8 Hz), 4.79 (s, 1H), 4.71 (s, 1H), 4.45 (d, 1H, *J* = 15.0 Hz), 4.10 (d, 1H, *J* = 15.0 Hz), 3.74 (dt, 1H, *J* = 10.8, 7.2 Hz), 3.44 (t, 1H, *J* = 10.2 Hz), 3.40 (t, 1H, *J* = 12.0 Hz), 3.09-3.04 (m, 2H), 2.55-2.50 (m, 1H), 2.29 (dd, 1H, *J* = 14.1, 5.7 Hz), 2.06 (dd, 1H, *J* = 13.8 Hz, 6.0 Hz), 1.96 (dd, 1H, *J* = 12.3, 6.9 Hz), 1.52 (q, 1H, *J* = 11.4 Hz); **IR** (thin film, $cm^{-1}$) 2921.8 (m), 2851.0 (w), 1699.4 (w), 1604.0 (w), 1529.2 (s), 1463.9 (w), 1350.0 (m), 1166.7 (s), 736.6 9m), 621.6 (m); **HRMS** (+APCI) calculated for $C_{28}H_{28}N_3O_4S$ 502.1801, found 502.1800 $[M + H]^+$; and tetrahydro-*β*-carboline **198** as a amorphous yellow solid (6.7 mg, 19%); $\mathbf{R_f}$ 0.55 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) δ 8.00 (d, 2H, *J* = 8.7 Hz), 7.61 (d, *J* = 8.7 Hz, 1H), 7.37-7.32 (m, 4H), 7.26 (d, 1H, *J* = 8.1 Hz), 7.18 (t, 1H, *J* = 7.6 Hz), 7.08 (t, 1H, *J* = 7.4 Hz), 7.00-6.99 (m, 2H), 5.47 (d, 1H, *J* = 17.0 Hz), 5.24 (dd, 1H, *J* = 10.0, 3.6 Hz), 5.21 (d, 1H, *J* = 16.9 Hz), 4.73 (s, 1H), 4.69 (s, 1H), 4.15 (dd, 1H, *J* = 15.1, 6.5 Hz), 3.58 (ddd, 1H, *J* = 14.9, 12.2, 5.1 Hz), 2.65 (dd, 1H, *J* = 15.8, 5.1 Hz), 2.52-2.46 (m, 2H), 2.38 (dd, 1H, *J* = 14.4, 3.5 Hz), 1.69 (d, *J* = 13.7 Hz, 1H), 1.55 (d, *J* = 13.7 Hz, 1H), 0.01 (s, 9H); **IR** (thin film, $cm^{-1}$) 2922.2 (w), 2852.1 (w), 1634.0 (w), 1605.6 (w), 1528.5 (m), 1463.5 (w), 1453.3 (w), 1346.4 (s), 1247.6 (w), 1161.1 (s), 853.3 (s), 737.3 (s); **HRMS** (+APCI) calculated for $C_{31}H_{36}N_3O_4SSi$ 574.2196, found 574.2197 $[M]^+$.

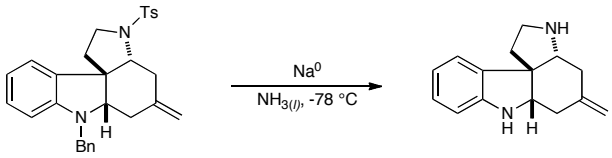
**Synthesis of Monoamine 217:**




**195** **217**

DME (4.4 mL) was added to a flask charged with naphthalene (0.728 g, 5.68 mmol) and sodium metal (0.106 g, 4.61 mmol). The resuling dark green mixture was stirred at r.t. for 1 h. In a separate flask, a solution of tetracyclic amine **195** (0.017 g, 0.035 mmol) in DME (1.7 mL) was cooled to -60 °C. The sodium napthalide solution (0.9 mL) was added slowly by syringe until the clear starting material solution turned green. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (0.3 mL). The resulting mixture was warmed to r.t. and stirred vigorously for 15 minutes. The organic layer was separated, and the aqueous layer was extracted with $CH_2Cl_2$ (2 x 1 mL). The organic extracts were combined, washed with brine (2 mL), dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (17:3 $CH_2Cl_2$/methanol) afforded monoamine **217** as a pale yellow oil (7.3 mg, 65%); $\mathbf{R_f}$ 0.35 (17:3 $CH_2Cl_2$/methanol); $^{1}$**H NMR** ($CDCl_3$, 400 MHz) δ 7.48 (d, 1H, *J* = 7.2 Hz), 7.40-7.27 (m, 5H), 7.08 (dt, 1H, *J* = 8.0, 1.2 Hz), 6.73 (t, 1H, *J* = 7.6 Hz), 6.38 (d, 1H, *J* = 8.0 Hz), 4.73 (s, 1H), 4.72 (s, 1H), 4.46 (d, 1H, *J* = 15.2 Hz), 4.19 (d, 1H, *J* = 15.2 Hz), 3.61 (t, 1H, *J* = 6.0 Hz), 3.52-3.42 (m, 2H), 3.39 (dd, 1H, *J* = 12.8, 4.8 Hz), 2.70 (dd, 1H, *J* = 13.2, 4.4 Hz), 2.47-2.34 (m, 2H), 2.13-1.97 (m, 3H); $^{13}$**C NMR** ($CDCl_3$, 100 MHz) δ 150.8, 142.2, 138.4, 131.4, 128.8, 128.5, 127.7, 127.4, 124.8, 118.1, 113.0, 107.7, 67.6, 61.2, 54.7, 49.2, 43.5, 43.5, 38.3, 34.2, 34.0; **IR** (thin film, $cm^{-1}$) 3400.0 (br, w), 3027.8 (w), 2924.2 (m), 1600.0 (s), 1492.3 (m), 1475.0 (m), 1451.7 9 (w), 1352.8 (w), 906.8 (m), 732.8 (s); **HRMS** (+APCI) calculated for $C_{22}H_{25}N_2$ 317.2018, found 317.2014 $[M+H]^+$.

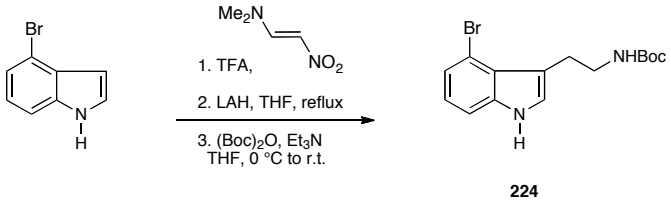
**Synthesis of diamine 218:**




**195** **218**

Sodium was added slowly to liquid ammonia (5.0 mL) at -78 °C until the color of the mixture remained dark blue. A solution of tetracyclic amine **195** (0.034 g, 0.072 mmol) in THF (0.8 mL) was added slowly to the sodium/liquid ammonia mixture. The reaction was stirred for 2.0 h at -78 °C. The reaction was quenched with $NH_4Cl$ (0.5 g), and the flask was allowed to reach r.t. in order to allow the ammonia to fully evaporate. $CH_2Cl_2$ (5 mL) was added to the residue, and the suspension was filtrated through a fritted funnel. The filtered cake was washed with $CH_2Cl_2$ (3 x 3 mL). The organic filtrate was concentrated *in vacuo*. Purification by chromatography on silica gel (90:10:1 $CH_2Cl_2$/methanol/$NH_4OH$) afforded diamine **218** as a colorless oil (0.011 g, 68%); **$R_f$** 0.18 (90:10:1 $CH_2Cl_2$/methanol/$NH_4OH$); **$^1$H NMR** ($CDCl_3$, 400 MHz) δ 7.27 (d, 1H, *J* = 7.2 Hz), 7.05 (dt, 1H, *J* = 7.6, 1.2 Hz), 6.74 (dt, 1H, *J* = 7.2, 1.2 Hz), 6.64 (dd, 1H, *J* = 7.6, 0.4 Hz), 4.70 (s, 1H), 4.65 (s, 1H), 3.69 (t, 1H, *J* = 8.4 Hz), 3.53-3.36 (m, 2H), 3.36-3.20 (m, 3H), 2.59-2.52 (m, 2H), 2.19 (t, 1H, *J* = 13.2 Hz), 2.00-1.91 (m, 3H); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) δ 150.6, 143.2, 132.3, 128.0, 125.5, 119.2, 111.6, 110.4, 63.4, 61.6, 55.4, 43.8, 40.5, 39.1, 34.6; **IR** (thin film, $cm^{-1}$) 3269.4 (br, w), 3069.6 (w), 2921.8 (m), 2867.6 (m), 1645.8 (w), 1603.5 (m), 1480.7 (m), 1462.4 (s), 1309.5 (w), 1265.3 (w), 889.0 (m), 745.5 (s); **HRMS** (+APCI) calculated for $C_{15}H_{19}N_2$ 227.1548, found 227.1542 $[M+H]^+$.

**Synthesis of carbamate 224**

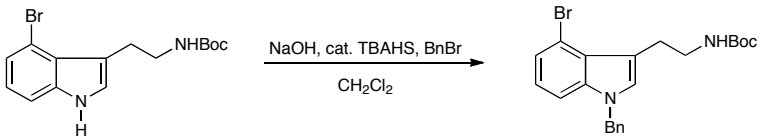



**224**

TFA (1.4 mL) was added slowly to a stirring suspension of 4-bromoindole (0.592 g, 3.02 mmol) and 2-dimethylamino-nitroethylene (0.351 g, 3.02 mmol). The resulting dark red suspension was stirred for 3.5 h. The reaction was quenched by slow addition into a stirring solution of saturated $NaHCO_3$ (18 mL) pre-cooled to 0 °C. The orange suspension was stirred at r.t. for 15 minutes, then it was extracted with EtOAc (3 x 25 mL), washed with brine, dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo*. The crude reaction mixture was dissolved in THF (20 mL) and cooled to 0 °C. LAH (2.0 M in THF, 9.05 mL, 18.1 mmol) was added over 30 minutes, and the dark red suspension was refluxed for 16 hours. The resulting orange suspension was cooled to 0 °C, and was quenched with saturated Rochelle's salt solution (8.0 mL). The mixture was filtrated through celite, and the filtered cake was washed with EtOAc (3 x 35 mL). The organic layer was separated, washed with brine (100 mL), dried over $Na_2SO_4$, and concentrated *in vacuo*. Crude 4-bromotryptamine was dissolved in THF (8.0 mL). Triethylamine (0.63 mL, 4.53 mmol) was added, and the resulting solution was cooled to 0 °C. A solution of di-*tert*-butyl carbonate (0.657 g, 3.02 mmol) in THF (2.0 mL) was added *via* cannula, and the mixture was stirred at r.t for 12 h. Aqueous 0.1 M HCl (5 mL) was added, and the mixture was stirred for 5 minutes. The organic layer was separated, and the aqueous layer was extracted with $CH_2Cl_2$ (3 x 5 mL). The organic extracts were combined, washed with brine (20 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo.*

Purification by chromatography on silica gel (9:1 → 3:2 hexanes/EtOAc) afforded carbamate **224** as a brown oil (0.514 g, 50%, over three steps); $\mathbf{R_f}$ 0.13 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) δ 8.14 (s, 1H), 7.32 (dd, 1H, *J* = 7.8, 0.6 Hz), 7.28 (d, 1H, *J* = 7.8 Hz), 7.10 (s, 1H), 7.02 (t, 1H, *J* = 7.8 Hz), 4.67 (s, 1H), 3.53-3.48 (m, 2H), 3.23-3.18 (t, 2H, *J* = 6.6 Hz), 1.45 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) δ 156.4, 138.0, 125.4, 124.4, 123.8, 122.8, 114.2, 113.5, 110.9, 79.5, 42.4, 28.6, 26.7; **IR** (thin film, $cm^{-1}$) 3420.3 (br, w), 3293.9 (br, w), 2976.4 (w), 2930.5 (w), 1686.0 (s), 1507.7 (m), 1365.4 (w), 1333.9 (w), 1246.0 (m), 1161.8 (s), 907.0 (m), 729.0 (s); **HRMS** (+APCI) calculated for $C_{11}H_{10}BrN_2O$ 264.9977, found 264.9971 $[M - O^tBu]^+$.

**Synthesis of tryptamine 234:**

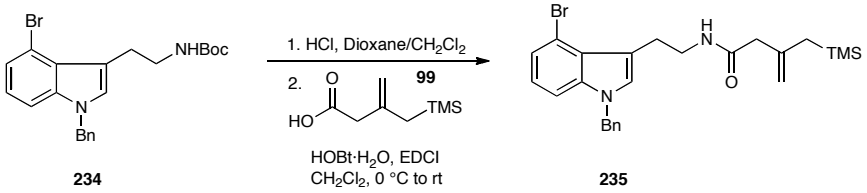



**224** **234**

Powdered NaOH (0.152 g, 3.80 mmol) and TBAHS (0.026 g, 0.076 mmol) were added to a solution of carbamate **224** (0.514 g, 1.52 mmol) in $CH_2Cl_2$ (15.0 mL), and the resulting suspension was stirred for 10 minutes. Benzyl bromide (0.200 mL, 1.67 mmol) was added dropwise and the reaction was vigorously stirred for 18 h. $H_2O$ (15 mL) was added, and the mixture was stirred for 10 minutes. The organic layer was separated, and the aqueous layer was extracted with $CH_2Cl_2$ (2 x 15 mL). The organic extracts were combined, washed with brine (40 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (9:1 → 4:1 hexanes/EtOAc) afforded tryptamine **234** as a brown oil (0.571 g, 87%); $\mathbf{R_f}$ 0.38 (7:3 hexanes/EtOAc); **$^1$H NMR**

($CDCl_3$, 400 MHz) δ 7.33-7.25 (m, 4H), 7.20 (d, 1H, *J* = 8.0 Hz), 7.10-7.08 (m, 2H), 7.02 (s, 1H), 7.00 (t, 1H, *J* = 8.0 Hz), 5.26 (s, 2H), 4.68-4.65 (br s, 1H), 3.50 (q, 2H, *J* = 6.8 Hz), 3.20 (t, 2H, *J* = 6.8 Hz), 1.43 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 156.2, 138.2, 137.1, 129.0, 128.5, 128.0, 126.9, 126.1, 123.9, 122.7, 114.6, 113.3, 109.3, 79.2, 50.3, 42.2, 28.6, 26.6; **IR** (thin film, $cm^{-1}$) 3350.0 (br, w), 2974.9 (w), 2929.4 (w), 1696.8 (s), 1496.6 (m), 1451.3 (w), 1433.6 (w), 1391.3 (w), 1364.8 (w), 1326.9 (w), 1248.3 (m), 1169.7 (s), 733.7 (m); **HRMS** (+APCI) calculated for $C_{22}H_{25}BrN_2O_2$ 428.1099, found 428.1095 $[M]^+$.

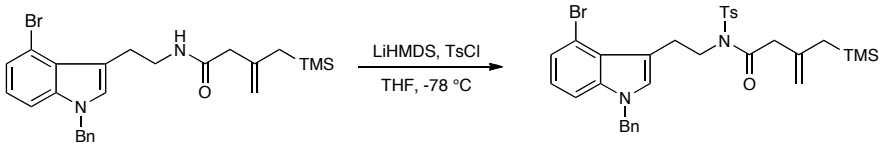
**Synthesis of amide 235:**




A solution of compound tryptamine **234** (0.571 g, 1.33 mmol) in $CH_2Cl_2$ (5.0 mL) was cooled to 0 °C. Hydrochloric acid (4.0 M in dioxane, 9.0 mL) was added dropwise, and the resulting mixture was stirred at 0 °C for 30 minutes, warmed to r.t. and stirred for 3 hours. The mixture was concentrated in vacuo. The crude hydrochloride salt was added to a stirring solution of $HOBt{\cdot}H_2O$ (0.183 g, 1.36 mmol) in $CH_2Cl_2$ (13.6 mL). The resulting mixture was stirred at r.t. for 5 minutes and then cooled to 0 °C. Carboxylic acid **99** (0.23 mL, 1.29 mmol) was added dropwise, followed by dropwise addition of EDCI (0.24 mL, 1.36 mmol) over 20 minutes. The reaction was stirred at 0 $^oC$ for 1 h, warmed to r.t. and stirred for 24 h. $Et_2O$ (27 mL) was added, and the reaction was stirred for 15 minutes. The mixture was washed with 0.1 M aqueous HCl (2 x 20 mL), saturated aqueous

$NaHCO_3$ (2 x 20 mL), and brine (20 mL). The organic layer was dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (4:1 → 7:3 hexanes/EtOAc) afforded amide **235** as a crystalline white solid (0.448 g, 70% over two steps); $\mathbf{R_f}$ 0.33 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 400 MHz) δ 7.35-7.27 (m, 4H), 7.22 (d, 1H, *J* = 6.4 Hz), 7.09 (dd, 2H, *J* = 7.6, 1.2 Hz), 7.04-6.95 (m, 2H), 6.14 (t, 1H, *J* = 5.2 Hz), 5.24 (s, 2H), 4.71 (d, 1H, *J* = 1.2 Hz), 4.68 (d, 1H, *J* = 1.2 Hz), 3.66 (q, 2H, *J* = 6.4 Hz), 3.25 (t, 2H, *J* = 6.4 Hz), 2.91 (s, 2H), 1.52 (s, 2H), 0.05 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 170.3, 142.4, 138.0, 136.9, 128.9, 128.3, 127.9, 126.8, 126.0, 123.8, 122.7, 114.5, 113.0, 112.6, 109.3, 50.1, 47.0, 41.0, 26.8, 25.9, -1.4; **IR** (thin film, $cm^{-1}$) 3292.5 (br, w), 3066.9 (w), 2951.2 (w), 1645.1 (m), 1548.1 (m), 1432.7 (m), 1327.5 (w), 1246.5 (m), 1171.8 (m), 838.4 (s), 731 (s), 696.7 (m); **m.p.** 80-81 °C; **HRMS** (+ESI) calculated for $C_{25}H_{32}BrN_2OSi$ 483.1467, found 483.1459 $[M+H]^+$.

**Synthesis of amide 229:**

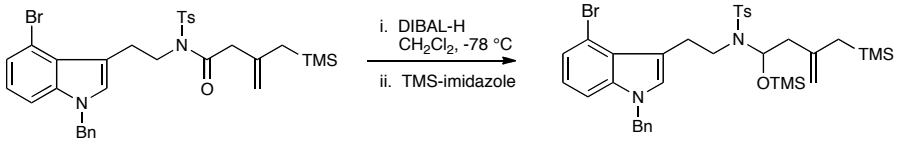



**235** **229**

A solution of amide **235** (0.448 g, 0.927 mmol) in THF (2.6 mL) was cooled to -78 °C. A freshly prepared LiHMDS solution (0.33 M in THF, 2.7 mL, 0.881 mmol) was cooled to -78 °C and added to the starting material solution *via* cannula. The reaction was stirred for 1 h at -78 °C. In a separate flask, a solution of tosyl chloride (0.248 g, 1.30 mmol) in THF (1 mL) was cooled to 0 °C and added into the reaction mixture *via* cannula. The mixture was stirred at -78 °C for 12 h. The reaction was quenched with saturated aqueous

$NaHCO_3$ (0.5 mL) and warmed to 0 °C. $H_2O$ (2 mL) was added, and the mixture was stirred for 5 minutes. The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (2 x 2 mL). The organic extracts were combined, washed with brine (6.0 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (9:1 → 7:3 hexanes/EtOAc) afforded tosylamide **229** as a colorless oil (0.193 g, 33%); $\mathbf{R_f}$ 0.44 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 400 MHz) δ 7.90 (d, 2H, *J* = 8.4 Hz), 7.34-7.24 (m, 6H), 7.21 (dd, 1H, *J* = 8.0, 0.4 Hz), 7.10-7.07 (m, 3H), 6.98 (t, 1H, *J* = 8.0 Hz), 5.23 (s, 2H), 4.59 (s, 1H), 4.31 (s, 1H), 4.21 (t, 2H, *J* = 6.4 Hz), 3.50 (t, 2H, *J* = 6.4 Hz), 2.73 (s, 2H), 2.42 (s, 3H), 1.36 (s, 2H), -0.14 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 171.2, 144.6, 139.9, 137.8, 136.8, 136.8, 130.0, 129.5, 129.0, 128.5, 127.9, 126.8, 126.0, 124.0, 122.8, 114.2, 111.6, 111.4, 109.6, 50.4, 49.3, 45.4, 27.2, 27.0, 21.7, -1.5; **IR** (thin film, $cm^{-1}$) 2952.1 (w), 1689.9 (m), 1635.0 (w), 1596.9 (w), 1451.3 (w), 1433.7 (w), 1349.6 (m), 1247.5 (m), 1161.4 (s), 842.5 (s), 730.9 (s), 681.2 (m); **HRMS** (+ESI) calculated for $C_{32}H_{38}BrN_2O_3SSi$ 637.1556, found 637.1566 $[M+H]^+$.

**Synthesis of *N*-tosyl-*O*-TMS-aminol 219:**

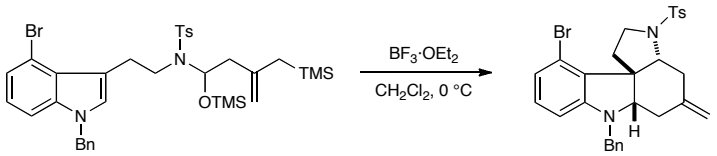



**229** **219**

A solution of tosylamide **229** (0.193 g, 0.305 mmol) in $CH_2Cl_2$ (3.0 mL) was cooled to -78 °C. DIBAL-H (1.0 M in $CH_2Cl_2$, 0.61 mL, 0.61 mmol) was added dropwise over 30 minutes. The reaction mixture was stirred for 20 minutes, then trimethylsilyl imidazole

(0.13 mL, 0.914 mmol) was added dropwise. The mixture was warmed to -25 $^{o}$C and stirred for 20 hrs. The mixture was warmed to 0 °C and stirred for 2 h. The reaction was quenched by slow addition of aqueous 15% Rochelle's salt solution (3 mL). The biphasic mixture was transferred to a 25 mL Erlenmeyer flask, and $Et_2O$ (6 mL) was added. The mixture was stirred vigorously at r.t. until both layers were clear. The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (2 x 3 mL). The organic extracts were combined, washed with brine (5 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (9:1 → 7:3 pentane/$Et_2O$, silica gel deactivated with 1% $Et_3N$) afforded *N*-tosyl-*O*-TMS-aminol **219** as a colorless oil (0.137 g, 63%); $\mathbf{R_f}$ 0.69 (7:3 hexanes/EtOAc); **$^{1}$H NMR** ($CDCl_3$, 400 MHz) δ 7.75 (d, 2H, *J* = 8.0 Hz), 7.36-7.23 (m, 6H), 7.19 (d, 1H, *J* = 7.6 Hz), 7.13-7.07 (m, 2H), 7.05 (s, 1H), 6.98 (t, 1H, *J* = 8.0 Hz), 5.55 (dd, 1H, *J* = 8.4, 4.0 Hz), 5.27 (s, 2H), 4.64 (s, 1H), 4.60 (s, 1H), 3.55 (m, 3H), 3.27 (m, 1H), 2.39 (m, 4H), 2.00 (dd, 1H, *J* = 13.2, 4.0 Hz), 1.58 (d, 1H, *J* = 13.6 Hz), 1.4 (d, 1H, 13.6 Hz), 0.15 (s, 9H), -0.01 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 143.1, 142.7, 138.6, 137.9, 137.1, 129.7, 129.0, 128.5, 127.9, 127.3, 126.9, 126.3, 123.8, 122.7, 114.4, 113.9, 111.1, 109.3, 82.1, 50.3, 45.6, 28.2, 27.1, 21.6, 0.3, -1.3; **IR** (thin film, cm$^{-1}$) 2954 (w), 1635.3 (w), 1604.7 (w), 1495.7 (w), 1474.8 (w), 1451.7 (w), 1434.2 (w), 1337.8 (m), 1249.3 (m), 1160.7 (m), 845.5 (s); **HRMS** (+ESI) calculated for $C_{32}H_{38}BrN_2O_2SSi$ 621.1607, found 621.1669 [M-OTMS]$^{+}$.

**Synthesis of tetracyclic amine 243:**

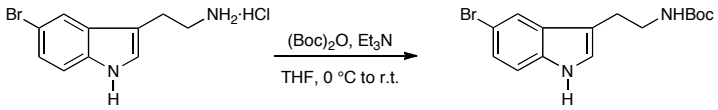



**219** **243**

A soluton of *N*-tosyl-*O*-TMS-aminol **219** (0.071 g, 0.109 mmol) in $CH_2Cl_2$ (3.0 mL) was cooled to 0 °C. $BF_3{\cdot}OEt_2$ (19 uL, 0.16 mmol) was added dropwise and the mixture was stirred at 0 °C for 2 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (3 mL). The resulting biphasic mixture was stirred vigorously for 15 minutes. The organic layer was separated, and the aqueous layer was extracted with $CH_2Cl_2$ (2 x 3 mL). The organic extracts were combined, washed with brine (5 mL), dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (4:1 hexanes/EtOAc) afforded the tetracyclic amine **243** as a crystalline white solid (0.026 g, 44%); $\mathbf{R_f}$ 0.54 (7:3 hexanes/EtOAc); $^{1}$**H NMR** ($CDCl_3$, 600 MHz) δ 7.71 (d, 2H, *J* = 7.8 Hz), 7.38-7.26 (m, 7H), 6.94-6.89 (m, 2H), 6.34 (d, 1H, *J* = 6.6 Hz), 4.87 (s, 1H), 4.70 (s, 1H), 4.37 (d, 1H, *J* = 15.0 Hz), 4.03 (d, 1H, *J* = 15.0 Hz), 3.80 (dt, 1H, *J* = 11.4, 6.6 Hz), 3.50 (t, 1H, *J* = 10.8 Hz), 3.22 (dd, *J* = 13.2, 3.6 Hz), 3.19 (t, 1H, *J* = 6.6 Hz), 3.09 (dd, *J* = 13.2, 3.6 Hz), 2.82 (t, 1H, *J* = 13.2 Hz), 2.44 (s, 3H), 2.35 (dd, 1H, *J* = 14.4, 5.4 Hz), 2.03 (dd, 1H, *J* = 12.6, 6.6 Hz), 1.98 (dd, 1H, *J* = 14.4, 7.8 Hz) 1.56 (q, 1H, *J* = 10.8 Hz); $^{13}$**C NMR** ($CDCl_3$, 100 MHz) δ153.1, 143.6, 143.3, 137.7, 133.6, 131.5, 129.9, 129.8, 128.9, 127.8, 127.7, 127.6, 124.5, 118.9, 112.7, 107.4, 69.7, 62.7, 58.6, 49.3, 49.3, 38.4, 36.2, 33.9, 21.8; **IR** (thin film, $cm^{-1}$) 3029.2 (w), 2925.1 (w), 1591.6 (m), 1562.7 (w), 1448.0 (m), 1433.0 (m), 1346.6 (m), 1333.3 (m), 1158.3 (s), 907.5 (m),

729.1 (s), 664.5 (s); **m.p.** 204.0-206.0 °C; **HRMS** (+ESI) calculated for $C_{29}H_{30}BrN_2O_2S$ 549.1211, found 549.1204 $[M+H]^+$.

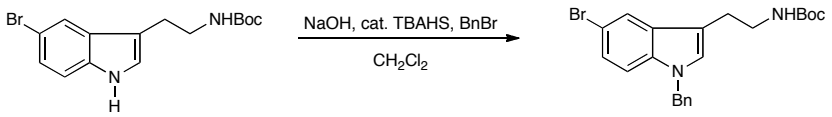
**Synthesis of carbamate 225:**




**225**

A solution of 5-bromotryptamine hydrochloride (0.227 g, 0.823 mmol) and triethylamine (0.30 mL, 2.17 mmol) in THF (13.6 mL) was cooled to 0 °C. A solution of di-*tert*-butyl dicarbonate (0.135 g, 0.823 mmol) in THF (1 mL) was added to the starting material mixture *via* cannula. The reaction was stirred at 0 °C for 10 minutes, warmed to r.t. and stirred for 12 h. The mixture was concentrated *in vacuo*. Purification by chromatography on silica gel (7:3 hexanes/EtOAc) afforded carbamate **225** as a colorless oil (0.278 g, 99%); $\mathbf{R_f}$ 0.36 (3:2 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 400 MHz) δ 8.22 (br s, 1H), 7.72 (d, 1H, $J$ = 2.0 Hz), 7.28 (dd, 1H, $J$ = 8.8, 2.0 Hz), 7.24 (d, 1H, $J$ = 8.8 Hz), 7.03 (s, 1H), 4.63 (br s, 1H), 3.44 (q, 2H, $J$ = 6.8 Hz), 2.91 (t, 2H, $J$ = 6.8 Hz), 1.45 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 156.3, 135.1, 129.3, 124.8, 123.6, 121.4, 112.9, 112.7, 112.6, 79.6, 41.2, 28.6, 25.8; **IR** (thin film, $cm^{-1}$) 3422.3 (br, w), 3304.2 (br, w), 2976.3 (w), 2930.4 (w), 1685.5 (s), 1507.4 (m), 1456.6 (m), 1365.3 (m), 1248.2 (m), 1161.0 (s), 907.2 (w), 793.2 (m), 730.0 (s); **HRMS** (+APCI) calculated for $C_{15}H_{19}BrN_2O_2$ 338.0630, found 338.0629 $[M]^+$.

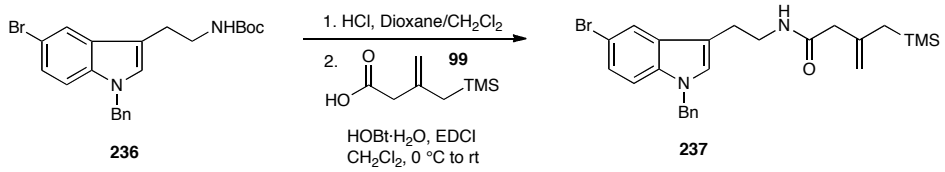
**Synthesis of tryptamine 236:**




**225** **236**

Powdered NaOH (0.260 g, 6.50 mmol) and TBAHS (0.044 g, 0.13 mmol) were added to a solution of carbamate **225** (0.831 g, 2.60 mmol) in $CH_2Cl_2$ (26.0 mL), and the resulting suspension was stirred for 10 minutes. Benzyl bromide (0.34 mL, 2.9 mmol) was added dropwise and the reaction was vigorously stirred for 18 h. $H_2O$ (20 mL) was added, and the mixture was stirred for 10 minutes. The organic layer was separated, and the aqueous layer was extracted with $CH_2Cl_2$ (2 x 10 mL). The organic extracts were combined, washed with brine (30 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (9:1 → 4:1 hexanes/EtOAc) afforded tryptamine **236** as a crystalline white solid (0.987 g, 81%); $\mathbf{R_f}$ 0.40 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 400 MHz) δ 7.72 (dd, 1H, *J* = 2.0, 0.4 Hz), 7.33-7.27 (m, 3H), 7.25 (dd, 1H, *J* = 8.8, 2.0 Hz), 7.12 (d, 1H, *J* = 8.8 Hz), 7.10-7.07 (m, 2H), 6.97 (s, 1H), 5.26 (s, 2H), 4.60 (br s, 1H), 3.43 (q, 2H, *J* = 6.8 Hz), 2.91 (t, 2H, *J* = 6.8 Hz), 1.45 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 156.0, 137.2, 135.4, 130.0, 128.9, 127.9, 127.5, 126.8, 124.8, 121.8, 112.7, 112.3, 111.4, 79.3, 50.2, 41.2, 28.6, 25.8; **IR** (thin film, $cm^{-1}$) 3351.7 (br, w), 2975.1 (w), 2928.6 (w), 1697.1 (s), 1507.6 (m), 1469.4 (m), 1453.4 (w), 1364.9 (m), 1249.2 (m), 1169.4 (s), 789.6 (w); **m.p.** 89.5-90.5 °C; **HRMS** (+APCI) calculated for $C_{22}H_{25}BrN_2O_2$ 428.1099, found 428.1094 $[M]^+$.

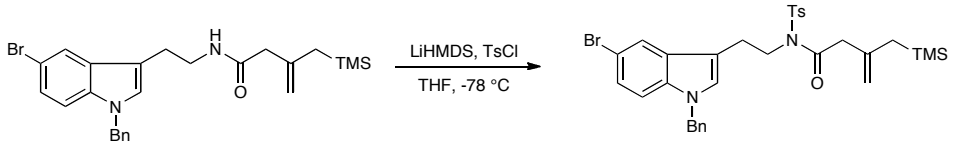
**Synthesis of amide 236:**




A solution of tryptamine **236** (0.987 g, 2.30 mmol) in $CH_2Cl_2$ (7.0 mL) was cooled to 0 °C. Hydrochloric acid (4.0 M in dioxane, 16.0 mL) was added dropwise, and the resulting mixture was stirred at 0 °C for 30 minutes, warmed to r.t. and stirred for 3 h. The mixture was concentrated *in vacuo*. The crude hydrochloride salt was added to a stirring solution of HOBt·$H_2O$ (0.311 g, 2.30 mmol) in $CH_2Cl_2$ (22.0 mL). The resulting mixture was stirred at r.t. for 5 minutes and then cooled to 0 °C. Carboxylic acid **99** (0.39 mL, 2.19 mmole) was added dropwise, followed by dropwise addition of EDCI (0.41 mL, 2.30 mmole) over 20 minutes. The reaction was stirred at 0 °C for 1 h, warmed to r.t. and stirred for 24 h. $Et_2O$ (40 mL) was added, and the reaction was stirred for 15 minutes. The mixture was washed with 0.10 M aqueous HCl (2 x 50 mL), saturated aqueous $NaHCO_3$ (2 x 50 mL), and brine (50 mL). The organic layer was dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (4:1 → 7:3 hexanes/EtOAc) afforded amide **237** as a crystalline white solid (0.742 g, 67% over two steps); $\mathbf{R_f}$ 0.16 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 400 MHz) δ 7.72 (d, 1H, *J* = 2.0 Hz), 7.34-7.27 (m, 3H), 7.25 (dd, 1H, *J* = 8.8, 2.0 Hz), 7.13 (d, 1H, *J* = 8.8 Hz), 7.10-7.06 (m, 2H), 6.96 (s, 1H), 5.96 (s, 1H), 5.26 (s, 2H), 4.66 (s, 1H), 4.64 (s, 1H), 3.55 (q, 2H, *J* = 6.8 Hz), 2.92 (t, 2H, *J* = 6.8 Hz), 2.88 (s, 2H), 1.45 (s, 2H), 0.01 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 170.4, 142.5, 137.1, 135.4, 129.9, 129.0, 128.0, 127.4, 126.8, 124.9, 121.6, 112.8, 112.7, 112.1, 111.4, 50.2, 47.0, 40.0, 26.8, 25.1, -1.4; **IR** (thin film,

$cm^{-1}$) 3294.9 (br, w), 3074.0 (w), 2951.7 (w), 1646.4 (s), 1522.3 (m), 1469.3 (m), 1247.4 (m), 1172.6 (w), 849.3 (s), 789.4 (w), 698.7 (m); **m.p.** 81.0-82.5 °C; **HRMS** (+ESI) calculated for $C_{25}H_{32}BrN_2OSi$ 483.1467, found 483.1453 $[M+H]^+$.

**Synthesis of tosylamide 230:**

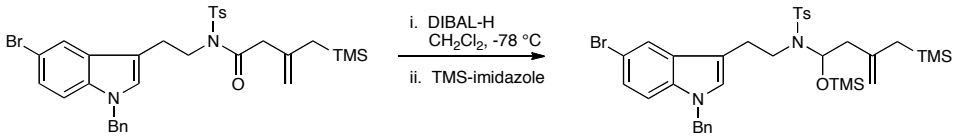



**237** **230**

A solution of amide **237** (0.742 g, 1.53 mmol) in THF (4.0 mL) was cooled to -78 °C. A freshly prepared LiHMDS solution (0.33 M in THF, 4.4 mL, 1.45 mmol) was cooled to -78 °C and added to the starting material solution *via* cannula. The reaction was stirred for 1 h at -78 °C. In a separate flask, a solution of tosyl chloride (0.321 g, 1.68 mmol) in THF (3.0 mL) was cooled to 0 °C and added to the reaction mixture via cannula. The mixture was stirred at -78 °C for 16 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (1 mL) and warmed to 0 °C. $H_2O$ (4 mL) was added, and the mixture was stirred for 5 minutes. The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (2 x 3 mL). The organic extracts were combined, washed with brine (6 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (9:1 → 4:1 hexanes/EtOAc) afforded tosylamide **230** as a colorless oil (0.293 g, 30%); $\mathbf{R_f}$ 0.46 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 400 MHz) δ 7.86-7.81 (m, 3H), 7.34-7.28 (m, 5H), 7.25 (dd, 1H, $J$ = 8.8, 2.0 Hz), 7.12 (d, 1H, $J$ = 8.8 Hz), 7.10-7.06 (m, 2H), 7.00 (s, 1H), 5.24 (s, 2H), 4.66 (s, 1H), 4.46 (s, 1H), 4.03-3.97 (m, 2H), 3.17-3.10 (m, 2H), 3.09 (s, 2H), 2.44 (s, 3H), 1.47 (s, 2H), -0.07 (s, 9H);

**$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 171.1, 145.0, 140.3, 137.1, 136.9, 135.4, 129.9, 129.9, 129.0, 128.2, 128.0, 128.0, 127.0, 125.0, 121.8, 113.0, 111.9, 111.6, 111.1, 50.4, 48.0, 45.8, 27.3, 26.1, 21.8, -1.3; **IR** (thin film, $cm^{-1}$) 2953.3 (w), 1692,7 (m), 1469.7 (m), 1453.1 (w), 1353.2 (s), 1248.2 (w), 1162.3 (s), 1088.3 (w), 848.4 (s), 670.0 (m); **HRMS** (+APCI) calculated for $C_{32}H_{38}BrN_2O_3SSi$ 637.1556, found 637.1554 $[M+H]^+$.

**Synthesis of *N*-tosyl-*O*-TMS-aminol 220**:

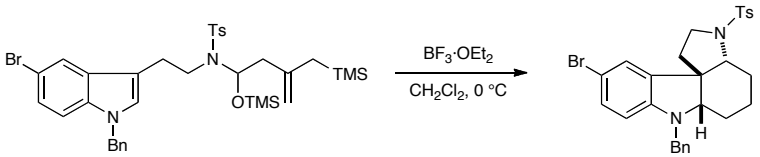



**230** **220**

A solution of tosylamide **230** (0.105 g, 0.165 mmol) in $CH_2Cl_2$ (1.6 mL) was cooled to -78 °C. DIBAL-H (1.0 M in $CH_2Cl_2$, 0.23 mL, 0.23 mmol) was added dropwise over 10 minutes. The reaction mixture was stirred for 1 h, then trimethylsilyl imidazole (73 μL, 0.50 mmol) was added dropwise. The mixture was warmed to -25 °C and stirred for 20 hours. The mixture was warmed to 0 °C and stirred for 2 hours. The reaction was quenched by slow addition of aqueous 15% Rochelle's salt solution (2 mL). The biphasic mixture was transferred to a 25 mL Erlenmeyer flask, and $Et_2O$ (6 mL) was added. The mixture was stirred vigorously at r.t. until both layers were clear. The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (2 x 2 mL). The organic extracts were combined, washed with brine (6 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (20:1 → 4:1 pentane/$Et_2O$, silica gel deactivated with 1% $Et_3N$) afforded *N*-tosyl-*O*-TMS-aminol **220** as a colorless oil (0.76 g, 65%); $\mathbf{R_f}$ 0.57 (7:3 hexanes/EtOAc, silica gel deactivated with

1% $Et_3N$); **$^1$H NMR** ($CDCl_3$, 600 MHz) δ 7.89 (d, 1H, *J* = 1.2 Hz), 7.74 (d, 2H, *J* = 8.4 Hz), 7.34-7.23 (m, 5H), 7.22 (dd, 1H, *J* = 9.0, 1.2 Hz), 7.10-7.04 (m, 3H), 6.93 (s, 1H), 5.54 (dd, 1H, *J* = 8.4, 4.2 Hz), 5.22 (s, 2H), 4.64 (s, 1H), 4.59 (s, 1H), 3.46 (ddd, 1H, *J* = 15.0, 11.4, 5.4 Hz), 3.32 (ddd, 1H, *J* = 15.0, 11.4, 4.8 Hz), 3.13 (td, 1H, *J* = 12.6, 4.8 Hz), 3.06 (td, 1H, *J* = 12.6, 5.4 Hz), 2.39 (s, 3H), 2.28 (dd, 1H, *J* = 13.8, 8.4 Hz), 1.97 (dd, 1H, *J* = 13.8, 4.2 Hz), 1.58 (d, 1H, *J* = 13.2 Hz), 1.39 (d, 1H, *J* = 13.2 Hz), 0.14 (s, 9H), -0.04 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) 143.3, 142.5, 138.4, 137.3, 135.5, 130.0, 129.8, 129.0, 128.0, 127.4, 127.4, 127.0, 124.9, 122.1, 112.8, 112.7, 111.4, 111.4, 81.9, 50.4, 45.8, 43.8, 27.6, 27.2, 21.7, 0.4, -1.3; **IR** (thin film, $cm^{-1}$) 2953.1 (w), 1632.9 (w), 1598.5 (w), 1337.8 (w), 1249.2 (m), 1159.1 (m), 934.5 (w), 841.5 (s), 733.4 (w), 699.7 (w), 660.0 (w), 549.4 (m); **HRMS** (+APCI) calculated for $C_{35}H_{47}BrN_2O_3SSi_2$ 710.2029, found 710.2026 $[M]^+$.

**Synthesis of tetracyclic amine 244**:

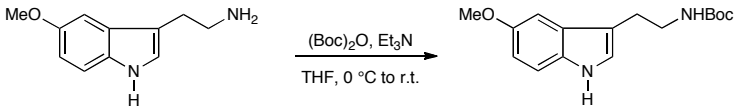



**220** **244**

A solution of *N*-tosyl-*O*-TMS-aminol **220** (0.050 g, 0.070 mmol) in $CH_2Cl_2$ (1.7 mL) was cooled to 0 °C. $BF_3{\cdot}OEt_2$ (13 μL, 0.11 mmol) was added dropwise and the mixture was stirred at 0 °C for 1 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (1.5 mL). The resulting biphasic mixture was stirred vigorously for 15 minutes. The organic layer was separated, and the aqueous layer was extracted with $CH_2Cl_2$ (2 x 2 mL). The organic extracts were combined, washed with brine (4 mL), dried over

anhydrous $Na_2SO_4$, and concentrated *in vacuo*. Purification by chromatography on basic alumina (4:1 hexanes/EtOAc) afforded tetracyclic amine **244** as a crystalline white solid (0.026 g, 68%); $\mathbf{R_f}$ 0.43 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) δ 7.71 (d, 2H, *J* = 7.8 Hz), 7.41 (d, 1H, *J* = 1.8 Hz), 7.34 (d, 2H, *J* = 7.8 Hz), 7.31-7.22 (m, 5H), 7.13 (dd, 1H, *J* = 8.4, 1.8 Hz), 6.20 (d, 1H, *J* = 8.4 Hz), 4.76 (s, 1H), 4.67 (s, 1H), 4.36 (d, 1H, *J* = 15.0 Hz), 4.06 (d, 1H, *J* = 15.0 Hz), 3.61 (dt, 1H, *J* = 10.8, 7.2 Hz), 3.44 (t, 1H, 10.8 Hz), 3.36 (t, 1H, *J* = 5.4 Hz), 3.06 (dd, 1H, *J* = 13.8, 5.4 Hz), 3.00 (dd, 1H, *J* = 12.0, 4.8 Hz), 2.45-2.40 (m, 4H), 2.24 (dd, 1H, *J* = 14.4, 6.0 Hz), 2.00 (dd, 1H, *J* = 14.4, 6.0 Hz), 1.86 (dd, 1H, *J* = 12.0, 7.2 Hz), 1.46 (q, 1H, *J* = 10.8 Hz); **$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 149.6, 144.1, 141.8, 137.7, 133.6, 131.4, 130.1, 128.8, 128.0, 127.8, 127.7, 127.6, 113.4, 109.6, 108.9, 67.3, 62.1, 55.1, 48.9, 47.7, 35.8, 35.4, 33.8, 21.8; **IR** (thin film, $cm^{-1}$) 3029.1 (w), 2950.0 (w), 1693.0 (w), 1596.5 (w), 1486.6 (m), 1452.6 (w), 1350.6 (m), 1161.9 (s), 665.8 (m); **m.p.** 138.5-140.0 °C; **HRMS** (+ESI) calculated for $C_{29}H_{30}BrN_2O_2S$ 549.1211, found 549.1195 $[M+H]^+$.

**Synthesis of carbamate 226:**

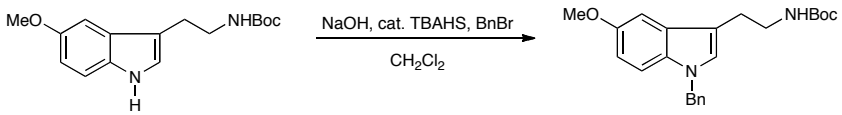



**226**

A solution of 5-methoxytryptamine (0.224 g, 1.18 mmol) and triethylamine (0.25 mL, 1.77 mmol) in THF (12.0 mL) was cooled to 0 °C. A solution of di-*tert*-butyl carbonate (0.257 g, 1.18 mmol) in THF (1.0 mL) was added to the starting material mixture *via* cannula. The reaction was stirred at 0 °C for 10 minutes, warmed to r.t. and stirred for 12 h. The mixture was concentrated *in vacuo*. Purification by chromatography on silica

gel (7:3 hexanes/EtOAc) afforded carbamate **226** as a green oil (0.337 g, 99%); $\mathbf{R_f}$ 0.28 (3:2 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 400 MHz) δ 8.03 (s, 1H), 7.27 (d, 1H, *J* = 8.4 Hz), 7.04 (d, 1H, *J* = 2.4 Hz), 7.02 (s, 1H), 6.88 (dd, 1H, *J* = 8.8, 2.4 Hz), 4.63 (br s, 1H), 3.88 (s, 3H), 3.47 (br s, 2H), 2.93 (t, *J* = 6.8 Hz, 2H), 1.45 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 156.2, 154.0, 131.7, 127.8, 123.1, 112.7, 112.3, 112.2, 100.6, 79.3, 56.0, 41.0, 28.6, 25.9; **IR** (thin film, $cm^{-1}$) 3331.8 (br w), 2976.2 (w), 2933.8 (w), 1687.7 (s), 1624.1 (w), 1584.0 (w), 1508.5 (m), 1484.7 (m), 1365.4 (m), 1214.7 (w), 1164.0 (s), 1031.6 (m), 907.7 (m), 795.3 (w), 728.1 (s); **HRMS** (+APCI) calculated for $C_{16}H_{23}N_2O_3$ 291.1709, found 291.1704 $[M+H]^+$.

**Synthesis of tryptamine 238:**

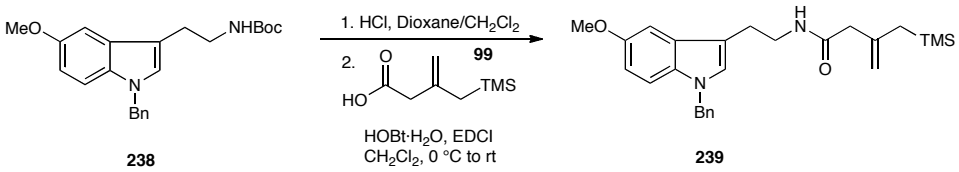



**226** **239**

Powdered NaOH (0.640 g, 16.0 mmol) and TBAHS (0.108 g, 0.319 mmol) were added to a solution of **226** (1.85 g, 6.37 mmol) in $CH_2Cl_2$ (60.0 mL), and the resulting suspension was stirred for 10 minutes. Benzyl bromide (0.83 mL, 7.01 mmol) was added dropwise and the reaction was vigorously stirred for 18 h. $H_2O$ (40 mL) was added and the mixture was stirred for 10 minutes. The organic layer was separated, and the aqueous layer was extracted with $CH_2Cl_2$ (2 x 30 mL). The organic extracts were combined, washed with brine (60 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (9:1 → 4:1 hexanes/EtOAc) afforded tryptamine **238** as a yellow oil (2.31 g, 95%); $\mathbf{R_f}$ 0.42 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) δ 7.32-7.25 (m, 3H), 7.15 (d, 1H, *J* = 9.0 Hz), 7.11 (d, 2H, *J* = 7.4 Hz), 7.05 (s, 1H), 6.95

(s, 1H), 6.85 (dd, 1H, *J* = 9.0, 2.4 Hz), 5.25 (s, 2H), 4.64 (s, 1H), 3.87 (s, 3H), 3.47 (d, 2H, *J* = 6.0 Hz), 2.93 (t, 2H, *J* = 6.0 Hz), 1.44 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) δ 156.1, 154.0, 137.8, 132.1, 128.8, 128.5, 127.7, 126.9, 126.8, 112.2, 111.9, 110.7, 101.0, 79.1, 56.0, 50.2, 41.0, 28.6, 25.9; **IR** (thin film, $cm^{-1}$) 3357.1 (br, w), 1974.9 (w), 2931.2 (w), 1693.6 (s), 1485.9 (s), 1451.5 (m), 1364.4 (m), 1227.7 (m), 1164.8 (s), 1040.9 (m), 732.0 (m), 703.4 (m); **HRMS** (+APCI) calculated for $C_{23}H_{28}N_2O_3$ 380.2100, found 380.2094 $[M]^+$.

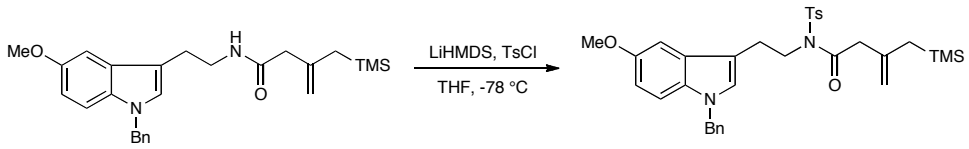
**Synthesis of amide 239:**




A solution of tryptamine **238** (2.31 g, 6.07 mmol) in $CH_2Cl_2$ (30.0 mL) was cooled to 0 °C. Hydrochloric acid (4.0 M in dioxane, 30.0 mL) was added dropwise, and the resulting mixture was stirred at 0 °C for 30 minutes, warmed to r.t. and stirred for 6 h. The mixture was concentrated *in vacuo*. The crude hydrochloride salt was added to a stirring solution of HOBt·$H_2O$ (0.821 g, 6.08 mmol) in $CH_2Cl_2$ (60.0 mL). The resulting mixture was stirred at r.t. for 5 minutes and then cooled to 0 °C. Carboxylic acid **99** (1.03 mL, 5.79 mmol) was added dropwise, followed by dropwise addition of EDCI (1.08 mL, 6.08 mmol) over 20 minutes. The reaction was stirred at 0 °C for 1 h, warmed to r.t. and stirred for 24 h. $Et_2O$ (200 mL) was added, and the reaction was stirred for 15 minutes. The mixture was washed with 0.10 M aqueous HCl (2 x 100 mL), saturated aqueous $NaHCO_3$ (2 x 100 mL), and brine (100 mL). The organic layer was dried over anhydrous

$MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (7:3 hexanes/EtOAc) afforded amide **239** as a crystalline white solid (1.79 g, 71% over two steps); $\mathbf{R_f}$ 0.17 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 400 MHz) δ 7.34-7.25 (m, 3H), 7.16 (dd, 1H, *J* = 8.8, *J* = 2.0 Hz), 7.13-7.09 (m, 2H), 7.06 (d, 1H, *J* = 2.4 Hz), 6.93 (s, 1H), 6.86 (dt, 1H, *J* = 8.8, 2.4 Hz), 6.02 (s, 1H), 5.24 (s, 2H), 4.66 (d, 1H, *J* = 0.8 Hz), 4.63 (d, 1H, *J* = 0.8 Hz), 3.88 (s, 3H), 3.59 (q, 2H, *J* = 6.8), 2.95 (t, 2H, *J* = 6.8 Hz), 2.88 (s, 2H), 1.46 (s, 2H), 0.01 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 170.4, 154.1, 142.5, 137.8, 132.2, 128.9, 128.5, 127.8, 126.9, 126.8, 112.7, 112.3, 111.7, 110.7, 100.8, 56.0, 50.2, 47.1, 39.8, 26.8, 25.3, -1.4; **IR** (thin film, $cm^{-1}$) 3295.5 (br, w), 3066.8 (w), 2950.0 (w), 1646.4 (m,), 1629.8 (m), 1486.1 (m), 1451.7 (w), 1436.4 (w), 1228.1 (m), 1039.7 (w), 839.4 (s), 701.6 (m); **m.p.** 64.5-65.5 °C; **HRMS** (+ESI) calculated for $C_{26}H_{35}N_2O_2Si$ 435.2468, found 435.2456 $[M+H]^+$.

**Synthesis of *N*-tosylamide 231:**

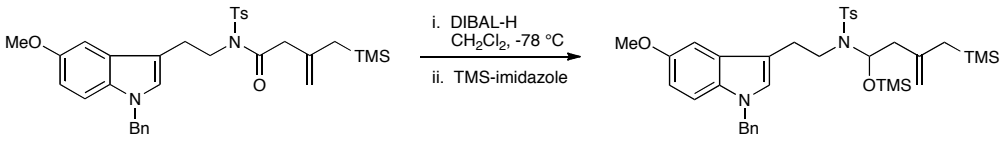



**239** **231**

A solution of amide **239** (0.973 g, 2.24 mmol) in THF (9.0 mL) was cooled to -78 °C. A freshly prepared LiHMDS solution (0.33 M in THF, 6.45 mL, 2.13 mmol) was cooled to -78 °C and added to the staring material solution *via* cannula. The reaction was stirred for 1 h at -78 °C. In a separate flask, a solution of tosyl chloride (0.470 g, 2.46 mmol) in THF (4.0 mL) was cooled to 0 °C and added to the reaction mixture *via* cannula. The mixture was stirred at -78 °C for 12 h. The reaction was quenched with saturated aqueous

$NaHCO_3$ (1 mL) and warmed to 0 °C. $H_2O$ (5 mL) was added, and the mixture was stirred for 5 minutes. The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (2 x 5 mL). The organic extracts were combined, washed with brine (12 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (20:1 → 9:1 hexanes/EtOAc) afforded tosylamide **231** as a colorless oil (0.305 g, 23%); $\mathbf{R_f}$ 0.50 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) δ 7.83 (d, 2H, *J* = 7.8 Hz), 7.32-7.25 (m, 6H), 7.14 (dd, 1H, *J* = 9.0, 0.6 Hz), 7.10 (d, 2H, *J* = 8.4 Hz), 6.95 (s, 1H), 6.84 (ddd, 1H, *J* = 9.0, 2.4, 0.6 Hz), 5.23 (s, 2H), 4.65 (s, 1H), 4.46 (s, 1H), 4.04 (t, 2H, *J* = 7.8 Hz), 3.88 (s, 3H), 3.19 (t, 2H, *J* = 7.8 Hz), 3.09 (s, 2H), 2.43 (s, 3H), 1.45 (s, 2H), -0.08 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) δ 171.1, 154.3, 144.9, 140.3, 137.7, 137.0, 132.0, 129.8, 128.9, 128.5, 128.0, 127.8, 127.4, 127.0, 112.5, 111.9, 110.9, 110.8, 100.8, 56.0, 50.3, 48.1, 45.7, 27.2, 26.5, 21.8, -1.3; **IR** (thin film, $cm^{-1}$) 2951.3 (w), 1693.5 (m), 1487.2 (m), 1452.5 (m), 1350.9 (s), 1233.0 (m), 1161.4 (s), 845.3 (s), 669.9 (m), 542.2 (m); **HRMS** (+ESI) calculated for $C_{33}H_{41}N_2O_4SSi$ 589.2556, found 589.2537 $[M+H]^+$.

**Synthesis of *N*-tosyl-*O*-TMS-aminol 221:**

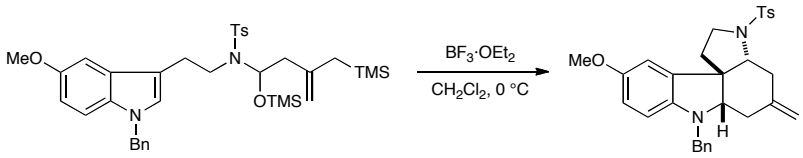



**231** **221**

A solution of tosylamide **231** (0.215 g, 0.366 mmol) in $CH_2Cl_2$ (3.7 mL) was cooled to -78 °C. DIBAL-H (1.0 M in $CH_2Cl_2$, 0.73 mL, 0.73 mmol) was added dropwise over 10 minutes. The reaction mixture was stirred for 45 minutes, then trimethylsilyl imidazole

(0.22 mL, 1.46 mmol) was added dropwise. The mixture was warmed to -25 °C and stirred for 20 hours. The mixture was warmed to 0 °C and stirred for 5 hours. The reaction was quenched by slow addition of aqueous 15% Rochelle's salt solution (3 mL). The biphasic mixture was transferred to a 25 mL Erlenmeyer flask, and $Et_2O$ (8 mL) was added. The mixture was stirred vigorously at r.t. until both layers were clear. The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (2 x 3 mL). The organic extracts were combined, washed with brine (7 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (7:3 pentane/$Et_2O$, silica gel deactivated with 1% $Et_3N$) afforded *N*-tosyl-*O*-TMS-aminol **221** as a colorless oil (0.181 g, 74%); $\mathbf{R_f}$ 0.52 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) δ 7.75 (d, 2H, *J* = 8.4 Hz), 7.34-7.25 (m, 5H), 7.23 (d, 1H, *J* = 2.4 Hz), 7.14 (d, 1H, *J* = 8.4 Hz), 7.13-7.10 (m, 2H), 6.94 (s, 1H), 6.84 (dd, 1H, *J* = 9.0, 2.4 Hz), 5.54 (dd, 1H, *J* = 8.4, 3.6 Hz), 5.24 (s, 1H), 4.64 (s, 1H), 4.60 (s, 1H), 3.89 (s, 3H), 3.54 (ddd, 1H, *J* = 14.4, 12.6, 5.4 Hz), 3.38 (ddd, 1H, *J* = 14.4, 12.6, 4.8 Hz), 3.20 (dt, 1H, *J* = 12.6, 4.8 Hz), 3.10 (dt, 1H, *J* = 12.6, 5.4 Hz), 2.40 (s, 3H), 2.31 (dd, 1H, *J* = 13.2, 8.4 Hz), 1.96 (dd, 1H, *J* = 13.2, 4.2 Hz), 1.57 (d, 1H, *J* = 13.8 Hz), 1.37 (d, *J* = 13.8 Hz), 0.15 (s, 9H), -0.0.3 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) 154.2, 143.2, 142.4, 138.6, 137.9, 132.1, 129.8, 128.9, 128.5, 127.8, 127.3, 127.0, 126.8, 112.4, 112.4, 111.3, 110.8, 101.0, 81.8, 56.0, 50.3, 45.8, 43.9, 28.0, 27.0, 21.7, 0.3, -1.3; **IR** (thin film, $cm^{-1}$) 2952.8 (w), 1622.2 (w), 1580.9 (w), 1487.9 (m), 1452.8 (w), 1339.5 (w), 1249.6 (m), 1160.7 (m), 934.1 (w), 845.4 (s); **HRMS** (+APCI) calculated for $C_{36}H_{50}N_2O_4SSi_2$ 662.3030, found 662.3030 $[M]^+$.

**Synthetic tetracyclic amine 245:**

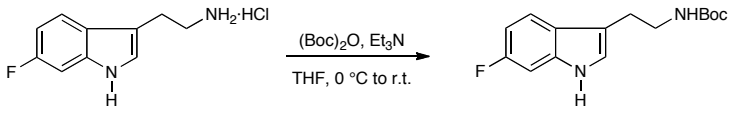



**221** **245**

A solution of *N*-tosyl-*O*-TMS-aminol **221** (0.180 g, 0.272 mmol) in $CH_2Cl_2$ (6.8 mL) was cooled to 0 °C. $BF_3{\cdot}OEt_2$ (50 μL, 0.41 mmol) was added dropwise and the mixture was stirred at 0 °C for 10 minutes. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (5 mL). The resulting biphasic mixture was stirred vigorously for 15 minutes. The organic layer was separated, and the aqueous layer was extracted with $CH_2Cl_2$ (2 x 4 mL). The organic extracts were combined, washed with brine (6 mL), dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo*. Purification by chromatography on basic alumina (4:1 hexanes/EtOAc) afforded tetracyclic amine **245** as a crystalline white solid (0.109 g, 80%); $\mathbf{R_f}$ 0.36 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) δ 7.72 (d, 2H, *J* = 9.6 Hz), 7.40-7.24 (m, 7H), 7.12 (d, 1H, *J* = 2.4 Hz), 6.67 (dd, 1H, *J* = 8.4, 2.4 Hz), 6.30 (d, 1H, *J* = 8.4 Hz), 4.79 (s, 1H), 4.68 (s, 1H), 4.35 (d, 1H, *J* = 15.0 Hz), 4.02 (d, 1H, *J* = 15.0 Hz), 3.77 (s, 3H), 3.65 (dt, 1H, *J* = 10.8, 7.2 Hz), 3.43 (t, 1 H, *J* = 10.2 Hz), 3.30 (t, 1H, *J* = 6.6 Hz), 3.07 (dd, 1H, *J* = 13.8, 4.2 Hz), 2.93 (dd, 1H, *J* = 12.6, 4.2), 2.48 (t, 1H, *J* = 13.2 Hz), 2.45 (s, 3H), 2.26 (dd, 1H, *J* = 14.4, 6.6 Hz), 2.03 (dd, 1H, *J* = 14.4, 7.2 Hz), 1.89 (dd, 1H, *J* = 12.0, 6.6 Hz), 1.47 (q, 1H, *J* = 10.2); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) δ 153.1, 144.7, 143.9, 143.0, 138.4, 133.2, 132.7, 130.0, 128.7, 128.0, 127.9, 127.4, 112.9, 112.7, 112.7, 108.4, 67.6, 62.8, 56.3, 55.1, 49.7, 47.9, 35.9, 35.6, 33.6, 21.8; **IR** (thin film, $cm^{-1}$) 3029.3 (w), 2936.2 (br, w), 2830.6 (w), 1646.7 (w), 1595.9 (w), 1480.1 (m), 1349.1 (m), 1273.2 (w), 1217.4 (w), 1160.4 (s), 665.5 (m);

**m.p.** 152.5-154.0 °C; **HRMS** (+APCI) calculated for $C_{30}H_{33}N_2O_3S$ 501.2212, found 501.2211 $[M+H]^+$.

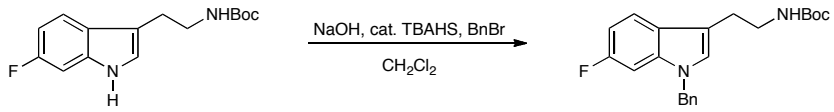
**Synthesis of carbamate 227:**




**227**

A solution of 6-fluorotryptamine hydrochloride (0.197 g, 0.920 mmol) and triethylamine (0.33 mL, 2.39 mmol) in THF (9.0 mL) was cooled to 0 °C. A solution of di-*tert*-butyl carbonate (0.200 g, 0.920 mmol) in THF (1.0 mL) was added to the starting material mixture *via* cannula. The reaction was stirred at 0 °C for 10 minutes, warmed to r.t. and stirred for 12 h. The mixture was concentrated *in vacuo*. Purification by chromatography on silica gel (7:3 hexanes/EtOAc) afforded carbamate **227** as a crystalline white solid (0.242 g, 95%); $\mathbf{R_f}$ 0.32 (3:2 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 400 MHz) δ 8.05 (s, 1H), 7.52 (dd, 1H, *J* = 8.8, 5.2 Hz), 7.06 (dd, 1H, *J* = 9.6, 2.4 Hz), 7.04-7.01 (m, 1H), 6.90 (ddd, 1H, *J* = 9.6, 8.8, 2.4 Hz,), 4.62 (br s, 1H), 3.52-3.38 (m, 2H), 2.94 (t, 2H, *J* = 6.8 Hz), 1.45 (m, 9H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 160.1 (d, $^1J_{C\text{-}F}$ = 237.34 Hz), 156.2, 136.4 (d, $^3J_{C\text{-}F}$ = 12.4 Hz), 124.2, 122.4 (d, $^4J_{C\text{-}F}$ = 1.18 Hz), 119.6 (d, $^3J_{C\text{-}F}$ = 10.4 Hz), 113.3 (d, $^4J_{C\text{-}F}$ 1.2 Hz), 108.2 (d, $^2J_{C\text{-}F}$ = 24.6 Hz), 97.7 (d, $^2J_{C\text{-}F}$ = 25.7 Hz), 79.5, 41.1, 28.6, 25.9; **IR** (thin film, $cm^{-1}$) 3310.4 (br, m), 2976.9 (w), 2931.2 (w), 1688.2 (s), 1627.5 (m), 1500.4 (m), 1456.7 (m), 1366.1 (w), 1341.4 (w), 1251.5 (m), 1165.7 (m), 1140.1 (m), 951.3 (w), 800.9 (m); **m.p.** 105.0-105.5 °C; **HRMS** (+APCI) calculated for $C_{15}H_{19}FN_2O_2$ 278.1431, found 278.1425 $[M]^+$.

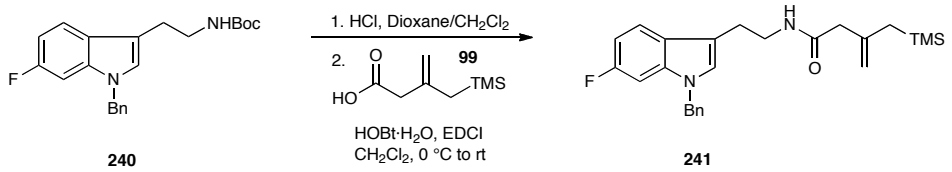
**Synthesis of tryptamine 240:**




**227** **240**

Powdered NaOH (0.824 g, 20.6 mmol) and TBAHS (0.140 g, 0.412 mmol) were added to a solution of carbamate **227** (2.29 g, 8.24 mmol) in $CH_2Cl_2$ (82.0 mL), and the resulting suspension was stirred for 10 minutes. Benzyl bromide (1.07 mL, 0.906 mmol) was added dropwise and the reaction was vigorously stirred for 18 h. $H_2O$ (60 mL) was added, and the mixture was stirred for 10 minutes. The organic layer was separated, and the aqueous layer was extracted with $CH_2Cl_2$ (2 x 40 mL). The organic extracts were combined, washed with brine (100 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (20:1 → 9:1 hexanes/EtOAc) afforded tryptamine **240** as a yellow oil (2.66 g, 88%); $\mathbf{R_f}$ 0.50 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) δ 7.54 (dd, 1H, *J* = 8.4, 5.4 Hz), 7.34-7.28 (m, 3H), 7.12 (d, 2H, *J* = 7.4 Hz), 6.96-6.93 (m, 2H), 6.89 (dt, 1H, *J* = 9.0, 1.8 Hz), 5.21 (s, 2H), 4.67 (s, 1H), 3.46 (d, 2H, *J* = 6.0 Hz), 2.95 (t, 2H, *J* = 6.0 Hz), 1.47 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) δ 160.2 (d, $^1J_{C\text{-}F}$ = 238.4 Hz), 156.1, 137.3, 137.0 (d, $^3J_{C\text{-}F}$ = 12.4 Hz), 129.1, 128.0, 127.0, 126.6, 124.9, 120.1 (d, $^3J_{C\text{-}F}$ = 9.9 Hz), 112.9, 108.1 (d, $^2J_{C\text{-}F}$ = 24.6 Hz), 96.4 (d, $^2J_{C\text{-}F}$ = 26.5 Hz), 79.3, 50.3, 41.2, 28.7, 26.0; **IR** (thin film, $cm^{-1}$) 3433.1 (br, w), 2976.4 (w), 2930.0 (w), 1696.9 (m), 1620.9 (w), 1487.6 (m), 1470.1 (w), 1453.2 (w), 1365.0 (w), 1332.6 (w), 1249.8 (m), 1164.3 (s), 906.8 (m), 727.9 (s), 705.6 (m); **HRMS** (+APCI) calculated for $C_{22}H_{25}FN_2O_2$ 368.1900, found 368.1895 $[M]^+$.

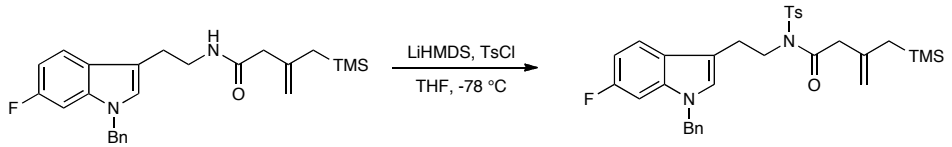
**Synthesis of amide 241:**




A solution of tryptamine **240** (1.45 g, 3.94 mmol) in $CH_2Cl_2$ (20.0 mL) was cooled to 0 °C. Hydrochloric acid (4.0 M in dioxane, 20.0 mL) was added dropwise, and the resulting mixture was stirred at 0 °C for 30 minutes, warmed to r.t. and stirred for 8 h. The mixture was concentrated *in vacuo*. The crude hydrochloride salt was added to a stirring solution of HOBt·$H_2O$ (0.559 g, 4.13 mmol) in $CH_2Cl_2$ (40 mL). The resulting mixture was stirred at r.t. for 5 minutes and then cooled to 0 °C. Carboxylic acid **7** (0.74 mL, 4.1 mmole) was added dropwise, followed by dropwise addition of EDCI (0.73 mL, 4.1 mmole) over 20 minutes. The reaction was stirred at 0 °C for 1 h, warmed to r.t. and stirred for 24 h. $Et_2O$ (80 mL) was added, and the reaction was stirred for 15 minutes. The mixture was washed with 0.10 M aqueous HCl (2 x 100 mL), saturated aqueous $NaHCO_3$ (2 x 100 mL), and brine (100 mL). The organic layer was dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (4:1 → 7:3 hexanes/EtOAc) afforded amide **241** as a crystalline white solid (1.14 g, 68% over two steps); $\mathbf{R_f}$ 0.26 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 400 MHz) δ 7.52 (dd, 1H, $J$ = 8.8, 5.2 Hz), 7.35-7.28 (m, 3H), 7.12-7.09 (m, 2H), 6.95-6.93 (m, 2H), 6.89 (ddd, 1H, $J$ = 9.6, 8.8, 2.0 Hz), 5.96 (s, 1H), 5.21 (s, 2H), 4.64 (s, 1H), 4.62 (s, 1H), 3.56 (q, 2H, $J$ = 6.4 Hz), 2.94 (t, 2H, $J$ = 6.4 Hz), 2.87 (s, 2H), 1.43 (s, 2H), 0 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 170.3, 160.0 (d, $^1J_{C\text{-}F}$ = 237.8 Hz), 142.3, 137.0, 136.7 (d, $^3J_{C\text{-}F}$ = 12.1 Hz), 128.8, 127.7, 126.7, 126.3 (d, $^4J_{C\text{-}F}$ = 3.5 Hz), 124.6, 119.8 (d, $^3J_{C\text{-}F}$ = 10.3 Hz), 112.5, 112.4, 107.8 (d, $^2J_{C\text{-}F}$ = 24.6

Hz), 96.2 (d, $^{2}J_{C\text{-}F}$ = 26.2 Hz), 49.9, 46.8, 39.8, 26.6, 25.1, -1.5; **IR** (thin film, $cm^{-1}$) 3306.1 (br, w), 3076.4 (w), 2952.6 (w), 1648.9 (m), 1622.5 (m), 1470.0 (w), 1332.7 (w), 1248.0 (m), 1168.1 (m), 907.9 (w), 838.5 (s), 728.4 (s), 705.3 (m); **m.p.** 54.5-55.5 °C; **HRMS** (+APCI) calculated for $C_{25}H_{32}FN_2OSi$ 423.2268, found 423.2269 $[M+H]^+$.

**Synthesis of *N*-tosylamide 232:**

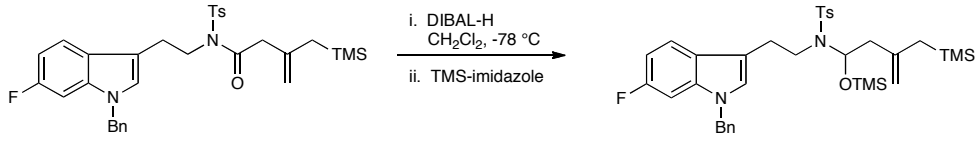



**241** **232**

A solution of amide **241** (0.837 g, 1.98 mmol) in THF (6.0 mL) was cooled to -78 °C. A freshly prepared LiHMDS solution (0.33 M in THF, 5.70 mL, 1.88 mmol) was cooled to -78 °C and added to the starting material solution *via* cannula. The reaction was stirred for 1 h at -78 °C. In a separate flask, a solution of tosyl chloride (0.415 g, 2.18 mmol) in THF (3.0 mL) was cooled to 0 °C and added to the reaction mixture *via* cannula. The mixture was stirred at -78 °C for 3 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (1 mL) and warmed to 0 °C. $H_2O$ (4 mL) was added, and the mixture was stirred for 5 minutes. The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (2 x 4 mL). The organic extracts were combined, washed with brine (6 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (9:1 → 4:1 pentane/$Et_2O$) afforded *N*-tosylamide **232** as a colorless oil (0.371 g, 33%); $\mathbf{R_f}$ 0.48 (7:3 hexanes/EtOAc); **$^{1}$H NMR** ($CDCl_3$, 400 MHz) δ 7.83 (d, 2H, *J* = 8.4 Hz), 7.68 (dd, 1H, *J* = 8.8, 5.2 Hz), 7.39-7.28 (m, 5H), 7.14-7.09 (m, 2H), 6.97 (s, 1H), 6.96-6.87 (m, 2H), 5.20 (s, 2H), 4.67 (s, 1H), 4.48 (s, 1H), 4.07-

4.00 (m, 2H), 3.22-3.16 (m, 2H), 3.13 (s, 2H), 2.44 (s, 3H), 1.46 (s, 2H), -0.07 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 171.2, 160.2 (d, $^1J_{C\text{-}F}$ = 236.6 Hz), 145.0, 140.3, 137.1, 137.0, 136.8 (d, $^3J_{C\text{-}F}$ = 11.8 Hz), 129.9, 129.1, 128.0, 127.9, 127.2 (d, $^4J_{C\text{-}F}$ = 3.8 Hz), 127.0, 124.7, 120.2 (d, $^3J_{C\text{-}F}$ = 10.4 Hz), 112.1, 111.7, 108.4 (d, $^2J_{C\text{-}F}$ = 24.4 Hz), 96.4 (d, $^2J_{C\text{-}F}$ = 26.1 Hz), 50.4, 48.2, 45.8, 27.2, 26.4, 21.8, -1.33; **IR** (thin film, $cm^{-1}$) 3031.7 (w), 2953.2 (w), 1694.1 (m), 1621.8 (w), 1352.3 (m), 1334.6 (m), 1248.5 (m), 1160.3 (s), 845.5 (s); **HRMS** (+ESI) calculated for $C_{32}H_{37}FN_2NaO_3SSi$ 599.2176, found 599.2180 $[M+Na]^+$.

**Synthesis of *N*-tosyl-*O*-TMS-aminol 222:**

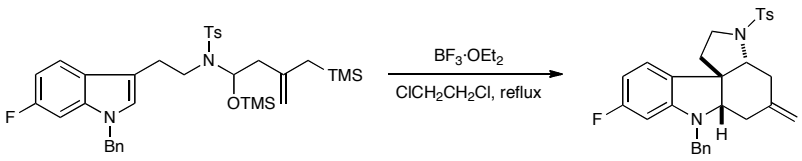



**232** **222**

A solution of tosylamide **232** (0.321 g, 0.557 mmol) in $CH_2Cl_2$ (5.6 mL) was cooled to -78 °C. DIBAL-H (1.0 M in $CH_2Cl_2$, 1.11 mL, 1.11 mmol) was added dropwise over 10 minutes. The reaction mixture was stirred for 30 minutes, then trimethylsilyl imidazole (0.33 mL, 2.23 mmol) was added dropwise. The mixture was warmed to -25 °C and stirred for 24 hours. The mixture was warmed to 0 °C and stirred for 5 hours. The reaction was quenched by slow addition of aqueous 15% Rochelle's salt solution (4 mL). The biphasic mixture was transferred to a 25 mL Erlenmeyer flask, and $Et_2O$ (8 mL) was added. The mixture was stirred vigorously at r.t. until both layers were clear. The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (2 x 3 mL). The organic extracts were combined, washed with brine (7 mL), dried over anhydrous

$MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (20:1 → 9:1 pentane/$Et_2O$, silica gel deactivated with 1% $Et_3N$) afforded *N*-tosyl-*O*-TMS-aminol **222** as a colorless oil (0.255 g, 70%); $\mathbf{R_f}$ 0.66 (7:3 hexanes/EtOAc, silica gel deactivated with 1% $Et_3N$); **$^1$H NMR** ($CDCl_3$, 400 MHz) δ 7.74 (d, 2H, *J* = 8.0 Hz), 7.62 (dd, 1H, *J* = 8.4, 5.6 Hz), 7.35-7.25 (m, 5H), 7.14-7.10 (m, 2H), 6.93 (s, 1H), 6.93-6.87 (m, 2H), 5.53 (dd, 1H, *J* = 8.8, 3.6 Hz), 5.21 (s, 2H), 4.63 (1H), 4.60 (1H), 3.52 (ddd, 1H, *J* = 14.8, 12.0, 5.6 Hz), 3.36 (ddd, 1H, *J* = 14.8, 11.6, 5.2 Hz), 3.20 (dt, 1H, *J* = 13.6, 4.8 Hz), 3.09 (ddd, 1H, *J* = 13.6, 11.6, 5.2 Hz), 2.40 (s, 3H), 2.29 (dd, 1H, *J* = 13.2, 8.8 Hz), 1.95 (dd, 1H, *J* = 13.2, 3.6 Hz), 1.58 (d, 1H, *J* = 13.6 Hz), 1.38 (d, 1H, *J* = 13.6 Hz), 0.14 (s, 9H), -0.03 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 160.1 (d, $^1J_{C\text{-}F}$ = 237.8 Hz), 143.3, 142.4, 138.5, 137.3, 136.8 (d, $^3J_{C\text{-}F}$ = 12.1 Hz), 129.8, 129.0, 127.9, 127.3, 127.0, 126.5 (d, $^4J_{C\text{-}F}$ = 4.0 Hz), 124.8, 120.2 (d, $^3J_{C\text{-}F}$ = 10.4 Hz), 113.2, 111.3, 108.1 (d, $^2J_{C\text{-}F}$ = 24.6 Hz), 96.3 (d, $^2J_{C\text{-}F}$ = 26.3 Hz), 81.8, 50.2, 45.7, 43.9, 27.8, 27.0, 21.6, 0.3, -1.3; **IR** (thin film, $cm^{-1}$) 2954.3 (w), 1621.7 (w), 1333.1 (m), 1249.7 (m), 1159.9 (m), 933.0 (m), 843.2 (s); **HRMS** (+APCI) calculated for $C_{35}H_{48}FN_2O_3SSi_2$ 651.2908, found 651.2942 $[M+H]^+$.

**Synthesis of tetracyclic amine 246:**

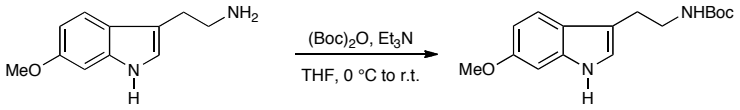



**222** **246**

A solution of *N*-tosyl-*O*-TMS-aminol **222** (0.056 g, 0.087 mmol) in $ClCH_2CH_2Cl$ (2.2 mL) was placed in an oil bath preheated to 90 °C and stirred for 5 minutes. $BF_3{\cdot}OEt_2$ (32 μL, 0.26 mmol) was added dropwise, and the resulting mixture was stirred for 15

minutes. The reaction was cooled to r.t., placed in an ice bath and quenched by addition of saturated aqueous $NaHCO_3$ (2 mL). The resulting biphasic mixture was stirred vigorously for 15 minutes. The organic layer was separated, and the aqueous layer was extracted with $CH_2Cl_2$ (2 x 2 mL). The organic extracts were combined, washed with brine (4 mL), dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (4:1 hexanes/EtOAc) afforded tetracyclic amine **246** as a crystalline white solid (0.026 g, 61%); $\mathbf{R_f}$ 0.53 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) δ 7.73 (t, 2H, $J$ = 7.8 Hz), 7.36 (d, 2H, $J$ = 7.8 Hz), 7.35-7.25 (m, 6H), 6.36 (dt, 1H, $J$ = 9.0, 2.4 Hz), 6.07 (dd, 1H, $J$ = 10.2, 2.4 Hz), 4.77 (s, 1H), 4.70 (s, 1H), 4.39 (d, 1H, $J$ = 15.0 Hz), 4.12 (d, 1H, $J$ = 15.0 Hz), 3.64 (dt, 1H, $J$ = 10.8, 7.2 Hz), 3.44-3.41 (m, 2H), 3.07 (dd, 1H, $J$ = 14.4, 4.8 Hz), 3.01 (dd, 1H, $J$ = 12.0, 4.8 Hz), 2.49-2.45 (m, 4H), 2.27 (dd, 1H, $J$ = 14.4, 6.0 Hz), 2.06 (dd, 1H, $J$ = 14.4, 5.4 Hz), 1.88 (dd, 1H, $J$ = 12.0, 6.6 Hz), 1.46 (q, 1H, $J$ = 10.8 Hz); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) δ 164.3 (d, $^1J_{C\text{-}F}$ = 242.7 Hz), 152.3 (d, $^3J_{C\text{-}F}$ = 12.4 Hz), 144.0, 141.8, 137.7, 132.6, 130.0, 128.7, 128.0, 127.7, 127.6, 126.7, 125.7 (d, $^3J_{C\text{-}F}$ = 10.4 Hz), 113.3, 103.6 (d, $^2J_{C\text{-}F}$ = 22.8 Hz), 95.5 (d, $^2J_{C\text{-}F}$ = 27.1 Hz), 67.6, 61.9, 54.4, 48.7, 47.8, 36.0, 35.3, 33.9, 21.8; **IR** (thin film, $cm^{-1}$) 2923.2 (br, w), 1610.4 (m), 1598.8 (m), 1493.0 (m), 1483.3 (m), 1451.6 (w), 1349.3 (m), 1162.7 (s), 1093.0 (m), 665.3 (m), 598.8 (m); **m.p.** 155.0-157.0 °C; **HRMS** (+APCI) calculated for $C_{29}H_{30}FN_2O_2S$ 489.2012, found 489.2014 $[M+H]^+$.

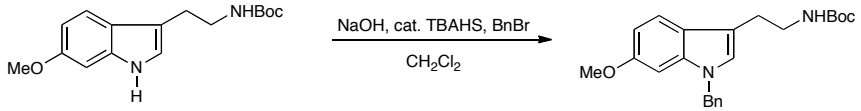
**Synthesis of carbamate 228:**




**228**

A solution of 6-methoxytryptamine (0.500 g, 2.63 mmol) and triethylamine (0.55 mL, 3.94 mmol) in THF (9.0 mL) was cooled to 0 °C. A solution of di-*t*butyl carbonate (0.573 g, 2.63 mmol) in THF (4.0 mL) was added to the starting material mixture *via* cannula. The reaction was stirred at 0 °C for 10 minutes, warmed to r.t. and stirred for 12 h. The mixture was concentrated *in vacuo*. Purification by chromatography on silica gel (7:3 hexanes/EtOAc) afforded carbamate **228** as a crystalline white solid (0.735 g, 96%); **$R_f$** 0.30 (3:2 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) δ 7.90 (s, 1H), 7.48 (d, 1H, *J* = 9.0 Hz), 6.93 (s, 1H), 6.87 (d, 1H, *J* = 1.8 Hz), 6.81 (dd, 1H, *J* = 9.0, 1.8 Hz), 4.62 (s, 1H), 3.86 (s, 3H), 3.46 (d, 2H, *J* = 4.8 Hz), 2.93 (t, 2H, *J* = 6.6 Hz), 1.45 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) δ 156.7, 156.2, 137.3, 122.0, 121.0, 119.6, 113.1, 109.5, 94.9, 79.3, 55.9, 41.1, 28.6, 26.0; **IR** (thin film, $cm^{-1}$) 3328.9 (br, w), 2975.6 (w), 2931.8 (w), 1686.7 (s), 1628.0 (m), 1501.5 (m), 1455.2 (m), 1253.4 (m), 1156.8 (s), 1083.7 (w), 1026.9 (m), 800.6 (m), 730.9 (m); **m.p.** 116.0-117.0 °C; **HRMS** (+APCI) calculated for $C_{16}H_{22}N_2O_3$ 290.1630, found 290.1626 $[M]^+$.

**Synthesis of tryptamine 407:**

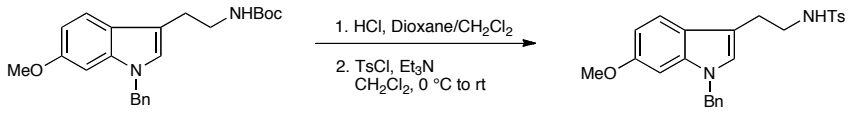



**238** **407**

Powdered NaOH (0.100 g, 2.50 mmol) and TBAHS (0.034 g, 0.101 mmol) were added to a solution of carbamate **238** (0.293 g, 1.01 mmol) in $CH_2Cl_2$ (10.0 mL), and the resulting

suspension was stirred for 10 minutes. Benzyl bromide (0.13 mL, 1.06 mmol) was added dropwise and the reaction was vigorously stirred for 18 h. $H_2O$ (10 mL) was added, and the mixture was stirred for 10 minutes. The organic layer was separated, and the aqueous layer was extracted with $CH_2Cl_2$ (2 x 10 mL). The organic extracts were combined, washed with brine (30 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (9:1 → 4:1 hexanes/EtOAc) afforded tryptamine **407** as a crystalline grey solid (0.343 g, 89%); $\mathbf{R_f}$ 0.42 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) δ 7.49 (d, 1H, *J* = 8.4 Hz), 7.33-7.25 (m, 3H), 7.13 (d, 2H, *J* = 7.2 Hz), 6.85 (s, 1H), 6.80 (dd, 1H, *J* = 9.0, 1.8 Hz), 6.73 (d, 1H, *J* = 1.8 Hz), 5.23 (s, 2H), 4.61 (s, 1H), 3.81 (s, 3H), 3.45-3.44 (m, 2H), 2.92 (t, 1H, *J* = 6.6 Hz), 1.44 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) δ 156.7, 156.1, 137.7, 137.7, 129.0, 127.8, 127.0, 125.2, 122.7, 119.9, 112.6, 109.1, 93.7, 79.3, 55.9, 50.1, 41.1, 28.6, 26.0; **IR** (thin film, $cm^{-1}$) 3359.4 (br, w), 2974.2 (w), 2931.8 (w), 1696.9 (m), 1621.8 (w), 1491.4 (m), 1452.9 (w), 1364.4 (w), 1262.9 (m), 1249.8 (m), 1166.4 (s); **m.p.** 92.5-93.0 °C; **HRMS** (+APCI) calculated for $C_{23}H_{29}N_2O_3$ 381.2178, found 381.2175 $[M+H]^+$.

**Synthesis of tosylamine 242:**

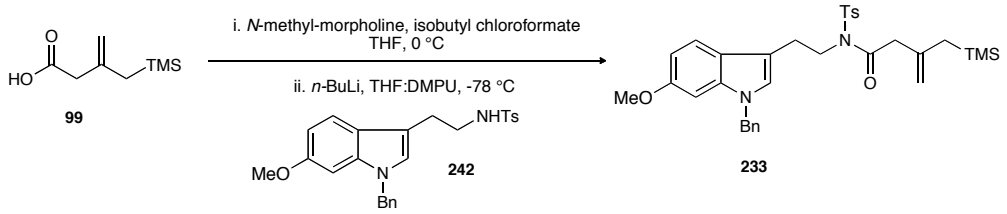



**407** **242**

A solution of tryptamine **407** (0.323 g, 0.861 mmol) in $CH_2Cl_2$ (4.5 mL) was cooled to 0 °C. Hydrochloric acid (4.0 M in dioxane, 4.5 mL) was added dropwise, and the resulting mixture was stirred at 0 °C for 30 minutes, warmed to r.t. and stirred for 45 minutes. The mixture was concentrated *in vacuo*. The crude hydrochloride salt was

dissolved in $CH_2Cl_2$ (5.0 mL), and the resulting suspension was cooled to 0 °C. Triethylamine (0.50 mL, 3.44 mmol) was added, followed by addition of a solution of tosyl chloride (0.172 g, 0.904 mmol) in $CH_2Cl_2$ (2.6 mL). The resulting mixture was stirred at 0 °C for 30 minutes, warmed to r.t. and stirred for 12 h. The reaction was quenched by addition of $H_2O$ (8 mL). The organic layer was separated, and the aqueous layer was extracted with $CH_2Cl_2$ (2 x 5 mL). The organic extracts were combined, washed with brine (15 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (3:2 hexanes/EtOAc) afforded tosylamine **242** as an amorphous white solid (0.342 g, 91%, over two steps); $\mathbf{R_f}$ 0.15 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 400 MHz) δ 7.63 (d, 2H, *J* = 8.0 Hz), 7.35-7.26 (m, 4H), 7.20 (dd, 2H, *J* = 8.0 Hz), 7.12 (dd, 2H, *J* = 8.0, 1.6 Hz), 6.75 (s, 1H), 6.74-6.70 (m, 2H), 5.20 (s, 2H), 4.39 (s, 1H), 3.26 (q, 2H, *J* = 6.4 Hz), 2.89 (dd, 2H, *J* = 6.4 Hz), 2.40 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 156.6, 143.3, 137.6, 137.5, 136.9, 129.7, 128.8, 127.7, 127.1, 126.9, 125.5, 122.1, 119.5, 110.9, 109.1, 93.5, 55.7, 49.9, 43.3, 25.5, 21.6; **IR** (thin film, $cm^{-1}$) 3280.3 (br, w), 3029.9 (w), 2937.2 (w), 1622.1 (w), 1558.0 (w), 1491.4, (w), 1453.0 (w), 1325.8 (m), 1156.4 (s), 1093.5 (w), 813.0 (m), 706.2 (m); **HRMS** (+APCI) calculated for $C_{25}H_{27}N_2O_3S$ 435.1742, found 435.1733 $[M+H]^+$.

**Synthesis of *N*-tosylamide 223:**

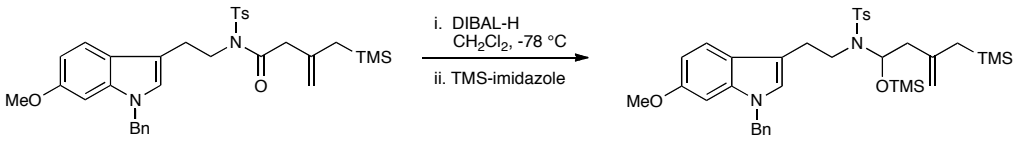



A solution of tosylamine **242** (0.251 g, 0.578 mmol) in THF:DMPU (12:1, 5.7 mL) was cooled to -78 °C. *n*-BuLi (1.6 M in hexanes, 0.38 mL, 0.61 mmol) was added over 15

minutes, and the resulting solution was stirred at -78 °C for 1 h. In a separate flask, a solution of carboxylic acid **99** (0.15 mL, 0.87 mmol) in THF (8.7 mL) was cooled to 0 °C. *N*-methyl-morpholine (0.10 mL, 0.93 mmol) was added to the carboxylic acid solution, followed by addition of isobutyl chloroformate (0.11 mL, 0.87 mmol) over 10 minutes. The resulting mixture was stirred for 30 minutes at 0 °C. Stirring was discontinued, and the suspension was allowed to settle for 30 minutes. The yellow supernatant was separated from the white precipitate, and was filtered through celite into a flask pre-cooled to -50 °C. The filtered cake was washed with dry THF (2 x 5 mL). The lithiate solution was added to the mixed anhydride solution *via* cannula, and the resulting orange solution was allowed to reach 0 °C over 2 h. The reaction was quenched with $H_2O$ (8 mL). The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (3 x 8 mL). The organic extracts were combined, washed with brine (20 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (9:1 hexanes/EtOAc) afforded *N*-tosylamide **233** as a colorless oil (0.177 g, 52%); $\mathbf{R_f}$ 0.48 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) δ 7.83 (d, 2H, *J* = 8.4 Hz), 7.63 (d, 1H, *J* = 8.6 Hz), 7.32-7.25 (m, 5H), 7.12 (d, 2H, *J* = 8.4 Hz), 6.86 (s, 1H), 6.81 (dd, 1H, *J* = 8.6, 2.1 Hz), 6.72 (d, 1H, *J* = 2.0 Hz), 5.21 (s, 2H), 4.66 (s, 1H), 4.47 (s, 1H), 4.03 (t, 1H, *J* = 7.8 Hz), 3.80 (s, 3H), 3.17 (t, 1H, *J* = 7.8 Hz), 3.09 (s, 2H), 2.43 (s, 3H), 1.46 (s, 2H), -0.05 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 171.2, 156.8, 145.0, 140.3, 137.6, 137.0, 129.9, 129.0, 128.1, 127.8, 127.1, 125.8, 122.6, 120.0, 112.0, 111.5, 109.3, 93.8, 55.9, 50.2, 48.3, 45.8, 27.2, 26.6, 21.8, -1.3; **IR** (thin film, $cm^{-1}$) 2952.0 (w), 1694.1 (m), 1623.0 (w), 1491.8 (w), 1453.6 (w), 1352.3 (m), 1162.8 (s), 846.4 (m), 705.3 (w),

670.1 (m); **HRMS** (+APCI) calculated for $C_{33}H_{41}N_2O_4SSi$ 589.2556, found 589.2544 $[M+H]^+$.

**Synthesis of *N*-tosyl-*O*-TMS-aminol 223:**

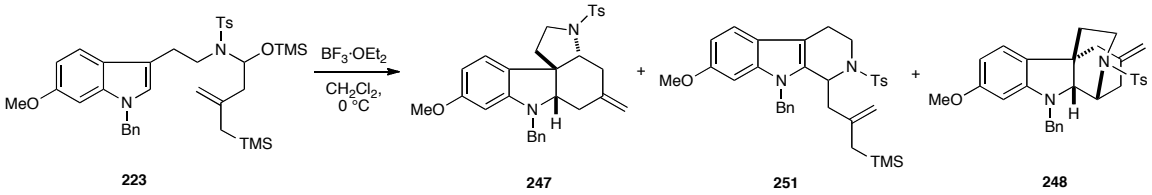



**233** **223**

A solution of tosylamide **233** (0.044 g, 0.074 mmol) in $CH_2Cl_2$ (1.0 mL) was cooled to -78 °C. DIBAL-H (1.0 M in $CH_2Cl_2$, 0.15 mL, 0.15 mmol) was added dropwise over 10 minutes. The reaction mixture was stirred for 45 minutes, then trimethylsilyl imidazole (44 uL, 0.22 mmol) was added dropwise. The mixture was warmed to -25 °C and stirred for 20 h. The mixture was warmed to 0 °C and stirred for 3 h. The reaction was quenched by slow addition of aqueous 15% Rochelle's salt solution (1 mL). $Et_2O$ (4 mL) was added, and the mixture was stirred vigorously at r.t. until both layers were clear. The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (2 x 1 mL). The organic extracts were combined, washed with brine (4 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica (20:1 → 9:1 pentane/$Et_2O$, silica gel deactivated with 1% $Et_3N$) afforded *N*-tosyl-*O*-TMS-aminol **223** as a colorless oil (0.032 g, 66%); $\mathbf{R_f}$ 0.54 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 400 MHz) δ 7.76-7.73 (d, 2H, *J* = 8.4 Hz), 7.58 (d, 1H, *J* = 8.6 Hz), 7.34-7.25 (m, 5H), 7.13 (dd, 2H, *J* = 8.0 Hz, 2.0 Hz), 6.83 (s, 1H), 6.81 (dd, 1H, *J* = 8.6, 2.0 Hz), 6.72 (d, 1H, *J* = 2.0 Hz), 5.54 (dd, 1H, *J* = 8.4, 3.8 Hz), 5.21 (s, 2H), 4.64 (s, 1H), 4.60 (s, 1H), 3.79 (s, 3H), 3.52 (ddd, 1H, *J* = 14.8, 12.0, 5.2 Hz), 3.37 (ddd, 1H, *J* = 14.8, 12.0, 4.8 Hz), 3.19

(dt, 1H, *J* = 12.8, 4.8 Hz), 3.07 (ddd, 1H, *J* = 13.6, 12.0, 5.2 Hz), 2.40 (s, 3H), 2.30 (dd, 1H, *J* = 13.6, 8.4 Hz), 1.97 (dd, 1H, *J* = 13.6, 3.8 Hz), 1.59 (d, 1H, *J* = 13.6 Hz), 1.41-1.38 (d, 1H, *J* = 13.6 Hz), 0.15 (s, 9H), -0.02 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) δ 156.7, 143.2, 142.6, 138.6, 137.8, 137.6, 129.8, 129.0, 127.8, 127.4, 127.0, 125.1, 122.7, 120.1, 113.0, 111.3, 109.1, 93.7, 81.9, 55.9, 50.1, 45.8, 44.1, 27.9, 27.1, 21.7, 0.3, -1.3; **IR** (thin film, $cm^{-1}$) 2953.6 (w), 1623.6 (w), 1491.7 (w), 1453.8 (w), 1334.9 (m), 1249.4 (m), 1229.3 (w), 1160.5 (m), 844.7 (s); **HRMS** (+APCI) calculated for $C_{33}H_{41}N_2O_3SSi$ 573.2607, found 573.2594 $[M+OTMS]^+$.

**Synthesis of tetracyclic amine 247:**



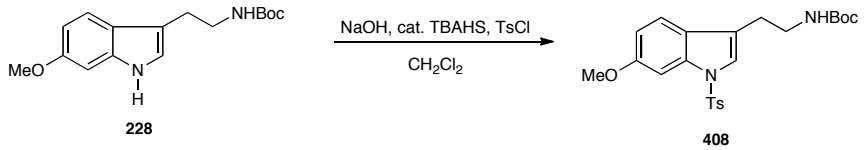

**223** **247** **251** **248**

A solution of *N*-tosyl-*O*-TMS-aminol **223** (0.031 g, 0.047 mmol) in $CH_2Cl_2$ (1.6 mL) was cooled to 0 °C. $BF_3{\cdot}OEt_2$ (88 μL, 0.71 mmol) was added dropwise and the mixture was stirred at 0 °C for 15 minutes. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (1.5 mL). The resulting biphasic mixture was stirred vigorously for 15 minutes. The organic layer was separated, and the aqueous layer was extracted with $CH_2Cl_2$ (2 x 1.5 mL). The organic extracts were combined, washed with brine (4 mL), dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (4:1 hexanes/$CH_2Cl_2$ → 100% $CH_2Cl_2$) afforded tetracyclic amine **247** as a colorless oil (4.5 mg, 23%); $\mathbf{R_f}$ 0.54 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) δ 7.72 (d, 2H, *J* = 8.4 Hz), 7.36 (d, 2H, *J* = 8.4 Hz), 7.33-7.25 (m,

6H), 6.23 (dd, 1H, *J* = 8.1, 2.2 Hz), 5.98 (d, 1H, *J* = 2.2 Hz), 4.77 (s, 1H), 4.68 (s, 1H), 4.41 (d, 1H, *J* = 15.1 Hz), 4.08 (d, 1H, *J* = 15.1 Hz), 3.74 (s, 3H), 3.66 (dt, 1H, *J* = 10.8, 6.6 Hz), 3.42 (t, 1H, *J* = 10.5 Hz), 3.37 (t, 1H, *J* = 5.9 Hz), 3.06 (dd, 1H, *J* = 14.1, 4.6 Hz), 2.97 (dd, 1H, *J* = 12.0, 4.8 Hz), 2.48 (t, 1H, *J* = 13.2 Hz), 2.46 (s, 3H), 2.26 (dd, 1H, *J* = 14.4, 6.0 Hz), 2.05 (dd, 1H, *J* = 14.1, 5.7 Hz), 1.86 (dd, 1H, *J* = 11.7, 6.9 Hz), 1.42 (q, 1H, *J* = 10.8 Hz); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) δ 161.0, 152.0, 143.9, 142.4, 138.1, 132.7, 130.0, 128.8, 128.0, 127.8, 127.4, 125.5, 124.0, 112.9, 101.4, 95.4, 67.4, 62.3, 55.4, 54.4, 48.8, 47.9, 36.0, 35.5, 34.0, 21.8; **IR** (thin film, $cm^{-1}$) 2923.4 (w), 1615.6 (m), 1494.1 (m), 1452.4 (w), 1348.5 (m), 1163.1 (s), 1095.7 (w), 1029.6 (w), 665.3 (m); **HRMS** (+APCI) calculated for $C_{30}H_{33}N_2O_3S$ 501.2212, found 501.2212 $[M+H]^+$; and tetrahydro-*β*-carboline **251** as a colorless oil (9.1 mg, 38%); $\mathbf{R_f}$ 0.63 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) δ 7.41 (d, 2H, *J*= 7.8 Hz), 7.33-7.27 (m, 3H), 7.21 (d, 1H, *J* = 8.7 Hz), 7.00 (d, 2H, *J* = 8.4 Hz), 6.98 (d, 2H, *J* = 7.2 Hz), 6.72 (dd, 1H, *J* = 8.7, 2.2 Hz), 6.64 (d, 1H, *J* = 2.2 Hz), 5.34 (d, 1H, *J* = 16.8 Hz), 5.22-5.17 (m, 2H), 4.71 (s, 1H), 4.66 (s, 1H), 4.06 (dd, 1H, *J* = 15.0, 6.0 Hz), 3.76 (s, 3H), 3.48 (ddd, 1H, *J* = 15.0, 12.0, 4.8 Hz), 2.51 (d, 1H, *J* = 15.6, 4.8 Hz), 2.47-2.41 (m, 2H), 2.31-2.28 (m, 4H), 1.66 (d, 1H, *J* = 13.7 Hz), 1.51 (d, 1H, *J* = 13.7 Hz), -0.03 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) δ 156.6, 143.1, 142.8, 138.2, 138.0, 137.3, 133.6, 129.3, 129.2, 127.9, 127.2, 126.3, 121.4, 119.0, 112.0, 108.9, 107.8, 94.1, 55.9, 51.3, 47.1, 44.4, 38.5, 26.3, 21.6, 20.0, -1.2; **IR** (thin film, $cm^{-1}$) 2922.0 (w), 2850.3 (w), 1625.1 (w), 1492.8 (w), 1452.7 (w), 1334.5 (w), 1153.7 (s), 840.3 (m); **HRMS** (+APCI) calculated for $C_{33}H_{41}N_2O_3SSi$ 573.2607, found 573.2593 $[M+H]^+$; and regioisomeric tetracyclic amine **248** as colorless oil (4.6 mg, 23%); $\mathbf{R_f}$ 0.54 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600

MHz) δ 7.63 (d, 2H, *J* = 8.4 Hz), 7.36-7.24 (m, 7H), 6.88 (d, 1H, *J* = 7.8 Hz), 6.27 (dd, 1H, *J* = 7.8, 2.4 Hz), 6.15 (d, 1H, *J* = 2.4 Hz), 4.56 (d, 1H, *J* = 2.4 Hz), 4.47 (q, 1H, *J* = 3.0 Hz), 4.32 (d, 1H, *J* = 2.4 Hz), 4.29 (d, 1H, *J* = 15.6 Hz), 4.17 (d, 1H, *J* = 15.6 Hz), 3.91 (dt, 1H, *J* = 13.2, 4.6 Hz), 3.74 (dd, 1H, *J* = 13.2, 6.6 Hz), 3.68 (s, 3H), 2.95 (d, 1H, *J* = 3.6 Hz), 2.43-2.41 (m, 3H), 2.36-2.27 (m, 4H), 2.20 (dd, 1H, *J* = 12.9, 3.9 Hz), 1.94 (dt, 1H, *J* = 13.2, 7.2 Hz); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) δ 160.2, 153.1, 144.9, 143.3, 138.1, 138.0, 131.4, 129.8, 128.9, 127.8, 127.5, 127.1, 120.9, 109.5, 103.2, 98.5, 72.4, 55.5, 52.6, 52.5, 42.8, 42.3, 41.5, 33.8, 33.3, 21.7; **IR** (thin film, $cm^{-1}$) 2924.0 (w), 1621.5 (w), 1594.4 (w), 1491.3 (m), 1452.7 (w), 1333.7 (m), 1158.2 (s), 1127.0 (m), 1093.3 (m), 939.1 (m); **HRMS** (+APCI) calculated for $C_{30}H_{33}N_2O_3S$ 501.2212, found 501.2211 $[M+H]^+$.

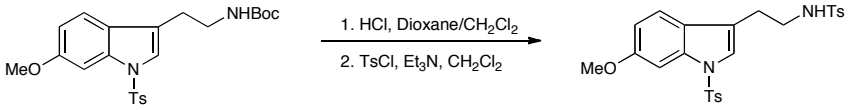
**Synthesis of tryptamine 408:**




Powdered NaOH (0.253 g, 6.32 mmol) and TBAHS (0.086 g, 0.253 mmol) were added to a solution of carbamate **228** (0.735 g, 2.53 mmol) in $CH_2Cl_2$ (20.0 mL), and the resulting suspension was stirred for 10 minutes. A solution of tosyl chloride (0.506 g, 2.66 mmol) in $CH_2Cl_2$ (5.0 mL) was added to the starting material suspension *via* cannula, and the reaction was stirred vigorously for 16 h. $H_2O$ (10 mL) was added, and the mixture was stirred for 10 minutes. The organic layer was separated, and the aqueous layer was extracted with $CH_2Cl_2$ (2 x 10 mL). The organic extracts were combined, washed with brine (30 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by

chromatography on silica gel (7:3 hexanes/EtOAc) afforded tryptamine **408** as a crystalline white solid (0.956 g, 88%); $\mathbf{R_f}$ 0.35 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 400 MHz) δ 7.74 (d, 2H, *J* = 8.0 Hz), 7.52 (d, 1H, *J* = 2.4 Hz), 7.35 (d, 1H, *J* = 8.8 Hz), 7.25 (s, 1H), 7.22 (d, 2H, *J* = 8.0 Hz), 6.86 (dd, 1H, *J* = 8.8, 2.4 Hz), 4.59-4.50 (br s, 1H), 3.91 (s, 1H), 3.39 (q, 2H, *J* = 6.9 Hz), 2.82 (t, 2H, *J* = 6.9 Hz), 2.35 (s, 3H), 1.5 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 158.0, 155.9, 144.8, 136.2, 134.9, 129.7, 126.6, 124.6, 122.0, 120.1, 120.0, 112.0, 98.1, 79.1, 55.6, 39.9, 28.3, 25.5, 21.4; **IR** (thin film, $cm^{-1}$) 3432.8 (br, w), 2976.7 (w), 1698.1 (m), 1615.1 (w), 1488.8 (m), 1364.6 (m), 1167.8 (s), 1110.8 (m), 906.9 (s), 727.0 (s), 670.0 (s), 583.9 (s), 540.7 (m); **m.p.** 104.0-105.0 °C; **HRMS** (+APCI) calculated for $C_{23}H_{28}N_2O_5S$ 444.1719, found 444.1714 $[M]^+$.

**Synthesis of tosylamine 255**

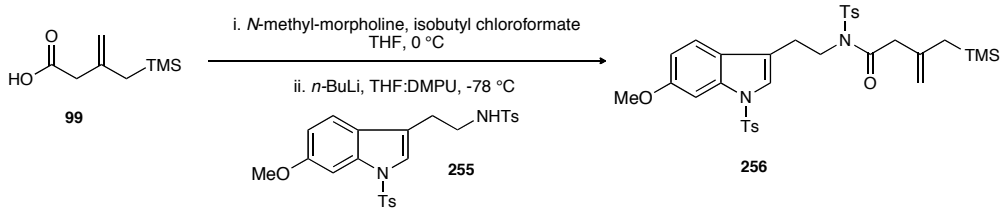



**408** **255**

A solution of tryptamine **408** (0.956 g, 2.22 mmol) in $CH_2Cl_2$ (11.0 mL) was cooled to 0 °C. Hydrochloric acid (4.0 M in dioxane, 11.0 mL) was added dropwise, and the resulting mixture was stirred at 0 °C for 30 minutes, warmed to r.t. and stirred for 2 h. The mixture was concentrated *in vacuo*. The crude hydrochloride salt was dissolved in $CH_2Cl_2$ (18.0 mL), and the resulting suspension was cooled to 0 °C. Triethylamine (1.23 mL, 8.86 mmol) was added, followed by addition of a solution of tosyl chloride (0.423 g, 2.22 mmol) in $CH_2Cl_2$ (4.0 mL). The resulting mixture was stirred at 0 °C for 30 minutes, warmed to r.t. and stirred for 12 h. The reaction was quenched by addition of $H_2O$ (10 mL). The organic layer was separated, and the aqueous layer was extracted with $CH_2Cl_2$

(2 x 10 mL). The organic extracts were combined, washed with brine (20 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (3:2 hexanes/EtOAc) afforded tosylamine **255** as a crystalline white solid (0.965 g, 87%, over two steps); $\mathbf{R_f}$ 0.15 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 400 MHz) δ 7.74 (d, 2H, *J* = 8.4 Hz), 7.60 (d, 2H, *J* = 8.0 Hz), 7.50 (d, 1H, *J* = 2.4 Hz), 7.27-7.21 (m, 4H), 7.18 (d, 1H, *J* = 8.4 Hz), 7.16 (s, 1H), 6.81 (dd, 1H, *J* = 8.4, 2.4 Hz), 4.31-4.26 (br s, 1H), 3.89 (s, 3H), 3.23 (q, 2H, *J* = 6.4 Hz), 2.80 (t, 2H, *J* = 6.4 Hz), 2.42 (s, 3H), 2.36 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz) 158.3, 145.2, 143.7, 136.8, 136.5, 135.2, 130.2, 129.9, 127.1, 126.9, 124.2, 122.7, 119.9, 119.0, 112.5, 98.3, 56.0, 42.5, 25.7, 21.8, 21.7; **IR** (thin film, $cm^{-1}$) 3278.4 (br, w), 2935.3 (w), 1616.2 (w), 1596.9 (w), 1488.6 (w), 1436.3 (w), 1363.2 (m), 1158.4 (s), 1114.7 (m), 1092.4 (m), 671.0 (s), 585.2 (m); **m.p**. 166.5-167 °C; **HRMS** (+APCI) calculated for $C_{25}H_{27}N_2O_5S_2$ 499.1361, found 499.1357 $[M+H]^+$.

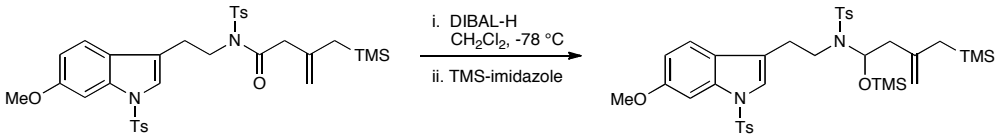
**Synthesis of *N*-tosylamide 256:**




A solution of tosylamine **255** (0.195 g, 0.391 mmol) in THF:DMPU (12:1, 4.0 mL) was cooled to -78 °C. *n*-BuLi (1.6 M in hexanes, 0.26 mL, 0.41 mmol) was added over 15 minutes, and the resulting solution was stirred at -78 °C for 1 h. In a separate flask, a solution of carboxylic acid **99** (91 μL, 0.51 mmol) in THF (5.0 mL) was cooled to 0 °C. *N*-methyl-morpholine (58 μL, 0.53 mmol) was added to the carboxylic acid solution,

followed by addition of isobutyl chloroformate (63 μL, 0.51 mmol) over 10 minutes. The resulting mixture was stirred for 30 minutes at 0 °C. Stirring was discontinued, and the suspension was allowed to settle for 30 minutes. The yellow supernatant was separated from the white precipitate, and was filtered through celite into a flask pre-cooled to -50 °C. The filtered cake was washed with dry THF (2 x 3 mL). The lithiate solution was added to the mixed anhydride solution *via* cannula, and the resulting orange solution was allowed to reach 0 °C over 2 h. The reaction was quenched with $H_2O$ (4 mL). The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (3 x 4 mL). The organic extracts were combined, washed with brine (15 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (9:1 hexanes/EtOAc) afforded *N*-tosylamide **256** as a colorless oil (0.117 g, 46%); $\mathbf{R_f}$ 0.31 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) δ 7.80 (d, 2H, *J* = 8.4 Hz), 7.73 (d, 2H, *J* = 8.4 Hz), 7.55 (d, 1H, *J* = 8.4 Hz), 7.51 (d, 1H, *J* = 2.4 Hz), 7.34 (d, 2H, *J* = 8.4 Hz), 7.25 (s, 1H), 7.22 (d, 2H, *J* = 8.4 Hz), 6.89 (dd, 1H, *J* = 8.4, 2.4 Hz), 4.69 (s, 1H), 4.52 (s, 1H), 3.99-3.97 (m, 2H), 3.88 (s, 3H), 3.18 (s, 2H), 3.07 (t, 2H, *J* = 8.1 Hz), 2.44 (s, 3H), 2.34 (s, 3H), 1.50 (s, 2H), -0.05 (m, 9H); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) δ 171.1, 158.4, 145.3, 145.1, 140.3, 136.8, 136.4, 135.4, 130.1, 130.1, 127.8, 127.0, 124.5, 122.7, 120.4, 119.0, 112.6, 112.3, 98.3, 56.0, 47.1, 45.8, 27.2, 26.1, 21.9, 21.8, -1.3; **IR** (thin film, $cm^{-1}$) 2953.9 (w), 1695.2 (w), 1615.1 (w), 1596.7 (w), 1489.3 (w), 1438.2 (w), 1355.6 (m), 1170.1 (s), 1112.5 (m), 1088.2 (w), 843.6 (m), 812.5 (w), 670.2 (s), 584.0 (m), 541.6 (m); **HRMS** (+APCI) calculated for $C_{33}H_{41}N_2O_6S_2Si$ 653.2175, found 653.2170 $[M+H]^+$.

**Synthesis of *N*-tosyl-*O*-TMS-aminol 254:**

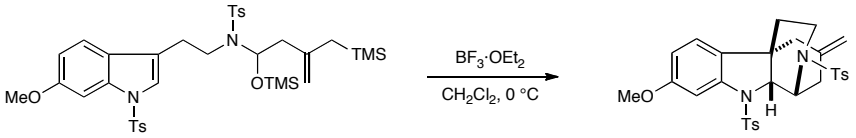



**256** **254**

A solution of tosylamide **256** (0.101 g, 0.155 mmol) in $CH_2Cl_2$ (1.5 mL) was cooled to -78 °C. DIBAL-H (1.0 M in $CH_2Cl_2$, 0.45 mL, 0.45 mmol) was added dropwise over 30 minutes. The reaction mixture was stirred for 2 h, then trimethylsilyl imidazole (0.123 mL, 0.620 mmol) was added dropwise. The mixture was warmed to -25 °C and stirred for 20 h. The mixture was warmed to 0 °C and stirred for 2 h. The reaction was quenched by slow addition of aqueous 15% Rochelle's salt solution (1 mL). The biphasic mixture was transferred to a 25 mL Erlenmeyer flask, and $Et_2O$ (4 mL) was added. The mixture was stirred vigorously at r.t. until both layers were clear. The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (2 x 1 mL). The organic extracts were combined, washed with brine (4 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica (9:1 hexanes/EtOAc, silica gel deactivated with 1% $Et_3N$) afforded *N*-tosyl-*O*-TMS-aminol **254** as a colorless oil (0.037 g, 33%); $\mathbf{R_f}$ 0.35 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) δ 7.75 (d, 2H, *J* = 8.4 Hz), 7.72 (d, 2H, *J* = 7.8 Hz), 7.52 (d, 1H, *J* = 2.4 Hz), 7.48 (d, 1H, *J* = 8.4 Hz,), 7.28 (d, 2H, *J* = 8.4 Hz), 7.24 (d, 2H, *J* = 7.8 Hz), 7.23 (s, 1H), 6.89 (dd, 1H, *J* = 8.4, 2.4 Hz), 5.52 (dd, 1H, *J* = 8.2, 4.2 Hz), 4.62 (s, 1H), 4.59 (s, 1H), 3.89 (s, 3H), 3.45 (ddd, 1H, *J* = 15.0, 12.0, 5.4 Hz), 3.30 (ddd, 1H, *J* = 15.0, 12.0, 4.8 Hz), 3.10 (dt, 1H, *J* = 12.9, 4.8 Hz), 3.01 (dt, 1H, *J* = 12.9, 5.4 Hz), 2.41 (s, 3H), 2.36 (s, 3H), 2.25 (dd, 1H, *J* = 13.2, 8.2 Hz), 1.92 (dd, 1H, *J* = 13.2, 4.2 Hz), 1.56 (d, 1H, *J* = 13.2 Hz), 1.36 (d, 1H, *J* =

13.2 Hz), 0.14 (s, 9H), -0.03 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) δ 158.3, 145.0, 143.5, 142.3, 138.2, 136.4, 135.5, 130.1, 129.9, 127.3, 127.0, 124.7, 122.0, 120.4, 120.3, 112.4, 111.4, 98.3, 81.8, 56.0, 45.7, 42.8, 27.7, 27.0, 21.8, 21.7, 0.3, -1.3; **IR** (thin film, $cm^{-1}$) 2953.8 (w), 1615.6 (w), 1597.3 (w), 1489.2 9 (w), 1368.7 (w), 1336.9 (w), 1248.6 (w), 1220.1 (w), 1160.2 (m), 1109.7 (m), 1085.3 (w), 933.3 (w), 838.7 (s), 669.6 (m), 542.1 (m); **HRMS** (+APCI) calculated for $C_{36}H_{50}N_2O_6S_2Si_2$ 726.2649, found 726.2644 $[M]^+$.

**Synthesis of regioisomeric tetracyclic amine 257:**

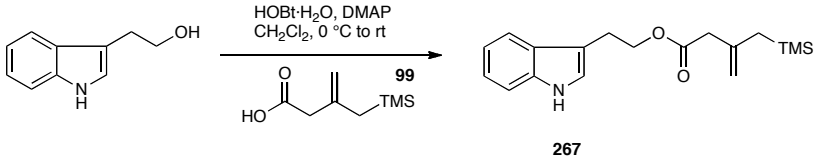



**254** **257**

A solution of *N*-tosyl-*O*-TMS-aminol **254** (0.037 g, 0.051 mmol) in $CH_2Cl_2$ (1.2 mL) was cooled to 0 °C. $BF_3{\cdot}OEt_2$ (31 μL, 0.254 mmol) was added dropwise and the mixture was stirred at 0 °C for 15 minutes. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (1 mL). The resulting biphasic mixture was stirred vigorously for 15 minutes. The organic layer was separated, and the aqueous layer was extracted with $CH_2Cl_2$ (2 x 1 mL). The organic extracts were combined, washed with brine (2 mL), dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (9:1 hexanes/EtOAc) afforded regioisomeric tetracyclic amine **257** as a crystalline white solid (0.018 g, 62%); $\mathbf{R_f}$ 0.23 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) δ 7.82 (d, 2H, *J* = 8.4 Hz), 7.78 (d, 2H, *J* = 7.8 Hz), 7.45 (d, 1H, *J* = 2.4 Hz), 7.36 (d, 2H, *J* = 7.8 Hz), 7.33 (d, 2H, *J* = 8.4 Hz), 6.89 (d, 1H, *J* = 8.4 Hz), 6.54 (dd, 1H, *J* = 8.4, 2.4 Hz), 5.20 (d, 1H, *J* = 3.0 Hz), 4.57 (s, 1H), 4.34 (s, 1H),

3.93 (dt, 1H, *J* = 13.2, 4.2 Hz), 3.87-3.79 (m, 4H), 3.10 (d, 1H, *J* = 3.6 Hz), 2.82 (d, 1H, *J* = 15.0 Hz), 2.49 (s, 3H), 2.42 (s, 3H), 2.30-2.18 (m, 4H), 1.91-1.85 (m, 1H); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) δ 160.1, 145.0, 144.1, 143.5, 143.0, 138.1, 131.7, 131.5, 130.2, 130.0, 128.4, 127.2, 121.4, 109.7, 109.1, 102.9, 69.8, 55.9, 53.1, 43.1, 42.3, 40.7, 33.9, 32.0, 21.8, 21.8; **IR** (thin film, $cm^{-1}$) 2923.7 (w), 1853.3 (w), 1610.7 (w), 1596.5 (w), 1353.9 (m), 1334.3 (w), 1282.5 (w), 1168.2 (s), 1157.5 (s), 1120.7 (w), 1092.0 (m), 814.2 (m), 666.5 (s), 657.2 (s), 621.3 (m), 547.6 (s); **HRMS** (+APCI) calculated for $C_{30}H_{33}N_2O_5S_2$ 565.1831, found 565.1831 $[M+H]^+$.

**Synthesis of ester 267:**

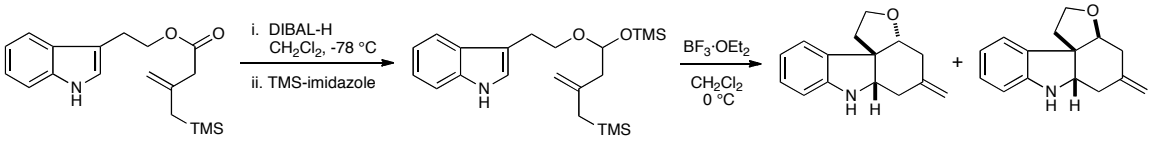



**267**

A solution of tryptophol (0.779 g, 4.83 mmol) and carboxylic acid **99** (0.78 mL, 4.39 mmol) in $CH_2Cl_2$ (38.0 mL) was cooled to 0 °C. EDCI (0.86 mL, 4.83 mmol) was added over 20 minutes, and the resulting mixture was stirred for 5 minutes. A solution of DMAP (0.590 g, 4.83 mmol) in $CH_2Cl_2$ (10.0 mL) was added via syringe over 15 minutes, and the resulting mixture was stirred at 0 °C for 1 h, warmed to r.t. and stirred for 24 h. $Et_2O$ (90.0 mL) was added, and the reaction was stirred for 15 minutes. The mixture was washed with 0.1 M aqueous HCl (2 x 100 mL), saturated aqueous $NaHCO_3$ (2 x 100 mL), and brine (100 mL). The organic layer was dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (40:1 → 9:1 hexanes/EtOAc) afforded ester **267** as a yellow oil (0.369 g, 27%); $\mathbf{R_f}$ 0.38 (7:3

hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) δ 8.00 (s, 1H), 7.66 (d, 1H, *J* = 7.6, Hz), 7.38 (d, 1H, *J* = 8.0, Hz), 7.21 (t, 1H, *J* = 8.0, Hz), 7.14 (t, 1H, *J* = 7.6, Hz), 7.07 (s, 1H), 4.78 (s, 1H), 4.72 (s, 1H), 4.39 (t, 2H, *J* = 7.2 Hz), 3.12 (t, 2H, *J* = 7.2 Hz), 3.00 (s, 2H), 1.62 (s, 2H), 0.04 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 171.9, 140.4, 136.3, 127.6, 122.3, 122.2, 119.5, 118.9, 111.9, 111.9, 111.3, 65.0, 44.2, 26.8, 24.9, -1.3; **IR** (thin film, $cm^{-1}$) 3410.2 (br, w), 2953.1 (w), 1718.0 (m), 1634.1 (w), 1457.1 (w), 1420.8 (w), 1247.2 (m), 1148.2 (m), 838.6 (s), 738.7 (s); **HRMS** (+ESI) calculated for $C_{18}H_{26}NO_2Si$ 316.1733, found 316.1728 $[M+H]^+$.

**Synthesis of tetracyclic ethers 266 and 265:**

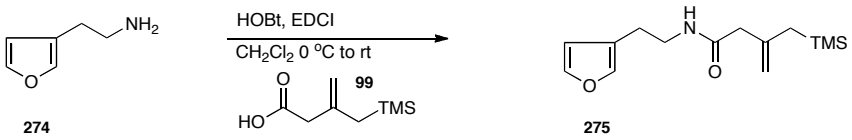



A solution of ester **267** (0.157 g, 0.498 mmol) in $CH_2Cl_2$ (5.0 mL) was cooled to -78 °C. DIBAL-H (1.0 M in $CH_2Cl_2$, 1.00 mL, 1.00 mmol) was added dropwise over 15 minutes. The reaction mixture was stirred for 50 minutes, then trimethylsilyl imidazole (0.22 mL, 1.5 mmol) was added dropwise. The mixture was warmed to -20 °C and stirred for 12 h. The mixture was warmed to 0 °C and stirred for 4 h. The reaction was quenched by slow addition of aqueous 15% Rochelle's salt solution (5 mL). The biphasic mixture was transferred to a 50 mL Erlenmeyer flask, and $Et_2O$ (10 mL) was added. The mixture was stirred vigorously at r.t. until both layers were clear. The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (2 x 5 mL). The organic extracts were combined, washed with saturated aqueous $CuSO_4$ (2 x 10 mL), brine (2 x 15 mL), dried

over anhydrous $Na_2SO_4$, and concentrated *in vacuo*. Crude acetal **262** was obtained as a colorless oil, and was used without further purification; $\mathbf{R_f}$ 0.65 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) δ 7.96 (d, 1H, *J* = 7.8 Hz), 7.63 (d, 1H, *J* = 7.8 Hz), 7.37 (d, 1H, *J* = 7.8 Hz), 7.20 (dt, 1H, *J* = 7.8, 0.6 Hz), 7.13 (dt, 1H, *J* = 7.8, 0.6 Hz), 7.07 (d, 1H, *J* = 1.8 Hz), 4.89 (t, 1H, *J* = 5.4 Hz), 4.67 (d, 1H, *J* = 1.8 Hz), 4.61 (t, 1H, *J* = 0.9 Hz), 3.96 (dt, 1H, *J* = 9.0, 7.2 Hz), 3.63 (dt, 1H, *J* = 9.0, 7.8 Hz), 3.06 (t, 2H, *J* = 7.4 Hz), 2.35 (dd, 1H, *J* = 14.4, 5.4 Hz), 2.22 (dd, 1H, *J* = 14.4, 5.4 Hz), 1.59 (d, 1H, *J* = 13.2 Hz), 1.56 (d, 1H, *J* = 13.2 Hz), 0.15 (s, 9H), 0.03 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 143.3, 136.3, 127.8, 122.2, 122.1, 119.4, 119.1, 113.3, 111.2, 110.3, 98.4, 67.4, 46.6, 27.8, 26.0, 0.7, -1.2; **IR** (thin film, $cm^{-1}$) 3415.0 (br, w), 2953.6 (w), 1634.2 (w), 1457.0 (w), 1419.5 (w), 1350.9 (w), 1249.4 (m), 1122.3 (w), 1030.0 (m), 947.1 (w), 840.2 (s), 739.3 (m); **HRMS** (+ESI) calculated for $C_{21}H_{36}NO_2Si_2$ 390.2285, found 390.2277 $[M+H]^+$. Crude acetal **262** was dissolved in $CH_2Cl_2$ (12.4 mL), and the resulting clear solution was cooled to 0 °C. $BF_3{\cdot}OEt_2$ (0.18 mL, 1.5 mmol) was added dropwise, and the resulting dark yellow mixture was stirred for 2.5 h. The reaction was quenched by addition into a stirring solution of saturated aqueous $NaHCO_3$ (15 mL) pre-cooled to 0 °C. The resulting biphasic mixture was stirred vigorously for 15 minutes. The organic layer was separated, and the aqueous layer was extracted with $CH_2Cl_2$ (2 x 10 mL). The organic extracts were combined, washed with brine (20 mL), dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (9:1 → 7:3 hexanes/EtOAc) afforded tetrahydrofuran **266** as a crystalline white solid (0.050 g, 44%, over two steps); $\mathbf{R_f}$ 0.21 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) δ 7.21 (d, 1H, *J* = 7.2 Hz), 7.06 (dt, 1H, *J* = 7.8, 1.2 Hz), 6.75 (t, 1H, *J* = 7.2 Hz), 6.65 (d, 1H, *J* = 7.8 Hz), 4.73 (s,

1H), 4.68 (s, 1H), 4.15-4.09 (m, 2H), 3.90 (dd, 1H, *J* = 12.6, 5.4 Hz), 3.81-3.75 (br s, 1H), 3.74 (t, 1H, *J* = 5.4 Hz), 2.68 (dd, 1H, *J* = 13.8, 5.4 Hz), 2.55 (dd, 1H, *J* = 14.4, 6.0 Hz), 2.33 (t, 1H, *J* = 12.6 Hz), 2.15 (dt, 1H, *J* = 11.4, 9.6 Hz), 2.03 (ddd, 1H, *J* = 12.0, 7.2, 3.0 Hz), 1.95 (dd, 1H, *J* = 14.4, 4.8 Hz); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) δ 150.3, 142.1, 132.1, 128.0, 125.4, 119.2, 112.5, 110.4, 79.7, 66.5, 62.1, 55.4, 40.4, 39.2, 34.0; **IR** (thin film, $cm^{-1}$) 3333.9 (br, w), 3071.7 (w), 2923.8 (m), 2881.3 (m), 1647.2 (w), 1604.1 (m), 1481.1 (m), 1463.1 (m), 1256.9 (w), 881.8 (m), 745.0 (s), 687.1 (m); **m.p.** 87.5-88.5; **HRMS** (+ESI) calculated for $C_{15}H_{18}NO$ 228.1388, found 228.1380 $[M+H]^+$; and tetrahydrofuran **265** as a colorless oil (0.022 g, 20%, over two steps); **$R_f$** 0.29 (7:3 hexanes/EtOAc); **$^1$H NMR** ($d_8$-toluene, 600 MHz) δ 7.00 (dt, 1H, *J* = 7.8, 1.2 Hz), 6.85 (d, 1H, *J* = 7.2 Hz), 6.70 (dt, 1H, *J* = 7.2, 1.2 Hz), 6.38 (d, 1H, *J* = 7.8 Hz), 4.82 (s, 2H), 3.89 (t, 1H, *J* = 3.7 Hz), 3.78-3.70 (m, 2H), 3.26-3.25 (m, 1H), 3.01-2.75 (br s, 1H), 2.47 (dd, 1H, *J* = 15.0, 3.7 Hz), 2.24-2.20 (m, 2H), 1.95 (dd, 1H, *J* = 14.4, 7.2 Hz), 1.88 (t, 2H, *J* = 7.2 Hz); **$^{13}$C NMR** ($d_8$-toluene, 150 MHz) δ 151.8, 142.6, 133.2, 129.2, 123.8, 120.0, 112.2, 110.7, 83.1, 67.4, 66.3, 54.4, 41.4, 37.0, 35.2; **IR** (thin film, $cm^{-1}$) 3354.3 (br, w), 3070.4 (w), 2926.0 (m), 2852.1 (m), 1656.4 (w), 1607.8 (m), 1482.3 (s), 1464.3 (s), 1261.2 (w), 1069.7 (m), 891.2 (m), 742.0 (s); **HRMS** (+ESI) calculated for $C_{15}H_{18}NO$ 228.1388, found 228.1380 $[M+H]^+$.

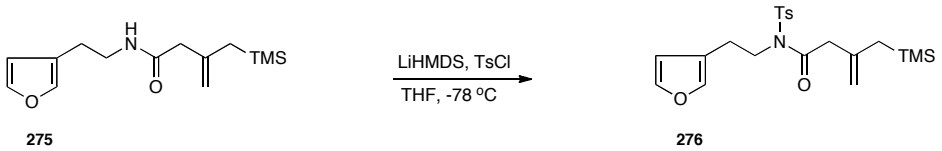
**Synthesis of amide 275:**




Carboxylic acid **99** (1.32 mL, 7.41 mmole) was added to a solution of HOBT·$H_2O$ (1.05 g, 7.78 mmol) and amine **274** (0.864 g, 7.78 mmol) in $CH_2Cl_2$ (78.0 mL) at 0 °C. EDCI

(1.38 mL, 7.78 mmole) was added over 20 minutes, and the resulting mixture was stirred at 0 $^{o}$C for 1 h, warmed to r.t. and stirred for 24 h. $Et_2O$ (160 mL) was added, and the reaction was stirred for 15 minutes. The mixture was washed with 0.1 M aq. HCl (2 x 100 mL), saturated aq. $NaHCO_3$ (2 x 100 mL), and brine (100 mL). The organic layer was dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (4:1 to 7:3 hexanes:EtOAc) afforded amide **275** as a viscous yellow oil (1.10 g, 56% over two steps); $\mathbf{R_f}$ 0.17 (7:3 hexanes/EtOAc); **$^{1}$H NMR** ($CDCl_3$, 400 MHz) δ 7.29 (s, 1H), 7.18 (s, 1H), 6.21 (s, 1H), 6.11 (br s, 1H), 4.68 (s, 2H), 3.37 (q, 2H, *J* = 6.8 Hz), 2.82 (s, 2H), 2.56 (t, 2H, *J* = 6.8 Hz), 1.47 (s, 2H), -0.04 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 170.3, 143.1, 142.3, 139.5, 121.7, 112.4, 110.7, 46.8, 39.4, 26.6, 24.8, -1.5; **IR** (thin film, cm$^{-1}$) 3291.9 (br, w), 3077.4 (br, w), 2952.5 (br, w), 1645.6 (m), 1540.9 (m), 1436.3, 1247.0 (m), 1158.9 (w), 1024.6 (w), 837.6 (s); **HRMS** (+ESI) calculated for $C_{14}H_{24}NO_2Si$ 266.1576, found 266.1590 $[M+H]^+$.

**Synthesis of *N*-tosylamide 276:**

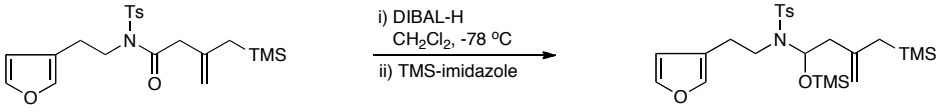



**275** **276**

A solution of amide **275** (0.256 g, 0.965 mmol) in THF (6.0 mL) was cooled to -78 °C. Freshly prepared LiHMDS solution (0.33 M in THF, 2.78 mL, 0.917 mmol) was cooled to -78 °C and added to the stating material solution via cannula. The mixture was stirred for 1 h at 78 °C. In a separate flask, a solution of tosyl chloride (0.900 g, 4.90 mmol) in THF (5.0 mL) was cooled to 0 °C and added into the reaction mixture *via* cannula. The mixture was stirred for 16 h. The reaction was quenched with saturated aq. $NaHCO_3$ (3

mL) and warmed to 0 °C. $H_2O$ (5 mL) was added, and the mixture was stirred for 5 minutes. The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (2 x 6 mL). The organic extracts were combined, washed with brine (12 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (9:1 to 7:3 hexanes:EtOAc) afforded compound **276** as a clear viscous oil (0.073 g, 18%); $\mathbf{R_f}$ 0.54 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 400 MHz) δ 7.81 (d, 2H, $J$ = 8.4 Hz), 7.37-7.33 (m, 3H), 7.28 (t, 1H, $J$ = 0.8 Hz), 6.34 (t, 1H, $J$ = 0.8 Hz), 4.69 (s, 1H), 4.53 (d, 1H), 3.97-3.93 (m, 2H), 3.20 (s, 2H), 2.91-2.84 (m, 2H), 2.44 (d, 3H), 1.50 (s, 2H), -0.3 (s, 9H); **IR** (thin film, $cm^{-1}$) 2921.5 (br, w), 1641.1 (w), 1597.1 (w), 1331.2 (m), 1158.6 (s), 1094.7 (m), 890.0 (m), 666.4 (m), 560.0 (m), 548.3 (m).

**Synthesis of *N*-tosyl-*O*-TMS-aminol 268:**

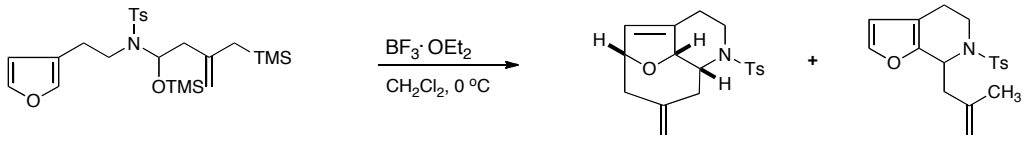



276 268

A solution of tosylamide **276** (0.124 g, 0.295 mmol) in $CH_2Cl_2$ (3.0 mL) was cooled to -78 °C. DIBAL-H (1.0 M in $CH_2Cl_2$, 0.60 mL, 0.60 mmol) was added dropwise over 15 minutes. The reaction mixture was stirred for 15 minutes, then trimethylsilyl imidazole (173 μL, 1.18 mmol) was added dropwise. The mixture was warmed to -25 °C and stirred for 20 h. The mixture was warmed to 0 °C and stirred for 2 h. The reaction was quenched by slow addition of aqueous 15% Rochelle's salt solution (3 mL). The biphasic mixture was transferred to a 25 mL Erlenmeyer flask, and $Et_2O$ (6 mL) was added. The mixture was stirred vigorously at r.t. until both layers were clear. The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (2 x 3 mL). The organic extracts were

combined, washed with brine (10.0 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (20:1 → 9:1 pentane/$Et_2O$, silica gel deactivated with 1% $Et_3N$) afforded *N*-tosyl-*O*-TMS-aminol **268** as a colorless oil (0.122 g, 83%); $\mathbf{R_f}$ 0.38 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) δ 7.74 (d, 2H, *J* = 8.4 Hz), 7.37 (t, 1H, *J* = 1.2 Hz), 7.29 (d, 2H, *J* = 8.4 Hz), 7.25 (s, 1H), 6.30 (dd, 1H, *J* = 1.2, 0.6 Hz), 5.51 (dd, 1H, *J* = 8.4, 4.2 Hz), 4.63 (s, 1H), 4.60 (s, 1H), 3.42 (ddd, 1H, *J* = 15.0, 12.0, 5.4 Hz), 3.27 (ddd, 1H, *J* = 15.0, 11.4 5.4 Hz), 2.88 (ddd, 1H, *J* = 13.8, 12.0, 5.4 Hz), 2.76 (ddd, 1H, *J* = 13.8, 11.4, 5.4 Hz), 2.42 (s, 3H), 2.24 (dd, 1H, *J* = 13.2, 8.4 Hz), 1.94 (dd, 1H, *J* = 13.2, 4.2 Hz), 1.56 (d, 1H, *J* = 13.2), 1.37 (d, 1H, *J* = 13.2), 0.12 (s, 9H), -0.02 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) δ 143.4, 143.1, 142.4, 139.3, 138.4, 129.8, 127.4, 122.2, 111.4, 111.14, 81.8, 45.7, 43.6, 27.1, 27.1, 21.7, 0.4, -1.3; **IR** (thin film, $cm^{-1}$) 2954.3 (br, w), 1634.0 (w), 1598.6 (w), 1340.6 (m), 1249.0 (m), 1159.6 (m), 932.7 (w), 840.6 (s); **HRMS** (+APCI) calculated for $C_{24}H_{40}NO_4SSi_2$ 494.2217, found 494.2220 $[M+H]^+$.

**Synthesis of caged-ether 270:**

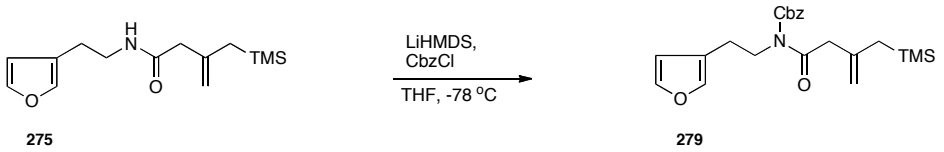



**268** **270** **272**

A solution of *N*-tosyl-*O*-TMS-aminol **268** (0.047 g, 0.096 mmol) in $CH_2Cl_2$ (2.4 mL) was cooled to 0 °C. $BF_3$·$OEt_2$ (18.0 uL, 0.144 mmol) was added dropwise and the mixture was stirred at 0 °C for 1 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ solution (2 mL). The resulting biphasic mixture was stirred vigorously for 15

minutes. The organic layer was separated, and the aqueous layer was extracted with $CH_2Cl_2$ (2 x 2 mL). The organic extracts were combined, washed with brine (4 mL), dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (7:3 → 3:2 hexanes/EtOAc) afforded ether **270** an amorphous white solid (0.012g, 37%); $\mathbf{R_f}$ 0.23 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 400 MHz) δ 7.73 (d, 2H, *J* = 8.0 Hz), 7.31 (d, 2H, *J* = 8.0 Hz), 5.49 (d, 1H, *J* = 1.6 Hz), 5.02 (d, 1H, *J* = 6.6 Hz), 4.78 (s, 1H), 4.68 (t, 1H, *J* = 1.0 Hz), 4.53 (d, 1H, *J* = 6.8 Hz), 4.38 (q, 1H, *J* = 6.2 Hz), 3.97 (dd, 1H, *J* = 13.0, 5.8 Hz), 3.20 (dt, 1H, *J* = 12.4, 3.6 Hz,), 2.64 (dd, 1H, *J* = 14.0, 6.0 Hz), 2.49 (dd, 1H, *J* = 12.8, 3.2 Hz), 2.43 (s, 3H), 2.39-2.35 (m, 2H), 2.31-2.20 (m, 2H); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) δ 143.6, 143.7, 138.3, 137.1, 130.0, 127.1, 123.8, 118.0, 85.6, 83.0, 56.2, 45.7, 43.4, 37.7, 28.0, 21.7; **IR** (thin film, $cm^{-1}$) 3067.8 (w), 2919.0 (w), 1641.1 (w), 1596.9 (w), 1443.3 (w), 1331.0 (m), 1158.3 (s), 1094.4 (s), 889.6 (m), 666.2 (m), 548.2 (m); **m.p.** 128.5-129.0 °C; **HRMS** (+ESI) calculated for $C_{18}H_{22}NO_3S$ 332.1320, found 332.1318 $[M+H]^+$; and furan **272** as a white solid (0.005g, 15%); $\mathbf{R_f}$ 0.30 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 400 MHz) δ 7.65 (d, 2H, *J* = 8.0 Hz), 7.23 (d, 1H, *J* = 2.0 Hz), 7.19 (d, 2H, *J* = 8.0 Hz), 6.05 (d, 1H, *J* = 2.0 Hz), 5.16 (t, 1H, *J* = 6.8 Hz), 4.85 (t, 1H, *J* = 1.7 Hz), 4.74 (t, 1H, *J* = 0.9 Hz), 3.96 (dd, 1H, *J* = 10.2, 5.4 Hz), 3.28 (ddd, 1H, *J* = 14.9, 11.2, 5.3 Hz), 2.55-2.44 (m, 2H), 2.38 (s, 3H), 2.26-2.16 (m, 2H), 1.80 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 148.9, 143.4, 141.4, 141.4, 129.6, 127.3, 127.2, 115.2, 114.8, 110.0, 52.2, 43.1, 39.6, 22.4, 21.7, 21.6; **IR** (thin film, $cm^{-1}$) 2923.7 (br, w), 1651.9 (w), 1597.5 (w), 1455.5 (w), 1339.8 (m), 1159.0 (s), 1112.5 (w), 1090.2 (w), 724.0 (m), 677.0 (m), 558.7 (m); **HRMS** (+ESI) calculated for $C_{18}H_{22}NO_3S$ 332.1320, found 332.1314 $[M+H]^+$.

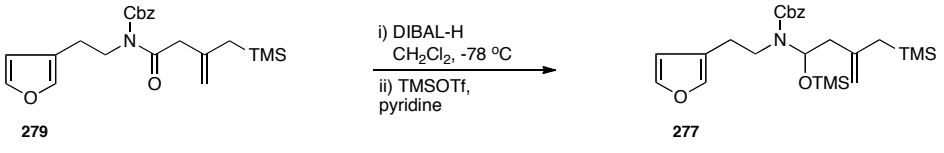
**Synthesis of *N*-Cbz-amide 279:**




**275** **279**

A solution of amide **275** (0.198 g, 0.772 mmol) in THF (0.5 mL) was cooled to -78 °C. A freshly prepared LiHMDS solution (0.73 M in THF, 1.0 mL, 0.73 mmol) was cooled to -78 °C and added to the staring material solution *via* cannula. The reaction was stirred for 1 h at -78 °C. Benzyl chloroformate (0.15 mL, 1.1 mmol) was added and the mixture was stirred for 12 h for -78 °C. The reaction was quenched with saturated aqueous $NH_4Cl$ (1 mL) and warmed to 0 °C. $H_2O$ (3 mL) was added and the mixture was stirred for 5 minutes. The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (2 x 4 mL). The organic extracts were combined, washed with brine (12 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (20:1 pentane/$Et_2O$) afforded *N*-Cbz-amide **279** as a colorless oil (0.159 g, 54%); $\mathbf{R_f}$ 0.46 (4:1 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 400 MHz) δ 7.43-7.36 (m, 5H), 7.33-7.32 (m, 1H), 7.18 (s, 1H), 6.23 (s, 1H), 5.20 (s, 2H), 4.70 (t, $J$ = 0.5 Hz, 1H), 4.63 (s, 1H), 3.95-3.91 (m, 2H), 3.57 (s, 2H), 2.67-2.64 (m, 2H), 1.61 (s, 2H), 0.03 (s, 9H).

**Synthesis of *N*-Cbz-*O*-TMS-aminol 277:**

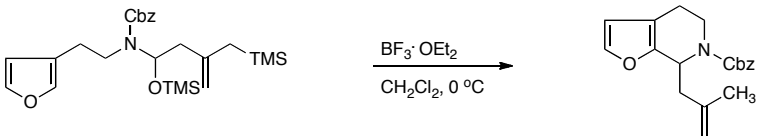



**279** **277**

A solution of *N*-Cbz amide **279** (0.159 g, 0.397 mmol) in $CH_2Cl_2$ (1.7 mL) was cooled to -78 °C. DIBAL-H (1.0 M in $CH_2Cl_2$, 0.54 mL, 0.54 mmol) was added dropwise over 10

minutes. The reaction mixture was stirred for 1 hour, then pyridine (0.13 mL, 1.6 mmol) was added dropwise and the reaction was stirred for 10 minutes. Trimethylsilyl triflate (0.18 mL, 0.99 mmole) was added dropwise and the mixture was stirred for 1 hour at -78 °C. The reaction was warmed to 0 °C and was quenched by slow addition of aqueous 15% Rochelle's salt solution (2 mL). The biphasic mixture was transferred to a 25 mL Erlenmeyer flask, and $Et_2O$ (6 mL) was added. The mixture was stirred vigorously at r.t. until both layers were clear. The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (2 x 2 mL). The organic extracts were combined, washed with brine (10 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (40:1 → 9:1 hexanes/EtOAc, silica gel deactivated with 1% $Et_3N$) afforded *N*-Cbz-*O*-TMS-aminol **277** as a colorless oil (0.161 g, 86%); $\mathbf{R_f}$ 0.68 (7:3 hexanes/EtOAc).

**Synthesis of furan 278:**

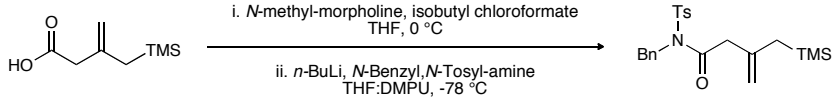



277 278

A solution of *N*-Cbz-*O*-TMS-aminol **277** (0.072 g, 0.152 mmol) in $CH_2Cl_2$ (3.8 mL) was cooled to 0 °C. $BF_3{\cdot}OEt_2$ (28 μL, 0.228 mmol) was added dropwise and the mixture was stirred at 0 °C for 10 minutes. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ solution (2 mL), and the resulting biphasic mixture was warmed stirred vigorously for 15 minutes. The organic layer was separated, and the aqueous layer was extracted with $CH_2Cl_2$ (2 x 2 mL). The organic extracts were combined, washed with brine (5 mL), dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo*. Purification by

chromatography on silica gel (7:3 hexanes/EtOAc) afforded tetracyclic amine **278** as a colorless oil (0.017 g, 36%); $\mathbf{R_f}$ 0.61 (7:3 hexanes/EtOAc); $^1$**H NMR** ($CDCl_3$, 600 MHz) (1.0:0.8 mixture of rotamers) δ 7.38-7.31 (m, 9H), 7.29 (d, 1.6H, *J* = 1.2 Hz), 6.26-6.21 (m, 1.6 H), 5.39-5.37 (m, 0.8H), 5.20-5.10 (m, 4.6H), 4.80 (s, 0.8H), 4.75 (s, 1H), 4.72 (s, 0.8H), 4.67 (s, 1H), 4.44 (dd, 1H, *J* = 13.4, 5.4 Hz), 4.28 (dd, 0.8H, *J* = 13.6, 5.1 Hz), 3.15-3.07 (m, 1.8H), 2.70-2.34 (m, 2.6H), 2.48-2.36 (m, 4.6H), 1.85 (s, 1.8H), 1.66 (s, 3H).

**Synthesis of *N*-tosylamide 282:**

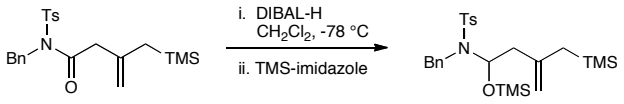



**99** **282**

A solution of *N*-benzyl,*N*-tosyl-amine (0.500 g, 1.91 mmol) in THF:DMPU (12:1, 20.0 mL) was cooled to -78 °C. *n*-BuLi (1.6 M in hexanes, 0.52 mL, 2.0 mmol) was added over 15 minutes, and the resulting solution was stirred at -78 °C for 1 h. In a separate flask, a solution of carboxylic acid **99** (0.39 mL, 2.2 mmol) in THF (22.0 mL) was cooled to 0 °C. *N*-methyl-morpholine (0.25 mL, 2.3 mmol) was added to the carboxylic acid solution, followed by addition of isobutyl chloroformate (0.28 mL, 2.2 mmol) over 10 minutes. The resulting mixture was stirred for 30 minutes at 0 °C. Stirring was discontinued, and the suspension was allowed to settle for 30 minutes. The yellow supernatant was separated from the white precipitate, and was filtered through celite into a flask pre-cooled to -50 °C. The filtered cake was washed with dry THF (2 x 7 mL). The lithiate solution was added to the mixed anhydride solution *via* cannula, and the resulting mixture was allowed to reach 0 °C over 2 h. The reaction was quenched with $H_2O$ (10.0

mL). The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (3 x 10 mL). The organic extracts were combined, washed with brine (30 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (20:1 hexanes/EtOAc) afforded *N*-tosylamide **282** as an amorphous white solid (0.156 g, 20%); $\mathbf{R_f}$ 0.57 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 400 MHz) δ 7.70 (d, 2H, *J* = 8.4 Hz), 7.39-7.24 (m, 7H), 5.10 (s, 2H), 4.64 (s, 1H), 4.48 (s, 1H), 3.13 (s, 2H), 2.39 (s, 3H), 1.44 (s, 2H), -0.11 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 171.1, 144.9, 140.0, 136.8, 136.6, 129.7, 128.8, 128.3, 127.8, 127.5, 112.1, 49.7, 45.7, 26.8, 21.7, -1.5; **IR** (thin film, $cm^{-1}$) 3033.2 (w), 2953.1 (w), 1700.5 (m), 1636.4 (w), 1597.0 (w), 1351.7 (m), 1247.6 (m), 1164.5 (s), 1119.9 (w), 1088.1 (m), 842.7 (s), 546.0 (s); **HRMS** (+APCI) calculated for $C_{22}H_{30}NO_3SSi$ 416.1716, found 416.1706 $[M+H]^+$.

**Synthesis of *N*-tosyl-O-TMS-aminol 280:**

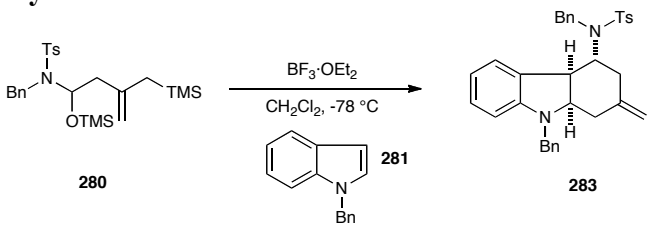



**282** **280**

A solution of *N*-tosylamide **282** (0.156 g, 0.374 mmol) in $CH_2Cl_2$ (3.7 mL) was cooled to -78 °C. DIBAL-H (1.0 M in $CH_2Cl_2$, 0.74 mL, 0.74 mmol) was added dropwise over 30 minutes. The reaction mixture was stirred for 10 minutes, then trimethylsilyl imidazole (0.22 mL, 1.1 mmol) was added dropwise. The mixture was warmed to -25 °C and stirred for 20 h. The mixture was warmed to 0 °C and stirred for 1 h. The reaction was quenched by slow addition of aqueous 15% Rochelle's salt solution (3 mL). The biphasic mixture was transferred to a 25 mL Erlenmeyer flask, and $Et_2O$ (10 mL) was added. The mixture was stirred vigorously at r.t. until both layers were clear. The organic layer was separated,

and the aqueous layer was extracted with $Et_2O$ (2 x 3 mL). The organic extracts were combined, washed with brine (10 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica (20:1 hexanes/EtOAc, silica gel deactivated with 1% $Et_3N$) afforded *N*-tosyl-*O*-TMS-aminol **280** as a colorless oil (0.130 g, 71%); $\mathbf{R_f}$ 0.73 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) δ 7.64 (d, 2H, *J* = 8.4 Hz), 7.35 (d, 2H, *J* = 8.4 Hz), 7.27-7.20 (m, 5H), 5.51 (dd, 1H, *J* = 8.4, 4.2 Hz), 4.55 (s, 1H), 4.52 (s, 1H), 4.45 (q, 2H, *J* = 16.2 Hz), 2.41 (s, 3H), 2.11 (dd, 1H, *J* = 13.5, 8.4 Hz), 2.02 (d, 1H, *J* = 13.5, 4.2 Hz), 1.46 (d, 1H, *J* = 13.2 Hz), 1.29 (d, 1H, *J* = 13.2 Hz), 0.03 (s, 9H), -0.07 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) δ 143.3, 142.5, 138.5, 138.3, 129.6, 129.1, 128.3, 127.5, 127.4, 111.2, 82.3, 46.5, 46.5, 27.2, 21.7, 0.2, -1.3; **IR** (thin film, $cm^{-1}$) 2954.8 (w), 1634.3 (w), 1598.7 (w), 1495.8 (w), 1455.8 (w), 1341.4 (w), 1249.8 (m), 1161.7 (m), 1102.5 (w), 1048.7 (w), 845.4 9 (s); **HRMS** (+APCI) calculated for $C_{22}H_{30}NO_2SSi$ 400.1767, found 400.1758 $[M\text{-}OTMS]^+$.

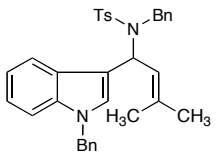
**Synthesis of tricyclic amine 283:**




A solution of *N*-tosyl-*O*-TMS-aminol **280** (0.057 g, 0.117 mmol) and *N*-benzyl indole **281** (0.025 g, 0.12 mmol) in $CH_2Cl_2$ (0.60 mL) was cooled to -78 °C. $BF_3{\cdot}OEt_2$ (43 μL, 0.35 mmol) was added dropwise and the mixture was stirred at 0 °C for 2 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (0.1 mL). The mixture was allowed to reach r.t., and was stirred vigorously for 15 minutes. The organic layer was

separated, and the aqueous layer was extracted with $CH_2Cl_2$ (2 x 0.5 mL). The organic extracts were combined, washed with brine (1 mL), dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo*. The resulting light pink solid was triturated in cold hexanes. Removal of the supernatant afforded the desired tricyclic amine **283** as a crystalline white solid (0.053 g, 85%); $\mathbf{R_f}$ 0.50 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) δ 7.62 (d, 2H, *J* = 8.4 Hz), 7.33-7.21 (m, 10H), 7.19 (d, 2H, *J* = 8.4 Hz), 7.17-7.10 (m, 2H), 7.00-6.94 (m, 2H), 6.51 (t, 1H, *J* = 7.2 Hz), 6.32 (d, 1H, *J* = 8.0 Hz), 4.57 (s, 1H), 4.52 (s, 1H), 4.51 (d, 1H, *J* = 14.8 Hz), 4.34 (d, 1H, *J* = 16.0 Hz), 4.19 (d, 1H, *J* = 14.8 Hz), 3.97 (d, 1H, *J* = 16.0 Hz), 3.61-3.50 (m, 2H), 3.42-3.33 (dd, 1H, *J* = 10.4, 6.8 Hz), 2.52 (d, 1H, *J* = 14.8 Hz), 2.44-2.34 (m, 4H), 2.25-2.14 (m, 2H); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) δ 152.3, 143.4, 143.1, 139.1, 138.3, 137.2, 130.6, 129.8, 129.3, 128.7, 128.5, 128.0, 127.9, 127.5, 127.4, 127.0, 125.2, 118.6, 111.7, 108.7, 67.1, 61.1, 51.0, 51.0, 44.5, 39.6, 33.7, 21.7; **IR** (thin film, $cm^{-1}$) 3028.9 (w), 2924.2 (w), 2852.4 (w), 1603.3 (w), 1478.0 (m), 1453.2 (w), 1337.7 (m), 1153.9 (s), 1091.4 (m), 907.6 (m), 728.9 (s), 700.9 (m), 545.1 (m); **m.p** 140.5-142.0 °C; **HRMS** (+APCI) calculated for $C_{34}H_{35}N_2O_2S$ 535.2419, found 535.2421 $[M+H]^+$.

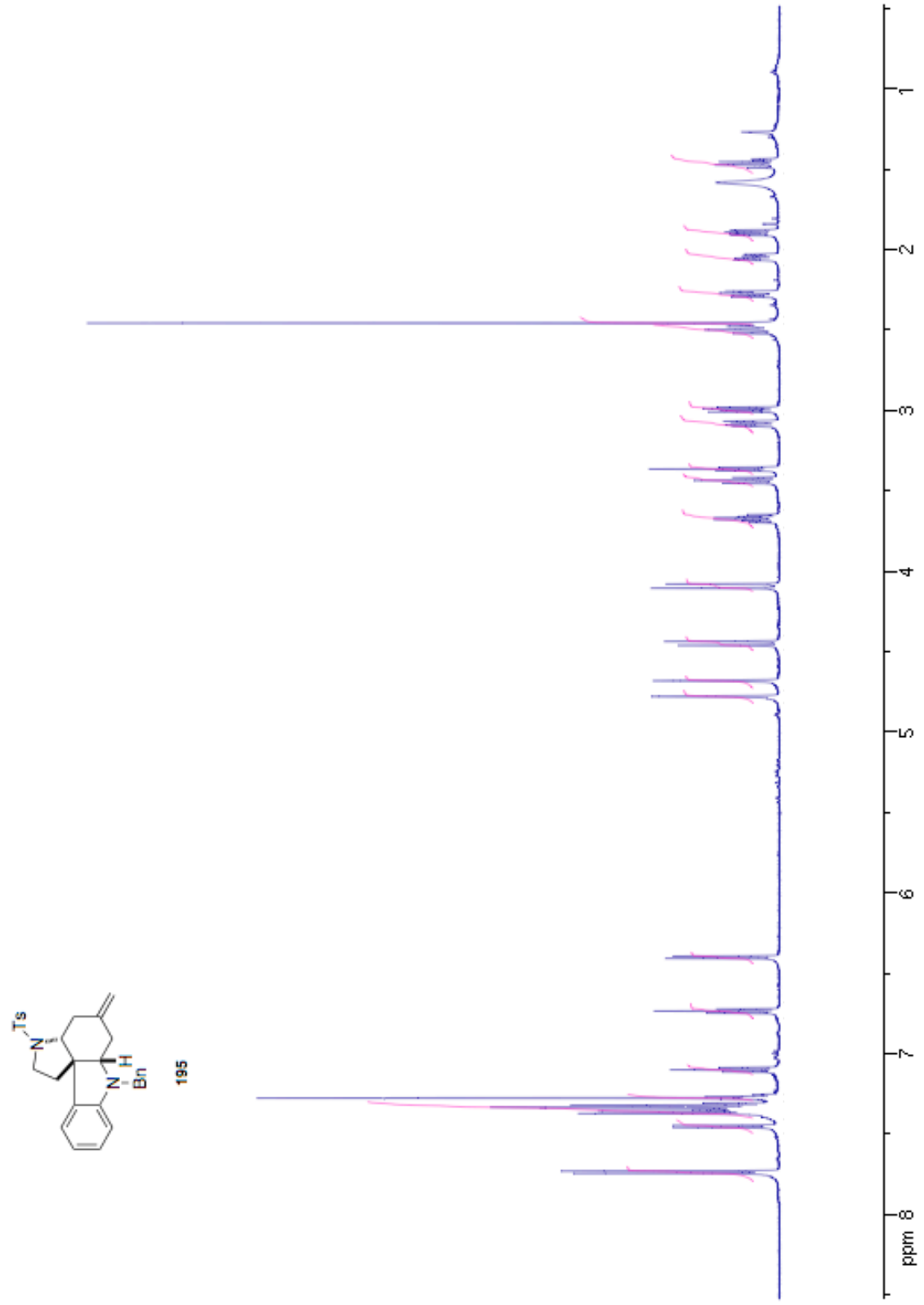
**Alkene 284** was generated as a side product of the intermolecular annulation reaction described above prior to its optimization as showen in Table 2.3.

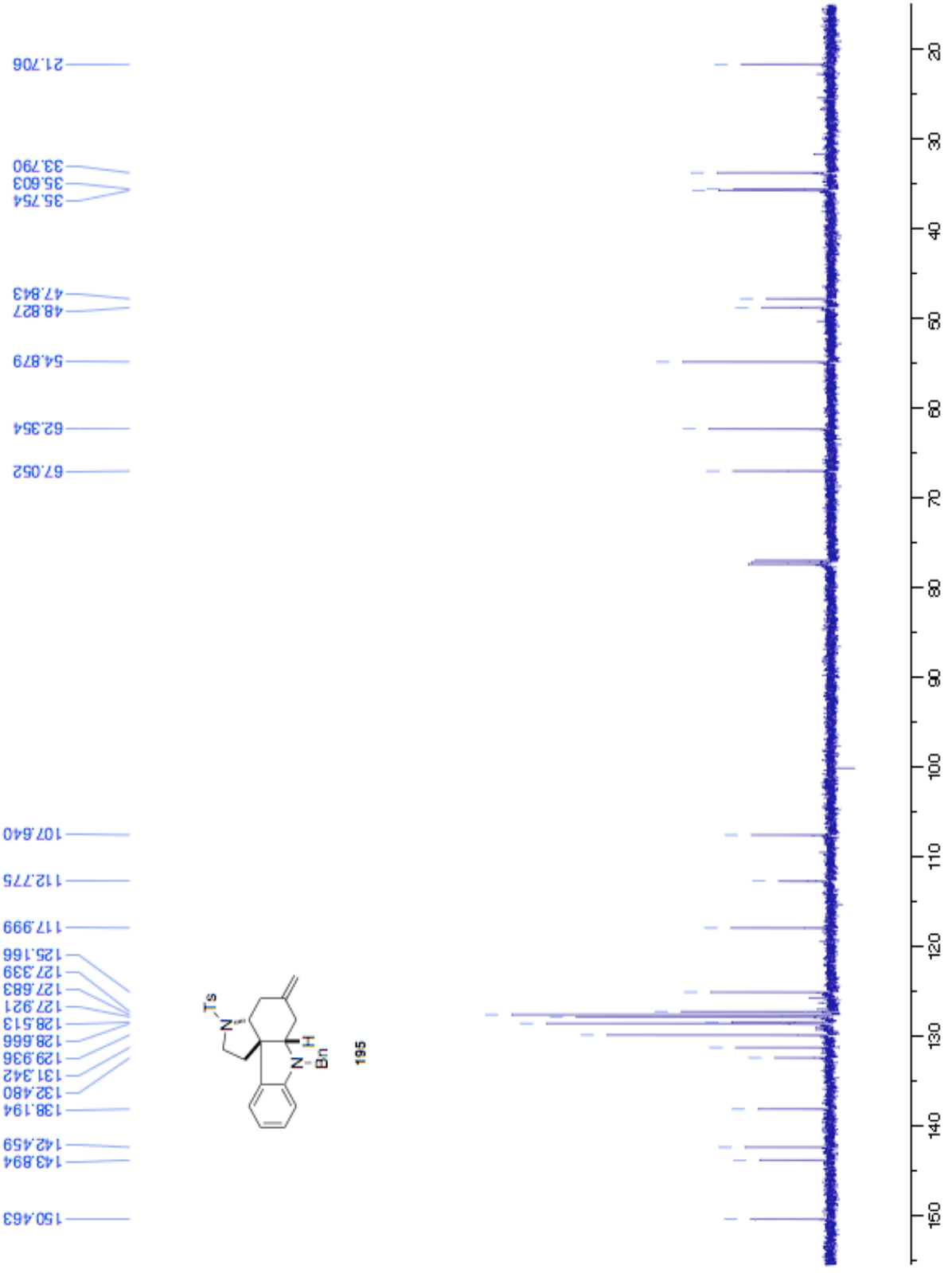


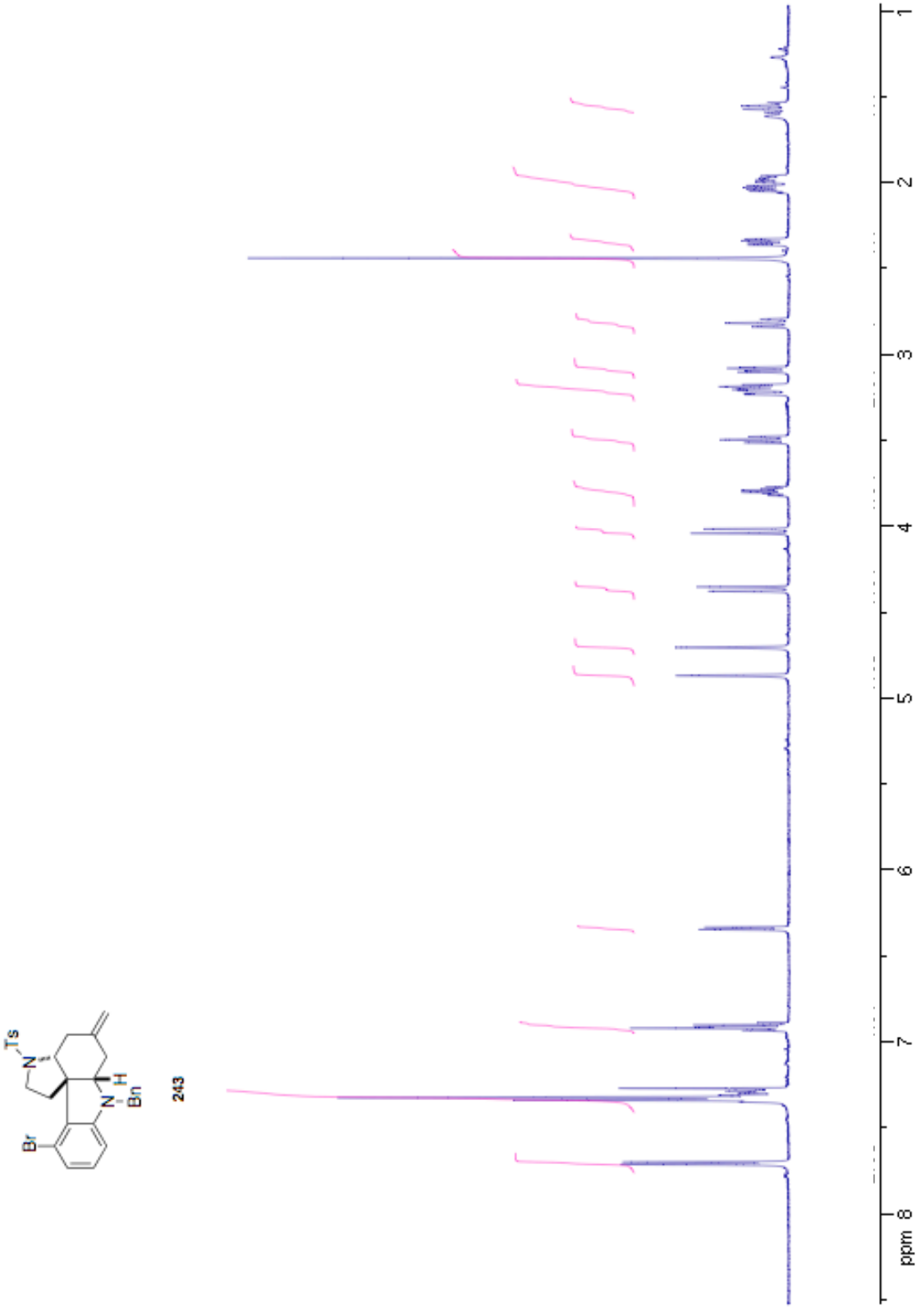

**284**

Amorphous white solid; **$R_f$** 0.51 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 400 MHz) δ 7.62 (d, 2H, *J* = 8.3 Hz), 7.41 (d, 1H, *J* = 8.0 Hz), 7.33-7.18 (m, 11H), 7.12 (dt, 1H, *J* = 7.6, 1.0 Hz), 7.05-7.03 (m, 2H), 6.93 (dt, 1H, *J* = 7.5, 0.9 Hz), 6.63 (d, 1H, *J* = 14.5 Hz), 6.47 (s, 1H), 5.19 (s, 2H), 5.09 (d, 1H, *J* = 14.5 Hz), 4.52 (s, 2H), 2.45 (s, 3H), 1.40 (s, 6H); **IR** (thin film, $cm^{-1}$) 3030.1 (w), 2961.3 (w), 2923.8 (w), 1651.4 (w), 1597.3 (w), 1495.7 (w), 1480.3 (w), 1465.6 (w), 1453.6 (w), 1354.1 (m), 1163.0 (s), 1091.0 (m), 733.8 (s); **HRMS** (+APCI) calculated for $C_{34}H_{35}N_2O_2S$ 535.2419, found 535.2428 $[M+H]^+$.

## 2.9. NMR Spectra


Ts
N
N
H
Bn
195
ppm
8
7
6
5
4
3
2
1


21.706
33.790
35.603
35.754
47.843
48.827
54.879
62.354
67.052
107.640
112.775
117.999
125.166
127.339
127.683
127.921
128.513
128.666
129.936
131.342
132.480
138.194
142.459
143.894
150.463
Ts
N
N
H
Bn
195
20
30
40
50
60
70
80
90
100
110
120
130
140
150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N
H
N
Bn
Br
243
ppm
8
7
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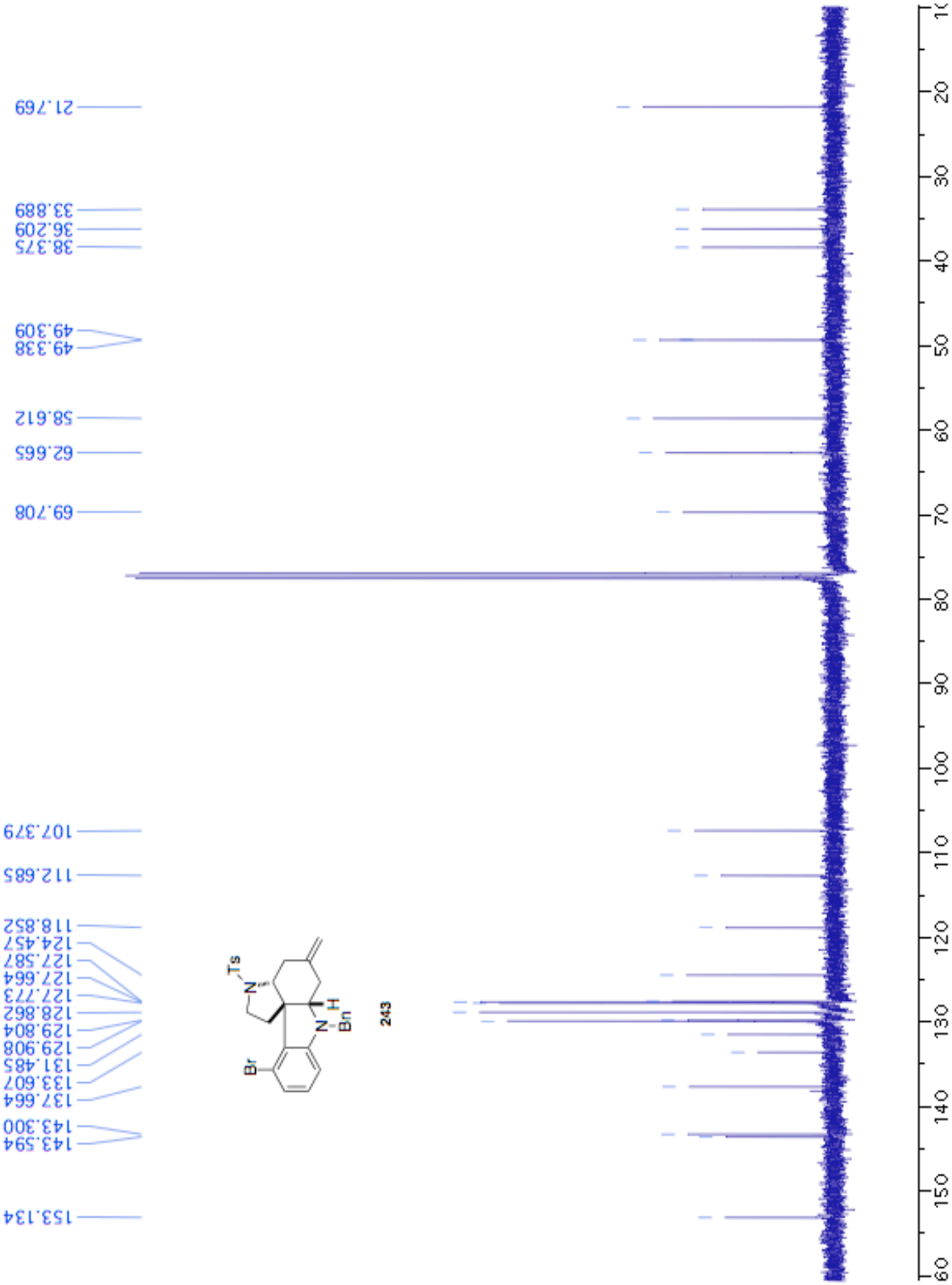
5
4
3
2
1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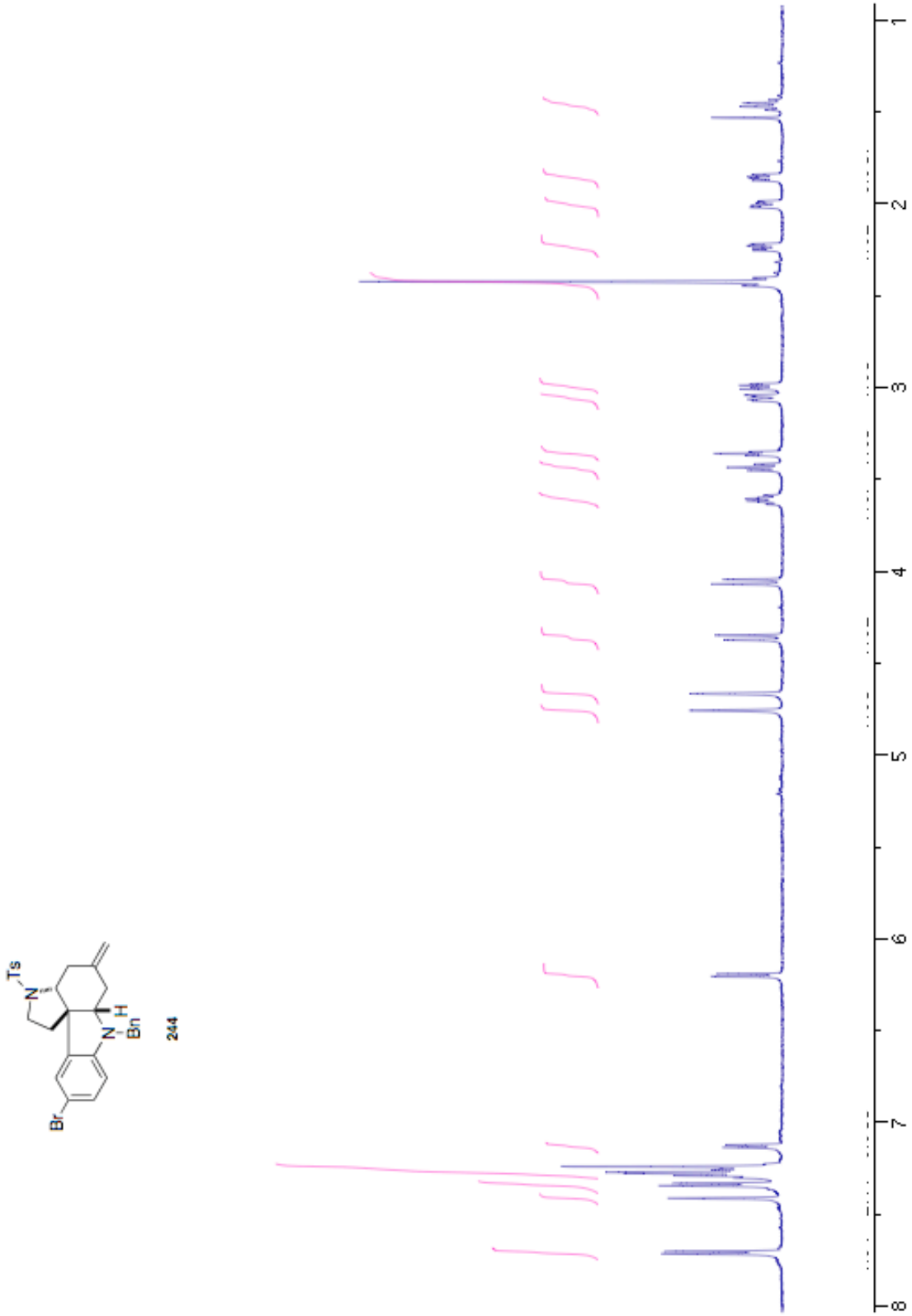
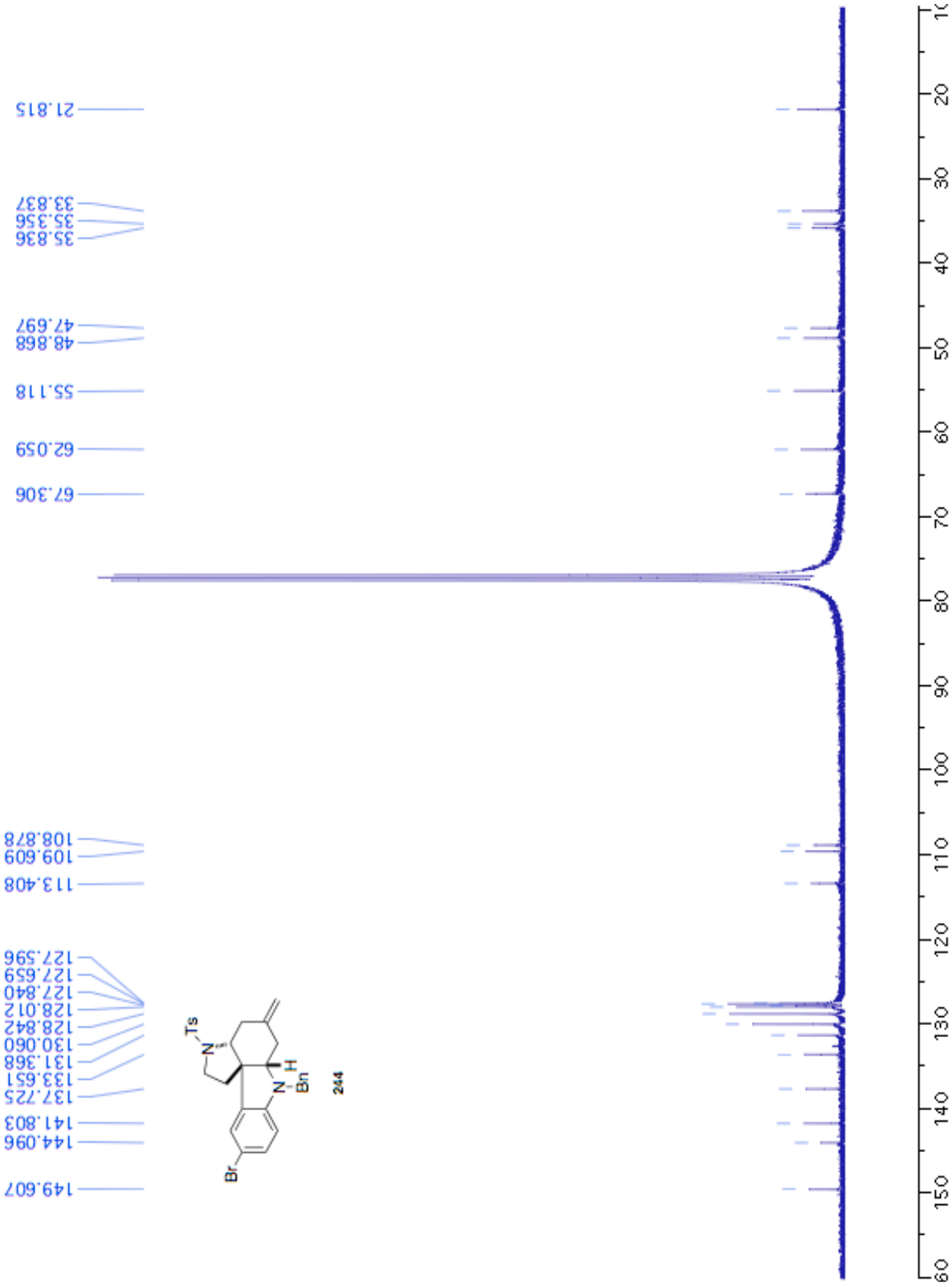
33.889
36.209
38.375
49.309
49.338
58.612
62.665
69.708
107.379
112.685
118.852
124.457
127.587
127.664
127.773
128.862
129.804
129.908
131.485
133.607
137.664
143.300
143.594
153.134
Ts
N
N
H
Bn
Br
243


Ts
N
N
H
Bn
Br
244
8
7
6
5
4
3
2
1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47.697
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67.306
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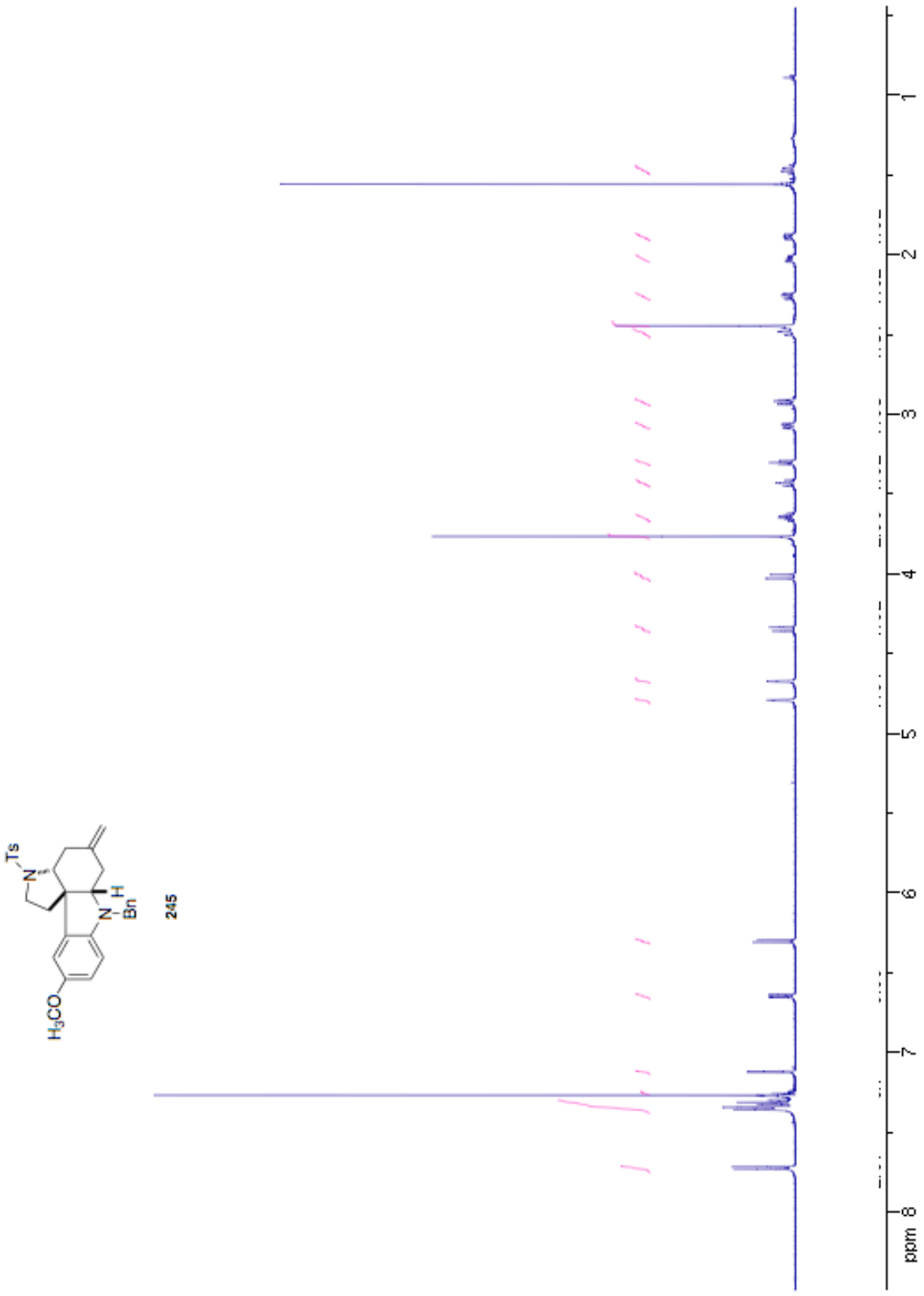
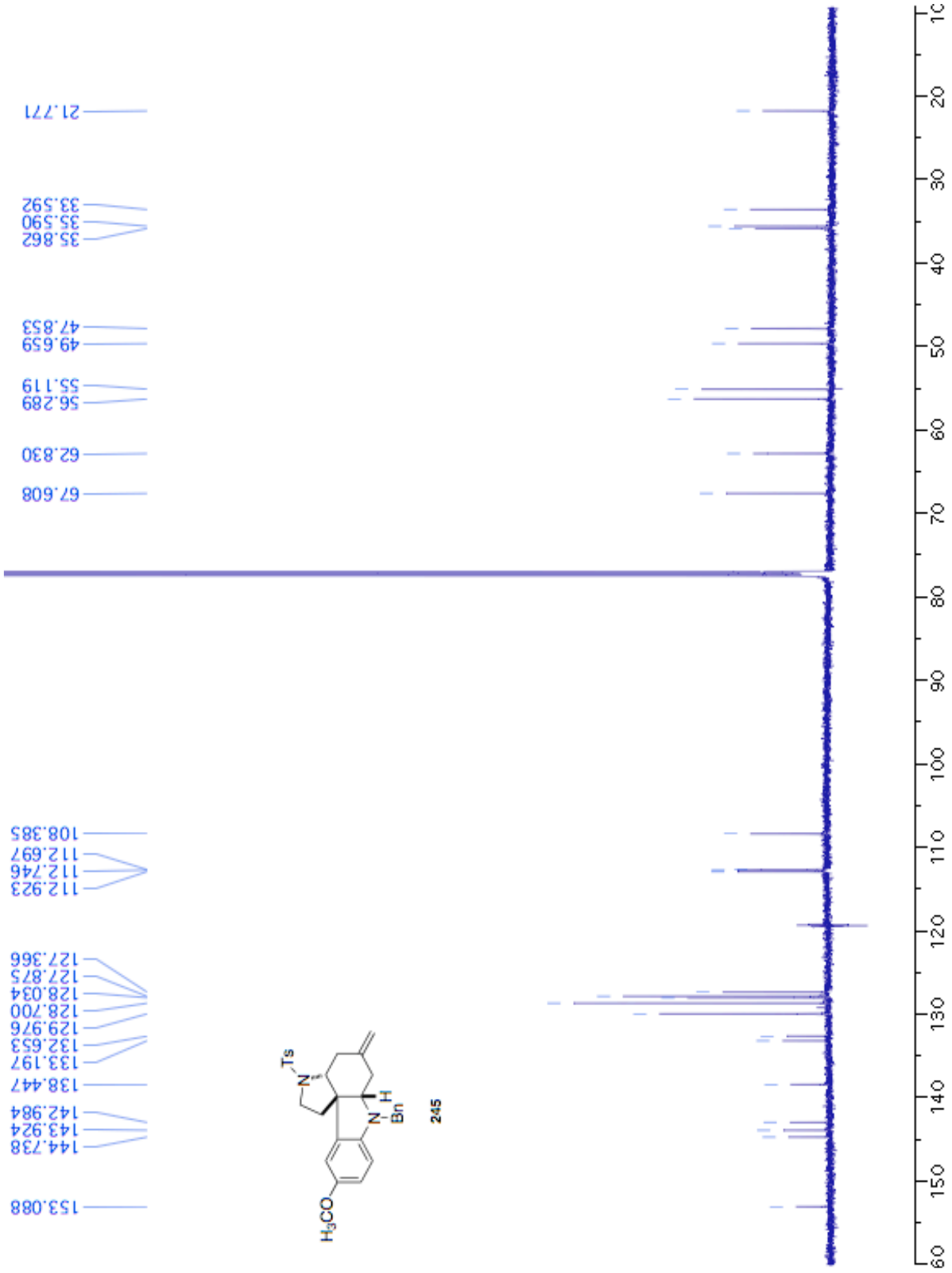
113.408
127.596
127.659
127.840
128.012
128.842
130.060
131.368
133.651
137.725
141.803
144.096
149.607
Ts
N
N
H
Bn
Br
244
60
70
80
90
100
110
120
130
140
150


Ts
N
N
H
Bn
H3CO
245
ppm
8
7
6
5
4
3
2
1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49.659
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112.923
127.366
127.875
128.034
128.700
129.976
132.653
133.197
138.447
142.984
143.924
144.738
153.088
Ts
N
N
H
Bn
H3CO
245
10
20
30
40
50
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150
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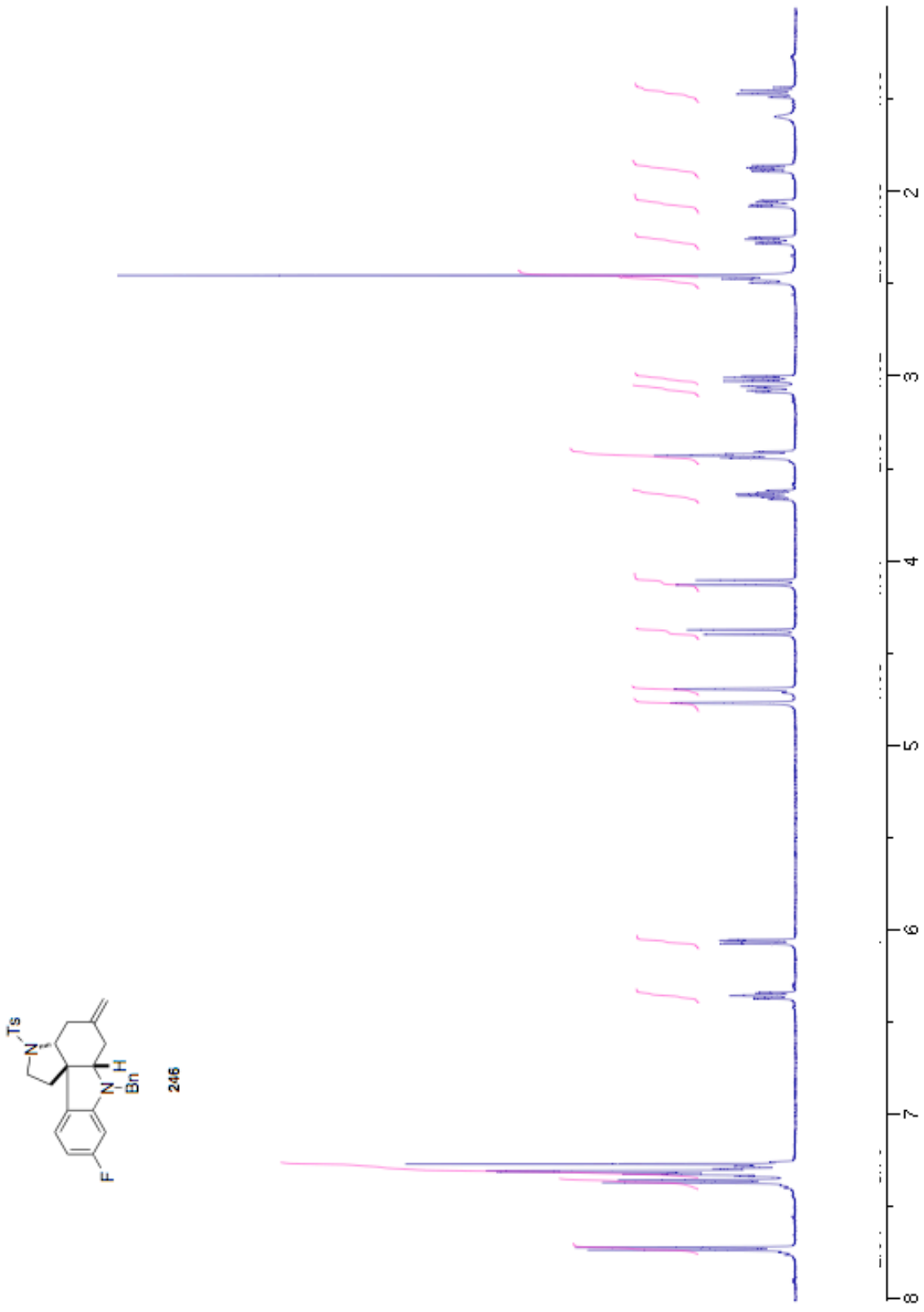
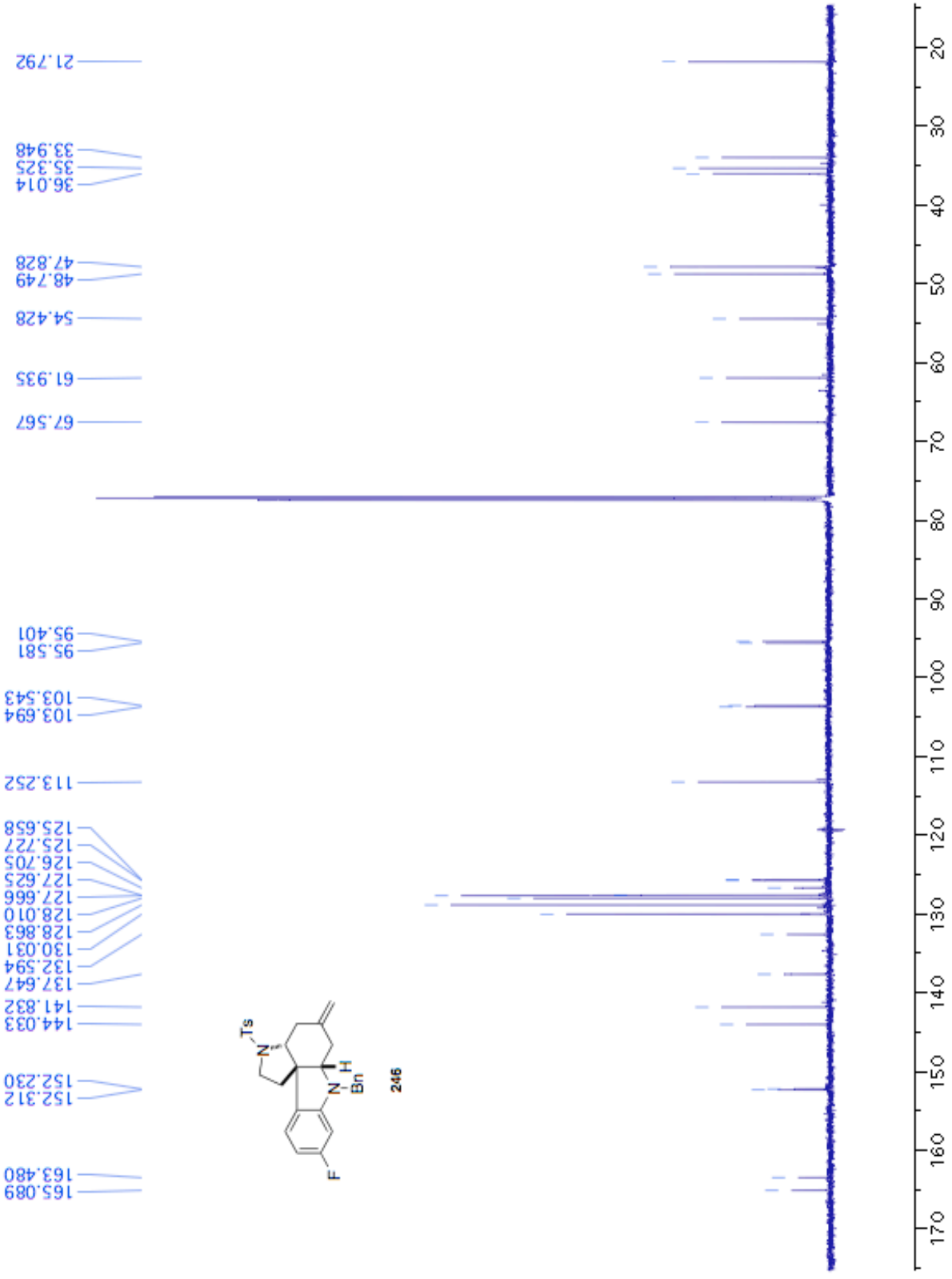

Ts
N
N
H
Bn
F
246
8
7
6
5
4
3
2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95.581
103.543
103.694
113.252
125.658
125.727
126.705
127.625
127.666
128.010
128.863
130.031
132.594
137.647
141.832
144.033
152.312
152.230
163.480
165.089
Ts
N
N
H
Bn
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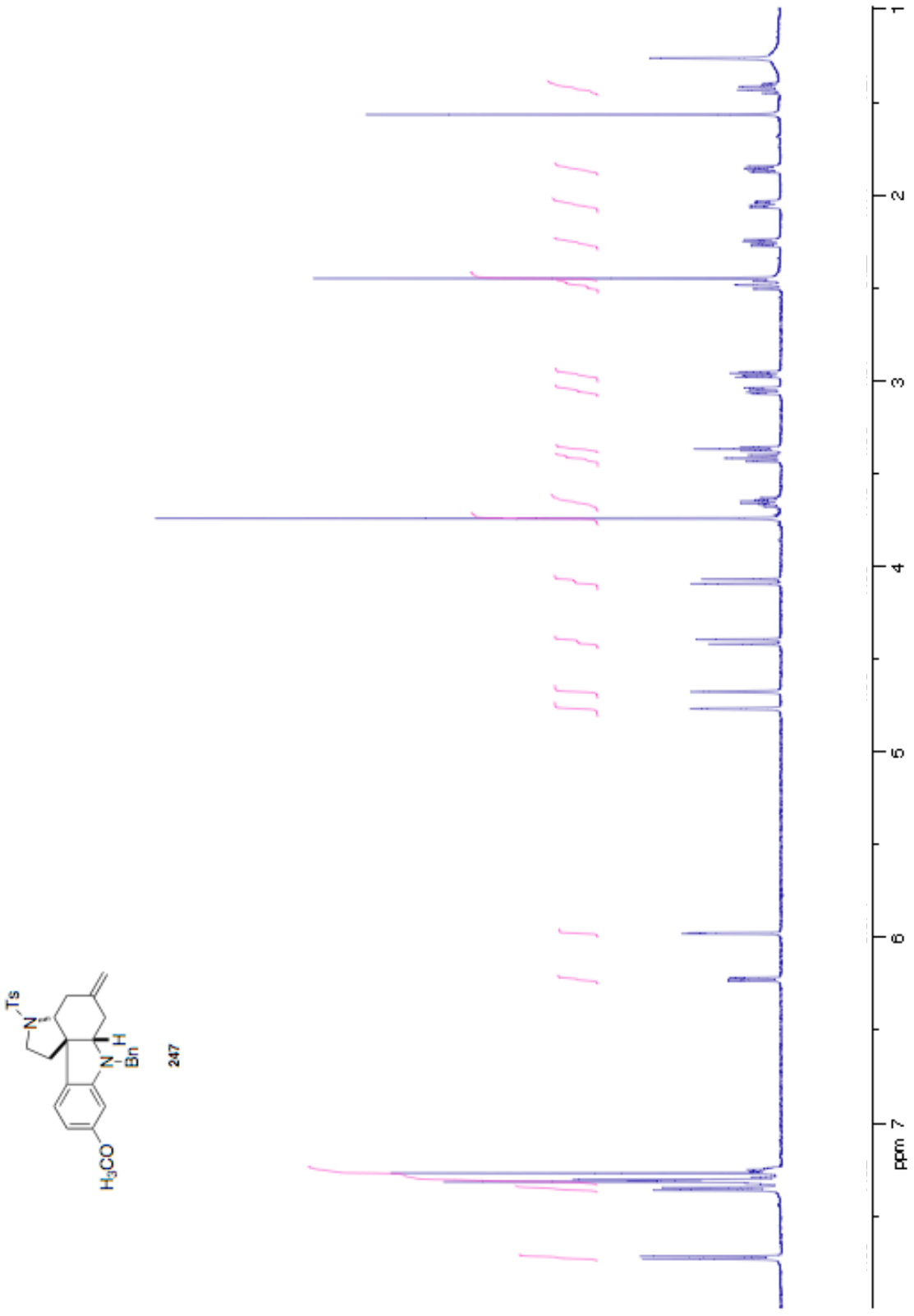
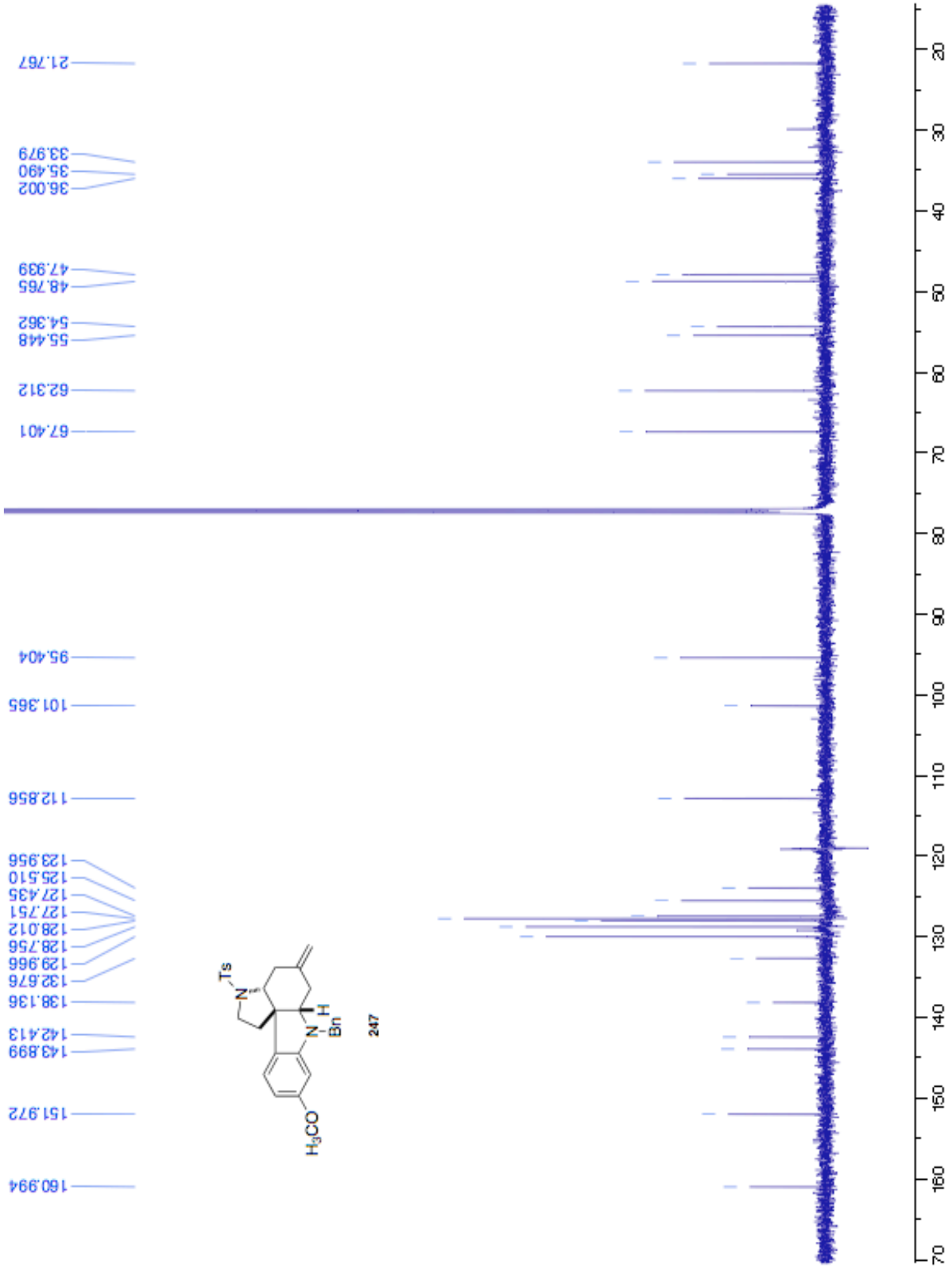
80
90
100
110
120
130
140
150
160
170


Ts
N
N
H
Bn
H3CO
247
ppm 7
6
5
4
3
2
1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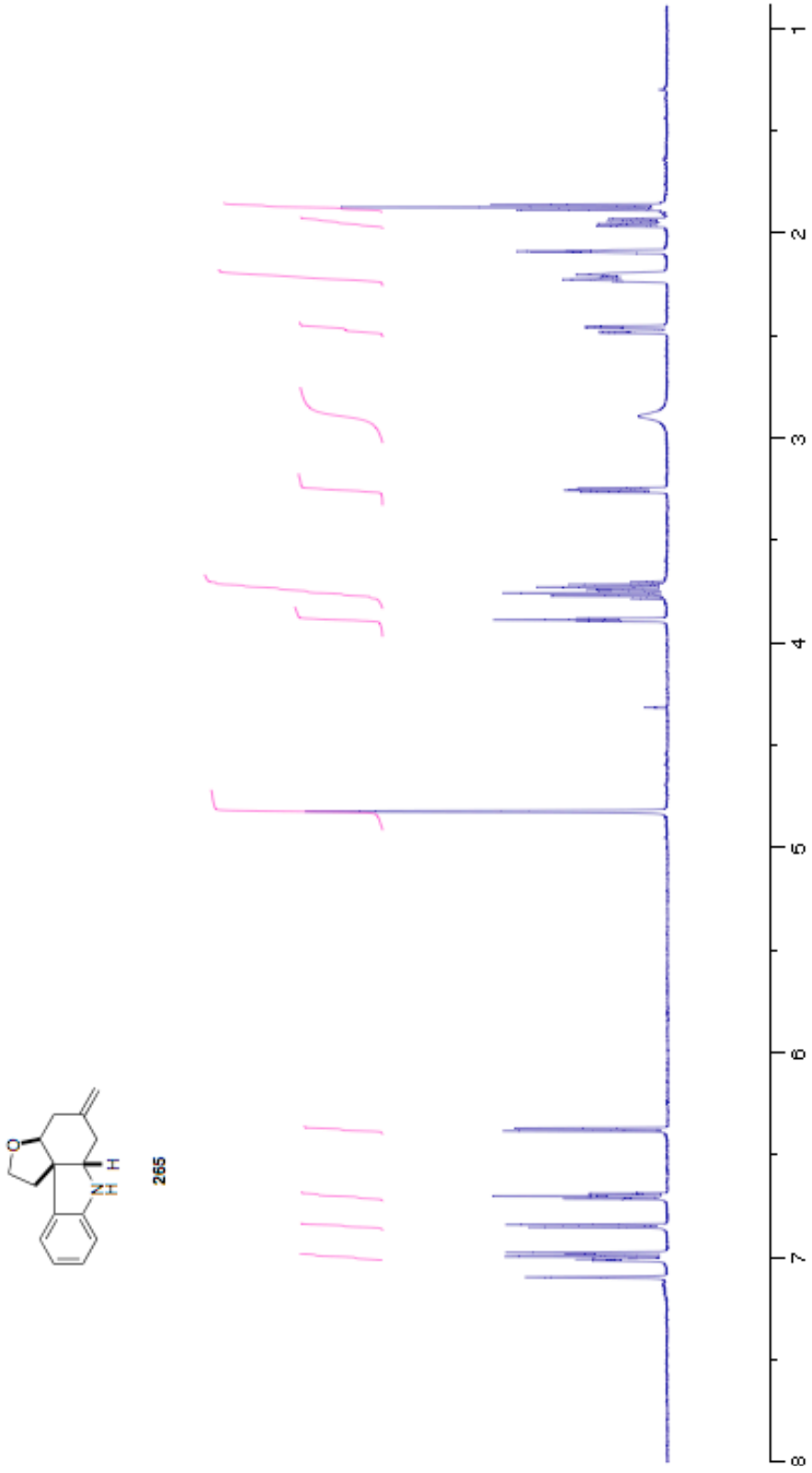
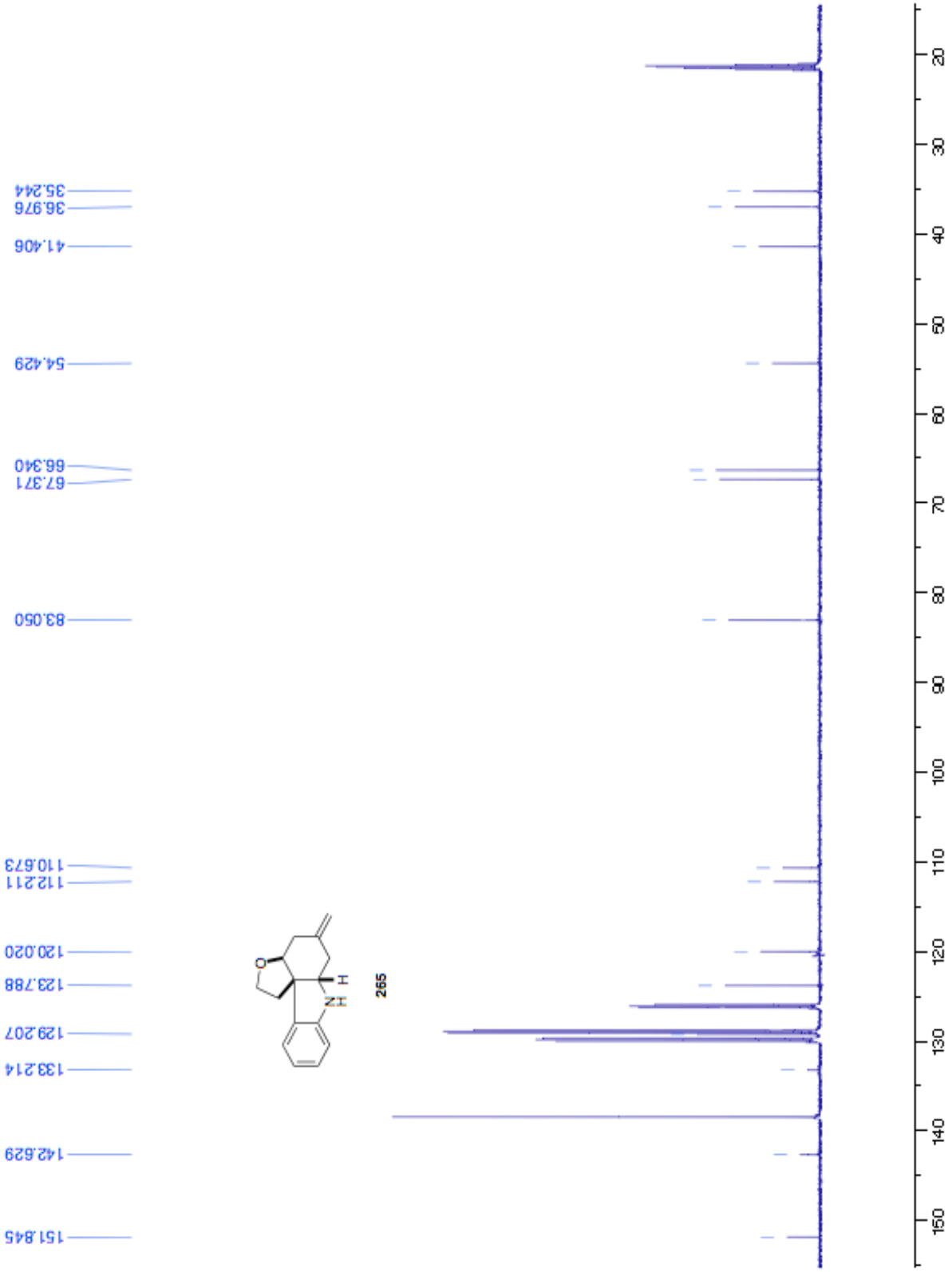
35.490
36.002
47.939
48.765
54.362
55.448
62.312
67.401
95.404
101.365
112.856
123.956
125.510
127.435
127.751
128.012
128.756
129.966
132.676
138.136
142.413
143.899
151.972
160.994
Ts
N
N
H
Bn
H3CO
247
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
70


O
N
H
H
265
1
2
3
4
5
6
7
8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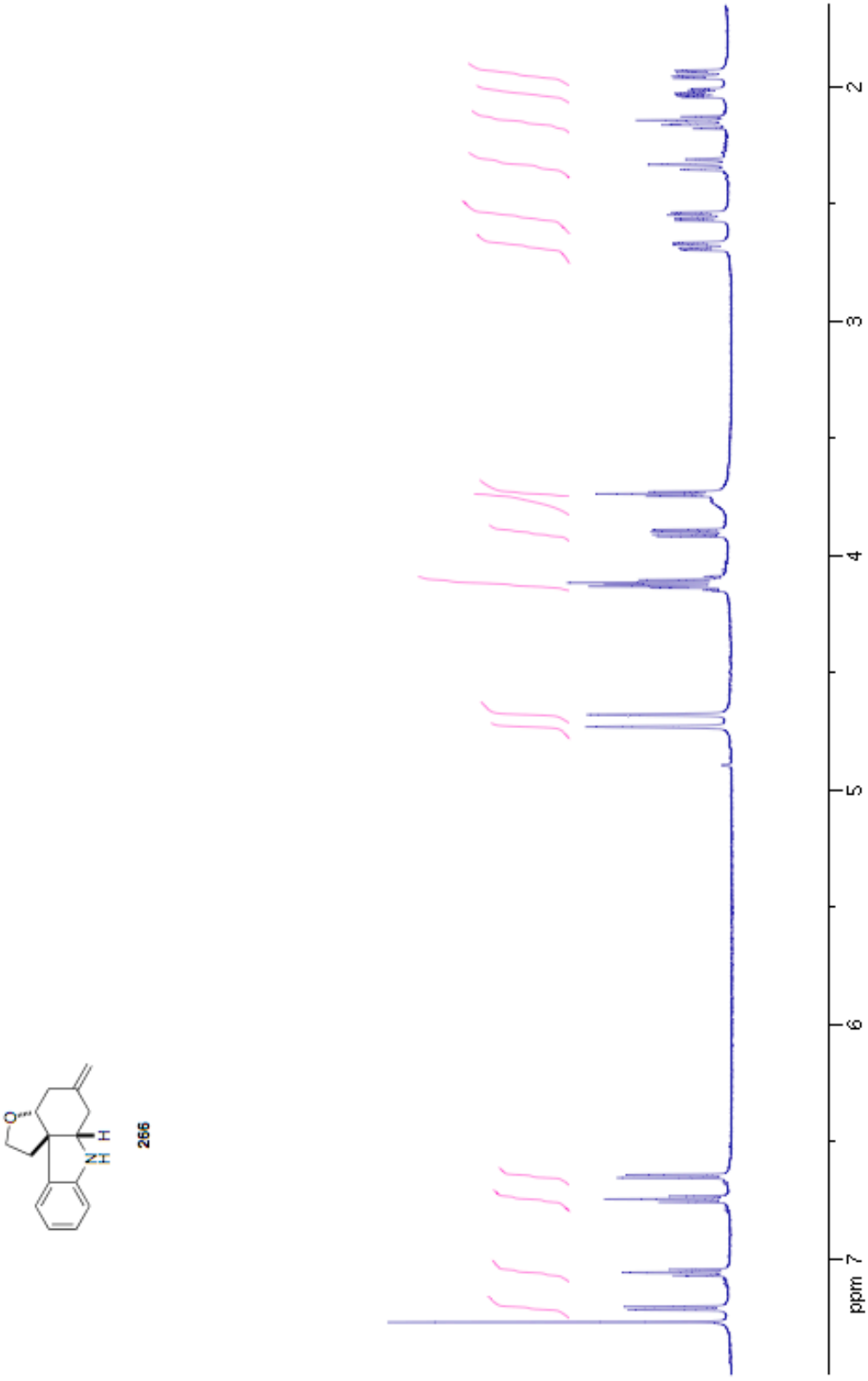
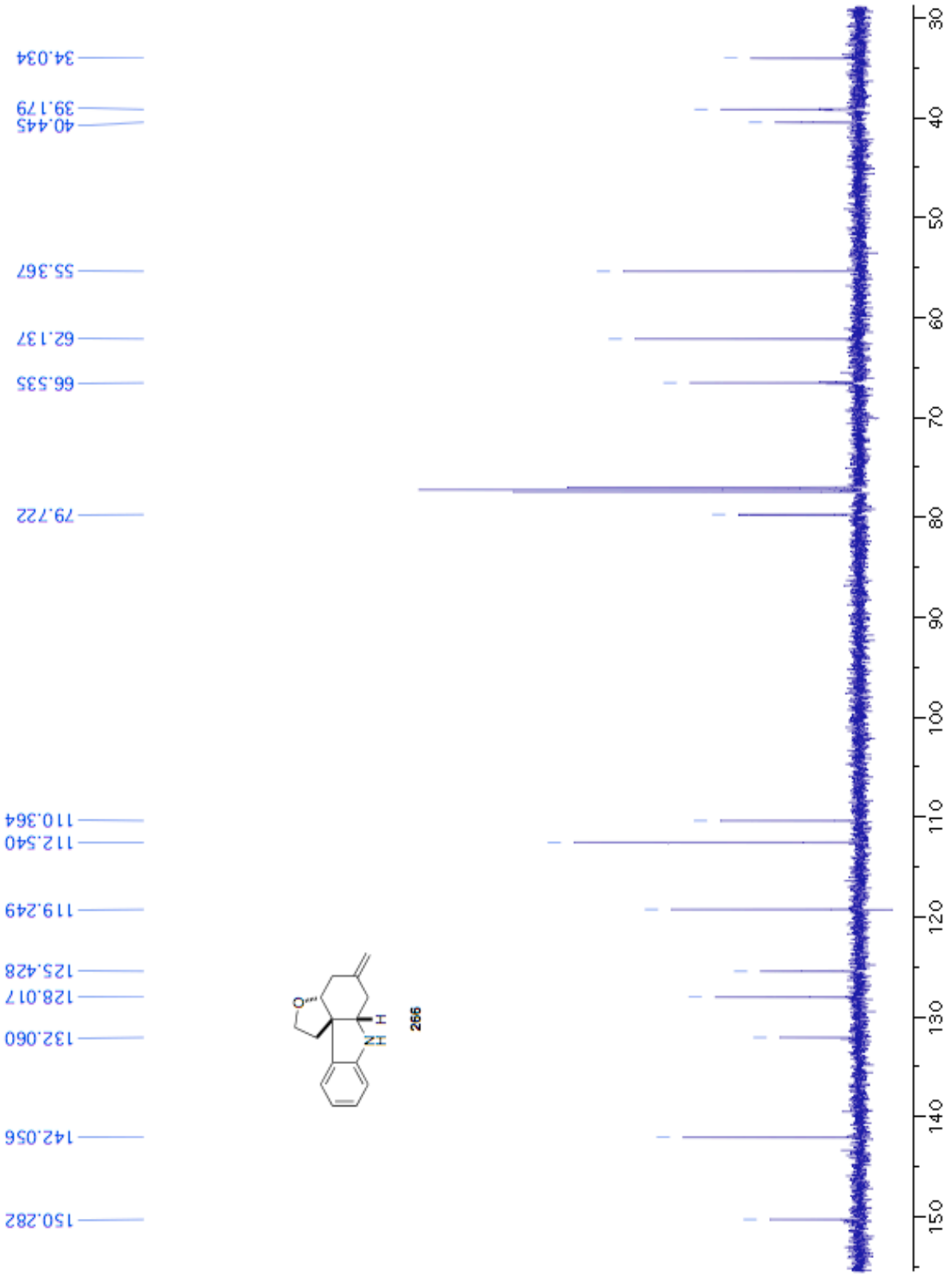
36.976
41.406
54.429
66.340
67.371
83.050
110.673
112.211
120.020
123.788
129.207
133.214
142.629
151.845
265
20
30
40
60
80
70
90
100
110
120
130
140
150


O
NH
H
266
2
3
4
5
6
7
ppm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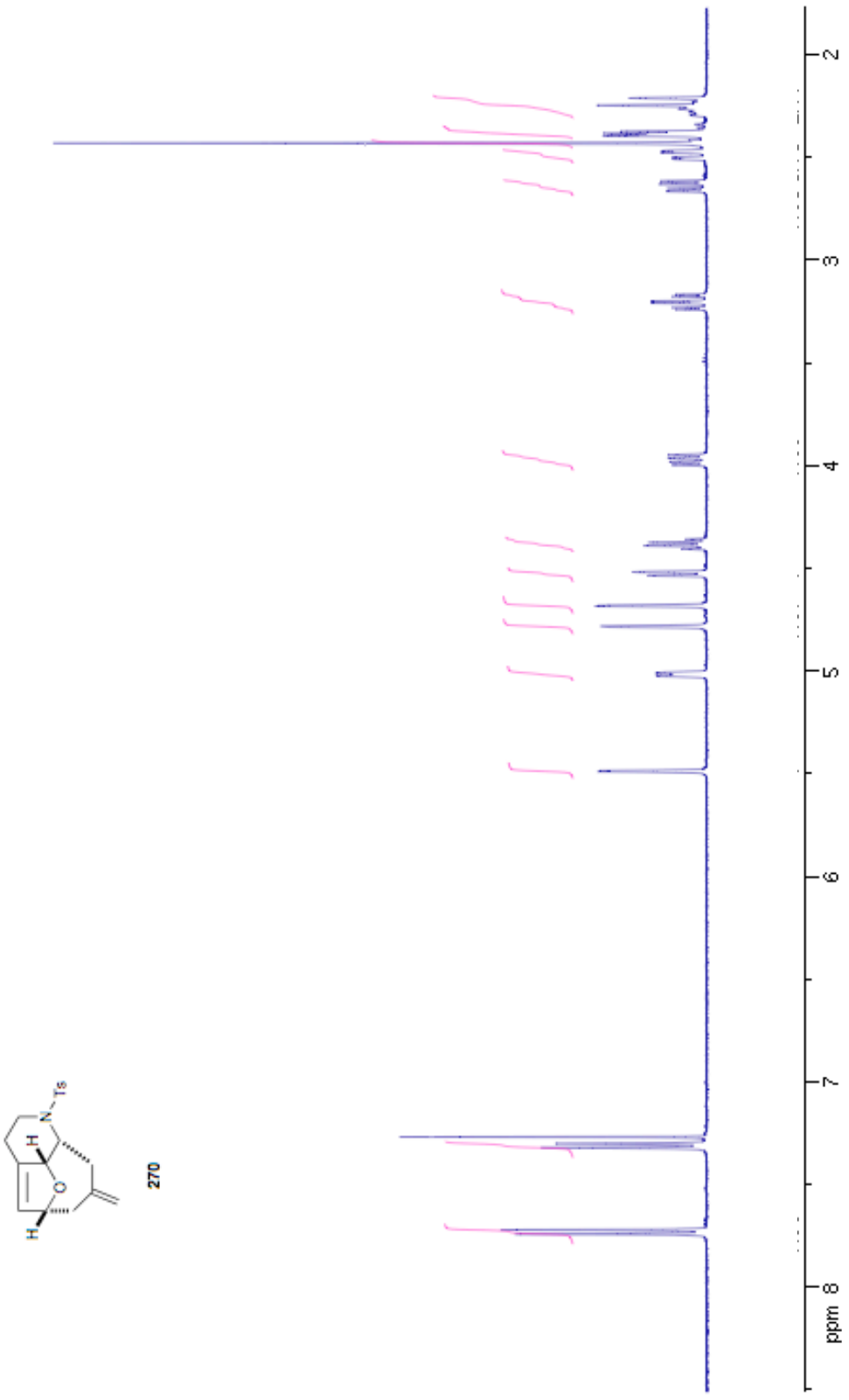
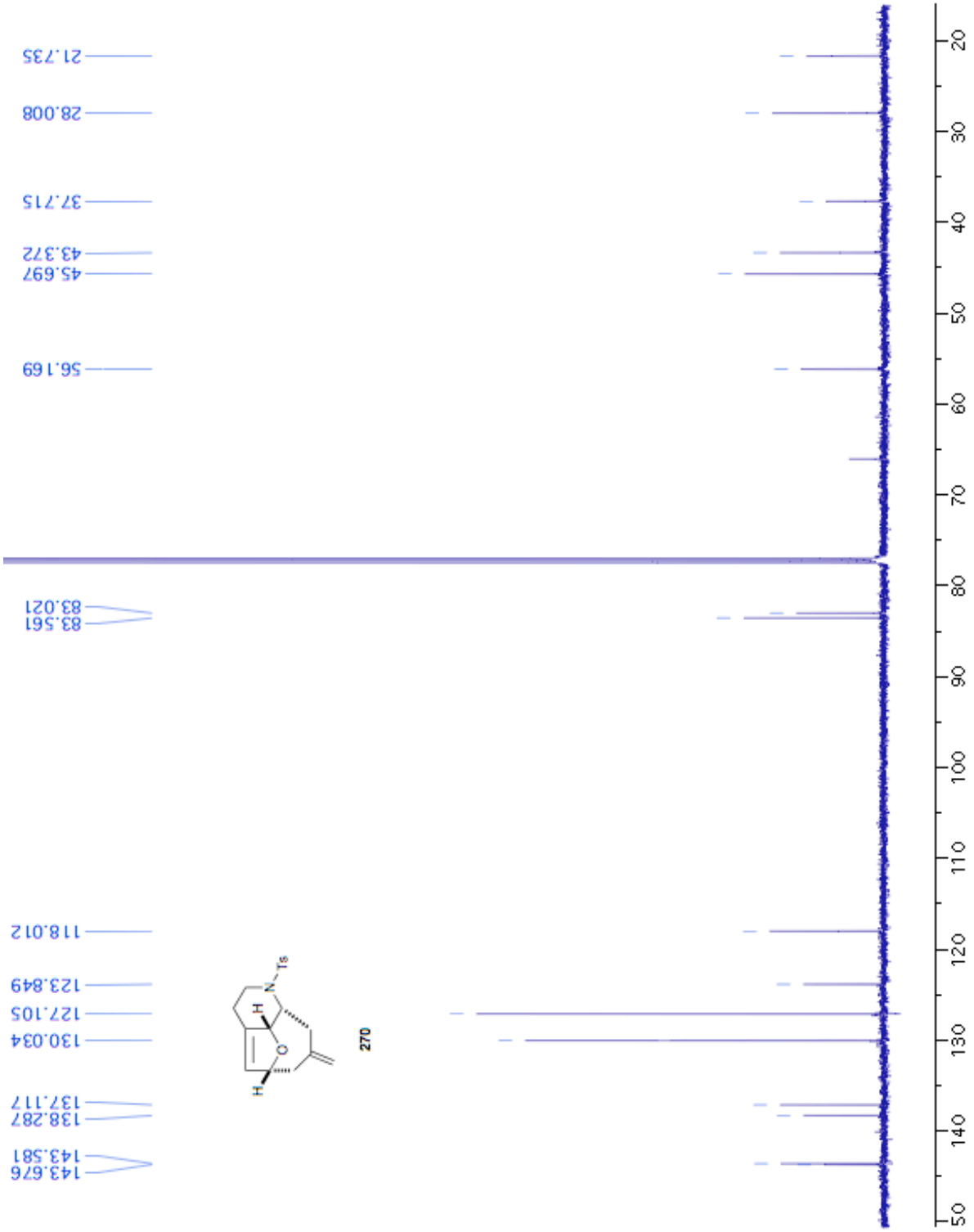
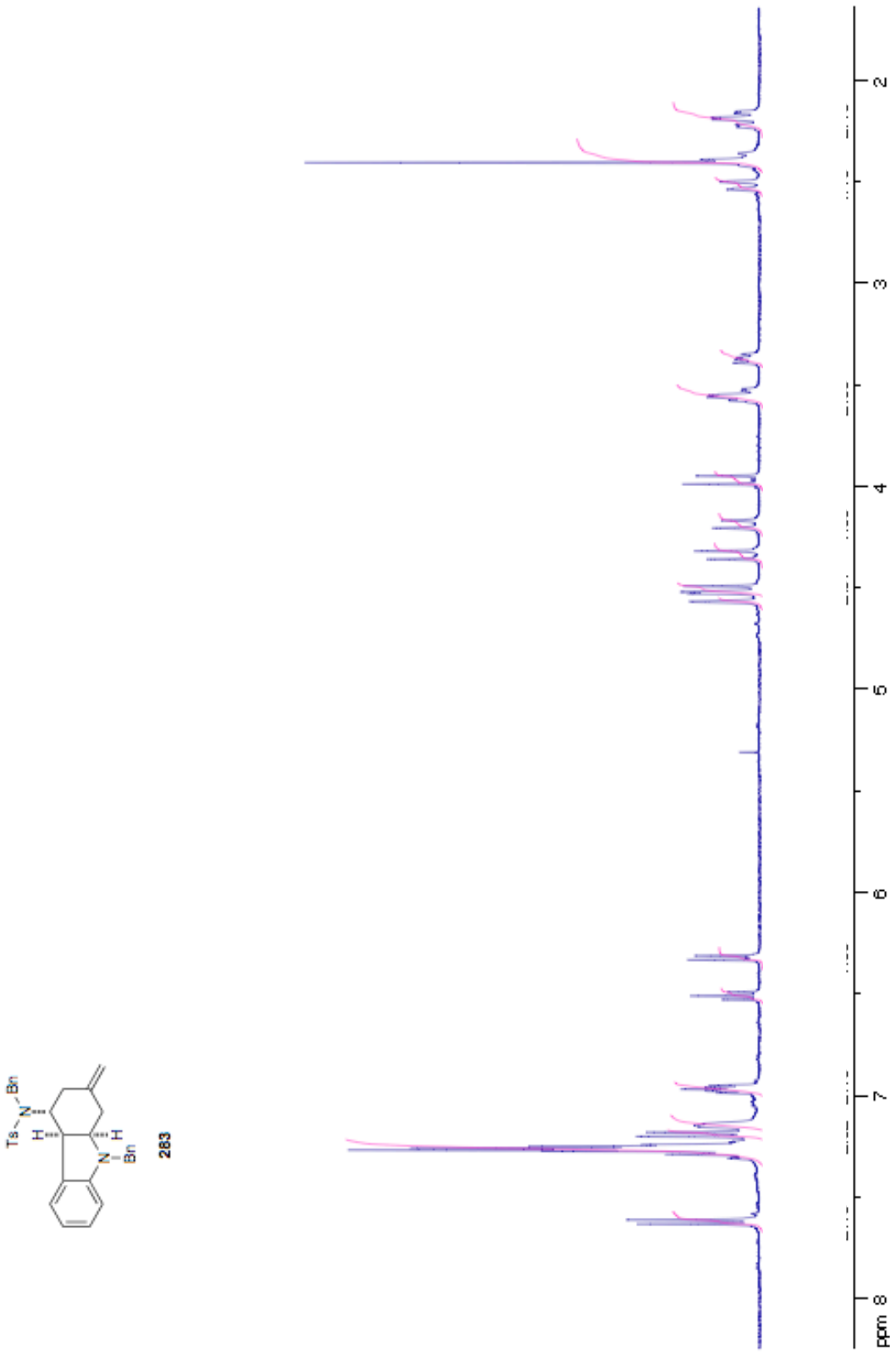
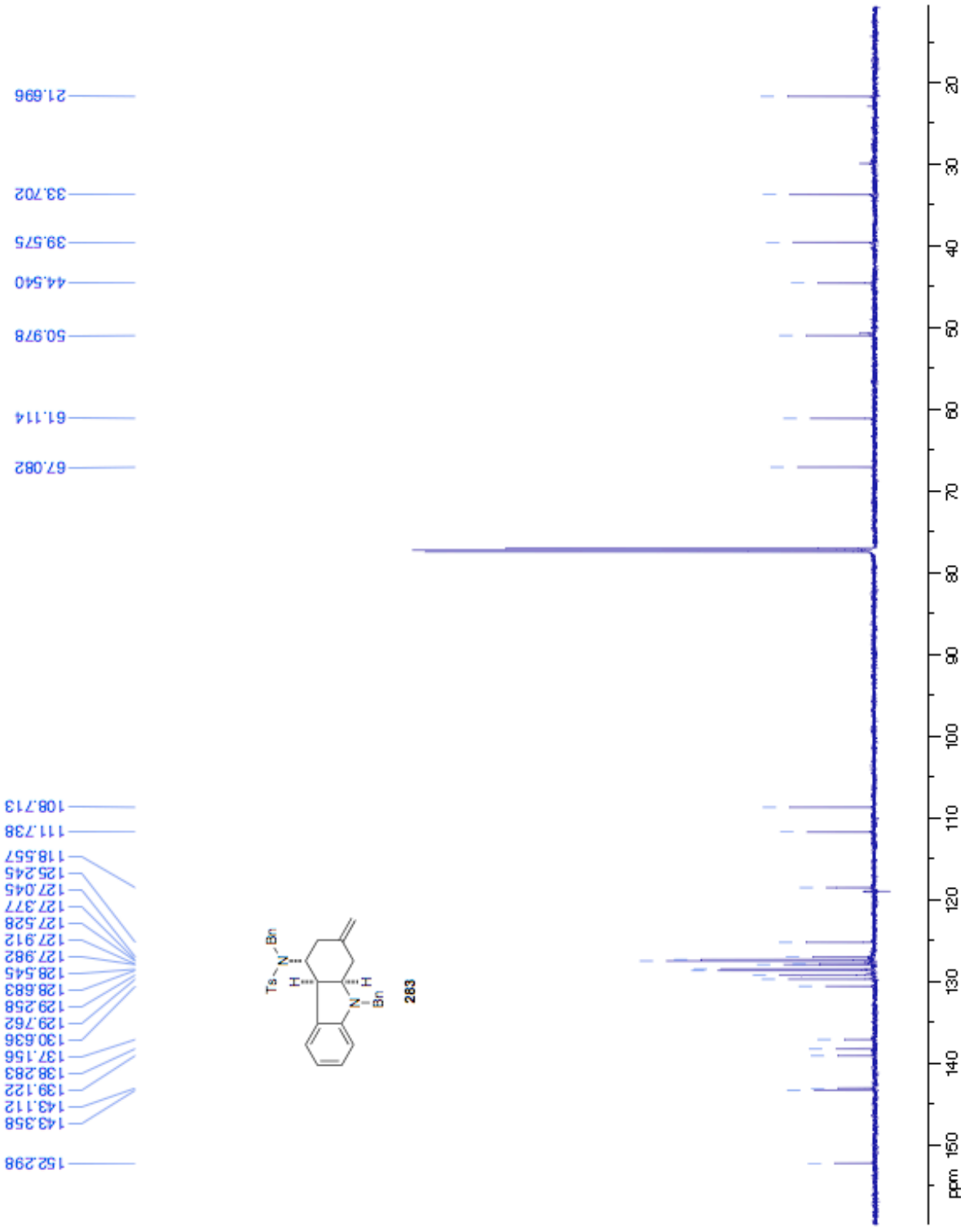
55.367
62.137
66.535
79.722
110.364
112.540
119.249
125.428
128.017
132.060
142.056
150.282
266


Ts
N
H
O
H
270
2
3
4
5
6
7
8
ppm

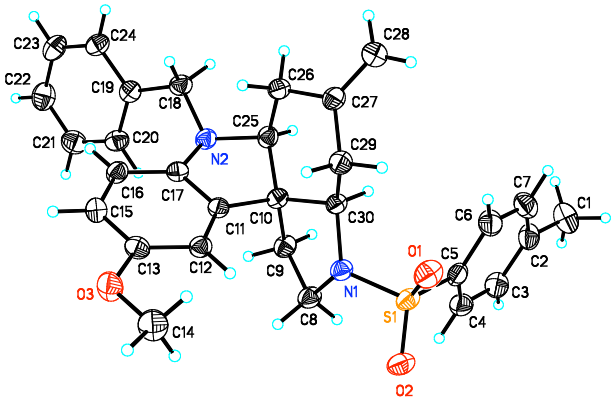

21.735
28.008
37.715
43.372
45.697
56.169
83.561
83.021
118.012
123.849
127.105
130.034
137.117
138.287
143.581
143.676
Ts
N
H
O
H
270
20
30
40
50
60
70
80
90
100
110
120
130
140
50

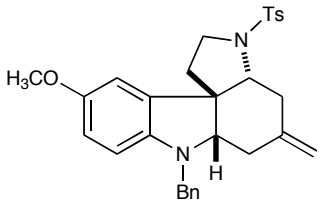

Ts
N
Bn
H
H
N
Bn
283
ppm
8
7
6
5
4
3
2


21.696
33.702
39.575
44.540
50.978
61.114
67.082
108.713
111.738
118.557
125.245
127.045
127.377
127.528
127.912
127.982
128.545
128.683
129.258
129.762
130.636
137.156
138.283
139.122
143.112
143.358
152.298
Ts
N
Bn
H
N
H
Bn
283
20
30
40
50
60
70
80
90
100
110
120
130
140
150
ppm

## 2.10. X-Ray Structures

**Compound 245**




**245**

Table 1. Crystal data and structure refinement for **245**.

| | | |
|---|---|---|
| Identification code | rd_05_263s | |
| Empirical formula | C30 H32 N2 O3 S | |
| Formula weight | 500.64 | |
| Temperature | 173(2) K | |
| Wavelength | 1.54178 Å | |
| Crystal system | Triclinic | |
| Space group | P-1 | |
| Unit cell dimensions | a = 8.5502(4) Å | α= 92.164(2)°. |
| | b = 10.2566(5) Å | β= 92.184(2)°. |
| | c = 16.4565(8) Å | γ = 113.149(2)°. |
| Volume | 1323.82(11) $Å^3$ | |
| Z | 2 | |
| Density (calculated) | 1.256 $Mg/m^3$ | |
| Absorption coefficient | 1.352 $mm^{-1}$ | |
| F(000) | 532 | |
| Crystal size | 0.24 x 0.20 x 0.04 $mm^3$ | |
| Theta range for data collection | 2.69 to 66.09°. | |
| Index ranges | -10<=h<=9, -11<=k<=11, -19<=l<=19 | |

| | |
|---|---|
| Reflections collected | 10496 |
| Independent reflections | 4017 [R(int) = 0.0167] |
| Completeness to theta = 66.09° | 86.8 % |
| Absorption correction | Semi-empirical from equivalents |
| Max. and min. transmission | 0.9479 and 0.7374 |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 4017 / 0 / 327 |
| Goodness-of-fit on $F^2$ | 1.048 |
| Final R indices [I>2sigma(I)] | R1 = 0.0334, wR2 = 0.0877 |
| R indices (all data) | R1 = 0.0353, wR2 = 0.0892 |
| Largest diff. peak and hole | 0.201 and -0.422 e.$Å^{-3}$ |

Table 2. Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters
($Å^2$x $10^3$) for **245**. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$
tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| C(1) | -1394(3) | 5447(2) | 6272(1) | 46(1) |
| C(2) | -358(2) | 4567(2) | 6144(1) | 34(1) |
| C(3) | -1084(2) | 3210(2) | 5765(1) | 35(1) |
| C(4) | -122(2) | 2413(2) | 5631(1) | 32(1) |
| C(5) | 1604(2) | 2980(2) | 5880(1) | 28(1) |
| C(6) | 2344(2) | 4324(2) | 6271(1) | 36(1) |
| C(7) | 1361(2) | 5100(2) | 6398(1) | 39(1) |
| C(8) | 1007(2) | -283(2) | 6537(1) | 29(1) |
| C(9) | 559(2) | -316(2) | 7429(1) | 27(1) |
| C(10) | 2326(2) | 464(2) | 7878(1) | 23(1) |
| C(11) | 3184(2) | -577(2) | 7977(1) | 23(1) |
| C(12) | 4062(2) | -1085(2) | 7443(1) | 24(1) |

| | | | | |
|---|---|---|---|---|
| C(13) | 4636(2) | -2107(2) | 7710(1) | 26(1) |
| C(14) | 6023(2) | -2126(2) | 6476(1) | 39(1) |
| C(15) | 4307(2) | -2610(2) | 8482(1) | 28(1) |
| C(16) | 3427(2) | -2100(2) | 9016(1) | 26(1) |
| C(17) | 2878(2) | -1070(2) | 8759(1) | 23(1) |
| C(18) | 2194(2) | -245(2) | 10077(1) | 28(1) |
| C(19) | 1236(2) | -1589(2) | 10496(1) | 26(1) |
| C(20) | -78(2) | -2762(2) | 10109(1) | 31(1) |
| C(21) | -957(2) | -3946(2) | 10538(1) | 37(1) |
| C(22) | -553(2) | -3971(2) | 11359(1) | 40(1) |
| C(23) | 757(2) | -2813(2) | 11749(1) | 36(1) |
| C(24) | 1652(2) | -1639(2) | 11318(1) | 29(1) |
| C(25) | 2363(2) | 959(2) | 8770(1) | 25(1) |
| C(26) | 4166(2) | 2081(2) | 9047(1) | 27(1) |
| C(27) | 5020(2) | 3175(2) | 8442(1) | 27(1) |
| C(28) | 5785(2) | 4547(2) | 8651(1) | 36(1) |
| C(29) | 4968(2) | 2598(2) | 7578(1) | 27(1) |
| C(30) | 3105(2) | 1711(2) | 7339(1) | 23(1) |
| N(1) | 2648(2) | 996(1) | 6509(1) | 25(1) |
| N(2) | 1990(2) | -380(1) | 9189(1) | 25(1) |
| O(1) | 4592(1) | 2950(1) | 5738(1) | 35(1) |
| O(2) | 2117(1) | 1003(1) | 5034(1) | 34(1) |
| O(3) | 5532(2) | -2691(1) | 7244(1) | 35(1) |
| S(1) | 2849(1) | 1976(1) | 5726(1) | 27(1) |

Table 3. Bond lengths [Å] and angles [°] for **245**.

| | |
|---|---|
| C(1)-C(2) | 1.507(2) |
| C(1)-H(1A) | 0.9800 |
| C(1)-H(1B) | 0.9800 |
| C(1)-H(1C) | 0.9800 |
| C(2)-C(7) | 1.392(2) |

| | |
|---|---|
| C(2)-C(3) | 1.392(2) |
| C(3)-C(4) | 1.386(2) |
| C(3)-H(3) | 0.9500 |
| C(4)-C(5) | 1.394(2) |
| C(4)-H(4) | 0.9500 |
| C(5)-C(6) | 1.389(2) |
| C(5)-S(1) | 1.7661(16) |
| C(6)-C(7) | 1.382(2) |
| C(6)-H(6) | 0.9500 |
| C(7)-H(7) | 0.9500 |
| C(8)-N(1) | 1.501(2) |
| C(8)-C(9) | 1.531(2) |
| C(8)-H(8A) | 0.9900 |
| C(8)-H(8B) | 0.9900 |
| C(9)-C(10) | 1.5453(19) |
| C(9)-H(9A) | 0.9900 |
| C(9)-H(9B) | 0.9900 |
| C(10)-C(30) | 1.525(2) |
| C(10)-C(11) | 1.525(2) |
| C(10)-C(25) | 1.530(2) |
| C(11)-C(12) | 1.389(2) |
| C(11)-C(17) | 1.396(2) |
| C(12)-C(13) | 1.399(2) |
| C(12)-H(12) | 0.9500 |
| C(13)-O(3) | 1.3800(18) |
| C(13)-C(15) | 1.387(2) |
| C(14)-O(3) | 1.420(2) |
| C(14)-H(14A) | 0.9800 |
| C(14)-H(14B) | 0.9800 |
| C(14)-H(14C) | 0.9800 |
| C(15)-C(16) | 1.391(2) |
| C(15)-H(15) | 0.9500 |
| C(16)-C(17) | 1.388(2) |
| C(16)-H(16) | 0.9500 |
| C(17)-N(2) | 1.4158(19) |
| C(18)-N(2) | 1.4588(19) |

| | |
|---|---|
| C(18)-C(19) | 1.508(2) |
| C(18)-H(18A) | 0.9900 |
| C(18)-H(18B) | 0.9900 |
| C(19)-C(20) | 1.393(2) |
| C(19)-C(24) | 1.394(2) |
| C(20)-C(21) | 1.388(2) |
| C(20)-H(20) | 0.9500 |
| C(21)-C(22) | 1.385(2) |
| C(21)-H(21) | 0.9500 |
| C(22)-C(23) | 1.386(3) |
| C(22)-H(22) | 0.9500 |
| C(23)-C(24) | 1.385(2) |
| C(23)-H(23) | 0.9500 |
| C(24)-H(24) | 0.9500 |
| C(25)-N(2) | 1.4861(19) |
| C(25)-C(26) | 1.556(2) |
| C(25)-H(25) | 1.0000 |
| C(26)-C(27) | 1.510(2) |
| C(26)-H(26A) | 0.9900 |
| C(26)-H(26B) | 0.9900 |
| C(27)-C(28) | 1.323(2) |
| C(27)-C(29) | 1.511(2) |
| C(28)-H(28A) | 0.9500 |
| C(28)-H(28B) | 0.9500 |
| C(29)-C(30) | 1.518(2) |
| C(29)-H(29A) | 0.9900 |
| C(29)-H(29B) | 0.9900 |
| C(30)-N(1) | 1.4889(18) |
| C(30)-H(30) | 1.0000 |
| N(1)-S(1) | 1.6365(12) |
| O(1)-S(1) | 1.4301(12) |
| O(2)-S(1) | 1.4335(11) |

| | |
|---|---|
| C(2)-C(1)-H(1A) | 109.5 |
| C(2)-C(1)-H(1B) | 109.5 |
| H(1A)-C(1)-H(1B) | 109.5 |

| | |
|---|---|
| C(2)-C(1)-H(1C) | 109.5 |
| H(1A)-C(1)-H(1C) | 109.5 |
| H(1B)-C(1)-H(1C) | 109.5 |
| C(7)-C(2)-C(3) | 118.23(16) |
| C(7)-C(2)-C(1) | 120.60(16) |
| C(3)-C(2)-C(1) | 121.17(15) |
| C(4)-C(3)-C(2) | 121.16(15) |
| C(4)-C(3)-H(3) | 119.4 |
| C(2)-C(3)-H(3) | 119.4 |
| C(3)-C(4)-C(5) | 119.46(15) |
| C(3)-C(4)-H(4) | 120.3 |
| C(5)-C(4)-H(4) | 120.3 |
| C(6)-C(5)-C(4) | 120.17(15) |
| C(6)-C(5)-S(1) | 119.56(12) |
| C(4)-C(5)-S(1) | 120.25(12) |
| C(7)-C(6)-C(5) | 119.39(15) |
| C(7)-C(6)-H(6) | 120.3 |
| C(5)-C(6)-H(6) | 120.3 |
| C(6)-C(7)-C(2) | 121.57(16) |
| C(6)-C(7)-H(7) | 119.2 |
| C(2)-C(7)-H(7) | 119.2 |
| N(1)-C(8)-C(9) | 104.75(11) |
| N(1)-C(8)-H(8A) | 110.8 |
| C(9)-C(8)-H(8A) | 110.8 |
| N(1)-C(8)-H(8B) | 110.8 |
| C(9)-C(8)-H(8B) | 110.8 |
| H(8A)-C(8)-H(8B) | 108.9 |
| C(8)-C(9)-C(10) | 102.23(12) |
| C(8)-C(9)-H(9A) | 111.3 |
| C(10)-C(9)-H(9A) | 111.3 |
| C(8)-C(9)-H(9B) | 111.3 |
| C(10)-C(9)-H(9B) | 111.3 |
| H(9A)-C(9)-H(9B) | 109.2 |
| C(30)-C(10)-C(11) | 119.17(12) |
| C(30)-C(10)-C(25) | 111.89(12) |
| C(11)-C(10)-C(25) | 99.81(11) |

| | |
|---|---|
| C(30)-C(10)-C(9) | 100.51(11) |
| C(11)-C(10)-C(9) | 109.15(12) |
| C(25)-C(10)-C(9) | 117.23(12) |
| C(12)-C(11)-C(17) | 121.28(13) |
| C(12)-C(11)-C(10) | 131.90(13) |
| C(17)-C(11)-C(10) | 106.75(12) |
| C(11)-C(12)-C(13) | 118.07(14) |
| C(11)-C(12)-H(12) | 121.0 |
| C(13)-C(12)-H(12) | 121.0 |
| O(3)-C(13)-C(15) | 115.45(13) |
| O(3)-C(13)-C(12) | 124.03(14) |
| C(15)-C(13)-C(12) | 120.51(14) |
| O(3)-C(14)-H(14A) | 109.5 |
| O(3)-C(14)-H(14B) | 109.5 |
| H(14A)-C(14)-H(14B) | 109.5 |
| O(3)-C(14)-H(14C) | 109.5 |
| H(14A)-C(14)-H(14C) | 109.5 |
| H(14B)-C(14)-H(14C) | 109.5 |
| C(13)-C(15)-C(16) | 121.28(14) |
| C(13)-C(15)-H(15) | 119.4 |
| C(16)-C(15)-H(15) | 119.4 |
| C(17)-C(16)-C(15) | 118.42(14) |
| C(17)-C(16)-H(16) | 120.8 |
| C(15)-C(16)-H(16) | 120.8 |
| C(16)-C(17)-C(11) | 120.42(13) |
| C(16)-C(17)-N(2) | 128.87(13) |
| C(11)-C(17)-N(2) | 110.70(12) |
| N(2)-C(18)-C(19) | 114.91(13) |
| N(2)-C(18)-H(18A) | 108.5 |
| C(19)-C(18)-H(18A) | 108.5 |
| N(2)-C(18)-H(18B) | 108.5 |
| C(19)-C(18)-H(18B) | 108.5 |
| H(18A)-C(18)-H(18B) | 107.5 |
| C(20)-C(19)-C(24) | 118.53(14) |
| C(20)-C(19)-C(18) | 123.24(14) |
| C(24)-C(19)-C(18) | 118.19(14) |

| | |
|---|---|
| C(21)-C(20)-C(19) | 120.41(15) |
| C(21)-C(20)-H(20) | 119.8 |
| C(19)-C(20)-H(20) | 119.8 |
| C(22)-C(21)-C(20) | 120.50(16) |
| C(22)-C(21)-H(21) | 119.7 |
| C(20)-C(21)-H(21) | 119.7 |
| C(21)-C(22)-C(23) | 119.59(16) |
| C(21)-C(22)-H(22) | 120.2 |
| C(23)-C(22)-H(22) | 120.2 |
| C(24)-C(23)-C(22) | 119.93(16) |
| C(24)-C(23)-H(23) | 120.0 |
| C(22)-C(23)-H(23) | 120.0 |
| C(23)-C(24)-C(19) | 121.02(15) |
| C(23)-C(24)-H(24) | 119.5 |
| C(19)-C(24)-H(24) | 119.5 |
| N(2)-C(25)-C(10) | 101.84(11) |
| N(2)-C(25)-C(26) | 110.83(12) |
| C(10)-C(25)-C(26) | 110.17(12) |
| N(2)-C(25)-H(25) | 111.2 |
| C(10)-C(25)-H(25) | 111.2 |
| C(26)-C(25)-H(25) | 111.2 |
| C(27)-C(26)-C(25) | 115.80(12) |
| C(27)-C(26)-H(26A) | 108.3 |
| C(25)-C(26)-H(26A) | 108.3 |
| C(27)-C(26)-H(26B) | 108.3 |
| C(25)-C(26)-H(26B) | 108.3 |
| H(26A)-C(26)-H(26B) | 107.4 |
| C(28)-C(27)-C(26) | 122.57(14) |
| C(28)-C(27)-C(29) | 121.84(15) |
| C(26)-C(27)-C(29) | 115.58(13) |
| C(27)-C(28)-H(28A) | 120.0 |
| C(27)-C(28)-H(28B) | 120.0 |
| H(28A)-C(28)-H(28B) | 120.0 |
| C(27)-C(29)-C(30) | 106.10(12) |
| C(27)-C(29)-H(29A) | 110.5 |
| C(30)-C(29)-H(29A) | 110.5 |

| | |
|---|---|
| C(27)-C(29)-H(29B) | 110.5 |
| C(30)-C(29)-H(29B) | 110.5 |
| H(29A)-C(29)-H(29B) | 108.7 |
| N(1)-C(30)-C(29) | 118.58(12) |
| N(1)-C(30)-C(10) | 101.81(11) |
| C(29)-C(30)-C(10) | 112.68(12) |
| N(1)-C(30)-H(30) | 107.7 |
| C(29)-C(30)-H(30) | 107.7 |
| C(10)-C(30)-H(30) | 107.7 |
| C(30)-N(1)-C(8) | 108.33(11) |
| C(30)-N(1)-S(1) | 118.59(10) |
| C(8)-N(1)-S(1) | 116.90(9) |
| C(17)-N(2)-C(18) | 118.58(12) |
| C(17)-N(2)-C(25) | 104.16(11) |
| C(18)-N(2)-C(25) | 116.28(12) |
| C(13)-O(3)-C(14) | 117.50(12) |
| O(1)-S(1)-O(2) | 119.58(7) |
| O(1)-S(1)-N(1) | 107.39(6) |
| O(2)-S(1)-N(1) | 105.90(7) |
| O(1)-S(1)-C(5) | 107.59(7) |
| O(2)-S(1)-C(5) | 108.44(7) |
| N(1)-S(1)-C(5) | 107.39(7) |

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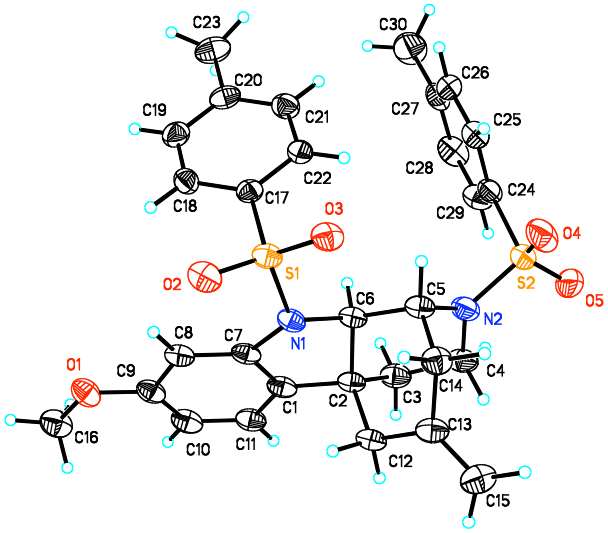
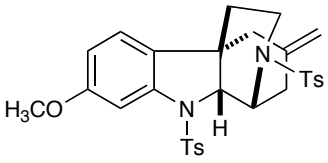
Symmetry transformations used to generate equivalent atoms:

**Compound 257**




**257**

Table 1. Crystal data and structure refinement for **257**.

| | | |
|---|---|---|
| Identification code | rd_06_234cs | |
| Empirical formula | C30 H32 N2 O5 S2 | |
| Formula weight | 564.70 | |
| Temperature | 173(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Orthorhombic | |
| Space group | Pbca | |
| Unit cell dimensions | a = 15.705(4) Å | α= 90°. |
| | b = 15.469(4) Å | β= 90°. |
| | c = 22.491(5) Å | γ = 90°. |
| Volume | 5464(2) $Å^3$ | |
| Z | 8 | |
| Density (calculated) | 1.373 $Mg/m^3$ | |
| Absorption coefficient | 0.239 $mm^{-1}$ | |
| F(000) | 2384 | |
| Crystal size | 0.29 x 0.20 x 0.03 $mm^3$ | |

| | |
|---|---|
| Theta range for data collection | 1.81 to 30.44°. |
| Index ranges | -22<=h<=22, -21<=k<=21, -32<=l<=31 |
| Reflections collected | 96169 |
| Independent reflections | 8098 [R(int) = 0.2105] |
| Completeness to theta = 30.44° | 97.8 % |
| Absorption correction | Semi-empirical from equivalents |
| Max. and min. transmission | 0.9929 and 0.9340 |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 8098 / 0 / 352 |
| Goodness-of-fit on $F^2$ | 1.001 |
| Final R indices [I>2sigma(I)] | R1 = 0.0631, wR2 = 0.1197 |
| R indices (all data) | R1 = 0.1826, wR2 = 0.1575 |
| Largest diff. peak and hole | 0.310 and -0.445 e.$Å^{-3}$ |

Table 2. Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters ($Å^2$x $10^3$) for **257**. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| C(1) | 2962(2) | 1614(2) | 9297(1) | 29(1) |
| C(2) | 2645(2) | 2080(2) | 8753(1) | 27(1) |
| C(3) | 2496(2) | 1556(2) | 8188(1) | 35(1) |
| C(4) | 2042(2) | 2099(2) | 7718(1) | 37(1) |
| C(5) | 1398(2) | 3052(2) | 8552(1) | 31(1) |
| C(6) | 1772(2) | 2380(2) | 8976(1) | 26(1) |
| C(7) | 2582(2) | 1984(2) | 9801(1) | 26(1) |
| C(8) | 2815(2) | 1752(2) | 10367(1) | 28(1) |
| C(9) | 3449(2) | 1120(2) | 10433(1) | 30(1) |
| C(10) | 3813(2) | 730(2) | 9943(1) | 33(1) |
| C(11) | 3578(2) | 989(2) | 9375(1) | 32(1) |
| C(12) | 3236(2) | 2876(2) | 8641(1) | 30(1) |
| C(13) | 2853(2) | 3634(2) | 8315(1) | 33(1) |
| C(14) | 1956(2) | 3858(2) | 8504(1) | 33(1) |

| | | | | |
|---|---|---|---|---|
| C(15) | 3270(2) | 4096(2) | 7916(1) | 44(1) |
| C(16) | 4272(2) | 269(2) | 11117(2) | 41(1) |
| C(17) | 491(2) | 2144(2) | 10178(1) | 26(1) |
| C(18) | 572(2) | 1626(2) | 10680(1) | 30(1) |
| C(19) | 12(2) | 946(2) | 10766(1) | 34(1) |
| C(20) | -639(2) | 776(2) | 10363(1) | 33(1) |
| C(21) | -713(2) | 1306(2) | 9869(1) | 34(1) |
| C(22) | -161(2) | 1985(2) | 9770(1) | 29(1) |
| C(23) | -1253(2) | 43(2) | 10463(2) | 44(1) |
| C(24) | -284(2) | 1960(2) | 7836(1) | 30(1) |
| C(25) | -957(2) | 2205(2) | 8194(1) | 33(1) |
| C(26) | -1517(2) | 1576(2) | 8394(1) | 34(1) |
| C(27) | -1410(2) | 714(2) | 8248(1) | 37(1) |
| C(28) | -731(2) | 484(2) | 7879(2) | 42(1) |
| C(29) | -175(2) | 1096(2) | 7676(1) | 40(1) |
| C(30) | -2018(2) | 41(2) | 8482(2) | 59(1) |
| N(1) | 1966(1) | 2626(1) | 9603(1) | 26(1) |
| N(2) | 1317(1) | 2590(2) | 7973(1) | 35(1) |
| O(1) | 3666(1) | 943(1) | 11010(1) | 36(1) |
| O(2) | 1622(1) | 3219(1) | 10596(1) | 36(1) |
| O(3) | 779(1) | 3642(1) | 9710(1) | 33(1) |
| O(4) | 127(1) | 3570(1) | 7733(1) | 48(1) |
| O(5) | 663(1) | 2531(2) | 6982(1) | 56(1) |
| S(1) | 1211(1) | 2995(1) | 10050(1) | 28(1) |
| S(2) | 464(1) | 2736(1) | 7583(1) | 39(1) |

Table 3. Bond lengths [Å] and angles [°] for **257**.

| | |
|---|---|
| C(1)-C(11) | 1.378(4) |
| C(1)-C(7) | 1.404(4) |
| C(1)-C(2) | 1.506(4) |
| C(2)-C(3) | 1.525(4) |
| C(2)-C(6) | 1.532(3) |

| | |
|---|---|
| C(2)-C(12) | 1.562(4) |
| C(3)-C(4) | 1.527(4) |
| C(3)-H(3A) | 0.9900 |
| C(3)-H(3B) | 0.9900 |
| C(4)-N(2) | 1.485(4) |
| C(4)-H(4A) | 0.9900 |
| C(4)-H(4B) | 0.9900 |
| C(5)-N(2) | 1.489(3) |
| C(5)-C(14) | 1.527(4) |
| C(5)-C(6) | 1.528(4) |
| C(5)-H(5) | 1.0000 |
| C(6)-N(1) | 1.493(3) |
| C(6)-H(6) | 1.0000 |
| C(7)-C(8) | 1.372(4) |
| C(7)-N(1) | 1.457(3) |
| C(8)-C(9) | 1.403(4) |
| C(8)-H(8) | 0.9500 |
| C(9)-O(1) | 1.369(3) |
| C(9)-C(10) | 1.381(4) |
| C(10)-C(11) | 1.387(4) |
| C(10)-H(10) | 0.9500 |
| C(11)-H(11) | 0.9500 |
| C(12)-C(13) | 1.509(4) |
| C(12)-H(12A) | 0.9900 |
| C(12)-H(12B) | 0.9900 |
| C(13)-C(15) | 1.321(4) |
| C(13)-C(14) | 1.511(4) |
| C(14)-H(14A) | 0.9900 |
| C(14)-H(14B) | 0.9900 |
| C(15)-H(15A) | 1.0617 |
| C(15)-H(15B) | 0.9750 |
| C(16)-O(1) | 1.433(3) |
| C(16)-H(16A) | 0.9800 |
| C(16)-H(16B) | 0.9799 |
| C(16)-H(16C) | 0.9800 |
| C(17)-C(18) | 1.391(4) |

| | |
|---|---|
| C(17)-C(22) | 1.395(4) |
| C(17)-S(1) | 1.760(3) |
| C(18)-C(19) | 1.384(4) |
| C(18)-H(18) | 0.9500 |
| C(19)-C(20) | 1.393(4) |
| C(19)-H(19) | 0.9500 |
| C(20)-C(21) | 1.385(4) |
| C(20)-C(23) | 1.505(4) |
| C(21)-C(22) | 1.381(4) |
| C(21)-H(21) | 0.9500 |
| C(22)-H(22) | 0.9500 |
| C(23)-H(23A) | 0.9800 |
| C(23)-H(23B) | 0.9800 |
| C(23)-H(23C) | 0.9800 |
| C(24)-C(25) | 1.383(4) |
| C(24)-C(29) | 1.394(4) |
| C(24)-S(2) | 1.773(3) |
| C(25)-C(26) | 1.387(4) |
| C(25)-H(25) | 0.9500 |
| C(26)-C(27) | 1.384(4) |
| C(26)-H(26) | 0.9500 |
| C(27)-C(28) | 1.396(4) |
| C(27)-C(30) | 1.507(4) |
| C(28)-C(29) | 1.367(4) |
| C(28)-H(28) | 0.9500 |
| C(29)-H(29) | 0.9500 |
| C(30)-H(30A) | 0.9800 |
| C(30)-H(30B) | 0.9800 |
| C(30)-H(30C) | 0.9800 |
| N(1)-S(1) | 1.655(2) |
| N(2)-S(2) | 1.617(2) |
| O(2)-S(1) | 1.430(2) |
| O(3)-S(1) | 1.4302(19) |
| O(4)-S(2) | 1.434(2) |
| O(5)-S(2) | 1.424(2) |

| | |
|---|---|
| C(11)-C(1)-C(7) | 118.8(3) |
| C(11)-C(1)-C(2) | 132.2(3) |
| C(7)-C(1)-C(2) | 108.6(2) |
| C(1)-C(2)-C(3) | 118.2(2) |
| C(1)-C(2)-C(6) | 100.1(2) |
| C(3)-C(2)-C(6) | 107.2(2) |
| C(1)-C(2)-C(12) | 108.2(2) |
| C(3)-C(2)-C(12) | 112.0(2) |
| C(6)-C(2)-C(12) | 110.3(2) |
| C(2)-C(3)-C(4) | 110.8(2) |
| C(2)-C(3)-H(3A) | 109.5 |
| C(4)-C(3)-H(3A) | 109.5 |
| C(2)-C(3)-H(3B) | 109.5 |
| C(4)-C(3)-H(3B) | 109.5 |
| H(3A)-C(3)-H(3B) | 108.1 |
| N(2)-C(4)-C(3) | 111.8(2) |
| N(2)-C(4)-H(4A) | 109.2 |
| C(3)-C(4)-H(4A) | 109.2 |
| N(2)-C(4)-H(4B) | 109.2 |
| C(3)-C(4)-H(4B) | 109.2 |
| H(4A)-C(4)-H(4B) | 107.9 |
| N(2)-C(5)-C(14) | 112.3(2) |
| N(2)-C(5)-C(6) | 104.6(2) |
| C(14)-C(5)-C(6) | 112.2(2) |
| N(2)-C(5)-H(5) | 109.2 |
| C(14)-C(5)-H(5) | 109.2 |
| C(6)-C(5)-H(5) | 109.2 |
| N(1)-C(6)-C(5) | 119.6(2) |
| N(1)-C(6)-C(2) | 101.75(19) |
| C(5)-C(6)-C(2) | 110.2(2) |
| N(1)-C(6)-H(6) | 108.2 |
| C(5)-C(6)-H(6) | 108.2 |
| C(2)-C(6)-H(6) | 108.2 |
| C(8)-C(7)-C(1) | 121.9(2) |
| C(8)-C(7)-N(1) | 129.8(2) |
| C(1)-C(7)-N(1) | 108.3(2) |

| | |
|---|---|
| C(7)-C(8)-C(9) | 118.0(3) |
| C(7)-C(8)-H(8) | 121.0 |
| C(9)-C(8)-H(8) | 121.0 |
| O(1)-C(9)-C(10) | 124.5(3) |
| O(1)-C(9)-C(8) | 114.5(3) |
| C(10)-C(9)-C(8) | 121.0(3) |
| C(9)-C(10)-C(11) | 119.9(3) |
| C(9)-C(10)-H(10) | 120.1 |
| C(11)-C(10)-H(10) | 120.1 |
| C(1)-C(11)-C(10) | 120.4(3) |
| C(1)-C(11)-H(11) | 119.8 |
| C(10)-C(11)-H(11) | 119.8 |
| C(13)-C(12)-C(2) | 117.0(2) |
| C(13)-C(12)-H(12A) | 108.0 |
| C(2)-C(12)-H(12A) | 108.0 |
| C(13)-C(12)-H(12B) | 108.0 |
| C(2)-C(12)-H(12B) | 108.0 |
| H(12A)-C(12)-H(12B) | 107.3 |
| C(15)-C(13)-C(12) | 123.6(3) |
| C(15)-C(13)-C(14) | 122.0(3) |
| C(12)-C(13)-C(14) | 114.3(2) |
| C(13)-C(14)-C(5) | 111.6(2) |
| C(13)-C(14)-H(14A) | 109.3 |
| C(5)-C(14)-H(14A) | 109.3 |
| C(13)-C(14)-H(14B) | 109.3 |
| C(5)-C(14)-H(14B) | 109.3 |
| H(14A)-C(14)-H(14B) | 108.0 |
| C(13)-C(15)-H(15A) | 122.8 |
| C(13)-C(15)-H(15B) | 115.6 |
| H(15A)-C(15)-H(15B) | 121.6 |
| O(1)-C(16)-H(16A) | 109.4 |
| O(1)-C(16)-H(16B) | 109.7 |
| H(16A)-C(16)-H(16B) | 109.5 |
| O(1)-C(16)-H(16C) | 109.3 |
| H(16A)-C(16)-H(16C) | 109.5 |
| H(16B)-C(16)-H(16C) | 109.5 |

| | |
|---|---|
| C(18)-C(17)-C(22) | 120.0(3) |
| C(18)-C(17)-S(1) | 120.3(2) |
| C(22)-C(17)-S(1) | 119.7(2) |
| C(19)-C(18)-C(17) | 119.5(3) |
| C(19)-C(18)-H(18) | 120.2 |
| C(17)-C(18)-H(18) | 120.2 |
| C(18)-C(19)-C(20) | 121.3(3) |
| C(18)-C(19)-H(19) | 119.4 |
| C(20)-C(19)-H(19) | 119.4 |
| C(21)-C(20)-C(19) | 118.2(3) |
| C(21)-C(20)-C(23) | 120.8(3) |
| C(19)-C(20)-C(23) | 121.0(3) |
| C(22)-C(21)-C(20) | 121.8(3) |
| C(22)-C(21)-H(21) | 119.1 |
| C(20)-C(21)-H(21) | 119.1 |
| C(21)-C(22)-C(17) | 119.3(3) |
| C(21)-C(22)-H(22) | 120.4 |
| C(17)-C(22)-H(22) | 120.4 |
| C(20)-C(23)-H(23A) | 109.5 |
| C(20)-C(23)-H(23B) | 109.5 |
| H(23A)-C(23)-H(23B) | 109.5 |
| C(20)-C(23)-H(23C) | 109.4 |
| H(23A)-C(23)-H(23C) | 109.5 |
| H(23B)-C(23)-H(23C) | 109.5 |
| C(25)-C(24)-C(29) | 120.5(3) |
| C(25)-C(24)-S(2) | 120.4(2) |
| C(29)-C(24)-S(2) | 119.0(2) |
| C(24)-C(25)-C(26) | 118.7(3) |
| C(24)-C(25)-H(25) | 120.6 |
| C(26)-C(25)-H(25) | 120.6 |
| C(27)-C(26)-C(25) | 121.5(3) |
| C(27)-C(26)-H(26) | 119.3 |
| C(25)-C(26)-H(26) | 119.3 |
| C(26)-C(27)-C(28) | 118.6(3) |
| C(26)-C(27)-C(30) | 120.4(3) |
| C(28)-C(27)-C(30) | 121.0(3) |

| | |
|---|---|
| C(29)-C(28)-C(27) | 120.7(3) |
| C(29)-C(28)-H(28) | 119.6 |
| C(27)-C(28)-H(28) | 119.6 |
| C(28)-C(29)-C(24) | 119.9(3) |
| C(28)-C(29)-H(29) | 120.1 |
| C(24)-C(29)-H(29) | 120.1 |
| C(27)-C(30)-H(30A) | 109.5 |
| C(27)-C(30)-H(30B) | 109.5 |
| H(30A)-C(30)-H(30B) | 109.5 |
| C(27)-C(30)-H(30C) | 109.5 |
| H(30A)-C(30)-H(30C) | 109.5 |
| H(30B)-C(30)-H(30C) | 109.5 |
| C(7)-N(1)-C(6) | 104.49(19) |
| C(7)-N(1)-S(1) | 121.70(18) |
| C(6)-N(1)-S(1) | 121.03(16) |
| C(4)-N(2)-C(5) | 121.1(2) |
| C(4)-N(2)-S(2) | 119.81(19) |
| C(5)-N(2)-S(2) | 118.56(18) |
| C(9)-O(1)-C(16) | 118.0(2) |
| O(2)-S(1)-O(3) | 120.28(12) |
| O(2)-S(1)-N(1) | 106.32(11) |
| O(3)-S(1)-N(1) | 104.81(12) |
| O(2)-S(1)-C(17) | 109.33(13) |
| O(3)-S(1)-C(17) | 107.87(12) |
| N(1)-S(1)-C(17) | 107.53(12) |
| O(5)-S(2)-O(4) | 120.28(15) |
| O(5)-S(2)-N(2) | 107.57(13) |
| O(4)-S(2)-N(2) | 107.72(13) |
| O(5)-S(2)-C(24) | 107.35(14) |
| O(4)-S(2)-C(24) | 106.85(13) |
| N(2)-S(2)-C(24) | 106.30(13) |

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Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **257**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| C(1) | 21(1) | 24(1) | 42(2) | -5(1) | -1(1) | -3(1) |
| C(2) | 18(1) | 29(2) | 35(2) | -3(1) | 3(1) | 1(1) |
| C(3) | 29(2) | 35(2) | 41(2) | -9(1) | 4(1) | 0(1) |
| C(4) | 26(2) | 47(2) | 39(2) | -11(2) | 0(1) | -6(1) |
| C(5) | 21(1) | 35(2) | 38(2) | -2(1) | 3(1) | 2(1) |
| C(6) | 18(1) | 27(1) | 34(2) | -4(1) | 0(1) | -1(1) |
| C(7) | 18(1) | 18(1) | 41(2) | -3(1) | -1(1) | -1(1) |
| C(8) | 21(1) | 25(1) | 38(2) | -6(1) | 2(1) | -1(1) |
| C(9) | 24(2) | 23(1) | 43(2) | 0(1) | -6(1) | -4(1) |
| C(10) | 24(1) | 22(1) | 52(2) | -5(1) | -2(1) | 4(1) |
| C(11) | 23(1) | 30(2) | 43(2) | -7(1) | 2(1) | 3(1) |
| C(12) | 18(1) | 33(2) | 40(2) | -4(1) | 0(1) | -2(1) |
| C(13) | 26(2) | 31(2) | 43(2) | -6(1) | 2(1) | -4(1) |
| C(14) | 31(2) | 27(2) | 41(2) | 0(1) | 3(1) | 4(1) |
| C(15) | 39(2) | 40(2) | 51(2) | 1(2) | 9(2) | -4(2) |
| C(16) | 34(2) | 30(2) | 59(2) | 8(2) | -6(2) | 2(1) |
| C(17) | 24(1) | 26(2) | 28(2) | -2(1) | 5(1) | 5(1) |
| C(18) | 27(2) | 36(2) | 28(2) | -1(1) | -2(1) | 5(1) |
| C(19) | 32(2) | 36(2) | 35(2) | 6(1) | 7(1) | 8(1) |
| C(20) | 30(2) | 30(2) | 38(2) | -7(1) | 12(1) | 2(1) |
| C(21) | 28(2) | 38(2) | 35(2) | -5(1) | -2(1) | -3(1) |
| C(22) | 24(1) | 33(2) | 30(2) | 3(1) | 1(1) | 5(1) |
| C(23) | 41(2) | 35(2) | 57(2) | -4(2) | 13(2) | -7(2) |
| C(24) | 24(1) | 33(2) | 33(2) | 3(1) | -6(1) | 1(1) |
| C(25) | 32(2) | 33(2) | 35(2) | -3(1) | -3(1) | 2(1) |
| C(26) | 30(2) | 41(2) | 32(2) | 6(1) | 1(1) | -2(1) |
| C(27) | 32(2) | 39(2) | 39(2) | 6(2) | -12(1) | -1(1) |
| C(28) | 42(2) | 28(2) | 56(2) | -7(2) | -10(2) | 2(1) |
| C(29) | 30(2) | 43(2) | 45(2) | -8(2) | 0(1) | 5(1) |
| C(30) | 50(2) | 54(2) | 73(3) | 16(2) | -9(2) | -20(2) |
| N(1) | 20(1) | 26(1) | 34(1) | -4(1) | -1(1) | 5(1) |

| | | | | | | |
|---|---|---|---|---|---|---|
| N(2) | 24(1) | 49(2) | 33(1) | -4(1) | -2(1) | -2(1) |
| O(1) | 33(1) | 30(1) | 45(1) | 1(1) | -9(1) | 4(1) |
| O(2) | 33(1) | 34(1) | 40(1) | -14(1) | -2(1) | 4(1) |
| O(3) | 30(1) | 25(1) | 45(1) | 2(1) | 3(1) | 8(1) |
| O(4) | 40(1) | 34(1) | 70(2) | 18(1) | -15(1) | -4(1) |
| O(5) | 41(1) | 99(2) | 29(1) | 11(1) | -3(1) | -13(1) |
| S(1) | 24(1) | 24(1) | 36(1) | -5(1) | 2(1) | 5(1) |
| S(2) | 28(1) | 51(1) | 37(1) | 11(1) | -5(1) | -6(1) |

Table 5. Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters ($Å^2$x $10^3$) for **257**.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(3A) | 2147 | 1041 | 8283 | 42 |
| H(3B) | 3050 | 1354 | 8029 | 42 |
| H(4A) | 2453 | 2509 | 7539 | 45 |
| H(4B) | 1830 | 1715 | 7398 | 45 |
| H(5) | 819 | 3223 | 8694 | 38 |
| H(6) | 1382 | 1868 | 8982 | 31 |
| H(8) | 2555 | 2011 | 10704 | 33 |
| H(10) | 4223 | 284 | 9994 | 39 |
| H(11) | 3843 | 734 | 9038 | 38 |
| H(12A) | 3444 | 3084 | 9031 | 36 |
| H(12B) | 3738 | 2675 | 8413 | 36 |
| H(14A) | 1703 | 4261 | 8212 | 39 |
| H(14B) | 1974 | 4153 | 8895 | 39 |
| H(15A) | 2990 | 4623 | 7685 | 52 |
| H(15B) | 3858 | 3922 | 7844 | 52 |
| H(16A) | 4061 | -273 | 10946 | 62 |
| H(16B) | 4355 | 197 | 11546 | 62 |
| H(16C) | 4815 | 422 | 10930 | 62 |

| | | | | |
|---|---|---|---|---|
| H(18) | 1008 | 1738 | 10962 | 36 |
| H(19) | 74 | 589 | 11107 | 41 |
| H(21) | -1155 | 1198 | 9590 | 40 |
| H(22) | -224 | 2341 | 9429 | 35 |
| H(23A) | -1346 | -34 | 10890 | 66 |
| H(23B) | -1018 | -489 | 10294 | 66 |
| H(23C) | -1797 | 177 | 10269 | 66 |
| H(25) | -1034 | 2794 | 8302 | 40 |
| H(26) | -1986 | 1741 | 8636 | 41 |
| H(28) | -656 | -103 | 7767 | 51 |
| H(29) | 286 | 933 | 7426 | 48 |
| H(30A) | -1948 | -496 | 8256 | 89 |
| H(30B) | -2604 | 249 | 8440 | 89 |
| H(30C) | -1896 | -68 | 8903 | 89 |

Table 6. Torsion angles [°] for **257**.

| | |
|---|---|
| C(11)-C(1)-C(2)-C(3) | 43.1(4) |
| C(7)-C(1)-C(2)-C(3) | -143.8(2) |
| C(11)-C(1)-C(2)-C(6) | 159.0(3) |
| C(7)-C(1)-C(2)-C(6) | -27.9(3) |
| C(11)-C(1)-C(2)-C(12) | -85.6(3) |
| C(7)-C(1)-C(2)-C(12) | 87.5(2) |
| C(1)-C(2)-C(3)-C(4) | 170.8(2) |
| C(6)-C(2)-C(3)-C(4) | 58.7(3) |
| C(12)-C(2)-C(3)-C(4) | -62.4(3) |
| C(2)-C(3)-C(4)-N(2) | -45.4(3) |
| N(2)-C(5)-C(6)-N(1) | 178.3(2) |
| C(14)-C(5)-C(6)-N(1) | 56.2(3) |
| N(2)-C(5)-C(6)-C(2) | 61.0(3) |
| C(14)-C(5)-C(6)-C(2) | -61.1(3) |

| | |
|---|---|
| C(1)-C(2)-C(6)-N(1) | 39.0(2) |
| C(3)-C(2)-C(6)-N(1) | 162.9(2) |
| C(12)-C(2)-C(6)-N(1) | -74.8(3) |
| C(1)-C(2)-C(6)-C(5) | 166.9(2) |
| C(3)-C(2)-C(6)-C(5) | -69.1(3) |
| C(12)-C(2)-C(6)-C(5) | 53.1(3) |
| C(11)-C(1)-C(7)-C(8) | 1.0(4) |
| C(2)-C(1)-C(7)-C(8) | -173.2(2) |
| C(11)-C(1)-C(7)-N(1) | 179.4(2) |
| C(2)-C(1)-C(7)-N(1) | 5.2(3) |
| C(1)-C(7)-C(8)-C(9) | -0.4(4) |
| N(1)-C(7)-C(8)-C(9) | -178.4(2) |
| C(7)-C(8)-C(9)-O(1) | 178.0(2) |
| C(7)-C(8)-C(9)-C(10) | -1.5(4) |
| O(1)-C(9)-C(10)-C(11) | -176.7(2) |
| C(8)-C(9)-C(10)-C(11) | 2.9(4) |
| C(7)-C(1)-C(11)-C(10) | 0.3(4) |
| C(2)-C(1)-C(11)-C(10) | 172.9(3) |
| C(9)-C(10)-C(11)-C(1) | -2.2(4) |
| C(1)-C(2)-C(12)-C(13) | -153.6(2) |
| C(3)-C(2)-C(12)-C(13) | 74.3(3) |
| C(6)-C(2)-C(12)-C(13) | -45.0(3) |
| C(2)-C(12)-C(13)-C(15) | -141.4(3) |
| C(2)-C(12)-C(13)-C(14) | 41.7(3) |
| C(15)-C(13)-C(14)-C(5) | 137.2(3) |
| C(12)-C(13)-C(14)-C(5) | -45.8(3) |
| N(2)-C(5)-C(14)-C(13) | -61.1(3) |
| C(6)-C(5)-C(14)-C(13) | 56.4(3) |
| C(22)-C(17)-C(18)-C(19) | 1.1(4) |
| S(1)-C(17)-C(18)-C(19) | -178.5(2) |
| C(17)-C(18)-C(19)-C(20) | -0.8(4) |
| C(18)-C(19)-C(20)-C(21) | 0.2(4) |
| C(18)-C(19)-C(20)-C(23) | -179.2(3) |
| C(19)-C(20)-C(21)-C(22) | 0.2(4) |
| C(23)-C(20)-C(21)-C(22) | 179.5(3) |
| C(20)-C(21)-C(22)-C(17) | 0.2(4) |

| | |
|---|---|
| C(18)-C(17)-C(22)-C(21) | -0.8(4) |
| S(1)-C(17)-C(22)-C(21) | 178.8(2) |
| C(29)-C(24)-C(25)-C(26) | 0.3(4) |
| S(2)-C(24)-C(25)-C(26) | -178.5(2) |
| C(24)-C(25)-C(26)-C(27) | 0.9(4) |
| C(25)-C(26)-C(27)-C(28) | -1.7(4) |
| C(25)-C(26)-C(27)-C(30) | 178.6(3) |
| C(26)-C(27)-C(28)-C(29) | 1.4(4) |
| C(30)-C(27)-C(28)-C(29) | -178.9(3) |
| C(27)-C(28)-C(29)-C(24) | -0.3(5) |
| C(25)-C(24)-C(29)-C(28) | -0.6(4) |
| S(2)-C(24)-C(29)-C(28) | 178.3(2) |
| C(8)-C(7)-N(1)-C(6) | -161.0(3) |
| C(1)-C(7)-N(1)-C(6) | 20.8(3) |
| C(8)-C(7)-N(1)-S(1) | -19.3(4) |
| C(1)-C(7)-N(1)-S(1) | 162.52(18) |
| C(5)-C(6)-N(1)-C(7) | -159.1(2) |
| C(2)-C(6)-N(1)-C(7) | -37.5(2) |
| C(5)-C(6)-N(1)-S(1) | 58.9(3) |
| C(2)-C(6)-N(1)-S(1) | -179.55(17) |
| C(3)-C(4)-N(2)-C(5) | 43.8(3) |
| C(3)-C(4)-N(2)-S(2) | -144.3(2) |
| C(14)-C(5)-N(2)-C(4) | 71.9(3) |
| C(6)-C(5)-N(2)-C(4) | -50.1(3) |
| C(14)-C(5)-N(2)-S(2) | -100.1(2) |
| C(6)-C(5)-N(2)-S(2) | 137.93(19) |
| C(10)-C(9)-O(1)-C(16) | -4.1(4) |
| C(8)-C(9)-O(1)-C(16) | 176.4(2) |
| C(7)-N(1)-S(1)-O(2) | 48.1(2) |
| C(6)-N(1)-S(1)-O(2) | -176.31(19) |
| C(7)-N(1)-S(1)-O(3) | 176.45(18) |
| C(6)-N(1)-S(1)-O(3) | -47.9(2) |
| C(7)-N(1)-S(1)-C(17) | -69.0(2) |
| C(6)-N(1)-S(1)-C(17) | 66.7(2) |
| C(18)-C(17)-S(1)-O(2) | -19.7(2) |
| C(22)-C(17)-S(1)-O(2) | 160.7(2) |

| | |
|---|---|
| C(18)-C(17)-S(1)-O(3) | -152.1(2) |
| C(22)-C(17)-S(1)-O(3) | 28.3(2) |
| C(18)-C(17)-S(1)-N(1) | 95.4(2) |
| C(22)-C(17)-S(1)-N(1) | -84.2(2) |
| C(4)-N(2)-S(2)-O(5) | -14.7(3) |
| C(5)-N(2)-S(2)-O(5) | 157.4(2) |
| C(4)-N(2)-S(2)-O(4) | -145.7(2) |
| C(5)-N(2)-S(2)-O(4) | 26.4(2) |
| C(4)-N(2)-S(2)-C(24) | 100.1(2) |
| C(5)-N(2)-S(2)-C(24) | -87.8(2) |
| C(25)-C(24)-S(2)-O(5) | -140.2(2) |
| C(29)-C(24)-S(2)-O(5) | 40.9(3) |
| C(25)-C(24)-S(2)-O(4) | -9.9(3) |
| C(29)-C(24)-S(2)-O(4) | 171.2(2) |
| C(25)-C(24)-S(2)-N(2) | 104.9(2) |
| C(29)-C(24)-S(2)-N(2) | -73.9(3) |

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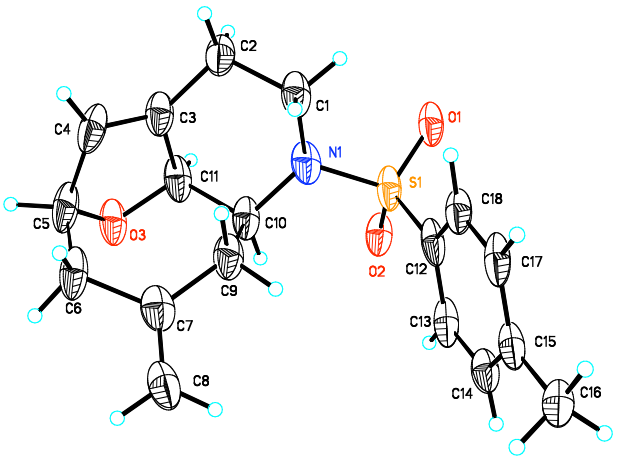
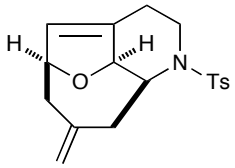
Symmetry transformations used to generate equivalent atoms:

**Compound 270**




**270**

Table 1. Crystal data and structure refinement for **270**.

| | | |
|---|---|---|
| Identification code | d6_016 | |
| Empirical formula | C18 H21 N O3 S | |
| Formula weight | 331.42 | |
| Temperature | 173(2) K | |
| Wavelength | 1.54178 Å | |
| Crystal system | Orthorhombic | |
| Space group | Pbca | |
| Unit cell dimensions | a = 10.7947(10) Å | α= 90°. |
| | b = 14.6736(16) Å | β= 90°. |
| | c = 20.2106(18) Å | γ = 90°. |
| Volume | 3201.3(5) $Å^3$ | |
| Z | 8 | |
| Density (calculated) | 1.375 $Mg/m^3$ | |
| Absorption coefficient | 1.921 $mm^{-1}$ | |
| F(000) | 1408 | |
| Crystal size | 0.41 x 0.13 x 0.03 $mm^3$ | |
| Theta range for data collection | 4.38 to 60.02°. | |
| Index ranges | -12<=h<=11, -13<=k<=15, -21<=l<=22 | |

| | |
|---|---|
| Reflections collected | 14955 |
| Independent reflections | 2289 [R(int) = 0.0787] |
| Completeness to theta = 60.02° | 96.3 % |
| Absorption correction | Semi-empirical from equivalents |
| Max. and min. transmission | 0.9446 and 0.5064 |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 2289 / 0 / 210 |
| Goodness-of-fit on $F^2$ | 1.018 |
| Final R indices [I>2sigma(I)] | R1 = 0.1156, wR2 = 0.2444 |
| R indices (all data) | R1 = 0.1816, wR2 = 0.3168 |
| Extinction coefficient | 0.0026(3) |
| Largest diff. peak and hole | 0.893 and -0.877 e.$Å^{-3}$ |

Table 2. Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters ($Å^2$x $10^3$) for **270**. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| C(1) | 3873(10) | 693(9) | 1783(4) | 74(3) |
| C(2) | 4651(10) | 211(9) | 1247(4) | 71(3) |
| C(3) | 4748(10) | 831(9) | 665(4) | 67(3) |
| C(4) | 5670(11) | 1279(9) | 383(5) | 79(4) |
| C(5) | 5154(11) | 1957(10) | -94(4) | 79(4) |
| C(6) | 5220(10) | 2955(9) | 162(4) | 75(4) |
| C(7) | 4148(10) | 3194(9) | 610(5) | 69(3) |
| C(8) | 3624(11) | 3991(9) | 530(6) | 84(4) |
| C(9) | 3769(10) | 2584(9) | 1156(4) | 71(3) |
| C(10) | 2948(9) | 1734(8) | 942(4) | 63(3) |
| C(11) | 3571(9) | 1177(8) | 385(4) | 64(3) |
| C(12) | 1560(9) | 2102(9) | 2424(4) | 73(4) |
| C(13) | 779(9) | 2859(9) | 2312(4) | 70(4) |
| C(14) | 833(9) | 3604(8) | 2728(5) | 65(3) |
| C(15) | 1699(9) | 3665(9) | 3232(4) | 67(3) |

| | | | | |
|---|---|---|---|---|
| C(16) | 1777(10) | 4479(8) | 3661(4) | 69(3) |
| C(17) | 2473(9) | 2920(9) | 3337(4) | 73(4) |
| C(18) | 2399(9) | 2163(9) | 2944(4) | 65(3) |
| N(1) | 2750(8) | 1088(7) | 1483(3) | 65(2) |
| O(1) | 1463(6) | 386(6) | 2330(3) | 72(2) |
| O(2) | 487(6) | 1302(5) | 1462(3) | 68(2) |
| O(3) | 3891(7) | 1704(6) | -181(3) | 73(2) |
| S(1) | 1484(2) | 1148(2) | 1913(1) | 68(1) |

Table 3. Bond lengths [Å] and angles [°] for **270**.

| | |
|---|---|
| C(1)-N(1) | 1.474(13) |
| C(1)-C(2) | 1.541(14) |
| C(1)-H(1A) | 0.9900 |
| C(1)-H(1B) | 0.9900 |
| C(2)-C(3) | 1.492(14) |
| C(2)-H(2A) | 0.9900 |
| C(2)-H(2B) | 0.9900 |
| C(3)-C(4) | 1.321(15) |
| C(3)-C(11) | 1.479(14) |
| C(4)-C(5) | 1.493(16) |
| C(4)-H(4) | 0.9500 |
| C(5)-O(3) | 1.424(13) |
| C(5)-C(6) | 1.553(16) |
| C(5)-H(5) | 1.0000 |
| C(6)-C(7) | 1.511(14) |
| C(6)-H(6A) | 0.9900 |
| C(6)-H(6B) | 0.9900 |
| C(7)-C(8) | 1.310(16) |
| C(7)-C(9) | 1.478(15) |
| C(8)-H(8A) | 0.9500 |
| C(8)-H(8B) | 0.9500 |
| C(9)-C(10) | 1.590(15) |

| | |
|---|---|
| C(9)-H(9A) | 0.9900 |
| C(9)-H(9B) | 0.9900 |
| C(10)-N(1) | 1.462(12) |
| C(10)-C(11) | 1.545(14) |
| C(10)-H(10) | 1.0000 |
| C(11)-O(3) | 1.423(11) |
| C(11)-H(11) | 1.0000 |
| C(12)-C(18) | 1.391(13) |
| C(12)-C(13) | 1.413(16) |
| C(12)-S(1) | 1.742(13) |
| C(13)-C(14) | 1.381(15) |
| C(13)-H(13) | 0.9500 |
| C(14)-C(15) | 1.385(13) |
| C(14)-H(14) | 0.9500 |
| C(15)-C(17) | 1.392(16) |
| C(15)-C(16) | 1.477(15) |
| C(16)-H(16A) | 0.9800 |
| C(16)-H(16B) | 0.9800 |
| C(16)-H(16C) | 0.9800 |
| C(17)-C(18) | 1.367(15) |
| C(17)-H(17) | 0.9500 |
| C(18)-H(18) | 0.9500 |
| N(1)-S(1) | 1.623(8) |
| O(1)-S(1) | 1.399(8) |
| O(2)-S(1) | 1.429(7) |

| | |
|---|---|
| N(1)-C(1)-C(2) | 109.8(7) |
| N(1)-C(1)-H(1A) | 109.7 |
| C(2)-C(1)-H(1A) | 109.7 |
| N(1)-C(1)-H(1B) | 109.7 |
| C(2)-C(1)-H(1B) | 109.7 |
| H(1A)-C(1)-H(1B) | 108.2 |
| C(3)-C(2)-C(1) | 108.2(10) |
| C(3)-C(2)-H(2A) | 110.0 |
| C(1)-C(2)-H(2A) | 110.0 |
| C(3)-C(2)-H(2B) | 110.0 |

| | |
|---|---|
| C(1)-C(2)-H(2B) | 110.0 |
| H(2A)-C(2)-H(2B) | 108.4 |
| C(4)-C(3)-C(11) | 108.1(10) |
| C(4)-C(3)-C(2) | 134.1(10) |
| C(11)-C(3)-C(2) | 116.8(9) |
| C(3)-C(4)-C(5) | 109.2(10) |
| C(3)-C(4)-H(4) | 125.4 |
| C(5)-C(4)-H(4) | 125.4 |
| O(3)-C(5)-C(4) | 105.2(10) |
| O(3)-C(5)-C(6) | 109.4(9) |
| C(4)-C(5)-C(6) | 113.4(9) |
| O(3)-C(5)-H(5) | 109.6 |
| C(4)-C(5)-H(5) | 109.6 |
| C(6)-C(5)-H(5) | 109.6 |
| C(7)-C(6)-C(5) | 112.5(10) |
| C(7)-C(6)-H(6A) | 109.1 |
| C(5)-C(6)-H(6A) | 109.1 |
| C(7)-C(6)-H(6B) | 109.1 |
| C(5)-C(6)-H(6B) | 109.1 |
| H(6A)-C(6)-H(6B) | 107.8 |
| C(8)-C(7)-C(9) | 120.9(11) |
| C(8)-C(7)-C(6) | 117.7(11) |
| C(9)-C(7)-C(6) | 121.3(11) |
| C(7)-C(8)-H(8A) | 120.0 |
| C(7)-C(8)-H(8B) | 120.0 |
| H(8A)-C(8)-H(8B) | 120.0 |
| C(7)-C(9)-C(10) | 115.2(8) |
| C(7)-C(9)-H(9A) | 108.5 |
| C(10)-C(9)-H(9A) | 108.5 |
| C(7)-C(9)-H(9B) | 108.5 |
| C(10)-C(9)-H(9B) | 108.5 |
| H(9A)-C(9)-H(9B) | 107.5 |
| N(1)-C(10)-C(11) | 105.3(9) |
| N(1)-C(10)-C(9) | 112.8(7) |
| C(11)-C(10)-C(9) | 111.7(8) |
| N(1)-C(10)-H(10) | 109.0 |

| | |
|---|---|
| C(11)-C(10)-H(10) | 109.0 |
| C(9)-C(10)-H(10) | 109.0 |
| O(3)-C(11)-C(3) | 106.5(8) |
| O(3)-C(11)-C(10) | 113.9(9) |
| C(3)-C(11)-C(10) | 106.1(7) |
| O(3)-C(11)-H(11) | 110.0 |
| C(3)-C(11)-H(11) | 110.0 |
| C(10)-C(11)-H(11) | 110.0 |
| C(18)-C(12)-C(13) | 117.3(12) |
| C(18)-C(12)-S(1) | 122.1(10) |
| C(13)-C(12)-S(1) | 120.6(8) |
| C(14)-C(13)-C(12) | 119.9(9) |
| C(14)-C(13)-H(13) | 120.0 |
| C(12)-C(13)-H(13) | 120.0 |
| C(13)-C(14)-C(15) | 121.9(11) |
| C(13)-C(14)-H(14) | 119.0 |
| C(15)-C(14)-H(14) | 119.0 |
| C(14)-C(15)-C(17) | 117.7(11) |
| C(14)-C(15)-C(16) | 121.5(11) |
| C(17)-C(15)-C(16) | 120.8(10) |
| C(15)-C(16)-H(16A) | 109.5 |
| C(15)-C(16)-H(16B) | 109.5 |
| H(16A)-C(16)-H(16B) | 109.5 |
| C(15)-C(16)-H(16C) | 109.5 |
| H(16A)-C(16)-H(16C) | 109.5 |
| H(16B)-C(16)-H(16C) | 109.5 |
| C(18)-C(17)-C(15) | 121.0(10) |
| C(18)-C(17)-H(17) | 119.5 |
| C(15)-C(17)-H(17) | 119.5 |
| C(17)-C(18)-C(12) | 121.9(11) |
| C(17)-C(18)-H(18) | 119.0 |
| C(12)-C(18)-H(18) | 119.0 |
| C(10)-N(1)-C(1) | 116.3(8) |
| C(10)-N(1)-S(1) | 119.2(7) |
| C(1)-N(1)-S(1) | 119.5(6) |
| C(11)-O(3)-C(5) | 105.9(7) |

| | |
|---|---|
| O(1)-S(1)-O(2) | 119.9(5) |
| O(1)-S(1)-N(1) | 107.0(5) |
| O(2)-S(1)-N(1) | 107.5(4) |
| O(1)-S(1)-C(12) | 106.6(4) |
| O(2)-S(1)-C(12) | 106.6(5) |
| N(1)-S(1)-C(12) | 108.8(5) |

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for **270**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| C(1) | 58(7) | 128(11) | 35(5) | 5(6) | -3(5) | -1(7) |
| C(2) | 55(7) | 109(10) | 49(5) | 5(6) | 6(5) | 14(6) |
| C(3) | 59(7) | 111(9) | 32(5) | -7(5) | 5(5) | -2(6) |
| C(4) | 57(7) | 144(12) | 36(5) | -10(6) | 4(5) | 17(7) |
| C(5) | 66(8) | 141(13) | 30(5) | -9(6) | 11(5) | 3(7) |
| C(6) | 54(7) | 139(12) | 33(5) | -2(6) | 1(4) | -2(7) |
| C(7) | 58(7) | 105(10) | 44(5) | 7(6) | -12(5) | -5(6) |
| C(8) | 60(8) | 114(12) | 79(8) | 30(8) | 9(6) | -9(7) |
| C(9) | 70(7) | 111(10) | 32(5) | -3(5) | -1(5) | 2(7) |
| C(10) | 48(6) | 112(10) | 31(4) | 4(5) | -7(4) | 2(6) |
| C(11) | 53(6) | 106(9) | 33(5) | -2(5) | -4(4) | -21(6) |
| C(12) | 36(6) | 148(12) | 34(5) | 23(6) | 3(4) | -1(6) |
| C(13) | 41(6) | 136(11) | 33(5) | 8(6) | 3(4) | 1(6) |
| C(14) | 42(6) | 107(10) | 46(5) | 18(6) | 7(5) | -4(5) |
| C(15) | 49(6) | 116(10) | 36(5) | 13(6) | 8(4) | 6(6) |
| C(16) | 63(7) | 98(10) | 46(5) | 0(6) | 13(5) | 0(6) |
| C(17) | 44(6) | 142(12) | 31(5) | 4(6) | 3(4) | 9(7) |
| C(18) | 44(6) | 116(10) | 35(5) | 8(6) | 4(4) | 1(6) |
| N(1) | 57(5) | 107(7) | 30(4) | 3(4) | -13(4) | -8(5) |
| O(1) | 62(5) | 123(7) | 31(3) | 5(4) | 2(3) | -6(4) |
| O(2) | 47(4) | 114(6) | 43(3) | -6(4) | -1(3) | -4(4) |

| | | | | | | |
|---|---|---|---|---|---|---|
| O(3) | 64(5) | 125(7) | 30(3) | 5(4) | 0(3) | -11(4) |
| S(1) | 46(2) | 127(3) | 31(1) | 3(1) | 0(1) | -4(2) |

Table 5. Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters ($Å^2$x $10^3$) for D6_016.

| | x | y | z | U(eq) |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| H(1A) | 3636 | 250 | 2130 | 89 |
| H(1B) | 4370 | 1181 | 1992 | 89 |
| H(2A) | 5487 | 71 | 1421 | 85 |
| H(2B) | 4249 | -368 | 1116 | 85 |
| H(4) | 6525 | 1184 | 469 | 95 |
| H(5) | 5601 | 1909 | -525 | 95 |
| H(6A) | 6006 | 3042 | 406 | 90 |
| H(6B) | 5223 | 3375 | -222 | 90 |
| H(8A) | 2991 | 4184 | 825 | 101 |
| H(8B) | 3876 | 4376 | 177 | 101 |
| H(9A) | 3299 | 2947 | 1483 | 85 |
| H(9B) | 4525 | 2356 | 1378 | 85 |
| H(10) | 2126 | 1958 | 783 | 76 |
| H(11) | 3028 | 656 | 254 | 77 |
| H(13) | 217 | 2855 | 1950 | 84 |
| H(14) | 260 | 4088 | 2668 | 78 |
| H(16A) | 2103 | 4993 | 3405 | 104 |
| H(16B) | 2329 | 4352 | 4035 | 104 |
| H(16C) | 949 | 4630 | 3827 | 104 |
| H(17) | 3062 | 2938 | 3686 | 87 |
| H(18) | 2936 | 1664 | 3030 | 78 |

Table 6. Torsion angles [°] for **270**.

| | |
|---|---|
| N(1)-C(1)-C(2)-C(3) | 46.7(13) |
| C(1)-C(2)-C(3)-C(4) | 113.1(15) |
| C(1)-C(2)-C(3)-C(11) | -54.1(13) |
| C(11)-C(3)-C(4)-C(5) | 0.8(13) |
| C(2)-C(3)-C(4)-C(5) | -167.1(12) |
| C(3)-C(4)-C(5)-O(3) | -14.2(12) |
| C(3)-C(4)-C(5)-C(6) | 105.3(12) |

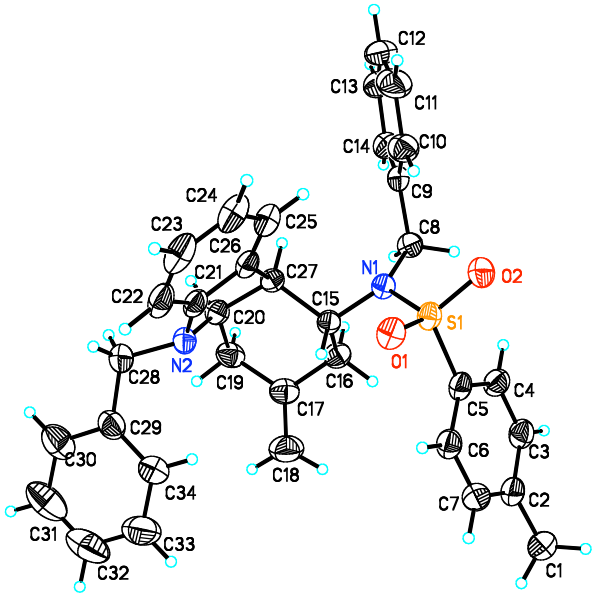
| | |
|---|---|
| O(3)-C(5)-C(6)-C(7) | 33.7(11) |
| C(4)-C(5)-C(6)-C(7) | -83.4(11) |
| C(5)-C(6)-C(7)-C(8) | -137.5(11) |
| C(5)-C(6)-C(7)-C(9) | 47.6(12) |
| C(8)-C(7)-C(9)-C(10) | 105.5(13) |
| C(6)-C(7)-C(9)-C(10) | -79.7(13) |
| C(7)-C(9)-C(10)-N(1) | 171.8(9) |
| C(7)-C(9)-C(10)-C(11) | 53.3(13) |
| C(4)-C(3)-C(11)-O(3) | 13.0(12) |
| C(2)-C(3)-C(11)-O(3) | -176.7(9) |
| C(4)-C(3)-C(11)-C(10) | -108.7(10) |
| C(2)-C(3)-C(11)-C(10) | 61.6(13) |
| N(1)-C(10)-C(11)-O(3) | -177.4(7) |
| C(9)-C(10)-C(11)-O(3) | -54.6(10) |
| N(1)-C(10)-C(11)-C(3) | -60.5(10) |
| C(9)-C(10)-C(11)-C(3) | 62.3(11) |
| C(18)-C(12)-C(13)-C(14) | -2.6(14) |
| S(1)-C(12)-C(13)-C(14) | 178.8(7) |
| C(12)-C(13)-C(14)-C(15) | 4.7(15) |
| C(13)-C(14)-C(15)-C(17) | -4.1(14) |
| C(13)-C(14)-C(15)-C(16) | 177.9(9) |
| C(14)-C(15)-C(17)-C(18) | 1.5(15) |
| C(16)-C(15)-C(17)-C(18) | 179.5(9) |
| C(15)-C(17)-C(18)-C(12) | 0.4(15) |
| C(13)-C(12)-C(18)-C(17) | 0.1(14) |
| S(1)-C(12)-C(18)-C(17) | 178.7(8) |
| C(11)-C(10)-N(1)-C(1) | 63.7(10) |
| C(9)-C(10)-N(1)-C(1) | -58.4(12) |
| C(11)-C(10)-N(1)-S(1) | -141.3(7) |
| C(9)-C(10)-N(1)-S(1) | 96.6(9) |
| C(2)-C(1)-N(1)-C(10) | -57.3(13) |
| C(2)-C(1)-N(1)-S(1) | 147.9(8) |
| C(3)-C(11)-O(3)-C(5) | -21.6(12) |
| C(10)-C(11)-O(3)-C(5) | 95.0(10) |
| C(4)-C(5)-O(3)-C(11) | 21.7(11) |
| C(6)-C(5)-O(3)-C(11) | -100.4(10) |

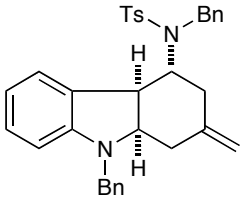
| | |
|---|---|
| C(10)-N(1)-S(1)-O(1) | 172.3(7) |
| C(1)-N(1)-S(1)-O(1) | -33.6(10) |
| C(10)-N(1)-S(1)-O(2) | 42.2(9) |
| C(1)-N(1)-S(1)-O(2) | -163.6(9) |
| C(10)-N(1)-S(1)-C(12) | -72.9(8) |
| C(1)-N(1)-S(1)-C(12) | 81.2(10) |
| C(18)-C(12)-S(1)-O(1) | 47.8(9) |
| C(13)-C(12)-S(1)-O(1) | -133.6(8) |
| C(18)-C(12)-S(1)-O(2) | 177.0(8) |
| C(13)-C(12)-S(1)-O(2) | -4.4(9) |
| C(18)-C(12)-S(1)-N(1) | -67.3(9) |
| C(13)-C(12)-S(1)-N(1) | 111.3(8) |

---

Symmetry transformations used to generate equivalent atoms:

**Compound 283**




**283**

Table 1. Crystal data and structure refinement for **283**.

| | | |
|---|---|---|
| Identification code | int_1s | |
| Empirical formula | C35.50 H37.50 N2 O2 S | |
| Formula weight | 556.23 | |
| Temperature | 173(2) K | |
| Wavelength | 1.54178 Å | |
| Crystal system | Monoclinic | |
| Space group | C2/c | |
| Unit cell dimensions | a = 26.9625(7) Å | α= 90°. |
| | b = 12.6832(4) Å | β= 101.767(2)°. |
| | c = 18.9477(5) Å | γ = 90°. |
| Volume | 6343.4(3) $Å^3$ | |
| Z | 8 | |
| Density (calculated) | 1.165 $Mg/m^3$ | |
| Absorption coefficient | 1.153 $mm^{-1}$ | |
| F(000) | 2372 | |
| Crystal size | 0.46 x 0.18 x 0.14 $mm^3$ | |
| Theta range for data collection | 3.35 to 65.83°. | |

| | |
|---|---|
| Index ranges | -30<=h<=31, -13<=k<=14, -22<=l<=21 |
| Reflections collected | 21329 |
| Independent reflections | 5033 [R(int) = 0.0245] |
| Completeness to theta = 65.83° | 91.5 % |
| Absorption correction | Semi-empirical from equivalents |
| Max. and min. transmission | 0.8553 and 0.6192 |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 5033 / 0 / 366 |
| Goodness-of-fit on $F^2$ | 1.076 |
| Final R indices [I>2sigma(I)] | R1 = 0.0722, wR2 = 0.2354 |
| R indices (all data) | R1 = 0.0790, wR2 = 0.2436 |
| Largest diff. peak and hole | 1.965 and -0.328 e.$Å^{-3}$ |

Table 2. Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters
($Å^2$x $10^3$) for **283**. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$
tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| C(1) | 659(2) | 6317(4) | -866(2) | 52(1) |
| C(2) | 1112(1) | 6310(3) | -251(2) | 40(1) |
| C(3) | 1489(1) | 7080(3) | -218(2) | 40(1) |
| C(4) | 1915(1) | 7063(3) | 322(2) | 38(1) |
| C(5) | 1973(1) | 6277(2) | 851(2) | 32(1) |
| C(6) | 1602(1) | 5522(3) | 835(2) | 36(1) |
| C(7) | 1173(1) | 5544(3) | 283(2) | 41(1) |
| C(8) | 2828(1) | 8241(2) | 1772(2) | 31(1) |
| C(9) | 3361(1) | 8435(3) | 2190(2) | 32(1) |
| C(10) | 3714(1) | 7632(3) | 2370(2) | 42(1) |
| C(11) | 4209(1) | 7863(4) | 2733(2) | 58(1) |
| C(12) | 4351(2) | 8896(4) | 2907(2) | 59(1) |
| C(13) | 4008(2) | 9696(4) | 2715(2) | 52(1) |
| C(14) | 3513(1) | 9470(3) | 2360(2) | 40(1) |
| C(15) | 2168(1) | 7467(2) | 2427(2) | 28(1) |
| C(16) | 1758(1) | 8243(3) | 2077(2) | 36(1) |
| C(17) | 1354(1) | 8305(3) | 2511(2) | 39(1) |
| C(18) | 873(1) | 8063(4) | 2244(3) | 57(1) |
| C(19) | 1549(1) | 8695(3) | 3266(2) | 40(1) |
| C(20) | 2015(1) | 8098(3) | 3661(2) | 34(1) |
| C(21) | 2326(1) | 6466(3) | 4064(2) | 35(1) |
| C(22) | 2451(2) | 5574(3) | 4497(2) | 47(1) |
| C(23) | 2922(2) | 5099(3) | 4515(2) | 49(1) |
| C(24) | 3247(2) | 5465(3) | 4105(2) | 46(1) |
| C(25) | 3114(1) | 6347(3) | 3654(2) | 38(1) |
| C(26) | 2659(1) | 6836(2) | 3641(2) | 31(1) |
| C(27) | 2413(1) | 7782(2) | 3212(2) | 28(1) |
| C(28) | 1644(1) | 7193(4) | 4597(2) | 50(1) |
| C(29) | 1079(1) | 7009(3) | 4433(2) | 42(1) |
| C(30) | 803(2) | 7303(4) | 4942(3) | 60(1) |
| C(31) | 289(2) | 7117(4) | 4832(4) | 79(2) |
| C(32) | 40(2) | 6626(5) | 4204(4) | 78(2) |
| C(33) | 309(2) | 6338(4) | 3695(3) | 70(1) |

| | | | | |
|---|---|---|---|---|
| C(34) | 827(2) | 6527(4) | 3808(2) | 54(1) |
| C(1S) | 487(3) | 581(7) | 3585(5) | 58(2) |
| C(2S) | 502(4) | 333(8) | 4392(5) | 67(2) |
| C(3S) | -21(3) | 59(7) | 4596(5) | 57(2) |
| N(1) | 2570(1) | 7309(2) | 2004(1) | 29(1) |
| N(2) | 1893(1) | 7089(2) | 3980(1) | 37(1) |
| O(1) | 2485(1) | 5361(2) | 1981(1) | 37(1) |
| O(2) | 2954(1) | 6268(2) | 1159(1) | 39(1) |
| S(1) | 2536(1) | 6236(1) | 1521(1) | 31(1) |

Table 3. Bond lengths [Å] and angles [°] for **283**.

| | |
|---|---|
| C(1)-C(2) | 1.504(5) |
| C(1)-H(1A) | 0.9800 |
| C(1)-H(1B) | 0.9800 |
| C(1)-H(1C) | 0.9800 |
| C(2)-C(7) | 1.388(5) |
| C(2)-C(3) | 1.402(5) |
| C(3)-C(4) | 1.374(5) |
| C(3)-H(3) | 0.9500 |
| C(4)-C(5) | 1.399(5) |
| C(4)-H(4) | 0.9500 |
| C(5)-C(6) | 1.380(5) |
| C(5)-S(1) | 1.769(3) |
| C(6)-C(7) | 1.393(5) |
| C(6)-H(6) | 0.9500 |
| C(7)-H(7) | 0.9500 |
| C(8)-N(1) | 1.482(4) |
| C(8)-C(9) | 1.514(4) |
| C(8)-H(8A) | 0.9900 |
| C(8)-H(8B) | 0.9900 |
| C(9)-C(10) | 1.389(5) |
| C(9)-C(14) | 1.393(5) |
| C(10)-C(11) | 1.402(5) |
| C(10)-H(10) | 0.9500 |
| C(11)-C(12) | 1.386(7) |
| C(11)-H(11) | 0.9500 |
| C(12)-C(13) | 1.373(7) |
| C(12)-H(12) | 0.9500 |
| C(13)-C(14) | 1.395(5) |
| C(13)-H(13) | 0.9500 |
| C(14)-H(14) | 0.9500 |
| C(15)-N(1) | 1.486(4) |
| C(15)-C(16) | 1.527(4) |
| C(15)-C(27) | 1.552(4) |
| C(15)-H(15) | 1.0000 |

| | |
|---|---|
| C(16)-C(17) | 1.497(5) |
| C(16)-H(16A) | 0.9900 |
| C(16)-H(16B) | 0.9900 |
| C(17)-C(18) | 1.328(5) |
| C(17)-C(19) | 1.503(5) |
| C(18)-H(18A) | 0.9500 |
| C(18)-H(18B) | 0.9500 |
| C(19)-C(20) | 1.527(5) |
| C(19)-H(19A) | 0.9900 |
| C(19)-H(19B) | 0.9900 |
| C(20)-N(2) | 1.481(4) |
| C(20)-C(27) | 1.553(4) |
| C(20)-H(20) | 1.0000 |
| C(21)-N(2) | 1.392(5) |
| C(21)-C(22) | 1.399(5) |
| C(21)-C(26) | 1.400(5) |
| C(22)-C(23) | 1.399(6) |
| C(22)-H(22) | 0.9500 |
| C(23)-C(24) | 1.366(6) |
| C(23)-H(23) | 0.9500 |
| C(24)-C(25) | 1.409(5) |
| C(24)-H(24) | 0.9500 |
| C(25)-C(26) | 1.370(5) |
| C(25)-H(25) | 0.9500 |
| C(26)-C(27) | 1.523(4) |
| C(27)-H(27) | 1.0000 |
| C(28)-N(2) | 1.469(4) |
| C(28)-C(29) | 1.508(5) |
| C(28)-H(28A) | 0.9900 |
| C(28)-H(28B) | 0.9900 |
| C(29)-C(34) | 1.382(6) |
| C(29)-C(30) | 1.386(5) |
| C(30)-C(31) | 1.379(7) |
| C(30)-H(30) | 0.9500 |
| C(31)-C(32) | 1.389(9) |
| C(31)-H(31) | 0.9500 |

| | |
|---|---|
| C(32)-C(33) | 1.368(8) |
| C(32)-H(32) | 0.9500 |
| C(33)-C(34) | 1.390(6) |
| C(33)-H(33) | 0.9500 |
| C(34)-H(34) | 0.9500 |
| C(1S)-C(2S) | 1.552(13) |
| C(1S)-H(1S1) | 0.9800 |
| C(1S)-H(1S2) | 0.9800 |
| C(1S)-H(1S3) | 0.9800 |
| C(2S)-C(3S) | 1.576(13) |
| C(2S)-H(2S1) | 0.9900 |
| C(2S)-H(2S2) | 0.9900 |
| C(3S)-C(3S)#1 | 1.519(17) |
| C(3S)-H(3S1) | 0.9900 |
| C(3S)-H(3S2) | 0.9900 |
| N(1)-S(1) | 1.631(3) |
| O(1)-S(1) | 1.434(2) |
| O(2)-S(1) | 1.437(2) |

| | |
|---|---|
| C(2)-C(1)-H(1A) | 109.5 |
| C(2)-C(1)-H(1B) | 109.5 |
| H(1A)-C(1)-H(1B) | 109.5 |
| C(2)-C(1)-H(1C) | 109.5 |
| H(1A)-C(1)-H(1C) | 109.5 |
| H(1B)-C(1)-H(1C) | 109.5 |
| C(7)-C(2)-C(3) | 118.5(3) |
| C(7)-C(2)-C(1) | 121.8(3) |
| C(3)-C(2)-C(1) | 119.8(3) |
| C(4)-C(3)-C(2) | 120.8(3) |
| C(4)-C(3)-H(3) | 119.6 |
| C(2)-C(3)-H(3) | 119.6 |
| C(3)-C(4)-C(5) | 120.0(3) |
| C(3)-C(4)-H(4) | 120.0 |
| C(5)-C(4)-H(4) | 120.0 |
| C(6)-C(5)-C(4) | 120.2(3) |
| C(6)-C(5)-S(1) | 120.5(3) |

| | |
|---|---|
| C(4)-C(5)-S(1) | 119.3(2) |
| C(5)-C(6)-C(7) | 119.4(3) |
| C(5)-C(6)-H(6) | 120.3 |
| C(7)-C(6)-H(6) | 120.3 |
| C(2)-C(7)-C(6) | 121.2(3) |
| C(2)-C(7)-H(7) | 119.4 |
| C(6)-C(7)-H(7) | 119.4 |
| N(1)-C(8)-C(9) | 115.3(3) |
| N(1)-C(8)-H(8A) | 108.5 |
| C(9)-C(8)-H(8A) | 108.5 |
| N(1)-C(8)-H(8B) | 108.5 |
| C(9)-C(8)-H(8B) | 108.5 |
| H(8A)-C(8)-H(8B) | 107.5 |
| C(10)-C(9)-C(14) | 118.6(3) |
| C(10)-C(9)-C(8) | 122.7(3) |
| C(14)-C(9)-C(8) | 118.6(3) |
| C(9)-C(10)-C(11) | 120.3(4) |
| C(9)-C(10)-H(10) | 119.8 |
| C(11)-C(10)-H(10) | 119.8 |
| C(12)-C(11)-C(10) | 120.2(4) |
| C(12)-C(11)-H(11) | 119.9 |
| C(10)-C(11)-H(11) | 119.9 |
| C(13)-C(12)-C(11) | 119.8(4) |
| C(13)-C(12)-H(12) | 120.1 |
| C(11)-C(12)-H(12) | 120.1 |
| C(12)-C(13)-C(14) | 120.2(4) |
| C(12)-C(13)-H(13) | 119.9 |
| C(14)-C(13)-H(13) | 119.9 |
| C(9)-C(14)-C(13) | 120.9(4) |
| C(9)-C(14)-H(14) | 119.6 |
| C(13)-C(14)-H(14) | 119.6 |
| N(1)-C(15)-C(16) | 113.3(2) |
| N(1)-C(15)-C(27) | 109.7(2) |
| C(16)-C(15)-C(27) | 112.3(3) |
| N(1)-C(15)-H(15) | 107.1 |
| C(16)-C(15)-H(15) | 107.1 |

| | |
|---|---|
| C(27)-C(15)-H(15) | 107.1 |
| C(17)-C(16)-C(15) | 109.9(3) |
| C(17)-C(16)-H(16A) | 109.7 |
| C(15)-C(16)-H(16A) | 109.7 |
| C(17)-C(16)-H(16B) | 109.7 |
| C(15)-C(16)-H(16B) | 109.7 |
| H(16A)-C(16)-H(16B) | 108.2 |
| C(18)-C(17)-C(16) | 122.9(3) |
| C(18)-C(17)-C(19) | 124.3(3) |
| C(16)-C(17)-C(19) | 112.8(3) |
| C(17)-C(18)-H(18A) | 120.0 |
| C(17)-C(18)-H(18B) | 120.0 |
| H(18A)-C(18)-H(18B) | 120.0 |
| C(17)-C(19)-C(20) | 113.4(3) |
| C(17)-C(19)-H(19A) | 108.9 |
| C(20)-C(19)-H(19A) | 108.9 |
| C(17)-C(19)-H(19B) | 108.9 |
| C(20)-C(19)-H(19B) | 108.9 |
| H(19A)-C(19)-H(19B) | 107.7 |
| N(2)-C(20)-C(19) | 113.5(3) |
| N(2)-C(20)-C(27) | 103.6(2) |
| C(19)-C(20)-C(27) | 116.9(3) |
| N(2)-C(20)-H(20) | 107.4 |
| C(19)-C(20)-H(20) | 107.4 |
| C(27)-C(20)-H(20) | 107.4 |
| N(2)-C(21)-C(22) | 128.5(3) |
| N(2)-C(21)-C(26) | 111.4(3) |
| C(22)-C(21)-C(26) | 120.1(3) |
| C(21)-C(22)-C(23) | 118.1(3) |
| C(21)-C(22)-H(22) | 120.9 |
| C(23)-C(22)-H(22) | 120.9 |
| C(24)-C(23)-C(22) | 121.6(3) |
| C(24)-C(23)-H(23) | 119.2 |
| C(22)-C(23)-H(23) | 119.2 |
| C(23)-C(24)-C(25) | 120.1(4) |
| C(23)-C(24)-H(24) | 120.0 |

| | |
|---|---|
| C(25)-C(24)-H(24) | 120.0 |
| C(26)-C(25)-C(24) | 119.1(4) |
| C(26)-C(25)-H(25) | 120.4 |
| C(24)-C(25)-H(25) | 120.4 |
| C(25)-C(26)-C(21) | 120.9(3) |
| C(25)-C(26)-C(27) | 131.0(3) |
| C(21)-C(26)-C(27) | 108.0(3) |
| C(26)-C(27)-C(15) | 111.3(2) |
| C(26)-C(27)-C(20) | 100.7(2) |
| C(15)-C(27)-C(20) | 112.7(2) |
| C(26)-C(27)-H(27) | 110.6 |
| C(15)-C(27)-H(27) | 110.6 |
| C(20)-C(27)-H(27) | 110.6 |
| N(2)-C(28)-C(29) | 115.4(3) |
| N(2)-C(28)-H(28A) | 108.4 |
| C(29)-C(28)-H(28A) | 108.4 |
| N(2)-C(28)-H(28B) | 108.4 |
| C(29)-C(28)-H(28B) | 108.4 |
| H(28A)-C(28)-H(28B) | 107.5 |
| C(34)-C(29)-C(30) | 118.4(4) |
| C(34)-C(29)-C(28) | 123.0(3) |
| C(30)-C(29)-C(28) | 118.6(4) |
| C(31)-C(30)-C(29) | 121.0(5) |
| C(31)-C(30)-H(30) | 119.5 |
| C(29)-C(30)-H(30) | 119.5 |
| C(30)-C(31)-C(32) | 120.1(5) |
| C(30)-C(31)-H(31) | 119.9 |
| C(32)-C(31)-H(31) | 119.9 |
| C(33)-C(32)-C(31) | 119.3(4) |
| C(33)-C(32)-H(32) | 120.3 |
| C(31)-C(32)-H(32) | 120.3 |
| C(32)-C(33)-C(34) | 120.4(5) |
| C(32)-C(33)-H(33) | 119.8 |
| C(34)-C(33)-H(33) | 119.8 |
| C(29)-C(34)-C(33) | 120.8(4) |
| C(29)-C(34)-H(34) | 119.6 |

| | |
|---|---|
| C(33)-C(34)-H(34) | 119.6 |
| C(2S)-C(1S)-H(1S1) | 109.5 |
| C(2S)-C(1S)-H(1S2) | 109.5 |
| H(1S1)-C(1S)-H(1S2) | 109.5 |
| C(2S)-C(1S)-H(1S3) | 109.5 |
| H(1S1)-C(1S)-H(1S3) | 109.5 |
| H(1S2)-C(1S)-H(1S3) | 109.5 |
| C(1S)-C(2S)-C(3S) | 116.2(8) |
| C(1S)-C(2S)-H(2S1) | 108.2 |
| C(3S)-C(2S)-H(2S1) | 108.2 |
| C(1S)-C(2S)-H(2S2) | 108.2 |
| C(3S)-C(2S)-H(2S2) | 108.2 |
| H(2S1)-C(2S)-H(2S2) | 107.4 |
| C(3S)#1-C(3S)-C(2S) | 112.6(9) |
| C(3S)#1-C(3S)-H(3S1) | 109.1 |
| C(2S)-C(3S)-H(3S1) | 109.1 |
| C(3S)#1-C(3S)-H(3S2) | 109.1 |
| C(2S)-C(3S)-H(3S2) | 109.1 |
| H(3S1)-C(3S)-H(3S2) | 107.8 |
| C(8)-N(1)-C(15) | 119.3(2) |
| C(8)-N(1)-S(1) | 118.4(2) |
| C(15)-N(1)-S(1) | 116.70(19) |
| C(21)-N(2)-C(28) | 118.0(3) |
| C(21)-N(2)-C(20) | 106.7(2) |
| C(28)-N(2)-C(20) | 115.0(3) |
| O(1)-S(1)-O(2) | 119.53(14) |
| O(1)-S(1)-N(1) | 107.86(13) |
| O(2)-S(1)-N(1) | 106.47(13) |
| O(1)-S(1)-C(5) | 106.55(15) |
| O(2)-S(1)-C(5) | 107.36(15) |
| N(1)-S(1)-C(5) | 108.73(14) |

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Symmetry transformations used to generate equivalent atoms:

#1 -x,-y,-z+1

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **283**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| C(1) | 45(2) | 71(3) | 39(2) | -4(2) | 4(2) | -8(2) |
| C(2) | 41(2) | 47(2) | 32(2) | -9(2) | 10(1) | 0(2) |
| C(3) | 47(2) | 42(2) | 30(2) | 3(1) | 8(1) | -1(2) |
| C(4) | 44(2) | 36(2) | 32(2) | -2(1) | 6(1) | -7(2) |
| C(5) | 41(2) | 30(2) | 26(2) | -4(1) | 8(1) | -1(1) |
| C(6) | 45(2) | 33(2) | 32(2) | -2(1) | 11(1) | -4(1) |
| C(7) | 42(2) | 41(2) | 41(2) | -6(2) | 11(2) | -7(2) |
| C(8) | 33(2) | 29(2) | 31(2) | 4(1) | 5(1) | -2(1) |
| C(9) | 33(2) | 39(2) | 25(2) | 0(1) | 8(1) | -3(1) |
| C(10) | 37(2) | 45(2) | 43(2) | 7(2) | 6(2) | 1(2) |
| C(11) | 35(2) | 82(3) | 56(2) | 20(2) | 4(2) | 9(2) |
| C(12) | 38(2) | 90(3) | 45(2) | 5(2) | -2(2) | -19(2) |
| C(13) | 47(2) | 65(3) | 43(2) | -12(2) | 7(2) | -20(2) |
| C(14) | 41(2) | 43(2) | 36(2) | -8(2) | 9(2) | -7(2) |
| C(15) | 32(2) | 26(2) | 27(2) | -1(1) | 7(1) | -2(1) |
| C(16) | 34(2) | 36(2) | 36(2) | 1(1) | 3(1) | 3(1) |
| C(17) | 33(2) | 35(2) | 48(2) | -2(2) | 6(2) | 4(1) |
| C(18) | 36(2) | 69(3) | 63(3) | -6(2) | 3(2) | -2(2) |
| C(19) | 34(2) | 39(2) | 50(2) | -10(2) | 14(2) | -1(1) |
| C(20) | 35(2) | 35(2) | 32(2) | -11(1) | 9(1) | -4(1) |
| C(21) | 45(2) | 34(2) | 23(2) | -6(1) | 3(1) | -9(2) |
| C(22) | 73(3) | 39(2) | 26(2) | -3(1) | 6(2) | -22(2) |
| C(23) | 80(3) | 31(2) | 30(2) | 0(1) | -4(2) | -1(2) |
| C(24) | 65(2) | 38(2) | 30(2) | -5(2) | -3(2) | 11(2) |
| C(25) | 48(2) | 38(2) | 26(2) | -2(1) | 3(1) | 7(2) |
| C(26) | 40(2) | 28(2) | 22(1) | -3(1) | 3(1) | -3(1) |
| C(27) | 29(2) | 25(2) | 29(2) | -2(1) | 6(1) | -2(1) |
| C(28) | 48(2) | 70(3) | 33(2) | -10(2) | 15(2) | -16(2) |
| C(29) | 45(2) | 42(2) | 42(2) | 4(2) | 15(2) | -6(2) |
| C(30) | 63(3) | 55(2) | 72(3) | -6(2) | 35(2) | -4(2) |
| C(31) | 62(3) | 77(3) | 112(5) | 6(3) | 51(3) | 4(3) |

| | | | | | | |
|---|---|---|---|---|---|---|
| C(32) | 43(2) | 84(4) | 111(4) | 34(3) | 23(3) | 0(2) |
| C(33) | 52(3) | 81(3) | 72(3) | 20(3) | 0(2) | -21(2) |
| C(34) | 47(2) | 68(3) | 49(2) | -1(2) | 13(2) | -17(2) |
| N(1) | 33(1) | 26(1) | 27(1) | 0(1) | 6(1) | -1(1) |
| N(2) | 41(2) | 44(2) | 28(1) | -6(1) | 11(1) | -12(1) |
| O(1) | 48(1) | 26(1) | 35(1) | 2(1) | 7(1) | 2(1) |
| O(2) | 41(1) | 42(1) | 37(1) | -5(1) | 13(1) | 2(1) |
| S(1) | 38(1) | 26(1) | 28(1) | -2(1) | 8(1) | 1(1) |

Table 5. Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters ($Å^2$x $10^3$) for **283**.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(1A) | 751 | 5998 | -1292 | 78 |
| H(1B) | 548 | 7046 | -975 | 78 |
| H(1C) | 383 | 5913 | -730 | 78 |
| H(3) | 1449 | 7619 | -573 | 47 |
| H(4) | 2169 | 7585 | 337 | 45 |
| H(6) | 1639 | 4994 | 1197 | 43 |
| H(7) | 918 | 5024 | 272 | 49 |
| H(8A) | 2621 | 8874 | 1813 | 38 |
| H(8B) | 2839 | 8155 | 1256 | 38 |
| H(10) | 3620 | 6924 | 2247 | 51 |
| H(11) | 4448 | 7309 | 2860 | 70 |
| H(12) | 4686 | 9050 | 3158 | 71 |
| H(13) | 4107 | 10406 | 2824 | 62 |
| H(14) | 3277 | 10029 | 2233 | 48 |
| H(15) | 2000 | 6769 | 2450 | 34 |
| H(16A) | 1910 | 8949 | 2048 | 43 |
| H(16B) | 1609 | 8008 | 1581 | 43 |

| | | | | |
|---|---|---|---|---|
| H(18A) | 773 | 7839 | 1757 | 68 |
| H(18B) | 628 | 8114 | 2540 | 68 |
| H(19A) | 1276 | 8630 | 3543 | 48 |
| H(19B) | 1634 | 9453 | 3247 | 48 |
| H(20) | 2190 | 8557 | 4066 | 41 |
| H(22) | 2223 | 5298 | 4772 | 56 |
| H(23) | 3018 | 4507 | 4820 | 59 |
| H(24) | 3563 | 5124 | 4123 | 56 |
| H(25) | 3337 | 6600 | 3363 | 46 |
| H(27) | 2666 | 8360 | 3216 | 33 |
| H(28A) | 1710 | 7910 | 4799 | 59 |
| H(28B) | 1802 | 6686 | 4973 | 59 |
| H(30) | 970 | 7637 | 5374 | 72 |
| H(31) | 105 | 7325 | 5187 | 95 |
| H(32) | -314 | 6491 | 4128 | 94 |
| H(33) | 140 | 6007 | 3263 | 84 |
| H(34) | 1009 | 6322 | 3451 | 65 |
| H(1S1) | 264 | 76 | 3283 | 87 |
| H(1S2) | 830 | 525 | 3488 | 87 |
| H(1S3) | 359 | 1297 | 3476 | 87 |
| H(2S1) | 648 | 951 | 4681 | 80 |
| H(2S2) | 736 | -267 | 4535 | 80 |
| H(3S1) | -268 | 623 | 4415 | 68 |
| H(3S2) | -151 | -607 | 4355 | 68 |

Table 6. Torsion angles [°] for **283**

| | |
|---|---|
| C(7)-C(2)-C(3)-C(4) | 1.4(5) |
| C(1)-C(2)-C(3)-C(4) | -177.4(3) |
| C(2)-C(3)-C(4)-C(5) | -0.6(5) |
| C(3)-C(4)-C(5)-C(6) | -0.6(5) |
| C(3)-C(4)-C(5)-S(1) | 177.5(3) |

| | |
|---|---|
| C(4)-C(5)-C(6)-C(7) | 0.9(5) |
| S(1)-C(5)-C(6)-C(7) | -177.2(2) |
| C(3)-C(2)-C(7)-C(6) | -1.1(5) |
| C(1)-C(2)-C(7)-C(6) | 177.7(3) |
| C(5)-C(6)-C(7)-C(2) | 0.0(5) |
| N(1)-C(8)-C(9)-C(10) | 43.9(4) |
| N(1)-C(8)-C(9)-C(14) | -140.4(3) |
| C(14)-C(9)-C(10)-C(11) | 1.7(5) |
| C(8)-C(9)-C(10)-C(11) | 177.4(3) |
| C(9)-C(10)-C(11)-C(12) | -0.8(6) |
| C(10)-C(11)-C(12)-C(13) | -0.8(6) |
| C(11)-C(12)-C(13)-C(14) | 1.4(6) |
| C(10)-C(9)-C(14)-C(13) | -1.1(5) |
| C(8)-C(9)-C(14)-C(13) | -177.0(3) |
| C(12)-C(13)-C(14)-C(9) | -0.5(6) |
| N(1)-C(15)-C(16)-C(17) | 176.5(3) |
| C(27)-C(15)-C(16)-C(17) | -58.5(3) |
| C(15)-C(16)-C(17)-C(18) | -120.1(4) |
| C(15)-C(16)-C(17)-C(19) | 61.5(4) |
| C(18)-C(17)-C(19)-C(20) | 130.4(4) |
| C(16)-C(17)-C(19)-C(20) | -51.3(4) |
| C(17)-C(19)-C(20)-N(2) | -81.8(3) |
| C(17)-C(19)-C(20)-C(27) | 38.7(4) |
| N(2)-C(21)-C(22)-C(23) | -177.5(3) |
| C(26)-C(21)-C(22)-C(23) | 2.5(5) |
| C(21)-C(22)-C(23)-C(24) | -2.3(5) |
| C(22)-C(23)-C(24)-C(25) | 0.6(5) |
| C(23)-C(24)-C(25)-C(26) | 0.8(5) |
| C(24)-C(25)-C(26)-C(21) | -0.5(5) |
| C(24)-C(25)-C(26)-C(27) | -179.3(3) |
| N(2)-C(21)-C(26)-C(25) | 178.8(3) |
| C(22)-C(21)-C(26)-C(25) | -1.2(5) |
| N(2)-C(21)-C(26)-C(27) | -2.1(3) |
| C(22)-C(21)-C(26)-C(27) | 177.9(3) |
| C(25)-C(26)-C(27)-C(15) | 79.0(4) |
| C(21)-C(26)-C(27)-C(15) | -99.9(3) |

| | |
|---|---|
| C(25)-C(26)-C(27)-C(20) | -161.3(3) |
| C(21)-C(26)-C(27)-C(20) | 19.7(3) |
| N(1)-C(15)-C(27)-C(26) | -75.1(3) |
| C(16)-C(15)-C(27)-C(26) | 158.0(3) |
| N(1)-C(15)-C(27)-C(20) | 172.7(2) |
| C(16)-C(15)-C(27)-C(20) | 45.8(3) |
| N(2)-C(20)-C(27)-C(26) | -29.2(3) |
| C(19)-C(20)-C(27)-C(26) | -154.9(3) |
| N(2)-C(20)-C(27)-C(15) | 89.4(3) |
| C(19)-C(20)-C(27)-C(15) | -36.3(4) |
| N(2)-C(28)-C(29)-C(34) | 15.5(6) |
| N(2)-C(28)-C(29)-C(30) | -166.8(4) |
| C(34)-C(29)-C(30)-C(31) | 0.2(7) |
| C(28)-C(29)-C(30)-C(31) | -177.6(4) |
| C(29)-C(30)-C(31)-C(32) | 0.2(8) |
| C(30)-C(31)-C(32)-C(33) | -0.5(8) |
| C(31)-C(32)-C(33)-C(34) | 0.5(8) |
| C(30)-C(29)-C(34)-C(33) | -0.2(7) |
| C(28)-C(29)-C(34)-C(33) | 177.4(4) |
| C(32)-C(33)-C(34)-C(29) | -0.1(7) |
| C(1S)-C(2S)-C(3S)-C(3S)#1 | -174.0(9) |
| C(9)-C(8)-N(1)-C(15) | 105.1(3) |
| C(9)-C(8)-N(1)-S(1) | -102.1(3) |
| C(16)-C(15)-N(1)-C(8) | 51.8(3) |
| C(27)-C(15)-N(1)-C(8) | -74.5(3) |
| C(16)-C(15)-N(1)-S(1) | -101.5(3) |
| C(27)-C(15)-N(1)-S(1) | 132.2(2) |
| C(22)-C(21)-N(2)-C(28) | 31.0(5) |
| C(26)-C(21)-N(2)-C(28) | -149.0(3) |
| C(22)-C(21)-N(2)-C(20) | 162.2(3) |
| C(26)-C(21)-N(2)-C(20) | -17.9(3) |
| C(29)-C(28)-N(2)-C(21) | -130.9(4) |
| C(29)-C(28)-N(2)-C(20) | 101.8(4) |
| C(19)-C(20)-N(2)-C(21) | 157.4(3) |
| C(27)-C(20)-N(2)-C(21) | 29.7(3) |
| C(19)-C(20)-N(2)-C(28) | -69.7(4) |

| | |
|---|---|
| C(27)-C(20)-N(2)-C(28) | 162.5(3) |
| C(8)-N(1)-S(1)-O(1) | 155.1(2) |
| C(15)-N(1)-S(1)-O(1) | -51.3(2) |
| C(8)-N(1)-S(1)-O(2) | 25.7(3) |
| C(15)-N(1)-S(1)-O(2) | 179.2(2) |
| C(8)-N(1)-S(1)-C(5) | -89.7(2) |
| C(15)-N(1)-S(1)-C(5) | 63.8(2) |
| C(6)-C(5)-S(1)-O(1) | -2.2(3) |
| C(4)-C(5)-S(1)-O(1) | 179.7(3) |
| C(6)-C(5)-S(1)-O(2) | 126.9(3) |
| C(4)-C(5)-S(1)-O(2) | -51.1(3) |
| C(6)-C(5)-S(1)-N(1) | -118.2(3) |
| C(4)-C(5)-S(1)-N(1) | 63.7(3) |

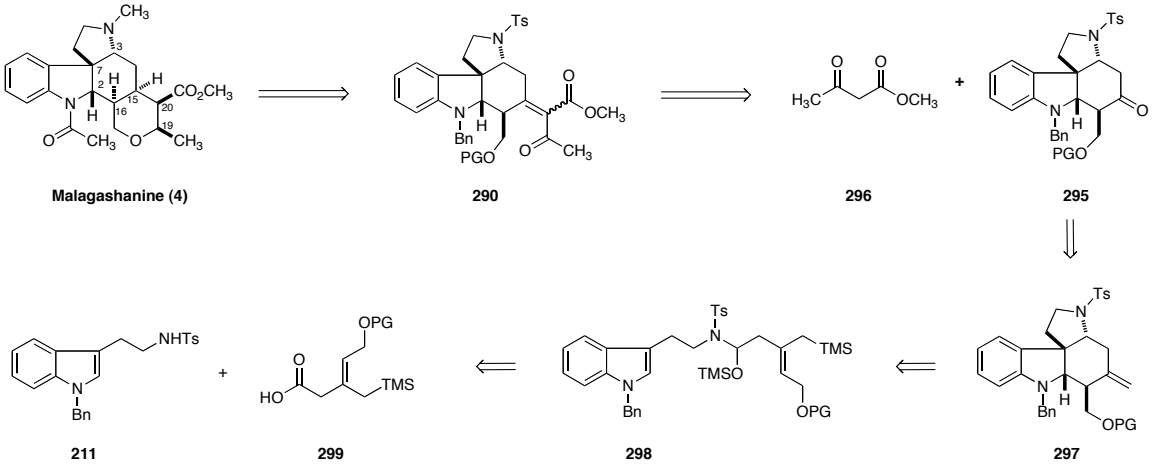
Symmetry transformations used to generate equivalent atoms:
#1 -x,-y,-z+1

# 3. Chapter Three: Efforts Towards the Total Synthesis of Malagashanine Using Our Cascade Cyclization Reaction Sequence

## 3.1. First Generation Approach: Accessing Malagashanine *via* a Knoevenagel Condensation and a Tandem Hydrogenation Reaction

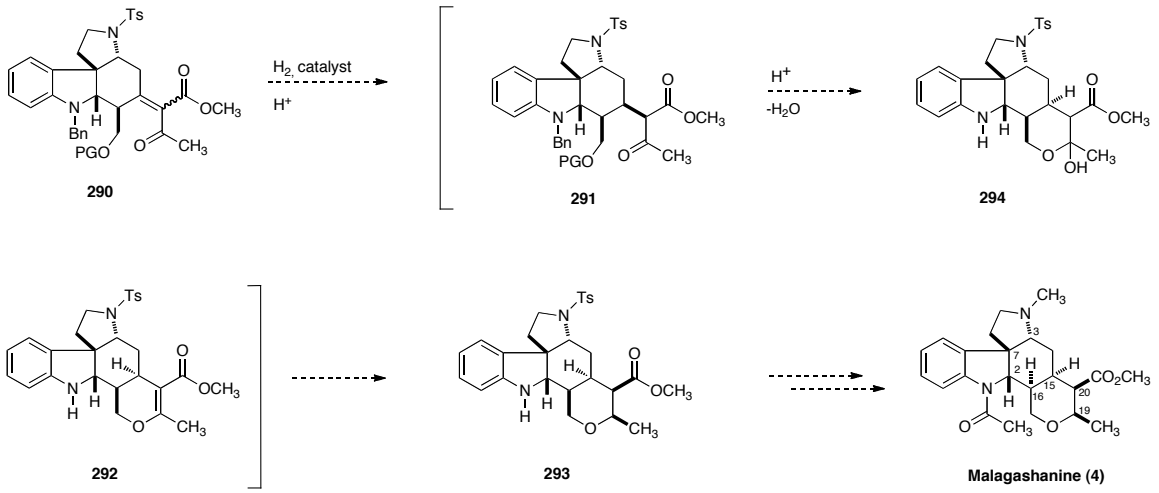
### 3.1.1. Retrosynthetic Analysis

With an efficient method in hand to construct the stereocenters at C(2), C(3), and C(7) in the malagashanine core, our focus turned to the development of a concise strategy for the total synthesis of malagashanine. Our retrosynthetic analysis is outlined in Scheme 3.1.




**Scheme 3.1** Overall synthetic strategy for the construction of malagashanine.

Our approach relied on the synthesis of $\alpha,\beta$-unsaturated ketoester **290**, which would allow the construction of the E ring and the installation of the C(19) and (20) stereocenter *via* an ambitious cascade sequence (Scheme 3.2).




**Scheme 3.2** Proposed tandem reaction to access malagashanine from $\alpha,\beta$-unsaturated ketoester **290**.

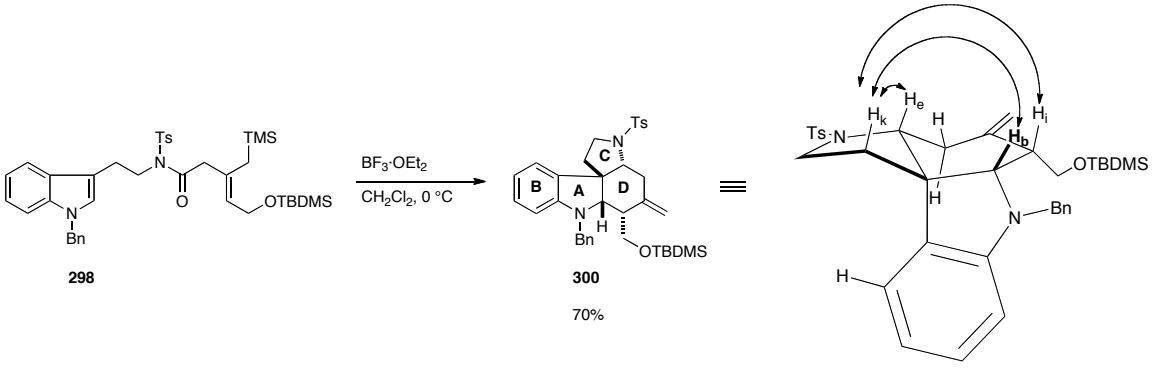
We envisioned that compound **290** could first undergo hydrogenation from the most accessible face of the olefin to generate the corresponding saturated ketoester **291** with the requisite stereochemistry at C(15). Carrying out this transformation under acidic conditions would allow the deprotection of the masked alcohol, which would then undergo an intramolecular hemiacetal formation with the more electrophilic ketone carbonyl, followed by *in situ* dehydration to produce $\alpha,\beta$-unsaturated ester **192**. A second *in situ* hydrogenation reaction would set the stereocenters at C(19) and C(20) to afford **293**.

In turn, $\alpha,\beta$-unsaturated ketoester **290** would be accessed through a Knoevonagel condensation[51] of ketone **295** with ketoester **296** (Scheme 3.1). Compound **295** would be

constructed from tetracyclic core **297** using our cascade annulation reaction.[52] Consequently, this strategy required us to extend the scope of our methodology by including an extra degree of olefin substitution in *N*-tosyl,*O*-TMS-aminol **298**, in order to install the fourth stereocenter at C(16). At the onset of our investigation, we predicted that the cyclization of *Z*-olefin isomer *N*-tosyl,*O*-TMS-aminol **298** would undergo cyclization *via* a chair transition (*vide infra*) to produce the requisite stereochemistry at this carbon center. Consequently, compound **298** was synthesized by Dr. Boudet in our laboratory and subjected to our standard cyclization reaction conditions.

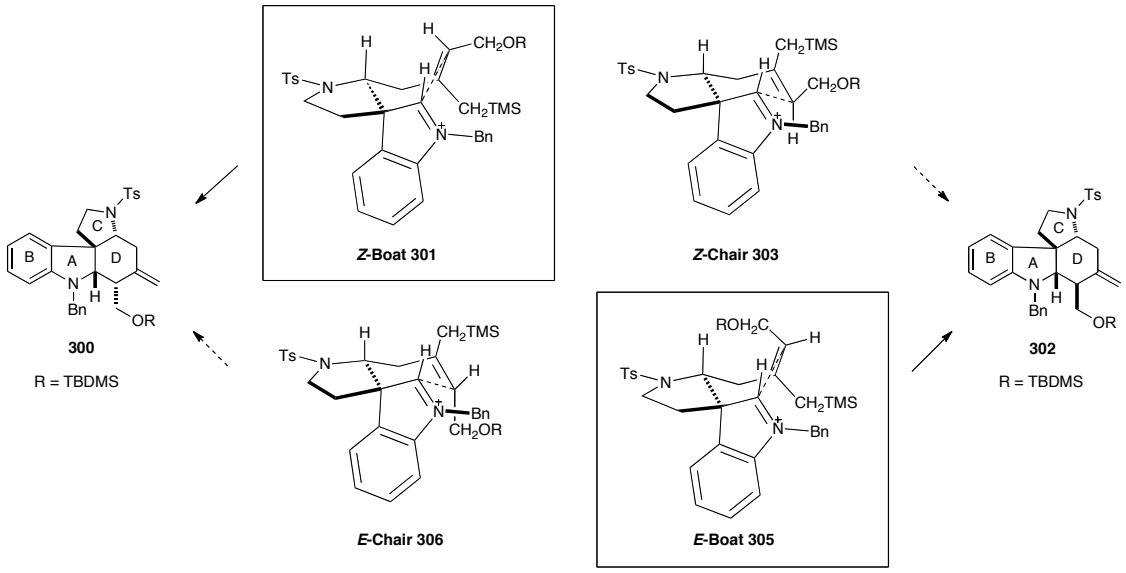
### 3.1.2. Initial Approach to Incorporate a Suitable C(16)-Substituent

Treatment of compound **298** with the previously developed cyclization conditions produced tetracyclic amine **300** as a single diastereomer (Scheme 3.3). The general structure of **300** was assigned based on COSY and HMQC experiments. We identified compound **300** as the C(16)-epimer of the desired tetracycle using NOESY experiments, which revealed key correlations between $H_k$ and proton signals $H_b$, $H_e$ and $H_i$, thus indicating that all four protons were located on the same face of the D-ring.




**Scheme 3.3** Cyclization of *Z*-isomer **298** and structural assignment of the product **300**.

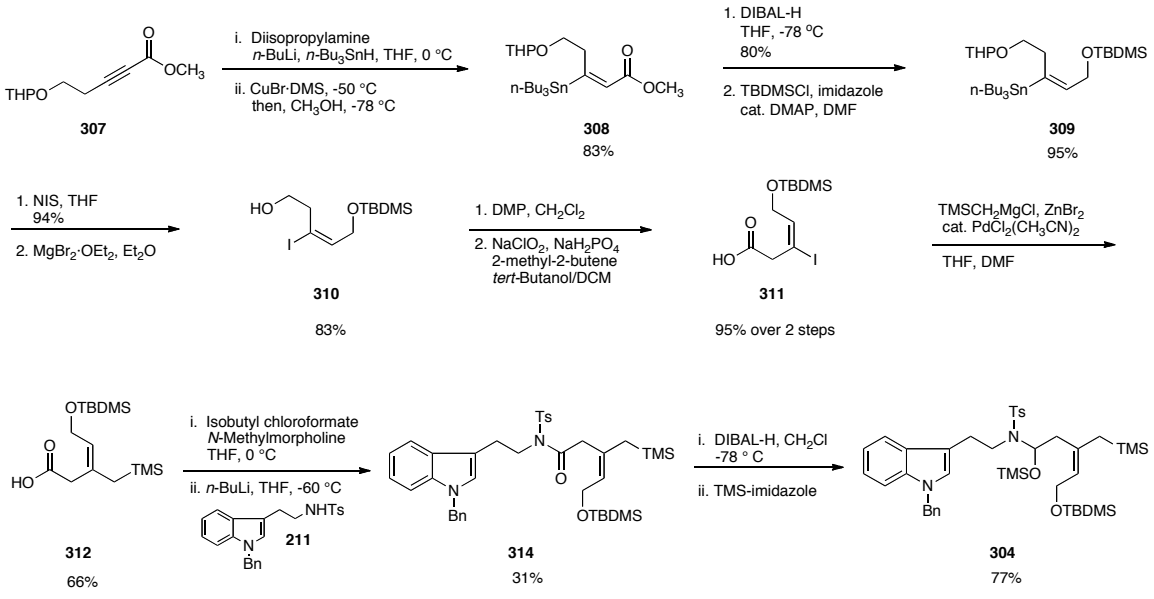
Despite obtaining the undesired epimer **300**, the exquisite diastereoselectivity observed in the transformation was very promising. We reasoned that the intermediate iminium ion underwent cyclization exclusively through boat transition state **301** (Scheme 3.4). The desired tetracycle **302**, which would have been generated *via* the corresponding *Z*-chair transition state **303**, was never observed. Consequently, we reasoned that the desired core **302** should be accessible from the *E*-olefin isomer *N*-tosyl-*O*-TMS-aminol **304**, as long as the intermediate iminium ion also underwent cyclization through boat transition state **305**.




**Scheme 3.4** Rationale for the observed stereochemical outcome.

### 3.1.3. Revised Approach to Incorporate a Suitable C(16)-Substituent: Synthesis of *E*-Olefin Isomer *N*-Tosyl-*O*-TMS-Aminol 304

The synthesis of *N*-tosyl,*O*-TMS-aminol **304** began with conjugate addition of tributylstannylcuprate[53] to known $\alpha,\beta$-unsaturated alkynylester **307**, followed by kinetic protonation of the intermediate enolate with methanol at -78 °C to generate the corresponding of *E*-olefin **308** in 83% yield (Scheme 3.5). Reduction of the ester with DIBAL-H and treatment of the ensuing alcohol with TBSCl and imidazole produced silyl ether **309** in 95% yield. Tin-iodine exchange using NIS[54] proceeded in 94% yield, followed by deprotection of the THP group with anhydrous magnesium bromide to afford alcohol **310** in 83% yield. Compound **310** was treated with Dess-Martin periodinane to produce a highly labile $\beta,\gamma$-unsaturated aldehyde intermediate, which was immediately subjected to a Pinnick oxidation[55] to afford the desired $\beta,\gamma$-unsaturated acid **311** in 95% yield over two steps.

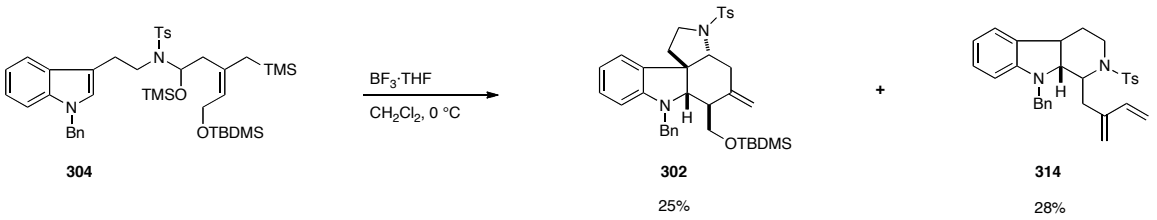



**Scheme 3.5** Synthesis of *N*-tosyl,*O*-TMS-aminol **304**.

Negishi cross-coupling of compound **311** with the allyl zinc reagent generated *in situ* from (trimethylsilyl)-methyl magnesium chloride produced the desired allylsilane in 66% yield.[56] Conversion of **312** to the corresponding mixed anhydride with isobutyl chloroformate and *N*-methyl morpholine, followed by treatment with the lithium anion of tosylamine **211** produced a disappointing 31% of compound **311**. Regardless, suffcient amounts of **311** were synthesized and subjected to our standard conditions to afford **304** in 77% yield.

### 3.1.4. Cyclization of *N*-Tosyl-*O*-TMS-Aminol 304

With *N*-tosyl,*O*-TMS-aminol **304** in hand, treatment with $BF_3{\cdot}OEt_2$ at 0 °C produced surprisingly low yields of the desired tetracyclic amine **302**, along with several other unidentified side products. Switching to the milder Lewis acid $BF_3{\cdot}THF$ increased the yield of **314** to 25% and also allowed the isolation of tetrahydrocarboline **314** in 28% yield (Scheme 3.6).




**304** **302** 25% **314** 28%

**Scheme 3.6** Cyclization of *N*-tosyl,*O*-TMS-aminol **304** to tetracyclic amine **302**.

Compound **302** was highly acid sensitive and decomposed readily in $CDCl_3$, which precluded the initial use of long 2D NMR experiments to assert the relative

stereochemical configuration at C(16). However, the structure of compound **302** was assigned based on comparisons of its $^1$H NMR spectrum to that of its C(16)-epimer **300** (Figure 3.1). More specifically, proton $H_b$ and its neighboring proton were not coupled to each other in compound **302,** while on C(16)-epimer **300** the equivalent protons displayed a coupling constant of 5.0 Hz. The lack of coupling in **302** suggested that the dihedral angle between $H_b$ and its neighbor was close to 90°, consistent with the assigned stereochemistry.

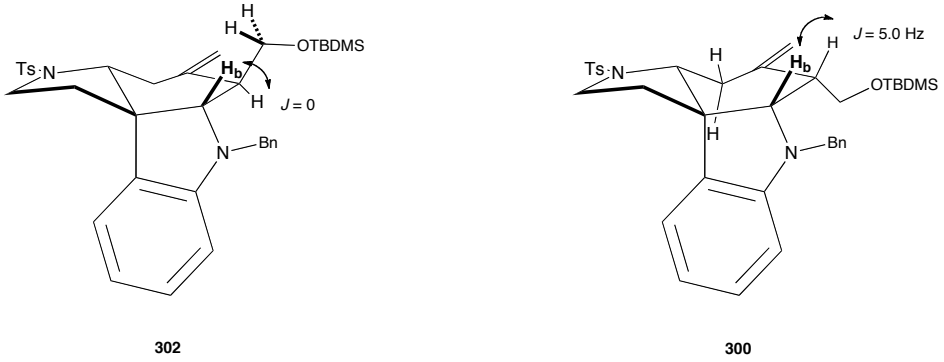
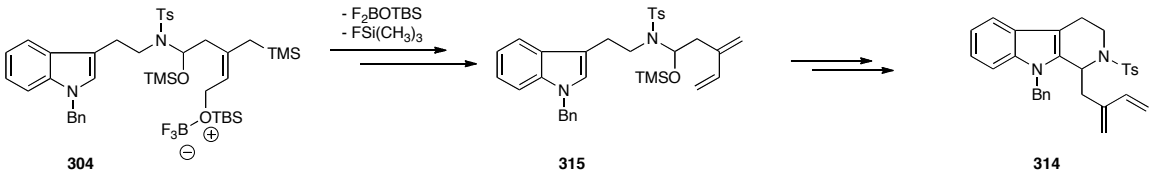



**Figure 3.1** Structural assignment of tetracyclic amine **302**.

The formation of tetrahydrocarboline **314** can be explained through the mechanism shown in Scheme 3.7, in which the *tert*-butyl-dimethylsilyloxy moeity first engages the Lewis acid. This is then followed by elimination of the *tert*-butyl-dimethylsilyloxy group, possibly promoted by the formation of a highly stable *β*-silyl allylic cation intermediate. Once compound **315** forms, it can eventually undergo spiroindolium fomation, followed by 1,2-alkyl migration and rearomatization to produce **314**.

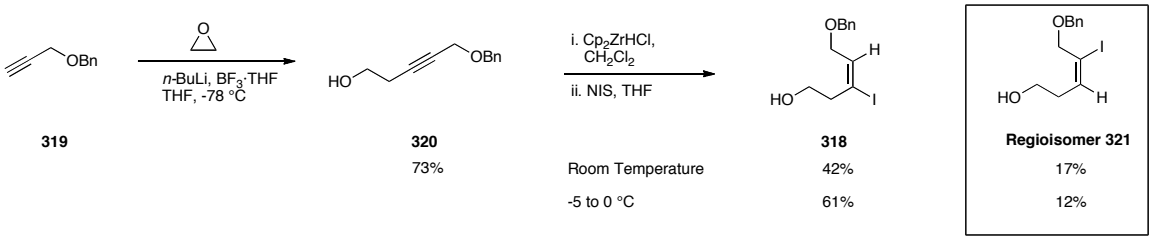



**Scheme 3.7** Mechanistic rationale for the formation of tetrahydrocarboline **314**.

The previous results, combined with the observed lability of the desired compound **302,** led us to rethink our functional group strategy. Consequently, we decided to replace the *tert*-butyl-dimethylsilyl protected substrate **304** for compounds **316** and **317** with the more robust benzyl and *tert*-butyl-diphenylsilyl groups.

### 3.1.5. Synthesis of *N*-Tosyl-*O*-TMS-Aminols 316 and 317 Containing the Benzyl and TBDPS Protecting Groups Respectively

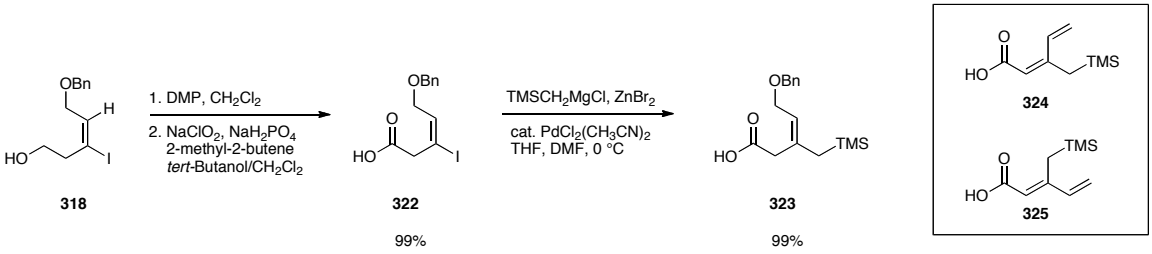
During the synthesis of *N*-Tosyl-*O*-TMS-Aminol **316,** we devised a more concise route to the requisite iodo-alcohol **318** (Scheme 3.8), starting from the corresponding propargyl ether **319**. This would reduce the overall number of steps in the sequence by three.




**Scheme 3.8** Second generation synthesis of iodo-alcohol **318**.

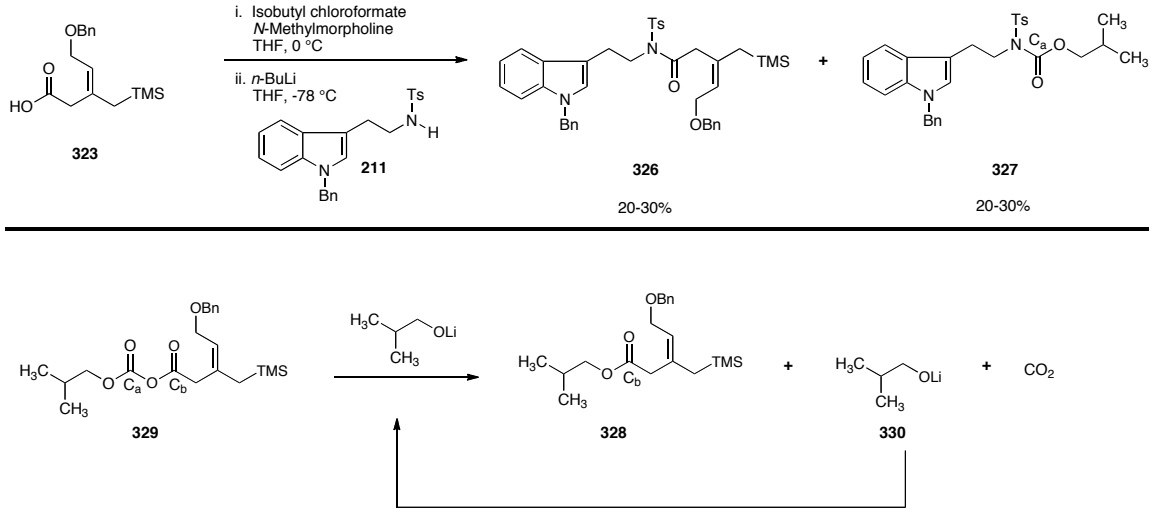
The synthesis of iodo-alcohol **318** began with the addition of known alkyne **319** to oxirane,[57] which produced homopropargylic alcohol **320** in 73% yield. This was followed by alkoxy-directed hydrozirconation[58] of **320,** and NIS quench of the intermediate vinylzirconocene to afford iodo-alcohol **318** in 42% yield. Regiosiomer **321** was also isolated in 17%. The ratio of desired product **318** to regioisomer **321** was increased to ~ 6:1 when the reaction was carried out at -5 °C instead of 25 °C. At temperatures lower than -5 °C, the initial hydrozirconation was prohibitively slow.

With **318** in hand, we carried out a Dess-Martin oxidation to produce the corresponding $\beta,\gamma$-unsaturated aldehyde, which was used directly in the subsequent Pinnick oxidation to generate acid **322** in nearly quantitative yield over two steps (Scheme 3.9). Negishi cross-coupling with the allylzinc reagent generated *in situ* from (trimethylsilyl)-methyl magnesium chloride initially afforded the required tri-substituted acid **323** in good yield, but as we gradually increased the scale of the reaction, large amounts of $\alpha,\beta,\gamma,\delta$-unsaturated acids **324** and **325** were produced. During the course of our optimization, we observed that the reaction mixture underwent a significant exotherm during the addition of the palladium catalyst. Fearing that this sharp increase in temperature was favoring the formation of elimination products like **324** and **325**, we carried out the reaction at 0 °C. Gratifyingly, this precaution solved the problem and allowed for the synthesis of multigram quantities of acid **323**.




**Scheme 3.9** Synthesis of $\beta,\gamma$-unsaturated acid **323**.

Treatment of acid **323** with isobutyl chloroformate and subsequent reaction with the lithium anion of **211** at -78 °C generated *N*-tosylamide **326** in only 20-30% yield (Scheme 3.10), along with equimolar amounts of compound **327**, as well as large amounts of ester **328** and unreacted staring material **323**.

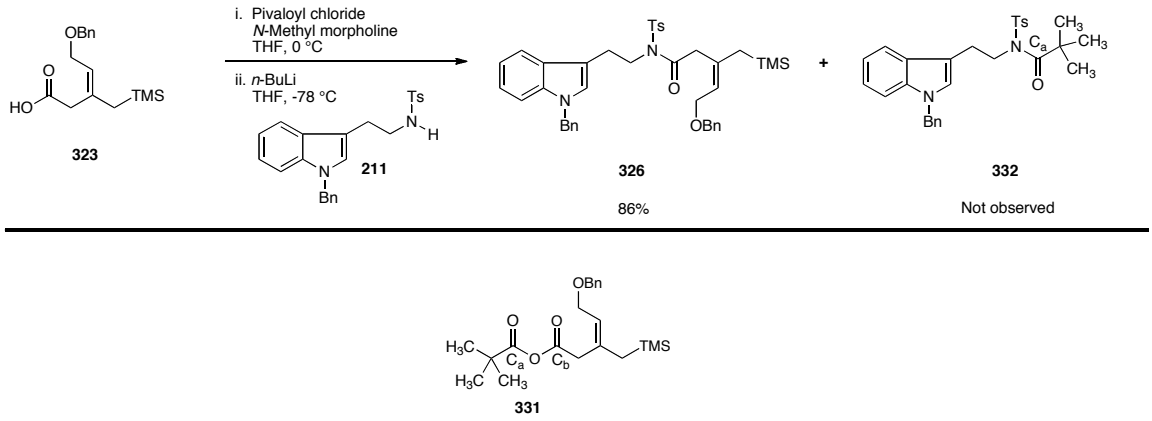



**Scheme 3.10** Initial attempts to couple acid **323** and tosylamide **211**.

Compound **327** was produced *via* nucleophilic attack of mixed anhydride **329** at carbonyl carbon $C_a$. Additionally, the formation of ester **328** (identified by comparison of its $^1$H NMR spectrum to that of the fully characterized TBDMS-protected analog)

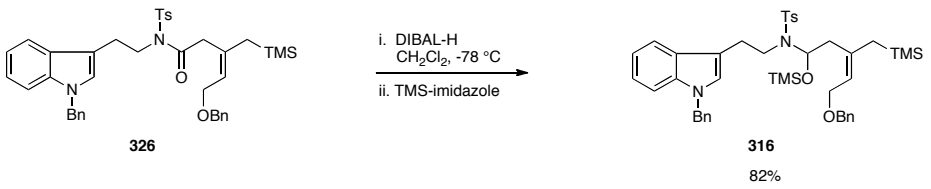
suggested that isobutoxide (**330**) was competing as a nucleophile with the tosylamide anion for the available mixed anhydride **329**.

At this stage, we decided to employ the more sterically congested mixed anhydride **331**,[47a] the bulk of which was expected to preclude nucleophilic attack at $C_a$ (Scheme 3.11). This change indeed produced the desired tosylamide **326** in 86% yield and completely suppressed the formation of regioisomer **332**, thus indicating that the nucleophilic attack occurred exclusively at $C_b$.



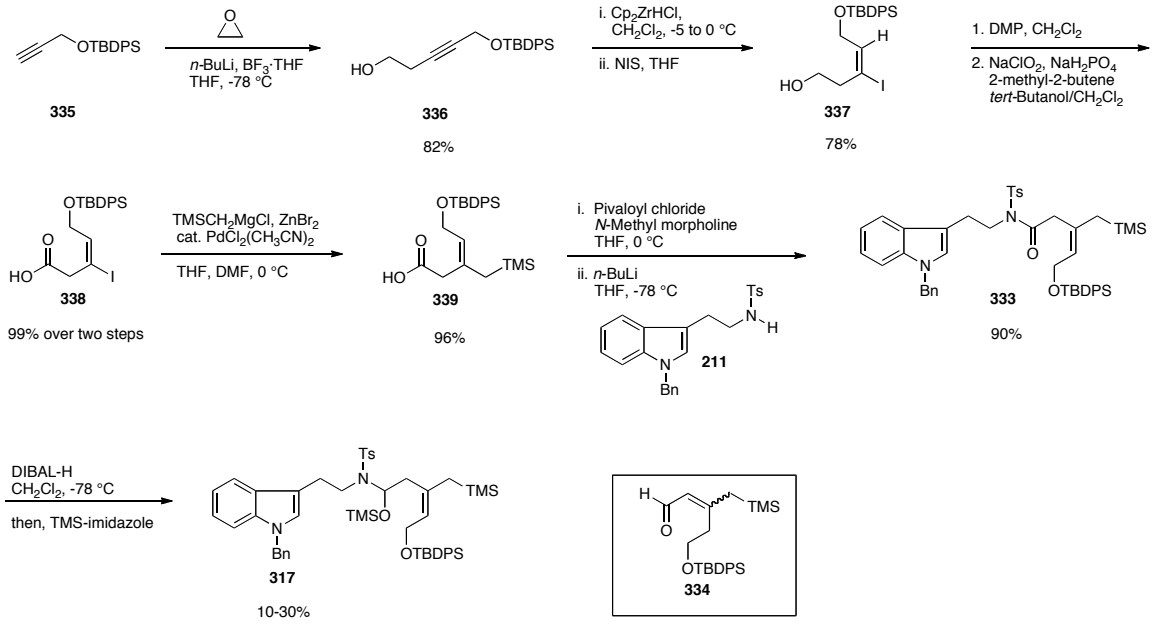

**Scheme 3.11** Improved procedure for the synthesis of *N*-tosylamide **326**.

With tosylamide **326** in hand, reduction with DIBAL-H and trapping with TMS-imidazole produced the corresponding *N*-tosyl,*O*-TMS-aminol **316** in 82% yield (Scheme 3.12).




**Scheme 3.12** Synthesis of *N*-tosyl,*O*-TMS-aminol **316**.

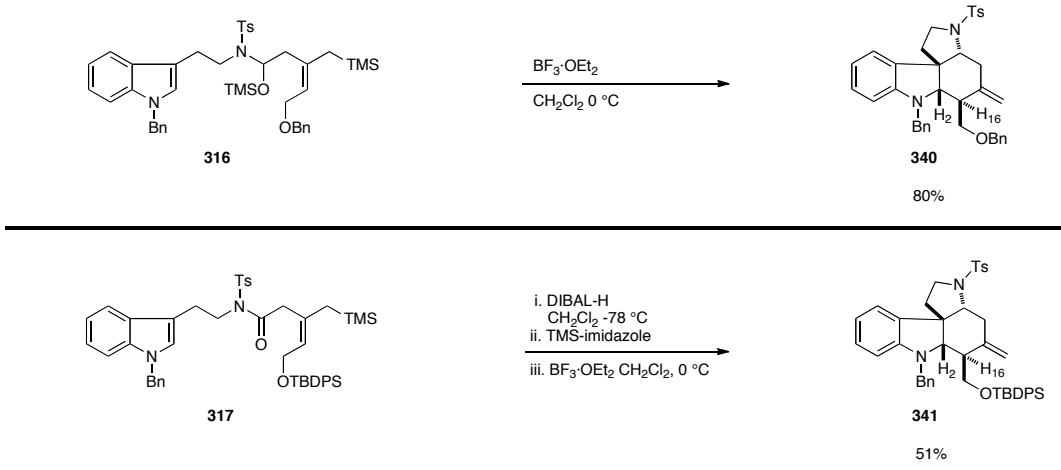
The synthesis of *N*-tosyl-*O*-TMS-aminol **317** was carried out in an analogous manner to that of *N*-tosyl-*O*-TMS-aminol **316**, as indicated in Scheme 3.13. The reduction of amide **333** with DIBAL-H and subsequent trapping with trimethylsilyl imidazole was problematic. Compound **317** decomposed extensively during the reaction work-up, producing large amounts of aldehyde **334** in the process. To circumvent the problem, a one-pot reduction/trapping/cyclization protocol was employed (*vida infra*).




**Scheme 3.13** Synthesis of *N*-tosyl-*O*-TMS-aminol **317**.

### 3.1.6. Synthesis of Malagashanine Cores 340 and 341 *via* Cyclization of *N*-Tosyl-*O*-TMS-Aminols 316 and 317 Respectively

With *N*-tosyl-*O*-TMS-aminol **316** at hand, the cyclization reaction was carried out using $BF_3{\cdot}OEt_2$ at 0 °C to afford tetracyclic amine **340** in 80% yield (Scheme 3.14). As mentioned earlier, *N*-tosyl-*O*-TMS-aminol **317** was cyclized *in situ* (following reduction with DIBAL-H and trapping with trimethylsilyl imidazole), which generated the desired product **341** in 51% yield.

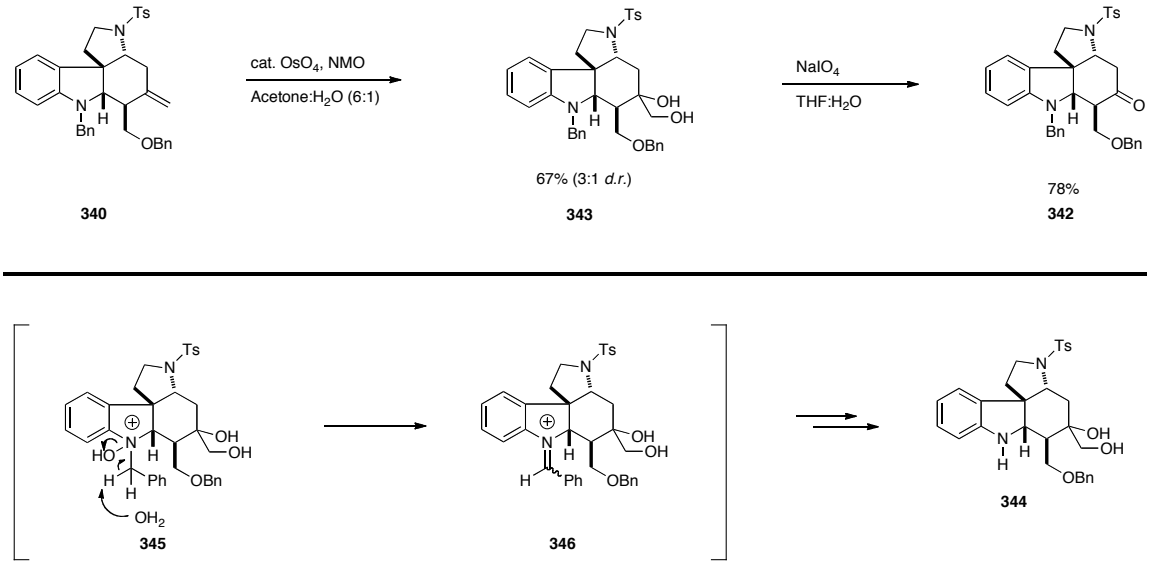



**Scheme 3.14** Cyclization of *N*-Tosyl-*O*-TMS-Aminols **316** and **317**.

The general structures of tetracyclic amines **340** and **341** were established by 1D and 2D NMR experiments. The relative stereochemistry at C(16) was established by analysis of the coupling constant of the indoline methine proton $H_2$ with $H_{16}$, which were 1.2 and 0 Hz for **340** and **341**, respectively. Indeed, using benzyl and TBDPS protecting groups in place of the more labile TBDMS group had a significant effect on the efficiency of the transformation.

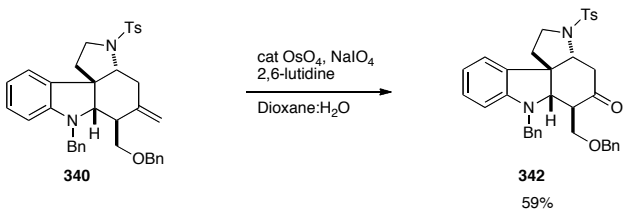
### 3.1.7. Synthesis of Ketone 342 for Knoevenagel Condensation

The synthesis of ketone **342** began with treatment of tetracyclic amine **340** with $OsO_4$ and NMO to afford **343** as a 3:1 inseparable mixture of diols in 67% yield (Scheme 3.15).[59] We also isolated 10% of de-benzylated product **344**, which presumably formed under the oxidative reaction conditions *via* *N*-oxide **345**,[60] which could undergo subsequent elimination of hydroxide to produce iminium ion **345**, followed by hydrolysis to afford **344**. With **344** in hand, treatment with $NaIO_4$ afforded the corresponding ketone **342** in 79% yield.[20]




**Scheme 3.15** Synthesis of ketone **342**.

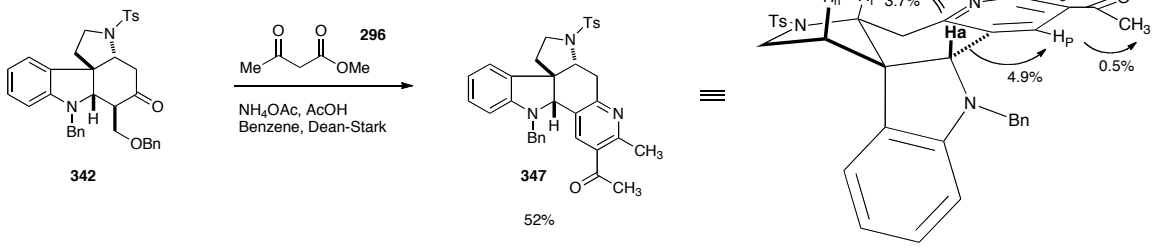
The previous route was eventually replaced with a more convenient one-pot protocol in which tetracyclic amine **340** was treated with $OsO_4$ in the presence of $NaIO_4$ and 2,6-lutidine to afford ketone **342** in 59% yield (Scheme 3.16).




**Scheme 3.16** Improved synthesis of ketone **342.**

### 3.1.8. Knoevenagel Condensation of Ketone 342 and Ketoester 296

The first attempts to carry out the Knoevenagel condensation of ketone **342** and ketoester **296** entailed standard conditions with $NH_4OAc$ and acetic acid in refluxing benzene.[51b] However, the desired product was never observed. Instead pyridine **347** was isolated in 52% yield (Scheme 3.17).

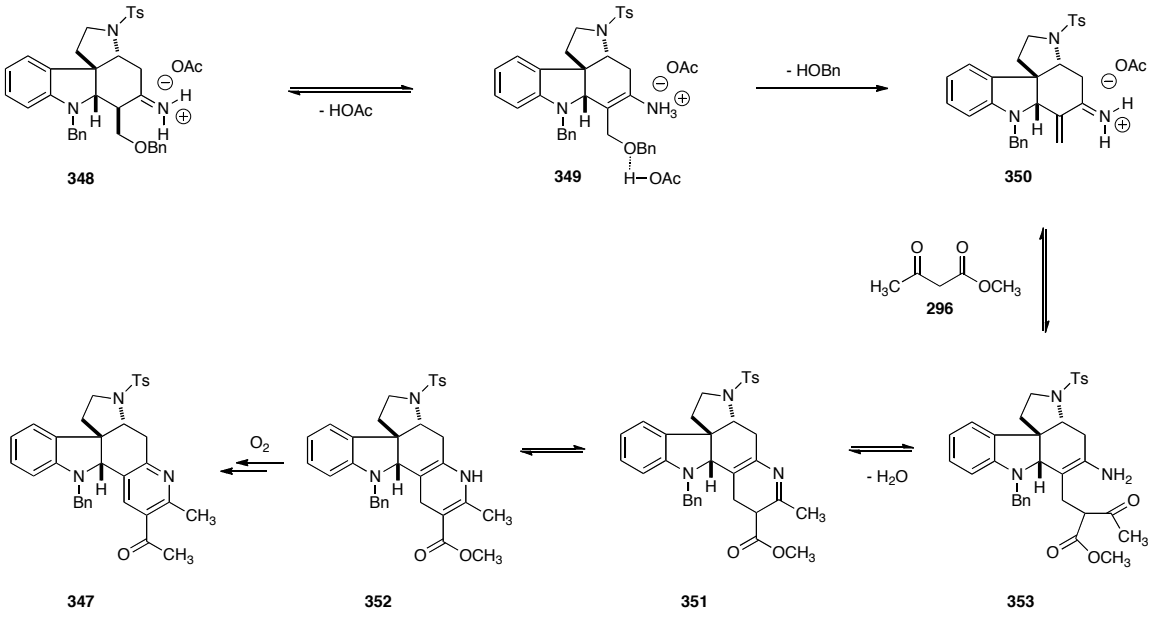



**Scheme 3.17** Early attempts to condense ketone **342** and ketoester **296**.

The structure of pyridine **347** was determined by 1D and 2D NMR experiments. Irradiation of $H_a$ produced enhancements of 3.7% and 3.0% on $H_f$ and $H_h$, respectively, which indicated that all three protons were located on the same face of the D-ring.

Additionally, the general structure was supported by NOE's between $H_a$ and $H_P$, and $H_P$ and the ester methyl group.

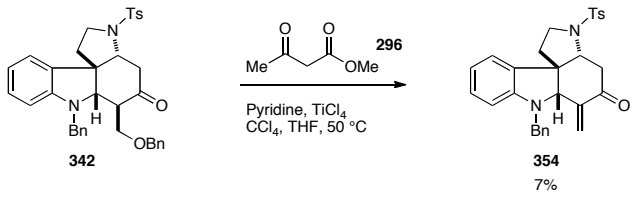
A possible explanation for the formation of pyridine **347** could involve initial formation of iminium ion **348**, followed by tautomerization to enaminium **349** and then $\beta$-elimination of benzyl alcohol to produce $\alpha,\beta$-unsaturated iminium ion **350** (Scheme 3.18). At this stage, Michael addition of ketoester **296** would be followed by intramolecular imine formation to generate **351**, which could then undergo air oxidation to produce pyridine **347**.




**Scheme 3.18** Possible mechanism for the formation of pyridine **347**.

At this stage, we switched to Lehnert conditions,[51d, e] which were known to work more efficiently in Knoevenagel condensations involving sterically congested ketones like **342** (Scheme 3.19). However, the combination of $TiCl_4$ with different amine bases ($Et_3N$ and pyridine), solvents (THF, $CH_2Cl_2$, $CCl_4$), as well as the use of various addition

protocols, mainly led to the recovery of unreacted starting material. When higher temperatures were employed we observed significant decomposition as well as the formation of side products, the major component of which was the $\alpha,\beta$-unsaturated ketone **354**.




**Scheme 3.19** Attempts to condense ketone **342** and $\beta$-ketoester **296** under Lehnert conditions.

Our observations indicated that under Knoevenagel condensation conditions, ketone **342** was not directly reacting with ketoester **296**. Moreover, when harsher reaction conditions were utilized, $\beta$-elimination of benzyl alcohol was occurring. Conformational studies with molecular models suggested that the sterically congested environment around the ketone carbonyl might be preventing large nucleophiles from adopting the necessary Bürgi-Dunitz trajectory. This notion was supported by NOESY experiments with **342** (Figure 3.2), which showed interactions between methine proton $H_a$ and the ethereal methylene protons, as well as with $H_f$ and $H_k$. This indicated that the D-ring existed in a half-chair conformation, with the ethereal methylene carbon projecting nearly perpendicularly from the plane of the carbonyl. A nucleophile approaching from the top face of the molecule (still the most accessible face) would experience large destabilizing steric interactions. In light of these observations, an alternate strategy to malagashanine was pursued.

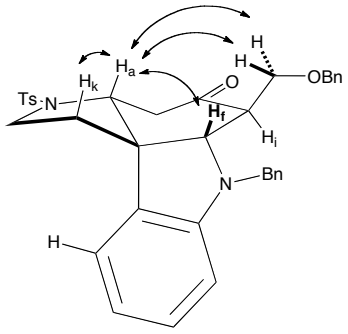
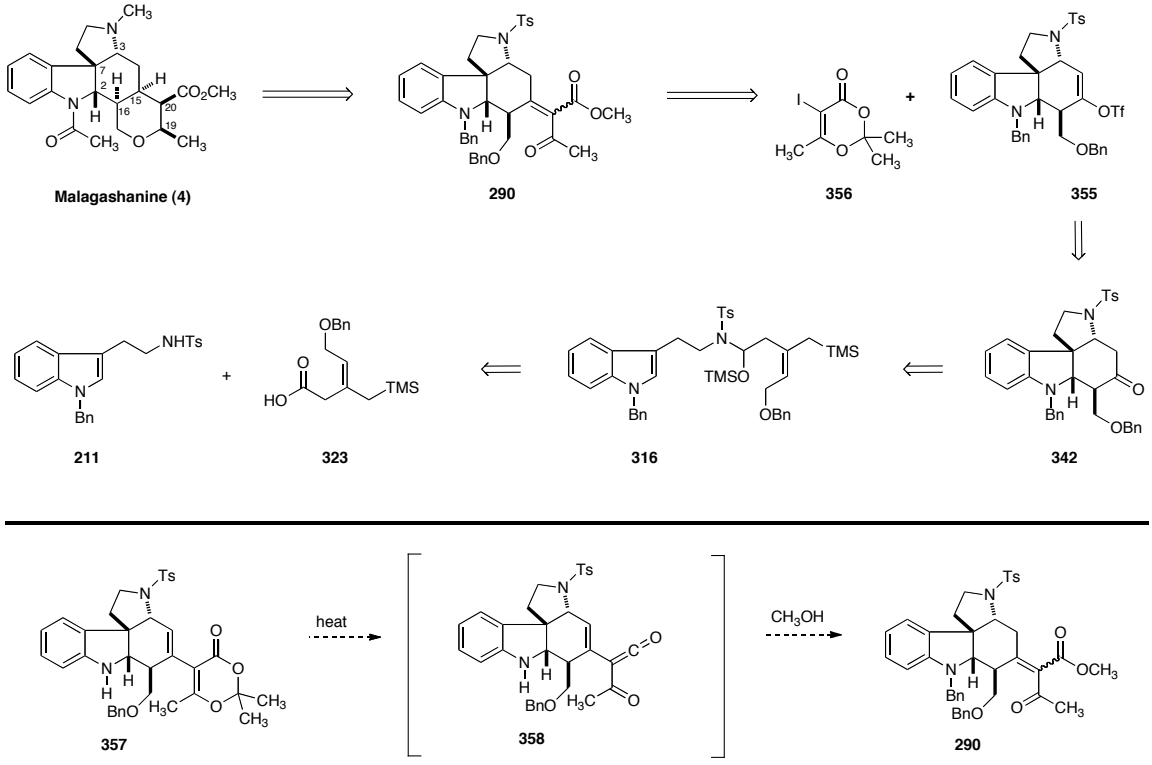



**Figure 3.2** NOE experiments with **342** suggest that the carbonyl D-ring exists in a half-chair conformation.

## 3.2. Second Generation Approach: Accessing Malagashanine *via* a Key Negishi Cross-Coupling and a Tandem Hydrogenation Reaction

### 3.2.1. Retrosynthetic Analysis

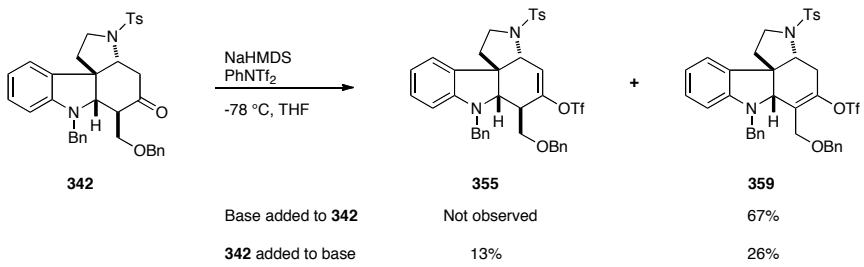
Our second approach to malagashanine incorporated a cross-coupling reaction between triflate **355** and vinyliodide **356** to generate the corresponding product **357** (Scheme 3.20). Thermolysis of **357** in the presence of methanol would afford key $\alpha,\beta$-unsaturated ketone **290**, which would then be converted into malagashanine (*vide supra*). In turn, triflate **355** would be accessed *via* ketone **342**.




**Scheme 3.20** Second generation approach to malagashanine.

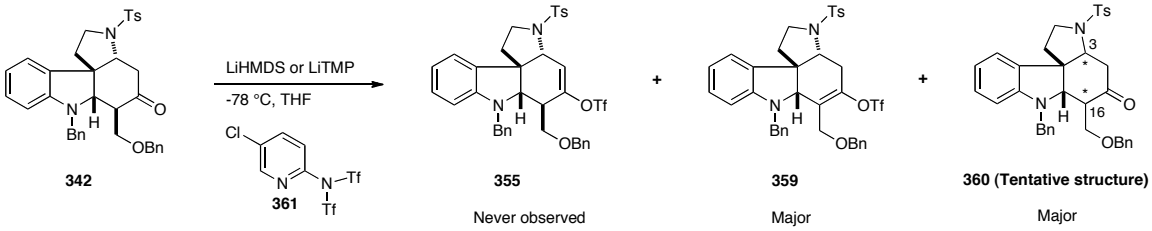
### 3.2.2. Synthesis of Kinetic Enol Triflate 355 for Key Negishi Cross-Coupling with 356

Subjecting ketone **342** to standard triflating conditions with NaHMDS[61] in THF at -78 °C, followed by trapping of the resulting enolate with *N*,*N*-di-triflylaniline only produced thermodynamic enol triflate **359** (Scheme 3.21). On the other hand, adding **342** to a solution of NaHMDS at -78 °C afforded the desired kinetic enol triflate **355**, albeit in only 13% yield, along with 26% of thermodynamic enol triflate **359**. Similar results were also observed with KHMDS.




**Scheme 3.21** Early attempts to synthesize kinetic enol triflate **355** using NaHMDS.

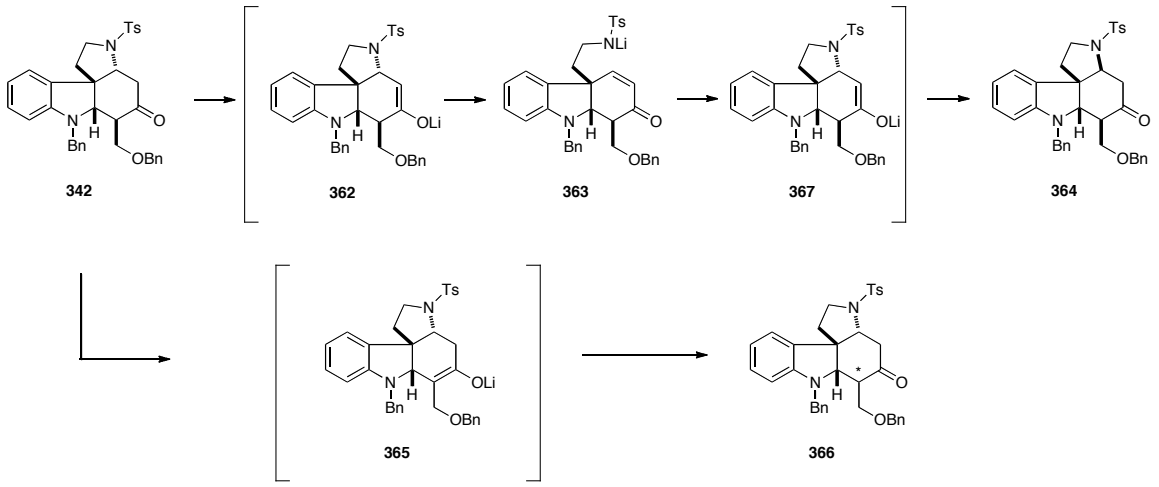
Switching to lithium bases[62] like LiHMDS produced[63] thermodynamic enol triflate **359**, along with significant amounts of compound **360**, which was tentatively assigned as either the C(3) or the C(16) epimer of **342** based on HRMS and NMR data (Scheme 3.22). Using the more hindered base LiTMP changed the product distribution in favor of compound **360**. Surprisingly, the kinetic enol triflate was never observed.[64] Additionally, employing a more reactive triflating reagent (**361**) did not have a significant effect on the reaction.




**Scheme 3.22** Early attempts to synthesize kinetic enol triflate **355** using lithium bases.

A possible explanation for the formation of a C(3) epimeric product entail a retro-Michael reaction of kinetic enolate **362** to open the strained *trans*-pyrrolidine moeity and generate $\alpha,\beta$-unsaturated ketone **363** (Scheme 3.23). Michael addition of the tosylamide anion could then generate the more stable *cis*-pyrrolidine **364** after workup. Additionally,

quenching of the thermodynamic enolate **365** during work-up could explain the formation of a C(16) epimer **366**.




**Scheme 3.23** Mechanistic rationale for the formation of C(3)/C(16) epimers of ketone **342**.

In light of the suspected epimerization of starting material under the reaction conditions, the stereochemical integrity of triflates **355** and **359** was checked using 2D NOE experiments (Figure 3.3). NOESY correlations in kinetic enol triflate **355** between $H_j$ and protons $H_d$ and $H_b$ indicated that the stereochemistry at C(2) and C(3) was conserved. Additionally, correlations between Hb and one of the benzylic ether protons showed that the stereochemistry at C(16) had not changed. Similarly, NOESY experiments corroborated the structure of thermodynamic enol triflate **359**.

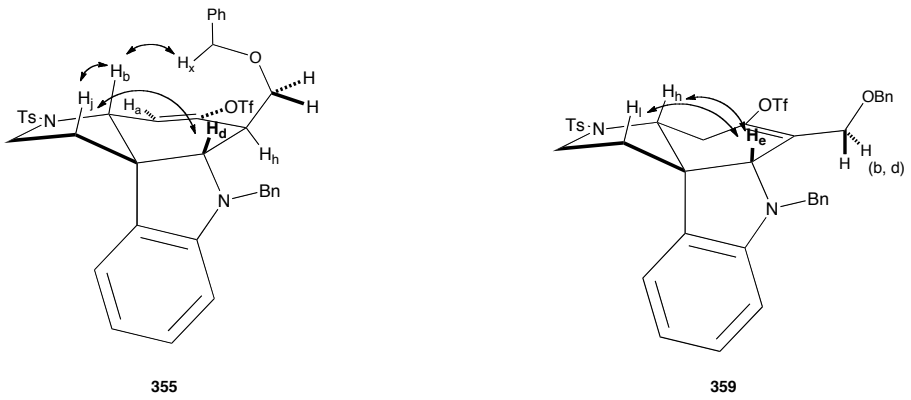
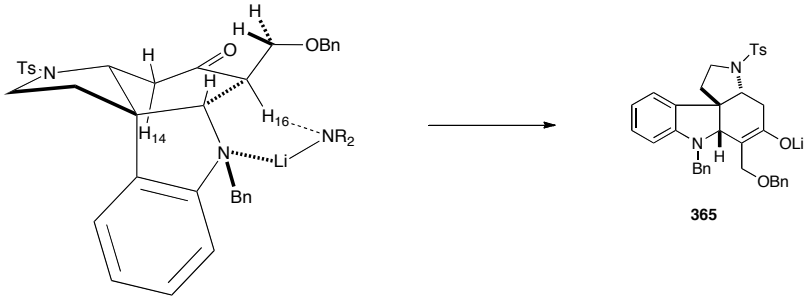



**Figure 3.3** NOESY correlations of triflates **355** and **359**.

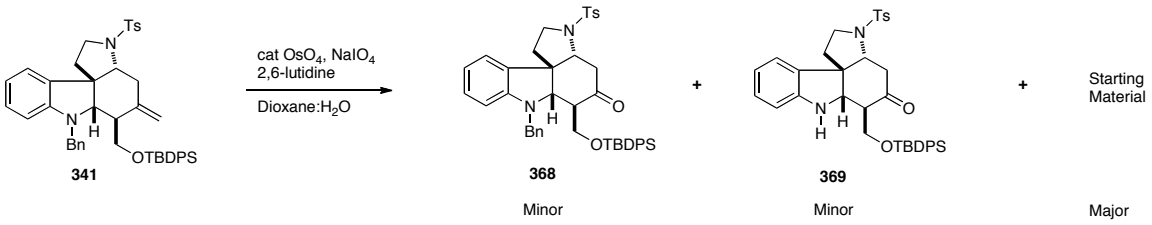
The formation of the thermodynamic enol triflate **59** under the reaction conditions was surprising considering how hindered the C(16) proton was in comparison to the axial C(14) proton. However, we thought of the possibility that the indoline nitrogen could be coordinating to the metal counterion, thus directing the deprotonation at C(16) and favoring the formation of the thermodynamic enolate **365** (Scheme 3.24). To test our hypothesis, we would need to employ the more hindered ketone **368** (*vide infra*), which was expected to decrease the directing effect of the indoline nitrogen *via* destabilizing steric interactions caused by the bulkier *tert*-butyldiphenylsilyl group.




**Scheme 3.24** Possible rationale for the formation of thermodynamic enolate **365**.

### 3.2.3. Synthesis of the More Hindered *β-tert*-Butyldiphenylsiloxy Ketone 368

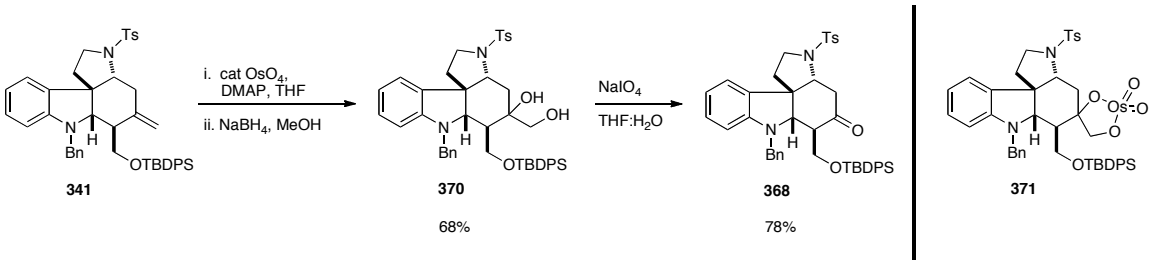
Our initial approach to the synthesis of ketone **368** (Scheme 3.25) relied on the same one-pot procedure employed in the conversion of **340** to **342**. However, the reaction produced only trace amounts of **368** along with debenzylated ketone **369**. Additionally, starting material was also recovered.




**Scheme 3.25** Initial attempts to synthesize ketone **368**.

Switching to a two-step procedure revealed that the intermediate dihydroxylation step was proceeding very slowly. Addition of stoichiometric amounts of $OsO_4$[20] in the presence of DMAP pushed the reaction to completion, but oddly, did not afford significant amounts of diol **370** after hydrolytic workup. Moreover, a conspicuous unidentified compound was being isolated in large amounts after purification, which we tentatively assigned as osmate ester **371** based on the similarities of its $^1$H NMR spectrum to that of diol **370** (Scheme 3.26). At this stage, we hypothesized that the large bulk of the TBDPS group might be responsible for the failure of osmate ester **371** to undergo hydrolysis, even after treatment with sodium sulfite solution. Employing a strong reductive work-up using $NaBH_4$ in methanol at 0 °C, indeed produced the desired diol

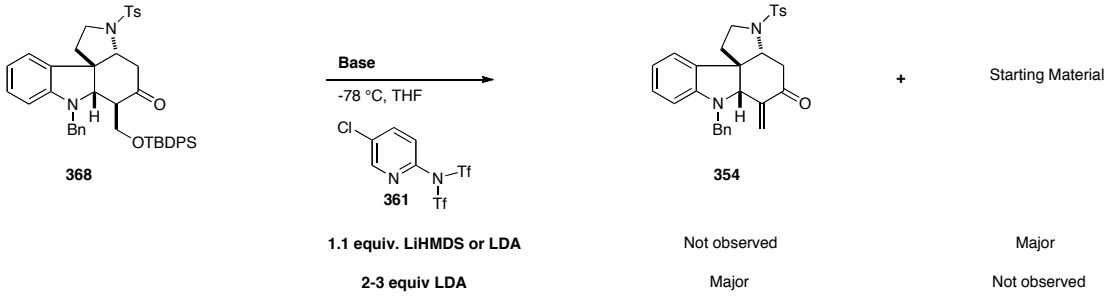
**370** as an inseparable 1.3:1 mixture of epimers in 68%. With **370** in hand, treatment with $NaIO_4$ afforded ketone **368** in 78% yield.




**Scheme 3.26** Improved synthesis of ketone **368**.

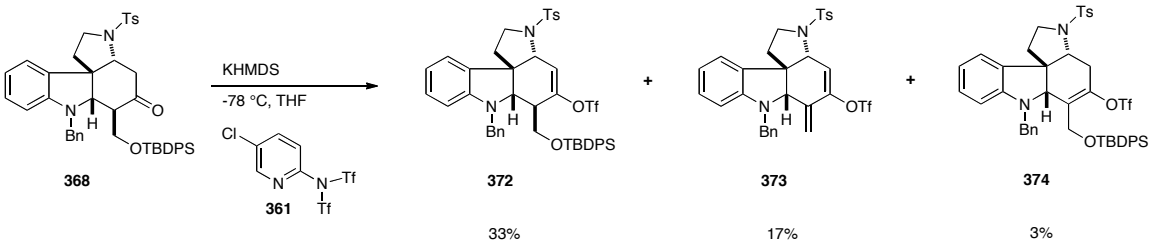
### 3.2.4. Synthesis of Kinetic Enol Triflate 372 and Key Negishi Cross-Coupling with 356

Addition of **368** to a solution of either LiHMDS or LDA at -78 °C consistently allowed the recovery of starting material (Scheme 3.27). In an effort to increase the reactivity of the base, additives like TMEDA and DMPU were used to sequester the lithium counterion, but the results were equally disappointing. Moreover, large amounts of $\alpha,\beta$-unsaturated ketone **354** were isolated when an excess of base was utilized.



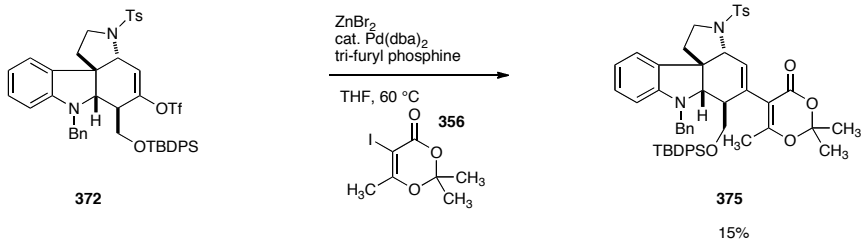

**Scheme 3.27** Attempts to synthesize kinetic enol triflate **372** using lithium bases.

Switching the counterion to potassium produced the best results, yielding 33% of the desired kinetic enol triflate **372**, along with 17% of the unsaturated kinetic enol triflate **373** and 3% of the thermodynamic enol triflate **374** (Scheme 3.28). Carrying out the reaction at -100 °C afforded lower yields of **372** and did not improve the product distribution.




**Scheme 3.28** Synthesis of **372** using KHMDS and Comins' reagent (**361**).

With triflate **372** in hand, the key cross-coupling reaction was undertaken (Scheme 3.29). Treatment of **372** with the zinc reagent of vinyliodide **356**[65] in the presence of $Pd(dba)_2$ and tri(2-furyl)phosphine (TFP) in refluxing THF afforded 15% of the desired product **375** along with 19% recovered starting material.



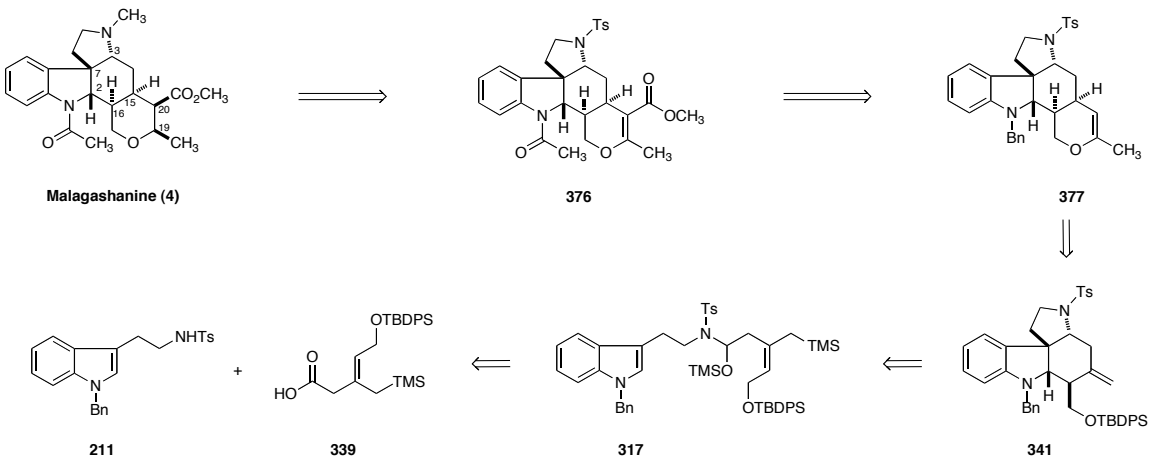

**Scheme 3.29** Negishi cross-coupling of triflate **372** and vinyliodide **356**.

Despite our initial success in the construction of the desired product **375**, we recognized that the improvement to the synthesis of triflate **372** by means of the bulkier *tert*-butyldiphenylsilylether was marginal at best, and was not amenable to large-scale synthesis. This limitation was significant, which prompted us to devise a more efficient approach to malagashanine.

## 3.3. Third Generation Approach: Accessing Malagashanine *via* a Formal Olefin Hydroacylation Reaction and a Late-Stage Hydrogenation

### 3.3.1. Retrosynthetic Analysis

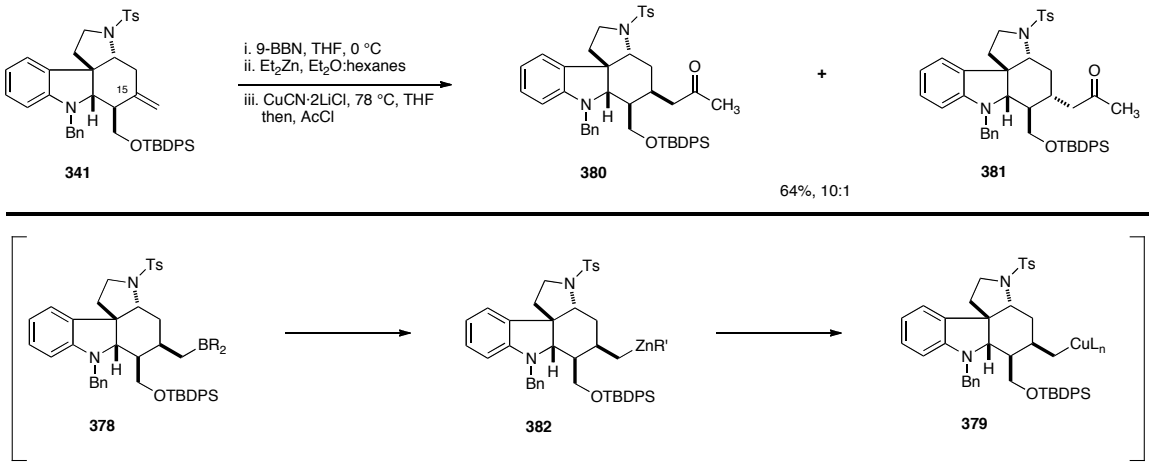
The difficulties of using ketones **342** and **368** as practical intermediates in the synthesis of the E ring of malagashanine led us to develop a third generation approach to the molecule (Scheme 30). Although we would still rely on a late stage hydrogenation reaction of unsaturated ester **376** to set the requisite stereochemistry at C(19) and C(20), compound **376** would now be synthesized from pyran **377**. In turn, compound **377** would be accessed from core **341** *via* a formal olefin hydroacylation reaction.




**Scheme 3.30** Third generation approach to malagashanine.

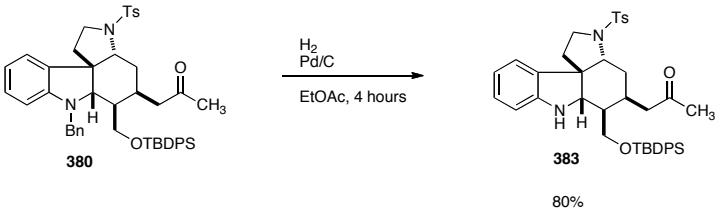
### 3.3.2. Synthesis of Pyran 377

The synthesis of the E ring began with the formal hydroacylation of the olefin using a method developed by Knochel and co-workers.[66] Hydroboration of **341** with 9-BBN set the stereocenter at C(15) and produced the corresponding alkyl-borane species **378** (Scheme 3.31). In order to functionalize C(20) by reaction with acetyl chloride, it was first necessary to transmetallate the alkyl-boron species to a more suitable metal like copper. This was accomplished by first exchanging the boron species with zinc, which then facilitated the subsequent exchange with copper to form the desired intermediate **379**. Treatment with acetyl chloride at -78 °C afforded ketone **380** in 64% yield and 10:1 diastereoselectivity. Interestingly, Dr. Boudet observed the inherent diastereoselectivity of the initial hydroboration reaction to be *ca.* 2.5:1, which suggests that the transmetallation steps involve a kinetic resolution.



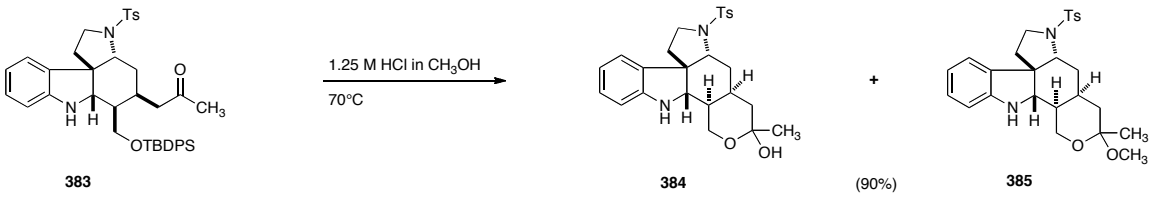

**Scheme 3.31** Formal hydroacylation of olefin **341**.

The relative stereochemistry at C(15) was indirectly determined through 2D NMR experiments of pyran **377** (*vide infra*). With ketone **380** in hand, hydrogenolysis of the benzyl group over palladium on carbon initially produced irreproducible yields of indoline **383** (Scheme 3.32).[67] However, during the course of our optimizations we observed that the product **383** would slowly decompose over the long reaction times. The problem was circumvented with the use of stoichiometric amounts of palladium on carbon, which allowed the reaction to reach completion within 4 hours. With this new procedure, indoline **383** was generated consistently in 80% yield.



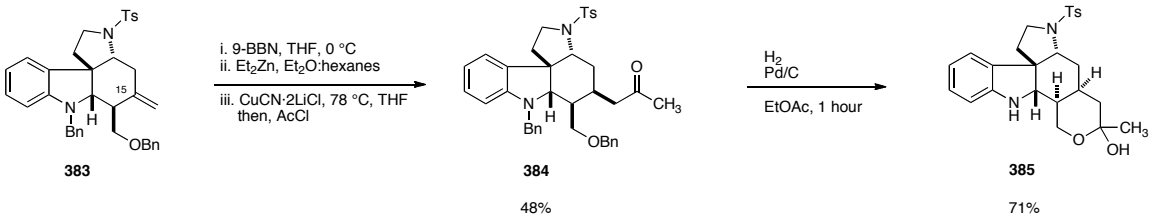

**Scheme 3.32** Hydrogenolysis of *N*-benzyl indoline **380**.

With indoline **383** in hand, hydrolysis of the silyl ether was accomplished using with HCl in methanol at 70 °C, which afforded a mixture of acetal **384** and hemiacteal **385** in 90% overall yield (Scheme 3.33).



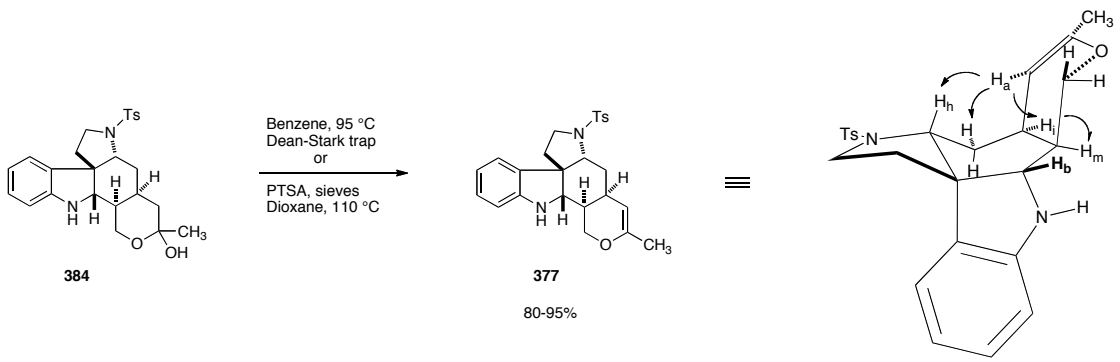

**Scheme 3.33** Hydrolysis of silyl ether **383**.

Hemiacetal **384** was also accessed from tetracyclic amine **340** as shown in Scheme 3.34, which reduced the overall synthetic sequence by one step.




**Scheme 3.34** Conversion of tetracyclic amine **340** to hemiacetal **384**.

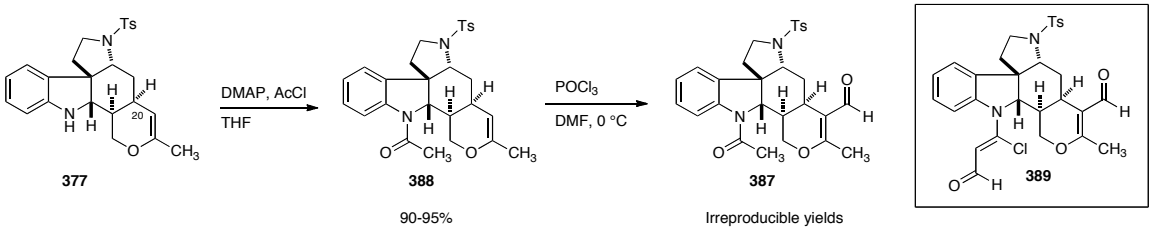
Hemiacetal **384** could be converted into the desired pyran **377** *via* dehydration in a Dean-Stark trap, or by heating in anhydrous dioxane at 110 °C in the presence of PTSA and activated molecular sieves (Scheme 3.35). Both methods could generate **377** in over 90% yield, but the latter method was preferred because it required shorter reaction times. The structure of **377** was assigned based on COSY, HMQC and NOESY experiments.




**Scheme 3.35** Synthesis and structural assignment of pyran **377**.

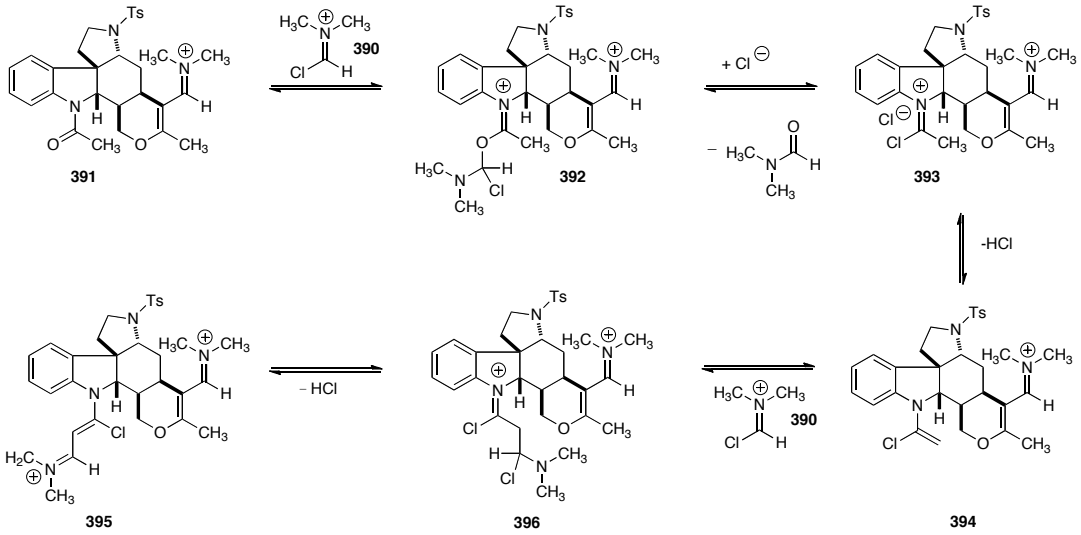
### 3.3.3. Synthesis of Ester 376 for Key Hydrogenation Reaction

The next step in the synthetic sequence required the installation of a formyl group at C(20) of pyran **377**, which would be subsequently oxidized to generate the requisite carboxylic acid. To construct aldehyde **387**, we first installed the acetyl group on indoline **377,** required for malagashanine, and then carried out a Vilsmeier formylation[68] on **388** (Scheme 3.36). However, despite extensive optimization, the yields were low and irreproducible. Additionally, the desired product **387** seemed to be undergoing a second transformation *in situ* to afford side product **389**.




**Scheme 3.36** Initial attempts to synthesize aldehyde **387**.

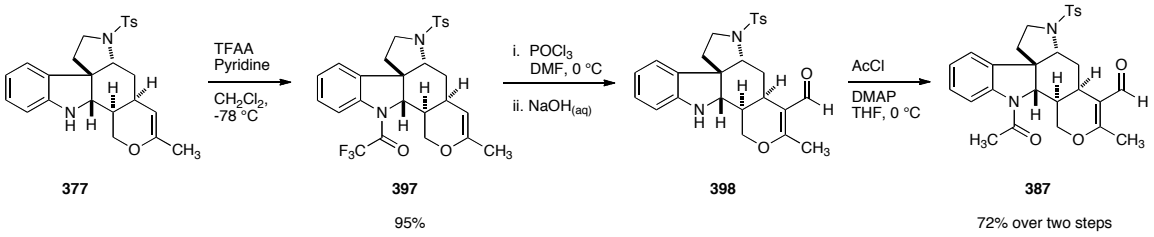
Compound **389** could be formed *via* nucleophilic attack of Vilsmeier reagent (**390**) by amide **391** to generate intermediate **392** (Scheme 3.37), followed by addition of chloride anion and elimination of dimethylformamide to afford indolium salt **393**. Loss of hydrogen chloride would afford enamine **394,** which could attack a second equivalent of Vilsmeier reagent (**390**) and undergo subsequent elimination of hydrogen chloride to generate $\alpha,\beta$,-unsaturated chloroiminium ion **395**. Hydrolysis of **395** during basic work-up would produce compound **389**.




**Scheme 3.37** Mechanistic rationale for the formation of side product **389**.

In order to circumvent the formation of **389**, it was necessary to protect the indoline moiety by installing a more electron deficient acyl group at the nitrogen atom. Treating pyran **377** with trifluoroacetic anhydride in the presence of pyridine at -78 °C afforded the corresponding trifluoroacetamide **397** in 95% yield, which was subjected to the Vilsmeier formylation conditions to afford the desired aldehyde with no detectable

side products (Scheme 3.38). Using a more basic work-up procedure allowed the *in situ* removal of the trifluoroacetyl moiety to generate indoline **398** in one step. Treatment with acetyl chloride and DMAP generated acetamide **387** in 72% from **397**.




**Scheme 3.38** Synthesis of aldehyde **387** from pyran **377**.

With aldehyde **387** in hand, we attempted the conversion to acid **399** using a variety of oxidizing reagents. However, TPAP, alkaline $KMnO_4$,[69] $AgNO_3$,[70] and $MnO_2$/NaCN/HOAc[71] (to produce the corresponding ester) were not successful. Even after extended reaction times, only starting material was recovered. Moreover, using Jones' reagent[72] afforded side products and none of the desired acid **399**. The overall lack of reactivity of aldehyde **387** towards standard oxidation protocols was not entirely surprising given that compound **387** could also be thought of as an vinylogous formate ester by virtue of its $\beta$-alkoxy substituent (Figure 3.4).

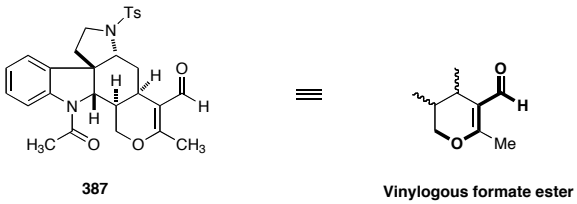
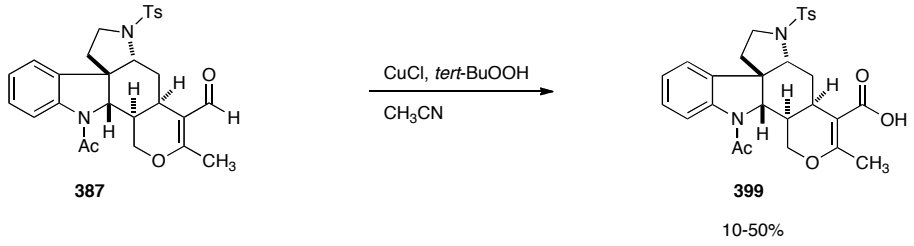


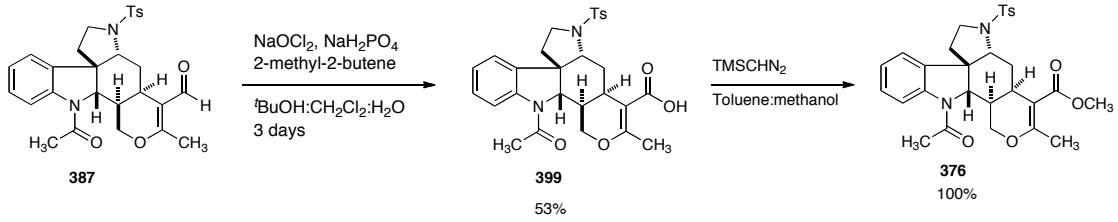

**Figure 3.4** Compound **387** is a vinylogous formate ester.

We had some success using radical-based chemistry with *tert*-butylhydroperoxide in the presence of catalytic amounts of copper(I) chloride,[73] which initially generated **399** in 50% yield (Scheme 3.39). However, as we attempted to scale up the reaction using this protocol we had great difficulty in obtaining reproducible yields.




**Scheme 3.39** Oxidation of aldehyde **387** *via* a radical-based protocol.

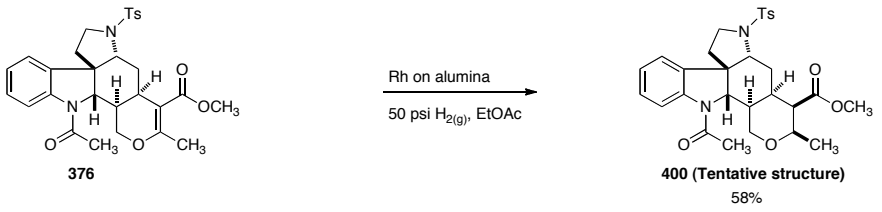
Ultimately, we were able to generate acid **399** by subjecting **387** to a 3 day-long Pinnick[74] oxidation protocol, which produced the desired product consistently in 53% yield. Compound **399** was then converted to the corresponding ester **376** using trimethylsilyl diazomethane (Scheme 3.40).




**Scheme 3.40** Synthesis of ester **376**.

### 3.3.4. Attempts to Synthesize Malagashanine by Hydrogenation of the C(19)-C(20) Olefin and Removal of the $N_b$ Tosyl Auxilliary.

With compound **376** in hand, we began our efforts towards the hydrogenation of the C(19)-C(20) olefin. During our first attempts, we subjected **376** to different heterogeneous palladium catalyst systems under an atmosphere of hydrogen gas (1–3 atm).[75] However, the starting material was always recovered unreacted. Searching the literature we discovered that 5% rhodium on alumina had been successfully used to effect the hydrogenation of tetrasubstituted electron-deficient olefins.[76] Treatment of **376** with an excess of this catalyst system under 50 psi of hydrogen gas produced compound **400** in 58% yield (Scheme 3.41).



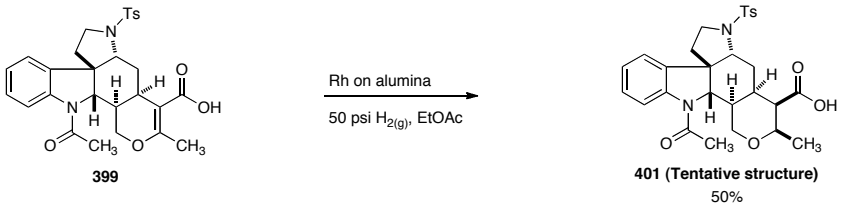

**Scheme 3.41** Hydrogenation of the C(19)-C(20) olefin in ester **376**.

Given that **400** existed as a 1:1 mixture of rotamers by $^1$H NMR, the signals of which did not coalesce even at a temperature of 120 °C, its was not possible to carry out 2D experiments to assess its structure. However, the $^1$H NMR data at 25 °C indicated that the rotameric allylic methyl signals (2.4 – 2.0 ppm) had been replaced by two rotameric methyl doublet signals (1.05 ppm), which was a good indication that the C(19)-C(20) double bond had undergone hydrogenation. Compound **400** was obtained as a single

diastereomer, and for the moment it was assumed that the hydrogenation had taken place from the most accessible convex face of the E ring.

With **400** in hand, the removal of the $N_b$ tosyl auxiliary was attempted using sodium naphthalide in 1,2-dimethoxyethane at -60 °C, which were conditions that had previously worked well with our model system **195** (*vide supra*, section 2.5). However, only unreacted starting material was recovered. Carrying out the reaction with excess reagent at 25 °C yielded similar results. Moreover, using stronger reducing reagents like LiDBB[77] led to the decomposition of the starting material. On the other hand, subjecting **400** to $SmI_2$[78] in the presence of $H_2O$ and pyrrolidine produced three major products, the structures of which were difficult to assign. The 1H NMR spectra for all three compounds indicated that the tosyl group was not present. However, the indoline aromatic signals had shifted upfield from their usual positions between 7 and 8 ppm. Also, the signals corresponding to the ester and amide methyls were not present. Additionally, all three compounds existed as single sets of proton signals, indicating the absence of rotamers (and possibly that of the amide groups). The HRMS data did not enhance our understanding of the structures further.

In light of our observations, which indicated that the ester functionality was not surviving the harsh reducing conditions necessary to remove the tosyl group, we decided to employ compound **401**, with the more resilient carboxyl functionality. Compound **401** was synthesized by treating **399** with 5% rhodium on alumina (Scheme 3.42).




**Scheme 3.42** Synthesis of acid **401**.

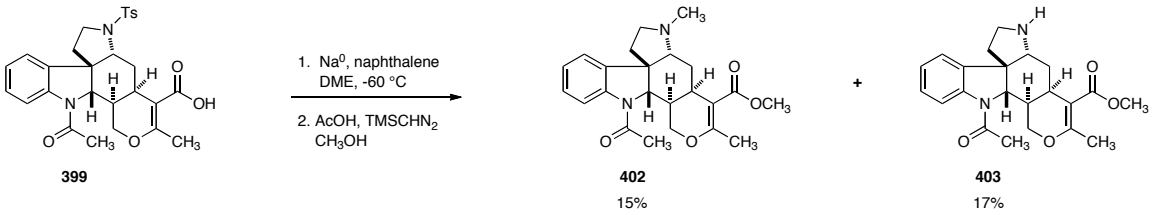
During the course of our investigation we noticed a discrepancy in the HRMS data for saturated acid **401**, which had also been previously observed in the HRMS for the corresponding saturated ester **400**. The data (+APCI, -APCI, +ESI, and -ESI) indicated that the molecular formula of compound **401** possessed four extra hydrogen atoms over that of its originally assigned structure.

In light of this evidence, a thorough inspection of the $^{1}H$ NMR spectrum of compound **401** revealed that, despite the presence of a misleading benzylic-like methyl singlet around 2.3 ppm, the corresponding toluene sulfonamide aromatic signals were not present. The latter fact had been initially overlooked because the strong $CHCl_3$ singlet from the NMR solvent had impeded a complete assessment of the aromatic region. The absence of these signals became obvious when $CD_2Cl_2$ was used as the NMR solvent instead.

This observation, in combination with an over-integration in the aliphatic region of the spectrum, as well as the presence of a methyl signal around 2.2 ppm, all led us to consider the possibility that the tosyl group might had been modified during the hydrogenation reaction. After all, of all the common metal used in heterogeneous hydrogenation catalysis, rhodium is the most reactive towards aromatic systems.

Furthermore, none of the methods used to cleave tosyl groups *(*vida supra) were effective in the removal of the tosyl group in **401** either.

As a measure of precaution, we opted to try cleaving the tosyl group in unsaturated acid **399** (Scheme 3.43). This was an approach that we had considered before, but had decided against for fears of also reducing the $\alpha,\beta$-unsaturated system in the process. Gratifyingly however, treating $\alpha,\beta$-unsaturated acid **399** with sodium naphthalide in DME at -60 °C, and then subjecting the crude reaction mixture to trimethylsilyl diazomethane in methanol afforded amines **402** and **403** in 15% and 17% yield, respectively. The structures of **402** and **403** were assigned based on 1H NMR and HRMS data. We also note that the formation of *N*-methylpyrrolidine **402** was unexpected given the scarce amount of literature on the use of trimethylsilyl diazomethane as an effective methylating reagent for secondary amines.




**Scheme 3.43** Synthesis of C(19)-C(20)dehydro-malagashanine **402** and $N_b$-desmethyl-C(19)-C(20)dehydro-malagashanine **403**.

These results lent some validity to the notion that the toluene sulfonamide groups in compounds **400** and **401** had been modified under the hydrogenation conditions. More importantly however, we were now one chemical transformation away from accessing malagashanine. To this end, preliminary attempts were made to set the C(19) and C(20) stereocenters in C(19)-C(20)dehydro-malagashanine **402**. Having removed the tosyl

auxiliary in the previous step, there was no reason to avoid using 5% rhodium on alumina to effect the requisite hydrogenation. However, only starting material was recovered when **402** was subjected to this system. There are still ongoing efforts in our laboratory to construct malagashanine *via* this overall strategy.

## 3.4. Conclusions

During this phase of our studies towards the total synthesis of malagashanine, we showed that *E*-olefin isomer *N*-tosyl-*O*-TMS-aminol **304** undergoes cyclization to afford core **302** with the necessary stereochemistry at C(2), C(3), C(7) and C(16) in modest yield. Moreover, switching the *tert*-butyldimethylsiloxy substituent in **304** for the lesser labile *tert*-butyldiphenylsiloxy and benzyloxy substituents in **316** and **317,** respectively, significantly increased the overall yield for the transformation.

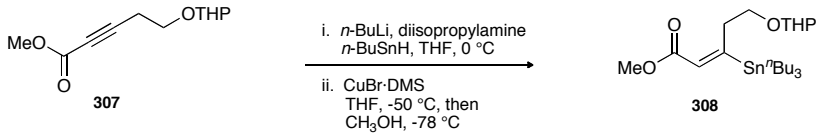
Our first generation approach to malagashanine, which centered on the construction of $\beta,\gamma$-unsaturated ketoester **290** *via* a Knoevonagel condensation, was precluded by the inherent tendency of ketone **342** to undergo $\beta$-elimination under the reaction conditions. Presumably, the highly sterically congested environment around the carbonyl moeity impeded the attack of the keto ester nucleophile (**296**), which favored side reactions when more forcing conditions were employed.

We attempted to circumvent the issue by constructing **290** *via* Negishi cross-coupling of vinyliodide **356** with either kinetic enol triflate **355** or **372**. However, the syntheses of the requisite kinetic enol trifates were hampered by the formation of side products generated *via* the intermediate thermodynamic enolates.

Our third generation approach to malagashanine permitted on the construction of the E-ring *via* a formal olefin hydroacylation of tetracyclic amine **341** and subsequent dehydration of hemiacetal **384**. Moreover, lowering the electron density of pyran **377** was necessary in order to suppress side reaction in the subsequent Vilsmeier formylation reaction. Additionally, the hydrogenations of acid **399** and ester **376** were complicated by possible side reactions involving the toluenesulfonamide moieties, which made impossible the subsequent removal of those groups. On the other hand, carrying out the cleavage of the tosyl auxilliary on unsaturated acid **399** generated the corresponding zwitterion, which was methylated *in situ* to afford C(19)-C(20)dehydro-malagashanine (**402**). The hydrogenation of **402** is currently being investigated in our laboratory.

## 3.5. Experimentals

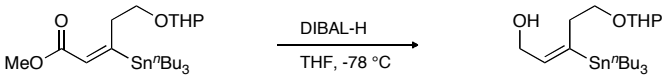
**Synthesis of $\beta$-stannyl-ester 308:**




*n*-BuLi (1.6 M in hexanes, 2.57 mL, 4.11 mmol) was added over 10 minutes to a solution of di-isopropylamine (0.58 mL, 4.14 mmol) in THF (7.0 mL) and the resulting mixture was stirred at 0 °C for 15 minutes. Tributyltin hydride (1.13 mL, 4.28 mmol) was added over 5 minutes and the resulting solution was stirred at 0 °C for 15 minutes. The mixture was cooled to -50 °C and copper(I) bromide dimethyl sulfide complex (0.883 g, 4.29 mmol) was added in portions. The resulting solution was stirred at -50 °C for 20 minutes, and then was cooled to -78 °C. A solution of alkynyl ester **307** (0.291 g, 1.37 mmol) in THF (5.8 mL) was added over 20 minutes, and the resulting mixture was stirred at -78 °C for 30 minutes. The reaction was quenched with methanol (4.5 mL) and was stirred at -78 °C for 30 minutes, warmed to 0°C and stirred for 30 minutes. $H_2O$ (5 mL) was added, and the mixture was filtrated through celite. The filtered cake was washed with EtOAc (3 x 20 mL). The filtrate was washed with brine (40 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (9:1 → 17:3 pentane/$Et_2O$) afforded $\beta$-stannyl-ester **308** as a colorless oil (0.573 g, 83%); **$^1$H NMR** ($CDCl_3$, 400 MHz) δ 6.01 (s, 1H), 4.59 (t, 1H, $J$ = 3.3 Hz), 3.87-3.76 (m, 2H), 3.68 (s, 3H), 3.51-3.41 (m, 2H), 3.16 (t, 2H, $J$ = 7.0 Hz), 1.83-1.25 (m, 19H), 1.04-0.86 (m, 14H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 170.5, 164.5, 129.4, 98.7 66.7, 62.2, 51.0, 35.6, 30.8,

29.1, 27.5, 25.6, 19.6, 13.8, 10.2; **IR** (thin film, $cm^{-1}$) 2952.9 (m), 2922.2 (m), 2870.5 (m), 2851.3 (m), 1717.1 (s), 1591.8 (w), 1455.8 (w), 1431.7 (w), 1350.0(w), 1164.9 (s), 1031.3 (s).

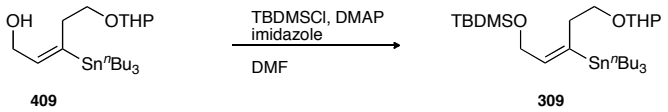
**Synthesis of allylic alcohol 409:**




**308** **409**

DIBAL-H (1 M in THF, 3.42 mL, 3.42 mmol) was added dropwise to a solution of ester **308** (0.573 g, 1.14 mmol) in THF (5.7 mL) at -78 °C, and the resulting mixture was stirred for 4 hours. The reaction was quenched with saturated aqueous $NH_4Cl$/methanol (1:1, 3 mL), warmed to room temperature and stirred for 20 minutes. The organic layer was separated, and the aqueous layer was extracted with pentane/$Et_2O$ (1:1, 3 x 3 mL). The organic extracts were combined, washed with brine (5 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (4:1 hexanes/EtOAc) afforded alcohol **409** as a colorless oil (0.432 g, 80%); **$^1$H NMR** ($CDCl_3$, 600 MHz) δ 6.01 (t, 1H, *J* = 6.6 Hz), 4.57 (t, 1H, *J* = 3.3 Hz), 4.15-4.08 (m, 2H), 3.81-3.75 (m, 2H), 3.49-3.48 (m, 1H), 3.32-3.28 (m, 1H), 2.73 (br s, 1H), 2.69-2.55 (m, 2H), 1.81-1.70 (m, 1H), 1.70-1.66 (m, 1H), 1.57-1.40 (m, 11H), 1.32-1.26 (m, 6H), 0.94-0.83 (m, 14H); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) δ 145.8, 141.8, 99.0, 66.2, 62.1, 57.7, 33.6, 30.3, 29.2, 27.6, 25.5, 19.4, 13.8, 9.7; **IR** (thin film, $cm^{-1}$) 3412.7 (br w), 2952.8 (m), 2921.3 (m), 2869.6 (m), 2851.6 (m), 1463.6 (w), 1120.5 (m), 1070.9 (m), 1028.1 (s).

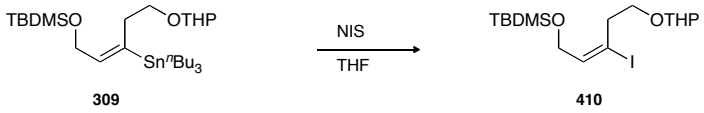
**Synthesis of silyl ether 309:**




**409** **309**

A solution of alcohol **409** (0.432 g, 0.913 mmol) in DMF (1.0 mL) was added *via* cannula to a solution of *tert*-butyl(chloro)dimethylsilane (0.412 g, 2.74 mmol), imidazole (0.224 g, 3.28 mmol) and DMAP (0.005 g, 0.045 mmol) in DMF (2.0 mL). The reaction was quenched with ether (15 mL). The mixture was washed with $H_2O$ (4 x 3 mL) and brine (3 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (20:1 hexanes/EtOAc) afforded silyl ether **309** as a colorless oil (0.509 g, 95%); **$^1$H NMR** ($CDCl_3$, 400 MHz) δ 5.73 (t, 1H, *J* = 5.6 Hz), 4.56 (t, 1H, *J* = 3.4 Hz), 4.32 (d, 2H, *J* = 5.6 Hz), 3.88-3.80 (m, 1H), 3.69-3.63 (m, 1H), 3.53-3.45 (m, 1H), 3.32-3.26 (m, 1H), 2.63-2.44 (m, 2H), 1.85-1.77 (m, 1H), 1.73-1.67 (m, 1H), 1.61-1.38 (m, 10H), 1.37-1.20 (m, 6H), 0.96-0.72 (m, 24H), 0.06 (s, 6H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 143.4, 140.2, 98.9, 67.1, 62.3, 60.4, 34.3, 30.8, 29.3, 27.6, 26.1, 25.6, 19.7, 18.5, 13.9, 9.8, -4.9; **IR** (thin film, cm$^{-1}$) 2953.3 (m), 2925.1 (m), 2854.1 (m), 1463.2 (w), 1252.9 (m), 1078.5 (s), 1031.9 (s), 834.5 (s), 773.8 (s).

**Synthesis of vinyliodide 410:**

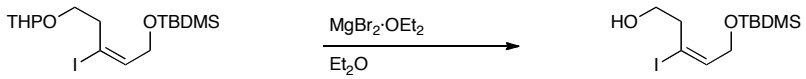



**309** **410**

A solution of *N*-iodosuccinimide (0.389 g, 1.73 mmol) in THF (3.5 mL) was added *via* cannula to a solution of vinylstannane **309** (0.928 g, 1.57 mmol) in THF (10.5 mL), and the resulting mixture was stirred for 30 minutes. The reaction was quenched with

saturated aqueous $NaHCO_3$/20% aqueous $Na_2SO_3$ (1:1, 25 mL), and the biphasic mixture was stirred for 15 minutes. The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (3 x 10 mL). The organic extracts were combined, washed with brine (30 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (40:1 → 9:1 hexanes/EtOAc) afforded vinyliodide **410** as a colorless oil (0.630 g, 94%); **$^1$H NMR** ($CDCl_3$, 400 MHz) δ 6.40 (t, 1H, *J* = 6.3 Hz), 4.60 (t, 1H, *J* = 3.5 Hz), 4.18 (d, 2H, *J* = 6.3 Hz), 3.88-3.79 (m, 2H), 3.54-3.46 (m, 2H), 2.71 (dt, 2H, *J* = 6.3, 2.1 Hz), 1.80-1.49 (m, 6H), 0.89 (s, 9H), 0.06 (s, 6H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 143.3, 99.5, 99.0, 65.7, 62.3, 61.4, 40.3, 30.7, 26.1, 25.6, 19.6, 18.5, -5.0; **IR** (thin film, $cm^{-1}$) 2927.3 (m), 2855.0 (m), 1633.3 (w), 1253.7 (m), 1078.1 (s), 1033.1 (s), 833.4 (s), 774.3 (s).

**Synthesis of homoallylic alcohol 310:**

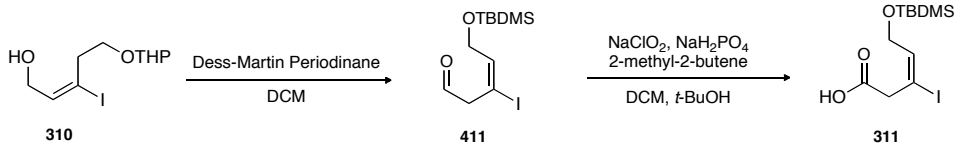



**410** **310**

A solution of vinyliodide **410** (0.630 g, 1.48 mmol) in $Et_2O$ (4.0 mL) was added *via* cannula to a solution of anhydrous magnesium bromide (2.0 g, 7.7 mmol) in $Et_2O$ (6.0 mL), and the resulting mixture was stirred for 3 hours. The reaction was quenched with $H_2O$ (10 mL), and the biphasic mixture was stirred for 5 minutes. The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (3 x 5 mL). The organic extracts were combined, washed with brine (10 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (4:1 → 7:3 hexanes/EtOAc) afforded homoallylic alcohol **310** as a colorless oil (0.418 g, 83%);

**$^1$H NMR** ($CDCl_3$, 400 MHz) δ 6.51 (t, 1H, *J* = 6.7 Hz), 4.12 (d, 2H, *J* = 6.7 Hz), 3.70 (t, 2H, *J* = 5.8 Hz), 2.71 (t, 2H, *J* = 5.8 Hz), 2.45 (br s, 1H), 0.88 (s, 9H), 0.07 (s, 6H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 143.0, 102.0, 60.8, 60.5, 42.7, 26.0, 18.5, -5.1; **IR** (thin film, $cm^{-1}$) 3354.3 (br w), 2952.0 (w), 2927.7 (w), 2882.8 (w), 2855.8 (w), 1632.1 (w), 1470.9 (w), 1253.6 (m), 1084.5 (m), 1040.7 (m), 832.5 (s), 811.5 (s), 774.6(s).

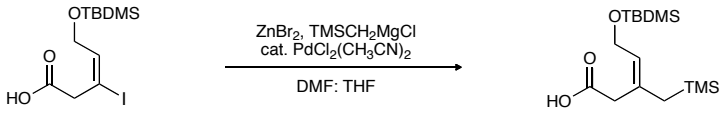
**Synthesis of iodo-acid 311:**




Dess-Martin periodinane (0.333 g, 0.785 mmol) was added to a solution of iodo-alcohol **310** (0.179 g, 0.524 mmol) in $CH_2Cl_2$ (5.25 mL), and the resulting suspension was stirred for 2 hours. The reaction was quenched with saturated aqueous $NaHCO_3$/20% aqueous $Na_2SO_3$ (1:1, 5 mL), and the biphasic mixture was stirred for 15 minutes. The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (3 x 5 mL). The organic extracts were combined, washed with brine (20 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to afford the unstable iodo-aldehyde **411** as a colorless oil (0.176 g, 99%); **$^1$H NMR** ($C_6D_6$, 400 MHz) δ 9.17 (s, 1H), 6.45 (t, 1H, *J* = 6.2 Hz), 3.66 (d, 2H, *J* = 6.1 Hz), 3.20 (s, 2H), 0.87 (s, 9H), -0.07 (s, 6H). Compound **411** was dissolved in $CH_2Cl_2$ (1.0 mL) and *tert*-BuOH (8.5 mL). 2-Methyl-2-butene (2.6 mL) was added, and the resulting mixture was stirred for 5 minutes. A solution of $NaClO_2$ (0.464 g, 5.13 mmol) and $NaH_2PO_4$ (0.564 g, 4.09 mmol) in $H_2O$ (4.7 mL) was added, and the resulting mixture was stirred for 1 hour. The reaction was quenched with brine (10 mL). The organic layer was separated, and the aqueous layer was extracted with $Et_2O$

(3 x 10 mL). The organic extracts were combined, washed with brine (2 x 10 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Crude iodo-acid **311** was obtained as a colorless oil (0.177 g, 95%), and was used without further purification; **$^1$H NMR** ($CDCl_3$, 400 MHz) δ 6.56 (t, 1H, *J* = 6.1 Hz), 4.18 (d, 1H, *J* = 6.1 Hz), 3.77 (s, 2H), 0.90 (s, 9H), 0.09 (s, 6H).

**Synthesis of acid 312:**

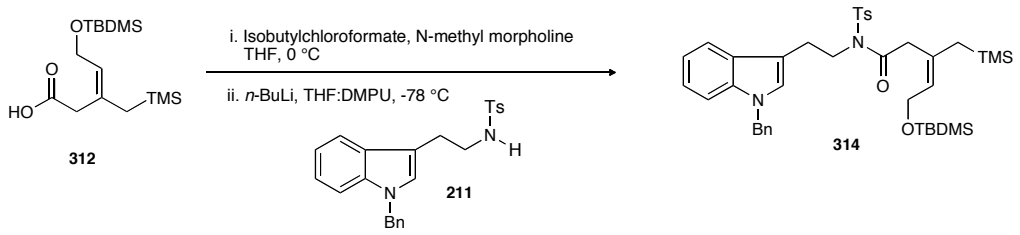



**311** **312**

Trimethylsilyl-methyl magnesium chloride (0.94 M in $Et_2O$, 1.60 mL, 1.50 mmol) was added to anhydrous $ZnBr_2$ (0.349 g, 1.55 mmol), and the resulting suspension was stirred vigorously for 14 hours. DMF (1.0 mL) was added, followed by $Et_2O$ (1.0 mL), and the mixture was stirred for 10 minutes. A solution of iodo-acid **311** (0.177 g, 0.498 mmol) in DMF (1.0 mL) was added *via* cannula. A solution of $Pd(CH_3CN)_2Cl_2$ (0.013 g, 0.05 mmol) in DMF (0.5 mL) was added over 5 minutes, and the resulting mixture was stirred for 1.5 hours. The reaction mixture was cooled to 0 °C and quenched with saturated aqueous $NH_4Cl$ (15 mL). EtOAc (10 mL) was added, and the mixture was stirred for 15 minutes. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 x 5 mL). The organic extracts were combined, washed with brine (3 x 5 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (9:1 → 7:3 hexanes/EtOAc, then 7:3:0.1 hexanes/EtOAc/methanol) afforded acid **312** as a colorless oil (0.104 g, 66%); **$^1$H NMR** ($CDCl_3$, 400 MHz) δ 5.52 (t, 1H, *J* =

6.9 Hz), 4.20 (d, 2H, *J* = 6.9 Hz), 3.13 (s, 2H), 1.65 (s, 2H), 0.92 (m, 9H), 0.04 (s, 6H), 0.03 (s, 9H);

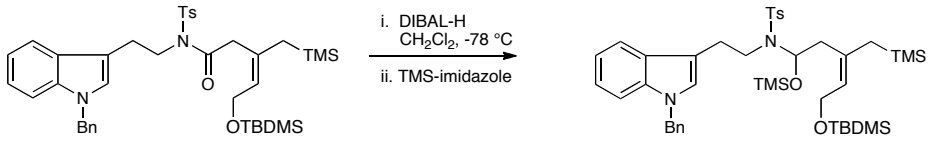
**Synthesis of *N*-tosylamide 314:**




A solution of carboxylic acid **312** (0.104 g, 0.327 mmol) in THF (1.9 mL) was cooled to 0 °C. *N*-methyl-morpholine (0.039 mL, 0.357 mmol) was added to the carboxylic acid solution, followed by slow addition of isobutyl chloroformate (0.041 mL, 0.327 mmol). The resulting mixture was stirred for 2 hour at 0 °C. Stirring was discontinued, and the suspension was allowed to settle for 1 hour. The resulting supernatant was transferred into a flask pre-cooled to -78 °C. THF (2.0 mL) was added to the remaining white precipitate, and the resulting suspension was stirred for 2 minutes, and then allowed to settle for 1 hour. The resulting supernatant was combined with the rest of the mixed anhydride solution. In a separate flask, a solution of tosylamine **211** (0.120 g, 0.297 mmol) in THF/DMPU (10:1, 1.65 mL) was cooled to -78 °C. *n*-BuLi (1.6 M in hexanes, 0.20 mL, 0.327 mmol) was added over 15 minutes, and the resulting solution was stirred at -78 °C for 1 hour. The mixture was added to the mixed anhydride solution *via* cannula, and the resulting orange solution was stirred at -78 °C for 12 hours. The reaction was quenched with saturated aqueous $NH_4Cl$ (4 mL), and was allowed to reach room temperature. The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (3 x 2 mL). The organic extracts were combined, washed with brine (2 x 5 mL),

dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (20:1 → 9:1 hexanes/EtOAc) afforded tosylamide **314** as an amorphous white solid (0.066 g, 31%); $\mathbf{R_f}$ 0.63 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 400 MHz) δ 7.82-7.80 (m, 3H), 7.37-7.26 (m, 6H), 7.21-7.12 (m, 4H), 7.00 (s, 1H), 5.35 (t, 1H, *J* = 6.8 Hz), 5.28 (s, 2H), 4.10-4.06 (m, 2H), 3.93 (d, 2H, *J* = 6.8 Hz), 3.31 (s, 2H), 3.23-3.19 (m, 2H), 2.44 (s, 3H), 1.42 (s, 2H), 0.87 (s, 9H), 0.02 (s, 6H), -0.05 (m, 9H).

**Synthesis of *N*-tosyl-*O*-TMS-aminol 304:**

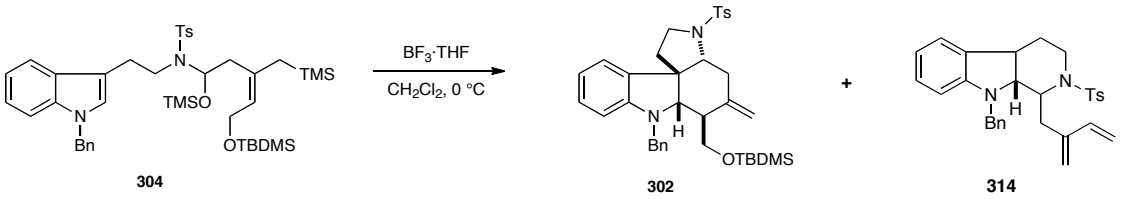



**314** **304**

A solution of *N*-tosylamide **314** (0.020 g, 0.029 mmol) in $CH_2Cl_2$ (0.3 mL) was cooled to -78 °C. DIBAL-H (1.0 M in $CH_2Cl_2$, 0.06 mL, 0.06 mmol) was added dropwise over 15 minutes, and the resulting mixture was stirred for 10 minutes at -78 °C. Trimethylsilyl imidazole (0.013 mL, 0.087 mmol) was added dropwise, and the solution was allowed to reach 0 °C over 12 hours. The reaction was quenched with aqueous 15% Rochelle's salt solution (1 mL). $Et_2O$ (3 mL) was added, and the mixture was stirred vigorously at r.t. until both layers were clear. The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (3 x 1 mL). The organic extracts were combined, washed with brine (5 mL), dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (9:1 hexanes/EtOAc, silica gel deactivated with 1% $Et_3N$) afforded *N*-tosyl-*O*-TMS-aminol **304** as a colorless oil (0.017 g, 77%); $\mathbf{R_f}$ 0.74 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 400 MHz) δ 7.74 (m, 3H), 7.34-7.26 (m, 5H), 7.22-7.13 (m, 5H), 6.98 (s, 1H), 5.39 (dd, 1H, *J* = 9.6, 2.5 Hz), 5.28 (s, 2H), 5.23 (t, 1H, *J* =

6.5 Hz), 4.24 (dd, 1H, *J* = 9.9, 5.1 Hz), 4.11 (dt, 1H, *J* = 12.2, 5.7 Hz), 3.58 (ddd, 1H, *J* = 14.6, 12.0, 5.6 Hz), 3.45 (ddd, 1H, *J* = 14.6, 12.0, 5.0 Hz), 3.24 (dt, 1H, *J* = 13.8, 5.3 Hz), 3.15 (dt, 1H, *J* = 12.6, 5.6 Hz), 2.53 (dd, 1H, *J* = 12.8, 9.6 Hz), 2.40 (s, 3H), 1.82 (dd, 1H, *J* = 12.7, 2.5 Hz), 1.54 (d, 1H, *J* = 13.2 Hz), 1.29 (d, 1H, *J* = 13.2 Hz), 0.89 (s, 9H), 0.12 (s, 9H), 0.06 (s, 6H), -0.05 (s, 9H).

**Synthesis of tetracyclic amine 302:**

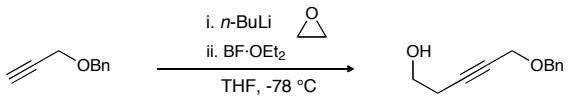



**304** **302** **314**

A solution of *N*-tosyl-*O*-TMS-aminol **304** (0.020 g, 0.0255 mmol) in $CH_2Cl_2$ (0.64 mL) was cooled to 0 °C. $BF_3$·THF (3 μL, 0.03 mmol) was added dropwise and the mixture was stirred at 0 °C for 30 minutes. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (1 mL). The resulting biphasic mixture was stirred vigorously for 15 minutes. The organic layer was separated, and the aqueous layer was extracted with $CH_2Cl_2$ (3 x 1 mL). The organic extracts were combined, washed with brine (3 mL), dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (7:3 hexanes/EtOAc) afforded tetracyclic amine **302** as a colorless oil (3.8 mg, 25%); $\mathbf{R_f}$ 0.65 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) δ 7.76 (d, 2H, *J* = 8.4 Hz), 7.37 (d, 2H, *J* = 8.4 Hz), 7.32-7.21 (m, 6H), 7.00 (t, 1H, *J* = 7.8 Hz), 6.61 (t, 1H, *J* = 7.2 Hz), 7.20 (d, 1H, *J* = 7.8 Hz), 4.70 (s, 1H), 4.68 (s, 1H), 4.41 (d, 1H, *J* = 15.6 Hz), 4.30 (d, 1H, *J* = 15.6 Hz), 3.71 (dt, 1H, *J* = 10.8, 6.8 Hz), 3.62 (s, 1H), 3.51 (t, 1H, *J* = 10.5 Hz), 3.43 (dd, 1H, *J* = 9.9, 6.3 Hz), 3.37 (dd, 1H, *J* = 11.4, 7.2 Hz),

3.31 (t, 1H, *J* = 9.6 Hz), 3.04-3.00 (m, 1H), 2.69 (dd, 1H, *J* = 16.7, 11.6 Hz), 2.50 (dd, 1H, *J* = 9.6, 6.6 Hz), 2.46 (s, 3H), 1.92 (dd, 1H, *J* = 11.7, 6.3 Hz), 1.45 (q, 1H, *J* = 11.0 Hz), 0.81 (s, 9H), 0.01 (s, 6H); and tetrahydrocarboline **314** as an amorphous white solid (3.5 mg, 28%); $\mathbf{R_f}$ 0.65 (7:3 hexanes/EtOAc).

**Synthesis of homopropargylic alcohol 320:**

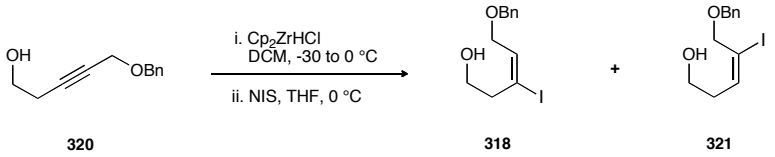



**319** **320**

A solution of benzyl ether **319** (3.52 g, 24.1 mmol) in THF (125.0 mL) was cooled to -78 °C. *n*-BuLi (1.6 M in hexanes, 19.6 mL, 31.3 mmol) was added over 15 minutes, and the resulting solution was stirred at -78 °C for 1 h. $BF_3{\cdot}OEt_2$ (3.86 mL, 31.3 mmol) was added over 10 minutes, and the solution was stirred for 15 minutes. In a separate flask, a solution of oxirane (1.43 mL, 28.9 mmol) in THF (3.0 mL) was cooled to -78 °C, and added to the reaction mixture *via* cannula. The resulting mixture was stirred at -78 0 °C for 2 hours. The reaction was quenched with saturated aqueous $NH_4Cl$ (45 mL). The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (3 x 100 mL). The organic extracts were combined, washed with brine (200 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (7:3 hexanes/EtOAc) afforded homopropargylic alcohol **320** as a colorless oil (3.35 g, 73%); $\mathbf{R_f}$ 0.18 (7:3 hexanes/EtOAc); $^{\mathbf{1}}\mathbf{H\ NMR}$ ($CDCl_3$, 400 MHz) δ 7.38-7.29 (m, 5H), 4.60 (s, 2H), 4.18 (t, 2H, *J* = 2.0 Hz), 3.75 (q, 2H, *J* = 6.3 Hz), 2.54 (tt, 2H, *J* = 6.2, 2.2 Hz), 1.75 (br t, 1H, *J* = 5.6 Hz); $^{\mathbf{13}}\mathbf{C\ NMR}$ ($CDCl_3$, 100 MHz) δ 137.3, 128.4, 128.1,

127.9, 84.0, 77.43, 71.6, 60.8, 57.7, 23.0; **IR** (thin film, $cm^{-1}$) 3390.4 (br, w), 3030.4 (w), 2857.4 (w), 1495.8 (w), 1453.6 (w), 1353.7 (m), 1261.5 (w), 1206.0 (w), 1131.9 (w), 1047.2 (s), 1026.9 (s), 736.9 (s), 696.7 (s); **HRMS** (+APCI) calculated for $C_{12}H_{15}O_2$ 191.1072, found 191.1063 $[M+H]^+$.

**Synthesis of iodo-alcohol 318:**

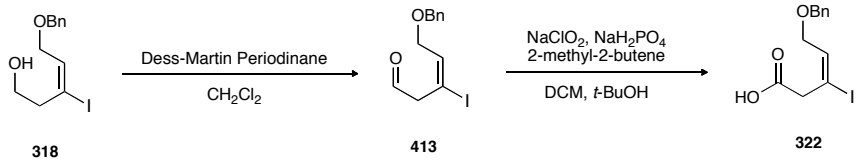



**320** **318** **321**

A solution of homopropargylic alcohol **320** (4.79 g, 25.2 mmol) in $CH_2Cl_2$ (126.0 mL) at -78 °C was added *via* cannula into a suspension of $Cp_2ZrHCl$ (19.5 g, 75.5 mmol) in $CH_2Cl_2$ (126.0 mL) at -5 °C, and the resulting mixture was stirred for 3 hours. A solution of NIS (11.3 g, 50.4 mole) in THF (126.0 mL) at 0 °C was added to the reaction mixture *via* cannula. The resulting suspension was stirred at 0 °C for 30 minutes. A solution of saturated aqueous $NaHCO_3$/20% aqueous $Na_2SO_3$ (1:1, 200 mL) was added, and the biphasic mixture was stirred for 15 minutes. The mixture was filtrated through a celite pad, and the filtered cake was washed with with $Et_2O$ (3 x 150 mL). The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (3 x 75 mL). The organic extracts were combined, washed with brine (300 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (4:1 hexanes/EtOAc) afforded iodo-alcohol **318** as a black oil (4.89 g, 61%); $\mathbf{R_f}$ 0.31 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) δ 7.38-7.30 (m, 5H), 6.62 (t, 1H, *J* = 6.9 Hz), 4.53 (s, 2H), 3.98 (d, 2H, *J* = 6.9 Hz), 3.74 (t, 2H, *J* = 5.1 Hz), 2.72 (t, 2H, *J* = 5.7 Hz), 2.01 (s, 1H); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) δ 140.1, 137.5, 128.6, 128.0, 128.0, 104.3, 72.6, 66.9, 60.6,

42.7; **IR** (thin film, $cm^{-1}$) 3376.8 (br w), 30329.0 (w), 2859.2 (w), 1629.1 (w), 1495.2 (w), 1452.8 (w), 1357.7 (w), 1042.5 (s), 1027.4 (s), 734.8 (s), 696.1 (s); **HRMS** (+APCI) calculated for $C_{12}H_{16}IO_2$ 319.0195, found 319.0190 $[M+H]^+$; and regioisomeric iodo-alcohol **321** as a red oil (0.962 g, 12%); $R_f$ 0.27 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) δ 7.41-7.30 (m, 5H), 6.49 (t, 1H, *J* = 7.8 Hz), 4.52 (s, 2H), 4.19 (s, 2H), 3.56 (dt, 2H, *J* = 6.0, 2.1 Hz), 2.74 (br s, 1H), 2.30 (q, 2H, *J* = 6.8 Hz); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) δ 141.9, 137.5, 128.5, 128.1, 127.9, 100.2, 71.6, 71.4, 60.9, 34.5; **IR** (thin film, $cm^{-1}$) 3377.5 (br w), 3029.2 (w), 2860.4 (w), 1628.6 (w), 495.5 (w), 1452.9 (w), 1355.9 (w), 1044.5 (s), 1027.3 (s), 734.2 (s), 696.3 (w); **HRMS** (+APCI) calculated for $C_{12}H_{16}IO_2$ 319.0195, found 319.0190 $[M+H]^+$.

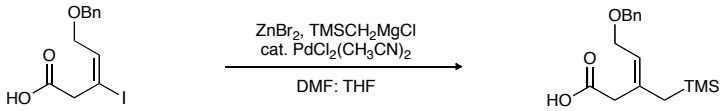
**Synthesis of iodo-acid 322:**




Dess-Martin periodinane (6.46 g, 15.2 mmol) was added to a stirring solution of iodo-alcohol **318** (3.23 g, 10.2 mmol) in $CH_2Cl_2$ (100.0 mL), and the resulting suspension was stirred for 3 hours. The reaction was quenched with saturated aqueous $NaHCO_3$/20% aqueous $Na_2SO_3$ (1:1, 100 mL), and the resulting biphasic mixture was stirred for 15 minutes. The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (3 x 100.0 mL). The organic extracts were combined, washed with brine (300 mL), dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo*. The unstable iodo-aldehyde **413** was dissolved in a solution of $CH_2Cl_2$ (20.3 mL) and *tert*-BuOH (84.6 mL). 2-Methyl-2-butene (46.0 mL) was added, and the resulting mixture was stirred for 5 minutes. A

solution of $NaClO_2$ (9.00 g, 99.5 mmol) and $NaH_2PO_4$ (10.9 g, 79.2 mmol) in $H_2O$ (90 mL) was added, and the resulting mixture was stirred for 1 hour. The reaction was quenched with brine (100 mL). The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (3 x 100 mL). The organic extracts were combined, washed with brine (2 x 100 mL), dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo*. Crude iodo-acid **322** was obtained as a yellow oil (3.37 g, 99%), and was used without further purification; $\mathbf{R_f}$ 0.48 (7:3 hexanes/EtOAc). **HRMS** (+APCI) calculated for $C_{12}H_{14}IO_3$ 332.9988, found 332.9987 $[M+H]^+$.

**Synthesis of Acid 323:**

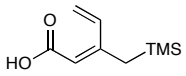



**322** **323**

Trimethylsilyl-methyl magnesium chloride (1.0 M in $Et_2O$, 40.7 mL, 40.7 mmol) was added to anhydrous $ZnBr_2$ (9.79 g, 43.5 mmol), and the resulting suspension was stirred vigorously for 14 hours. DMF (30.0 mL) was added, followed by $Et_2O$ (10.0 mL), and the mixture was stirred for 10 minutes. A solution of iodo-acid **322** (4.51 g, 13.6 mmol) in DMF (25.0 mL) was added *via* cannula, and the resulting suspension was cooled to 0 °C. A solution of $Pd(CH_3CN)_2Cl_2$ (0.352 g, 1.36 mmol) in DMF (5.0 mL) was added over 5 minutes, and the resulting mixture was stirred for 2 hours, warmed to room temperature and stirred for 30 minutes. The reaction mixture was cooled to 0 °C and quenched with saturated aqueous $NH_4Cl$ (100 mL). EtOAc (200 mL) was added, and the mixture was stirred for 15 minutes. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 x 125 mL). The organic extracts were combined,

washed with brine (300 mL), filtrated through celite, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Crude acid **323** was obtained as a yellow oil (3.76 g, 93%), and was used without further purification; $\mathbf{R_f}$ 0.20 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 400 MHz) δ 8.75 (br s, 1H), 7.39-7.28 (m, 5H), 5.51 (t, 1H, *J* = 6.9 Hz), 4.56 (s, 2H), 4.03 (d, 2H, *J* = 6.9 Hz), 3.06 (s, 2H), 1.67 (s, 2H), 0.06 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) δ 175.1, 137.8, 136.8 128.6, 128.1, 128.0, 122.6, 72.3, 66.3, 39.3, 28.1, -1.2; **IR** (thin film, $cm^{-1}$) 3550-2560 (br w), 2952.4 (w), 1706.8 (s), 1656.9 (w), 1247.2 (m), 839.7 (s); **HRMS** (+APCI) calculated for $C_{16}H_{25}O_3Si$ 293.1573, found 293.1565 $[M+H]^+$.

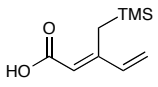
**Elimination products 324** was obtained when the procedure above was carried out at r.t. instead of at 0 °C.




**324**

**$^1$H NMR** ($CDCl_3$, 600 MHz) δ 7.85 (dd, 1H, *J* = 17.6, 11.0 Hz), 5.58 (d, 2H, *J* = 17.6 Hz), 5.57 (s, 1H), 5.49 (dd, 1H, *J* = 11.0, 1.2 Hz), 1.95 (s, 2H), 0.06 (s, 9H).

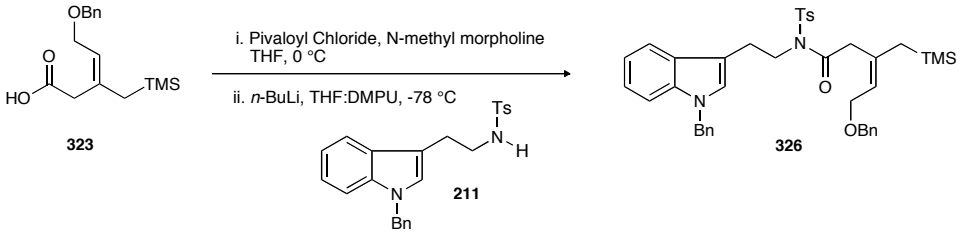
**Elimination products 325** was obtained when the procedure above was carried out at r.t. instead of at 0 °C.




**325**

**$^1$H NMR** ($CDCl_3$, 600 MHz) δ 6.38 (dd, 1H, *J* = 17.4, 10.7 Hz), 5.71 (s, 1H), 5.60 (d, 1H, *J* = 17.3 Hz), 5.42 (d, 1H, *J* = 10.7 Hz), 2.59 (s, 2H), 0.05 (s, 9H).

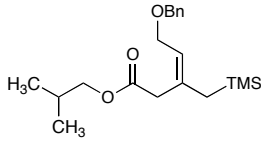
**Synthesis of *N*-tosylamide 326:**




A solution of tosylamine **211** (0.339 g, 0.838 mmol) in THF (10.8 mL) was cooled to -78 °C. *n*-BuLi (1.59 M in hexanes, 0.63 mL, 1.00 mmol) was added over 15 minutes, and the resulting solution was stirred at -78 °C for 1 h. DMPU (1.2 mL) was added, and the solution was stirred for 30 minutes. In a separate flask, a solution of carboxylic acid **323** (0.319 g, 1.09 mmol) in THF (11.0 mL) was cooled to 0 °C. *N*-methyl-morpholine (0.13 mL, 1.2 mmol) was added to the carboxylic acid solution, followed by addition of pivaloyl chloride (0.13 mL, 1.1 mmol). The resulting mixture was stirred for 45 minutes at 0 °C. Stirring was discontinued, and the suspension was allowed to settle for 1 hour to allow the morpholinium salts to precipitate. The yellow supernatant was transferred to a flask pre-cooled to -78 °C. THF (11.0 mL) was added to the white precipitate, and the resulting suspension was stirred for 2 minutes. Stirring was discontinued, and the suspension was allowed to settle for 1 hour. The yellow supernatant was separated by syringe and combined with the first extraction. The lithiate solution was quickly added to the mixed anhydride solution *via* cannula, and the solution was stirred at -78 °C for 4 hours. The reaction was quenched with $H_2O$ (20 mL). The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (3 x 20 mL). The organic extracts were combined, washed with brine (50 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (17:3 hexanes/EtOAc) afforded tosylamide **326** as a colorless oil (0.488 g, 86%); $\mathbf{R_f}$ 0.56 (7:3 hexanes/EtOAc); **$^1$H NMR**

($CDCl_3$, 400 MHz) δ 7.82-7.76 (m, 3H), 7.30-7.27 (m, 15H), 6.98 (s, 1H), 5.43 (t, 1H, *J* = 6.7 Hz), 5.26 (s, 2H), 4.35 (s, 2H), 4.06-4.02 (m, 2H), 3.78 (d, 2H, *J* = 6.7 Hz), 3.32 (s, 2H), 3.21-3.17 (m, 2H), 2.42 (s, 3H), 1.49 (s, 2H), -0.03 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 170.5, 145.0, 138.6, 137.7, 137.1, 136.8, 135.1, 130.1, 128.9, 128.5, 128.2, 127.8, 127.8, 127.7, 127.7, 127.1, 126.8, 123.5, 122.1, 119.6, 119.5, 111.5, 109.9, 71.7, 66.5, 50.1, 48.2, 40.4, 28.5, 26.3, 21.8, -1.2; **IR** (thin film, $cm^{-1}$) 3029.7 (w), 2952.0 (w), 1697.7 9 (m), 1495.1 (w), 1467.2 (w), 1453.0 (w), 1351.9 (s), 1247.1 (w), 1158.7 (s), 1088.1 (m), 850 (s), 738.8 (s); **HRMS** (+ESI) calculated for $C_{40}H_{50}N_3O_4SSi$ 696.3291, found 696.3299 $[M+NH_4]^+$.

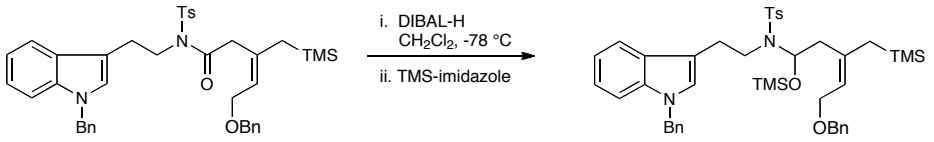
**Ester 328** was obtained when the above procedure employed isobutyl chloroformate in place of pivaloyl chloride.




**328**

**$R_f$** 0.66 (9:1 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) δ 7.38-7.30 (m, 5H), 5.43 (t, 1H, *J* = 6.8 Hz), 4.50 (s, 2H), 4.08 (d, 1H, *J* = 6.8 Hz), 3.85 (d, 2H, *J* = 6.6 Hz), 3.04 (s, 2H), 1.95-1.88 (m, 1H), 1.65 (s, 2H), 0.92 (d, 6H, *J* = 7.2 Hz), 0.06 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) δ 171.3, 138.7, 135.2, 128.6, 128.0, 127.7, 123.2, 71.9, 71.1, 66.7, 38.7, 28.3, 27.9, 19.3, -1.1; **IR** (thin film, $cm^{-1}$) 2925.1 (m), 1731.5 (m), 1064.3 (s), 848.9 (s), 789.0 (s); **HRMS** (+ESI) calculated for $C_{20}H_{32}NaO_3Si$ 371.2018, found 371.2012 $[M+Na]^+$.

**Synthesis of *N*-tosyl-*O*-TMS-aminol 316:**

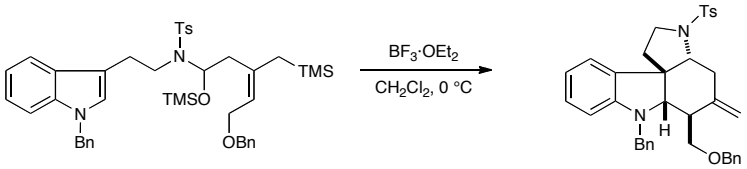



**326** **316**

A solution of tosylamide **326** (1.54 g, 2.27 mmol) in $CH_2Cl_2$ (23.0 mL) was cooled to -78 °C. DIBAL-H (1.0 M in $CH_2Cl_2$, 4.54 mL, 4.54 mmol) was added dropwise over 15 minutes. The reaction mixture was stirred for 45 minutes, then trimethylsilyl imidazole (1.81 mL, 9.07 mmol) was added dropwise, and the reaction was warmed to -25 °C and stirred for 12 hours. The mixture was warmed to 0 °C, trimethylsilyl imidazole (1.81 mL, 9.07 mmol) was added and the reaction was stirred for 8 hours. The reaction was quenched by slow addition of aqueous 15% Rochelle's salt solution (20 mL). $Et_2O$ (80 mL) was added, and the mixture was stirred vigorously at r.t. until both layers were clear. The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (3 x 25 mL). The organic extracts were combined, washed with brine (100.0 mL), dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (9:1 hexanes/EtOAc, silica gel deactivated with 1% $Et_3N$) afforded *N*-tosyl-*O*-TMS-aminol **316** as a colorless oil (1.39 g, 82%); $\mathbf{R_f}$ 0.62 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 400 MHz) δ 7.78-7.76 (m, 3H), 7.36-7.20 (m, 12H), 7.18-7.14 (m, 3H), 6.98 (s, 1H), 5.33 (dd, 1H, *J* = 9.6, 2.4 Hz), 5.35 (t, 1H, *J* = 6.8 Hz), 5.31 (s, 2H), 4.48 (q, 2H, *J* = 10.3 Hz), 4.14 (dd, 1H, *J* = 12.4, 7.6 Hz), 4.01 (dd, 1H, *J* = 12.4, 6.4 Hz), 3.60 (ddd, 1H, *J* = 14.6, 11.8, 5.6 Hz), 3.45 (ddd, 1H, *J* = 14.6, 11.8, 4.8 Hz), 3.25 (dt, 1H, *J* = 12.6, 4.8 Hz), 3.16 (dt, 1H, *J* = 12.6, 5.6 Hz), 2.56 (dd, 1H, *J* = 12.8, 9.6 Hz), 2.39 (s, 3H), 1.90 (dd, 1H, *J* = 12.8, 2.4 Hz), 1.64 (d, 1H, *J* = 13.4 Hz), 1.40 (d, 1H, *J* = 13.4 Hz), 0.12 (s, 9H), 0.01 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 143.2, 138.7, 138.6, 137.7, 137.0,

136.7, 129.8, 128.8, 128.4, 128.1, 127.7, 127.6, 127.5, 127.1, 126.9, 126.2, 126.1, 122.9, 121.9, 119.3, 112.6, 109.9, 81.4, 71.6, 66.7, 49.9, 44.0, 40.2, 28.0, 27.8, 21.5, 0.1, -1.3; **IR** (thin film, $cm^{-1}$) 3029.5 (w), 2953.1 (w), 1466.9 (w), 1453.2 (w), 1333.7 (m), 1248.5 9 (m), 1158.9 (m), 843.4 (s), 735.6 (s); **HRMS** (+ESI) calculated for $C_{43}H_{60}N_3O_4SSi_2$ 770.3843, found 770.4864 $[M+NH_4]^+$.

**Synthesis of tetracyclic amine 340:**

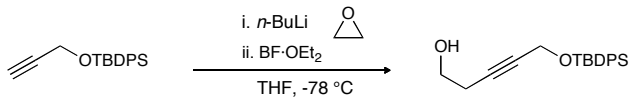



**316** **340**

A solution of *N*-tosyl-*O*-TMS-aminol **316** (1.393 g, 1.849 mmol) in $CH_2Cl_2$ (46.0 mL) was cooled to 0 °C. $BF_3{\cdot}OEt_2$ (1.14 mL, 9.25 mmol) was added dropwise over 3 minutes and the mixture was stirred at 0 °C for 45 minutes. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (30 mL). The resulting biphasic mixture was stirred vigorously for 15 minutes. The organic layer was separated, and the aqueous layer was extracted with $CH_2Cl_2$ (3 x 30 mL). The organic extracts were combined, washed with brine (100 mL), dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (4:1 hexanes/EtOAc) afforded tetracyclic amine **340** as an amorphous white solid (0.876 g, 80%); $\mathbf{R_f}$ 0.50 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) δ 7.69 (d, 2H, *J* = 8.2 Hz), 7.34-7.19 (m, 13H), 7.02 (dt, 1H, *J* = 7.4, 1.2 Hz), 6.63 (t, 1H, *J* = 7.4 Hz), 6.26 (d, 1H, *J* = 7.8 Hz), 4.73 (s, 2H), 4.47-4.42 (m, 2H), 4.40 (d, 1H, *J* = 12.0 Hz), 4.25 (d, 1H, *J* = 15.6 Hz), 3.66 (dt, 1H, *J* = 10.8, 7.0 Hz), 3.48 (d, 1H, *J* = 1.8 Hz), 3.41 (t, 1H, *J* = 10.2 Hz), 3.36-3.29 (m, 2H), 3.26 (dd,

1H, *J* = 9.6, 7.8 Hz), 3.06 (dd, 1H, *J* = 16.2, 6.6 Hz), 2.69 (dd, 1H, *J* = 16.2, 11.4 Hz), 2.59 (t, 1H, *J* = 6.9 Hz), 2.45 (s, 3H), 1.82 (dd, 1H, *J* = 12.0, 6.6 Hz), 1.36 (q, 1H, *J* = 10.8 Hz); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) 150.3, 143.8, 142.3, 138.5, 138.0, 132.6, 130.7, 129.8, 128.6, 128.5, 128.5, 127.8, 127.8, 127.6, 127.4, 127.2, 124.8, 117.1, 114.6, 106.0, 73.0, 73.0, 68.9, 59.3, 55.0, 48.6, 47.8, 46.1, 36.5, 33.6, 21.7.

**Synthesis of homopropargylic alcohol 336:**




335 336

A solution of silyl ether **335** (2.00 g, 6.79 mmol) in THF (45.0 mL) was cooled to -78 °C. *n*-BuLi (1.59 M in hexanes, 5.55 mL, 8.83 mmol) was added over 15 minutes, and the resulting solution was stirred at -78 °C for 1 h. $BF_3{\cdot}OEt_2$ (1.90 mL, 8.83 mmol) was added over 5 minutes, and the solution was stirred for 15 minutes. In a separate flask, a solution of oxirane (0.40 mL, 8.15 mmol) in THF (1.0 mL) was cooled to -78 °C, and added to the reaction mixture *via* cannula. The resulting mixture was stirred at -78 °C for 2 hours. The reaction was quenched with saturated aqueous $NH_4Cl$ (45 mL). The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (3 x 50 mL). The organic extracts were combined, washed with brine (200 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (7:3 hexanes/EtOAc) afforded homopropargylic alcohol **336** as a colorless oil (1.89 g, 82%); **$R_f$** 0.30 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 400 MHz) δ 7.76-7.73 (m, 4H), 7.48-7.39 (m, 6H), 4.36 (t, 2H, *J* = 2.1 Hz), 3.63 (q, 2H, *J* = 6.3 Hz), 2.42 (tt, 2H, *J* = 6.2, 2.1 Hz), 1.79 (br s, 1H), 1.08 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 135.8, 133.4, 130.0,

127.9, 82.4, 80.7, 61.1, 53.0, 26.9, 23.4, 19.3; **IR** (thin film, $cm^{-1}$) 3346.9 (br, w), 3070.8 (w), 2930.5 (w), 2857.5 (w), 1472.1 (w), 1427.5 (w), 1372.8 (w), 1111.3 (m), 1060.7 (m), 700.8 (s), 612.6 (m); **HRMS** (+ESI) calculated for $C_{21}H_{26}NaO_2Si$ 361.1600, found 361.1598 $[M+Na]^+$.

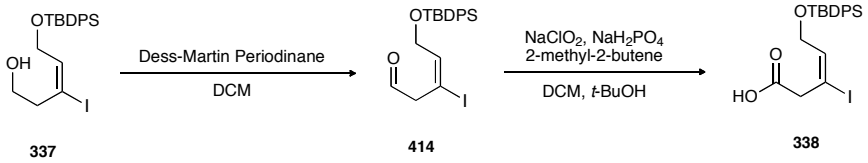
**Synthesis of iodo-alcohol 337:**


**336** **337**

A solution of homopropargylic alcohol **336** (1.89 g, 5.57 mmol) in $CH_2Cl_2$ (28.0 mL) at -78 °C was added *via* cannula into a suspension of $Cp_2ZrHCl$ (4.31 g, 16.7 mmol) in $CH_2Cl_2$ (28.0 mL) at -5 °C, and the resulting mixture was stirred for 3 hours. A solution of NIS (2.50 g, 11.1 mmol) in THF (28 mL) at 0 °C was added to the reaction mixture *via* cannula. The resulting suspension was stirred at 0 °C for 30 minutes. The reaction was quenched with saturated aqueous $NaHCO_3$/20% aqueous $Na_2SO_3$ (1:1, 100 mL), and the resulting biphasic mixture was stirred for 15 minutes. The mixture was filtrated through a celite pad, and the filtered cake was washed with with $Et_2O$ (3 x 50 mL). The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (3 x 50 mL). The organic extracts were combined, washed with brine (150 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (9:1 hexanes/EtOAc) afforded iodo-alcohol **337** as a colorless oil (2.02 g, 78%); $\mathbf{R_f}$ 0.28 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 400 MHz) 7.71-7.65 (m, 4H), 7.47-7.39 (m, 6H), 6.56 (t, 1H, $J$ = 6.7 Hz), 4.15 (d, 2H, $J$ = 6.7 Hz), 3.65 (q, 2H, $J$ = 5.9 Hz), 2.54 (t, 2H, $J$ = 5.8 Hz), 1.62 (t, 1H, $J$ = 6.1 Hz), 1.05 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 143.0,

135.7, 133.2, 130.0, 127.9, 101.6, 61.6, 60.8, 42.5, 26.9, 19.3; **IR** (thin film, $cm^{-1}$) 3367.1 (br, w), 3070.2 (w), 2929.8 (w), 2856.4 (w), 1632.8 (w), 1588.7 (w), 1471.4 (w), 1427.0 (w), 1372.8 (w), 1105.5 (m), 1039.9 (m), 733.2 (m), 699.2 (s), 611.8 (m); **HRMS** (+ESI) calculated for $C_{21}H_{27}INaO_2Si$ 489.0723, found 489.0726 $[M+Na]^+$.

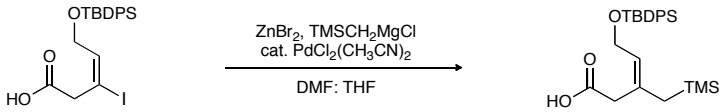
**Synthesis of iodo-acid 338:**




Dess-Martin periodinane (10.9 g, 25.6 mmol) was added to a solution of iodo-alcohol **337** (7.97 g, 17.1 mmol) in $CH_2Cl_2$ (171.0 mL), and the resulting suspension was stirred for 3 hours. The reaction was quenched with saturated aqueous $NaHCO_3$/20% aqueous $Na_2SO_3$ (1:1, 200 mL), and the resulting biphasic mixture was stirred for 15 minutes. The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (3 x 150 mL). The organic extracts were combined, washed with brine (300 mL), dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo*. The unstable iodo-aldehyde **414** was dissolved in a solution of $CH_2Cl_2$ (34.0 mL) and *tert*-BuOH (143.0 mL). 2-Methyl-2-butene (78.0 mL) was added, and the resulting mixture was stirred for 5 minutes. A solution of $NaClO_2$ (15.15 g, 167.5 mmol) and $NaH_2PO_4$ (18.4 g, 133.3 mmol) in $H_2O$ (151.0 mL) was added, and the resulting mixture was stirred for 1 hour. The reaction was quenched with brine (200 mL). The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (3 x 150 mL). The organic extracts were combined, washed with brine (2 x 150 mL), dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo*. Crude iodo-acid **338** was obtained as an orange oil (8.18 g, 99%), and was used without further purification;

**$R_f$** 0.28 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) δ 7.66 (d, 4H, *J* = 7.0 Hz), 7.46-7.39 (m, 6H), 6.59 (t, 1H, *J* = 6.2 Hz), 4.14 (d, 2H, *J* = 6.3 Hz), 3.52 (s, 2H), 1.04 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 175.1, 144.5, 135.7, 133.1, 130.1, 128.0, 89.3, 62.1, 45.2, 26.9, 19.3; **IR** (thin film, $cm^{-1}$) 3500-2500 (br w), 3069.9 (w), 2929.4 (w), 2856.0 (w), 1711.5 (s), 1426.9 (m), 1105.5 (s), 699.8 (s); **HRMS** (+ESI) calculated for $C_{21}H_{25}INaO_3Si$ 503.0515, found 503.0510 $[M+Na]^+$.

**Synthesis of acid 339:**

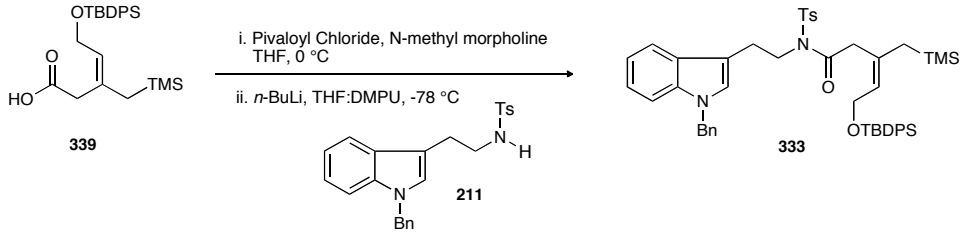



**338** **339**

Trimethylsilyl-methyl magnesium chloride (1.0 M in $Et_2O$, 54.5 mL, 54.5 mmol) was added to anhydrous $ZnBr_2$ (13.09 g, 58.12 mmol), and the resulting suspension was stirred vigorously for 14 hours. DMF (50.0 mL) was added, followed by $Et_2O$ (30.0 mL), and the mixture was stirred for 10 minutes. A solution of iodo-acid **338** (8.73 g, 18.2 mmol) in DMF (50.0 mL) was added *via* cannula, and the resulting suspension was cooled to 0 °C. A solution of $Pd(CH_3CN)_2Cl_2$ (0.441 g, 1.70 mmol) in DMF (5.0 mL) was added over 5 minutes, and the resulting mixture was stirred for 30 minutes, warmed to room temperature and stirred for 2 hours. The reaction mixture was cooled to 0 °C and quenched with saturated aqueous $NH_4Cl$ (150 mL). EtOAc (300 mL) was added, and the mixture was stirred for 15 minutes. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 x 200 mL). The organic extracts were combined, washed with brine (300 mL), filtered through celite, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Crude acid **339** was obtained as a yellow oil (7.69 g, 96%), and

was used without further purification; **$R_f$** 0.23 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) δ 10.67 (br s, 1H), 7.68-7.66 (m, 4H), 7.43-7.36 (m, 6H), 5.46 (s, 1H, *J* = 6.9 Hz), 4.17 (d, 2H, *J* = 6.9 Hz), 2.95 (s, 1H), 1.61 (s, 2H), 1.02 (s, 9H), 0.01 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 177.2, 135.7, 133.8, 132.6, 129.8, 127.9, 126.1, 60.9, 38.5, 27.9, 27.0, 19.3, -1.2; **IR** (thin film, $cm^{-1}$) 3300-2700 (br, w), 2953.8 (w), 2856.8 (w), 1706.1 (m), 1248.0 (w), 1110.0 (m), 1044.9 (m), 841.5 (m), 823.0 (m), 699.6 (s), 612.2 (m); **HRMS** (-ESI) calculated for $C_{25}H_{35}O_3Si_2$ 439.2125, found 439.2136 $[M-H]^-$.

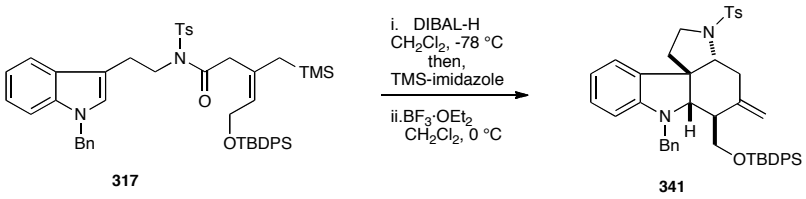
**Synthesis of *N*-tosylamide 333:**




A solution of carboxylic acid **339** (4.44 g, 10.1 mmol) in THF (100.0 mL) was cooled to 0 °C. *N*-methyl-morpholine (1.19 mL, 10.9 mmol) was added to the carboxylic acid solution, followed by addition of pivaloyl chloride (1.24 mL, 10.1 mmol). The resulting mixture was stirred for 1 hour at 0 °C. Stirring was discontinued, and the suspension was allowed to settle for 1 hour. The resulting supernatant was transferred into a flask pre-cooled to -78 °C. THF (100.0 mL) was added to the remaining white precipitate, and the resulting suspension was stirred for 2 minutes, and then allowed to settle for 1 hour. The resulting supernatant was combined with the rest of the mixed anhydride solution. In a separate flask, a solution of tosylamine **211** (3.13 g, 7.75 mmol) in THF (100.0 mL) was cooled to -78 °C. *n*-BuLi (1.6 M in hexanes, 5.81 mL, 9.30 mmol) was added over 15 minutes, and the resulting solution was stirred at -78 °C for 1 hour. DMPU was added

over 5 minutes, and the solution was stirred for 15 minutes. The mixture was added to the mixed anhydride solution *via* cannula, and the resulting orange solution was stirred at -78 °C for 2 hours. The reaction was quenched with saturated aqueous $NH_4Cl$ (150 mL), and was warmed to room temperature. The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (3 x 150 mL). The organic extracts were combined, washed with brine (2 x 150 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (9:1 → 4:1 hexanes/EtOAc) afforded *N*-tosylamide **333** as an amorphous white solid (5.79 g, 90%); $\mathbf{R_f}$ 0.62 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) δ 7.75 (d, 1H, *J* = 7.9 Hz), 7.67 (d, 2H, *J* = 8.4 Hz), 7.66-7.64 (m, 4H), 7.42-7.35 (m, 6H), 7.31-7.24 (m, 4H), 7.17-7.15 (m, 3H), 7.11-7.09 (m, 3H), 6.93 (s, 1H), 5.43 (t, 1H, *J* = 6.5 Hz), 5.23 (s, 2H), 4.00 (d, 2H, *J* = 6.5 Hz), 3.98-3.95 (m, 2H), 3.20 (s, 2H), 3.14-3.11 (m, 2H), 2.34 (s, 3H), 1.41 (s, 2H), 1.01 (s, 9H), -0.03 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) δ 170.5, 144.8, 137.6, 136.9, 136.7, 135.6, 134.0, 131.9, 129.9, 129.7, 128.8, 128.1, 127.8, 127.7, 127.5, 127.0, 126.7, 126.5, 122.0, 119.5, 119.4, 111.4, 109.8, 60.9, 50.0, 48.1, 40.2, 27.9, 26.9, 26.3, 21.6, 19.3, -1.3; **IR** (thin film, $cm^{-1}$) 3068.7 (w), 2954.3 (w), 2856.2 (w), 1698.8 (m), 1495.2 (w), 1427.5 (w), 1352.7 (s), 1247.3 (w), 1157.8 (s), 1110.3 (m), 1088.4 (m), 1046.2 (w), 849.2 (s), 738.2 (s), 701.8 (s); **HRMS** (+ESI) calculated for $C_{49}H_{58}N_2NaO_4SSi_2$ 849.3554, found 849.3532 $[M+Na]^+$.

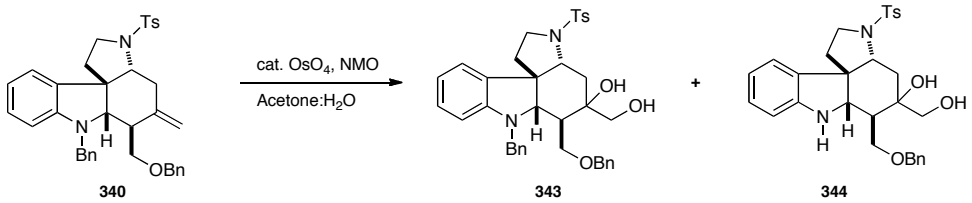
**Synthesis of tetracyclic amine 341:**




A solution of *N*-tosylamide **317** (5.81 g, 7.02 mmol) in $CH_2Cl_2$ (70.0 mL) was cooled to -78 °C. DIBAL-H (1.0 M in $CH_2Cl_2$, 14.0 mL, 14.1 mmol) was added dropwise over 15 minutes, and the resulting mixture was stirred for 45 minutes. Trimethylsilyl imidazole (8.4 mL, 42.1 mmol) was added dropwise, and the solution was warmed to 0 °C over 2 hours. Additional trimethylsilyl imidazole (8.4 mL, 42.1 mmol) was added and the mixture was stirred for 4 hours. $BF_3{\cdot}OEt_2$ (13.0 mL, 105.4 mmol) was added over 5 minutes, and the resulting deep orange solution was stirred for 5 minutes. The reaction was quenched by slow addition of aqueous 15% Rochelle's salt solution/aqueous saturated $NaHCO_3$ (1:1, 200 mL). $Et_2O$ (200 mL) was added, and the mixture was stirred vigorously at r.t. until both layers were clear. The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (3 x 100 mL). The organic extracts were combined, washed with brine (200 mL), dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (17:3 → 4:1 hexanes/EtOAc,) afforded tetracycle **341** as an amorphous white solid (2.65 g, 51%); $\mathbf{R_f}$ 0.47 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) 7.60 (d, 2H, *J* = 8.2 Hz), 7.57 (d, 2H, *J* = 7.2 Hz), 7.50 (d, 2H, *J* = 7.2 Hz), 7.48-7.37 (m, 4H), 7.28-7.18 (m, 8H), 7.16 (d, 2H, *J* = 7.8 Hz), 7.00 (t, 1H, *J* = 7.7 Hz), 6.60 (t, 1H, *J* = 7.4 Hz), 6.19 (d, 1H, *J* = 7.8 Hz), 4.70 (s, 1H), 4.69 (s, 1H), 4.39 (d, 1H, *J* = 16.0 Hz), 4.28 (d, 1H, *J* = 16.0 Hz), 3.64 (dt, 1H, *J* = 10.9, 7.1 Hz), 3.52 (dd, 1H, *J* = 10.1, 6.6 Hz), 3.41-3.37 (m, 2H), 3.35 (t, 1H, *J* = 10.2

Hz), 3.17 (dd, 1H, *J* = 11.6, 7.0 Hz), 2.98 (dd, 1H, *J* = 17.0 Hz, 6.9 Hz), 2.66 (dd, 1H, *J* = 16.8, 11.7 Hz), 2.57 (t, 1H, *J* = 7.6 Hz), 2.40 (s, 3H), 1.77 (dd, 1H, *J* = 11.9, 6.9 Hz), 1.08 (q, 1H, *J* = 11.0 Hz), 1.00 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) δ 150.7, 143.8, 141.5, 138.7, 135.8, 135.7, 133.7, 133.5, 132.6, 130.4, 130.1, 130.0, 129.9, 128.7, 128.6, 128.0, 127.9, 127.9, 127.2, 127.2, 124.9, 117.0, 115.5, 105.5, 68.8, 67.4, 58.8, 54.9, 49.4, 48.2, 47.9, 36.7, 32.9, 27.1, 21.8, 19.4; **IR** (thin film, $cm^{-1}$) 3069.3(w), 2928.9 (w), 2856.8 (w), 1600.7 (m), 1484.2 (m), 1351.4 (m), 1164.5 (s), 1109.0 (s), 736.2 (s), 702.3 (s); **HRMS** (+ESI) calculated for $C_{46}H_{51}N_2O_3SSi$ 739.3390, found 739.3381 $[M+H]^+$.

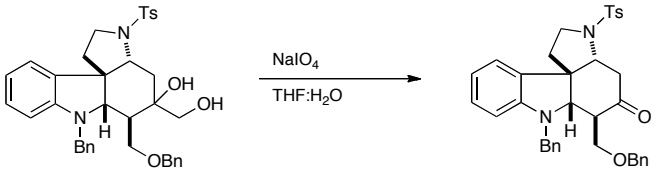
**Synthesis of diol 343:**




Osmium tetroxide (2.5% wt in *tert*-butanol, 0.12 mL, 0.0092 mmol) and *N*-methyl morpholine oxide (0.011 g, 0.096 mmol) were sequentially added to a solution of tetracycle **340** (0.054 g, 0.092 mmol) in acetone:$H_2O$ (4:1, 0.65 mL), and the resulting mixture was stirred for 4 hours. $CH_2Cl_2$ (1 mL) was added, followed by $H_2O$ (1 mL). The resulting biphasic mixture was stirred vigorously for 15 minutes. The organic layer was separated, and the aqueous layer was extracted with $CH_2Cl_2$ (3 x 1 mL). The organic extracts were combined, washed with brine (2 mL), dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (13:7 → 1:1 hexanes/EtOAc) afforded **343** as an amorphous white solid (0.039 g, 67%); $\mathbf{R_f}$ 0.56 (1:1 hexanes/EtOAc); and debenzylated diol **344** as an amorphous light pink solid (0.007 g,

15%); **$R_f$** 0.30 (1:1 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) (5:1 mixture of diastereomers) δ 7.84 (d, 1.6H, *J* = 7.5 Hz), 7.77 (d, 0.4H, *J* = 7.2 Hz), 7.59-7.53 (m, 1H), 7.42-7.31 (m, 7H), 7.10 (t, 1H, *J* = 7.5 Hz), 6.83 (t, 1H, *J* = 6.9 Hz), 6.67 (d, 1H, *J* = 7.8 Hz), 4.55-4.48 (m, 3H), 3.73-3.50 (m, 5H), 3.43-3.29 (m, 3H), 2.98 (d, 2H, *J* = 11.4 Hz), 2.52-2.50 (m, 1H), 2.46 (s, 3H), 1.84 (t, 1H, *J* = 13.2 Hz), 1.74-1.64 (m, 2H), 1.44 (q, 1H, *J* = 10.7 Hz); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) (5:1 mixture of diastereomers) δ 144.0, 137.3, 132.0, 130.0, 128.9, 128.9, 128.5, 128.4, 128.4, 128.1, 128.0, 125.7, 120.1, 111.9, 74.9, 74.0, 68.6, 65.3, 65.2, 59.7, 55.9, 49.1, 47.7, 36.4, 35.3, 21.8; **IR** (thin film, $cm^{-1}$) 3418.7 (br w), 3373.1 (br w), 3041.7 (w), 2924.0 (w), 2875.5 (w), 1597.8 (w), 1476.6 (w), 1454.9 (w), 1342.8 (m), 1297.4 (w), 1159.2 (s), 1089.2 (w), 1051.3 (s), 664.9 (s); **HRMS** (+APCI) calculated for $C_{30}H_{35}N_2O_5S$ 535.2267, found 535.2262 $[M+H]^+$.

**Synthesis of ketone 342:**

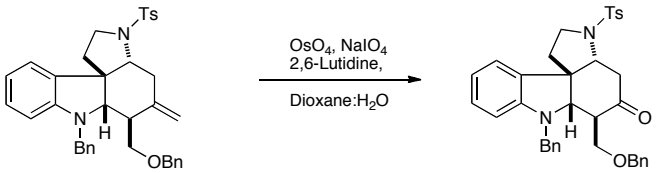



**343** **342**

Sodium periodate (0.050 g, 0.23 mmol) was added to a solution of diol **343** (0.039 g, 0.062 mmol) in THF:$H_2O$ (4:1, 1.0 mL), and the mixture was stirred for 5 hours. $Et_2O$ (2 mL) was added, followed by $H_2O$ (1 mL). The resulting biphasic mixture was stirred vigorously for 15 minutes. The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (3 x 1 mL). The organic extracts were combined, washed with brine (3 mL), dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (7:3 hexanes/EtOAc) afforded ketone **342** as a colorless oil

(0.029 g, 78%); **$R_f$** 0.30 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) δ 7.66 (d, 2H, *J* = 8.2 Hz), 7.33-7.29 (m, 4H), 7.27-7.21 (m, 7H), 7.10-7.05 (m, 3H), 6.71 (dt, 1H, *J* = 7.5, 0.6 Hz), 6.36 (d, 1H, *J* = 7.8 Hz), 4.42 (d, 1H, *J* = 15.0 Hz), 4.38 (d, 1H, *J* = 12.5 Hz), 4.28 (d, 1H, *J* = 12.5 Hz), 4.00 (d, 1H, *J* = 15.0 Hz), 3.88 (dd, 1H, *J* = 12.0, 6.1 Hz), 3.68 (dt, 1H, *J* = 11.2, 6.7 Hz), 3.54-3.51 (m, 3H), 3.19 (dd, 1H, *J* = 8.8, 4.4 Hz), 3.15 (dd, 1H, *J* = 18.8, 6.1 Hz), 2.85 (dd, 1H, *J* = 18.7, 12.1 Hz), 2.42 (t, 1H, *J* = 4.1 Hz), 2.37 (s, 3H), 1.93 (dd, 1H, *J* = 11.9, 6.4 Hz), 1.51 (q, 1H, *J* = 10.8 Hz); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) δ 208.9, 150.0, 144.1, 137.5, 137.4, 132.9, 130.0, 129.5, 128.9, 128.8, 128.8, 128.2, 128.1, 127.8, 127.7, 127.7, 125.8, 118.9, 107.6, 73.5, 72.0, 68.6, 58.0, 54.9, 51.1, 48.3, 48.2, 43.2, 36.0, 21.8; **IR** (thin film, $cm^{-1}$) 3030.4 (w), 2918.6 (m), 2849.9 (w), 1705.1 (m), 1599.9 (m), 1478.9 (m), 1453.1 (w), 1350.4 (m), 1162.4 (s), 1092.1 (m), 733.6 (s); **HRMS** (+APCI) calculated for $C_{36}H_{37}N_2O_4S$ 593.2474, found 593.2474 $[M+H]^+$.

**Synthesis of ketone 342 (One Pot procedure):**

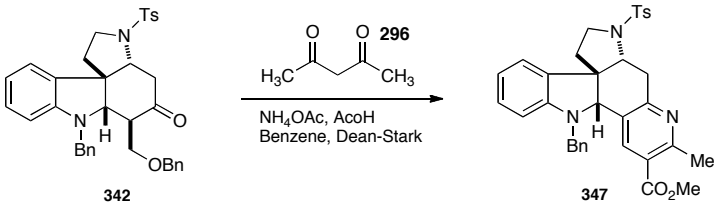



**340** **342**

Sodium periodate (0.220 g, 1.029 mmol) and osmium tetroxide (2.5% wt in *tert*-butanol, 0.081 mL, 0.0064 mmol) were sequentially added to a suspension of tetracycle **340** (0.076 g, 0.13 mmol) and 2,6-lutidine (0.060 mL, 0.51 mmol) in dioxane:$H_2O$ (3:1, 1.4 mL), and the mixture was stirred for 6 hours. $CH_2Cl_2$ (3 mL) was added, followed by $H_2O$ (1 mL). The resulting biphasic mixture was stirred vigorously for 15 minutes. The

organic layer was separated, and the aqueous layer was extracted with $CH_2Cl_2$ (3 x 1 mL). The organic extracts were combined, washed with brine (3 mL), dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (7:3 hexanes/EtOAc) afforded ketone **342** as a colorless oil (0.045 g, 59%). The product was identical to that obtained by the two-step procedure as judged by $^1$H NMR.

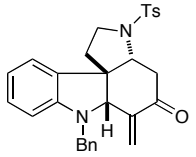
**Synthesis of pyridine 347:**




Ammonium acetate (0.069 g, 0.90 mmol) was added to a solution of ketone **342** (0.023 g, 0.038 mmol) and methyl acetoacetate (0.010 mL, 0.093 mmol) in benzene/acetic (4:1, 2.0 mL), and the resulting mixture was placed in a Dean-Stark trap and heated at reflux for 18 hours. $CH_2Cl_2$ (4 mL) was added, and the mixture was filtered through celite and concentrated *in vacuo*. Purification by chromatography on silica gel (13:1 → 7:3 hexanes/EtOAc) afforded pyridine **347** as an amorphous white solid (0.012 g, 52%); $\mathbf{R_f}$ 0.30 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) δ 7.97 (s, 1H), 7.74 (d, 2H, *J* = 8.1 Hz), 7.49 (d, 1H, *J* = 7.4 Hz), 7.43-7.36 (m, 4H), 7.34-7.29 (m, 3H), 7.07 (t, 1H, *J* = 7.7 Hz), 6.75 (t, 1H, *J* = 7.5 Hz), 6.41 (d, 1H, *J* = 7.9 Hz), 4.64 (d, 1H, *J* = 15.3 Hz), 4.42 (s, 1H), 4.23 (d, 1H, *J* = 15.3 Hz), 3.93 (s, 3H), 3.82 (dt, 1H, *J* = 10.9, 7.1 Hz), 3.65 (dd, 1H, *J* = 16.8, 4.2 Hz), 3.59 (t, 1H, *J* = 10.3 Hz), 3.40 (dd, 1H, *J* = 16.9, 12.0 Hz), 3.23 (dd, 1H, *J* = 12.0, 4.2 Hz), 2.75 (s, 3H), 2.41 (s, 3H), 2.06 (dd, 1H, *J* = 11.7, 6.8 Hz), 1.69 (q, 1H, *J* = 10.9 Hz); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) δ 168.9, 158.7, 158.5, 149.6, 144.0,

140.0, 137.5, 132.9, 130.0, 130.0, 129.2, 129.0, 128.3, 128.0, 127.9, 127.7, 125.7, 122.6, 119.1, 108.6, 67.0, 61.1, 55.1, 52.4, 49.9, 48.0, 37.2, 35.8, 24.8, 21.8; **IR** (thin film, $cm^{-1}$) 2951.8 (w), 1722.9 (s), 1597.3 (m), 1548.2 (w), 1480.5 (m), 1448.6 (m), 1348.8 (m), 1265.5 (m), 1158.6 (s), 1094.0 (w), 730.6 (s); **HRMS** (+APCI) calculated for $C_{34}H_{34}N_3O_4S$ 580.2270, found 580.2269 $[M+H]^+$.

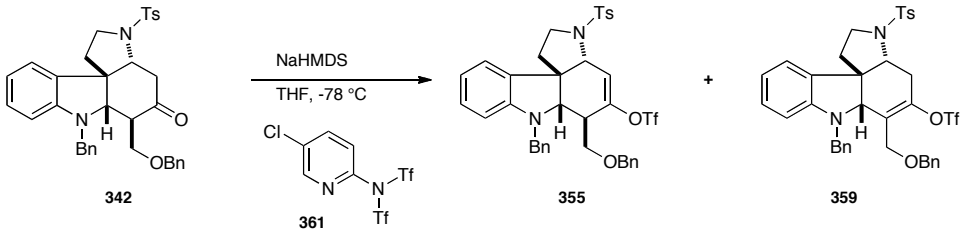
**Elimination products 354** was obtained when Lehnert conditions were employed to carry out the Knoevenagel condensation of ketone **342** with methyl acetoacetate.




**354**

**$R_f$** 0.34 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) δ 7.73 (d, 2H, *J* = 8.4 Hz), 7.34 (d, 2H, *J* = 8.4 Hz), 7.31-7.27 (m, 3H), 7.24-7.23 (m, 3H), 7.07 (t, 1H, *J* = 7.8 Hz), 6.69 (t, 1H, *J* = 7.5 Hz), 6.35 (d, 1H, *J* = 7.8 Hz), 5.85 (d, 1H, *J* = 0.6 Hz), 5.08 (s, 1H), 4.46 (d, 1H, *J* = 16.2 Hz), 4.12 (s, 1H), 4.00 (d, 1H, *J* = 16.2 Hz), 3.81 (dt, 1H, *J* = 10.8, 7.1 Hz), 3.62 (t, 1H, *J* = 10.5 Hz), 3.43 (dd, 1H, *J* = 12.6, 5.4 Hz), 3.12-3.07 (dd, 1H, *J* = 18.9, 5.4 Hz), 2.76 (dd, 1H, *J* = 18.9, 12.6 Hz), 2.43 (s, 3H), 2.14 (dd, 1H, *J* = 12.0, 7.2 Hz), 1.72 (q, 1, *J* = 18.3 Hz); **IR** (thin film, $cm^{-1}$) 3029.6 (w), 2922.6 (w), 1724.2 (w), 1696.9 (m), 1598.2 (m), 1480.5 (m), 1347.7 (m), 1161.2 (s), 1091.2 (m), 732.4 (s); **HRMS** (+APCI) calculated for $C_{29}H_{29}N_2O_3S$ 485.1899, found 485.1894 $[M+H]^+$.

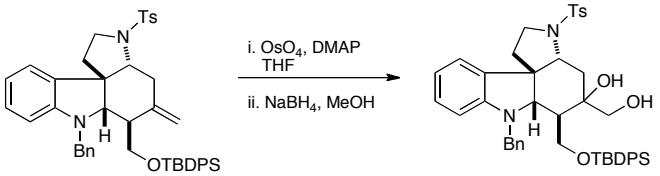
**Synthesis of kinetic enol triflate 355**:




A solution of ketone **342** (0.012 g, 0.021 mmol) in THF (0.2 mL) was added over 15 minutes to a stirring solution of NaHMDS (0.19 M in THF, 0.12 mL, 0.023 mmol) at -78 °C, and the resulting mixture was stirred for 30 minutes. A solution of triflating reagent **361** (9.0 mg, 0.023 mmol) in THF (0.2 mL) was added over 5 minutes, and the resulting mixture was stirred at -78 °C for 4 hours. The reaction was quenched by addition of aqueous saturated $NaHCO_3$ (0.2 mL). $Et_2O$ (3 mL) was added and the crude reaction mixture washed with brine (2 x 1 mL), dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (9:1 → 4:1 hexanes/EtOAc,) afforded kinetic enol triflate **355** as an amorphous white solid (2.0 mg, 13%); $\mathbf{R_f}$ 0.48 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) δ 7.68 (d, 2H, *J* = 8.2 Hz), 7.33-7.23 (m, 11H), 7.12-7.10 (m, 2H), 7.05 (t, 1H, *J* = 7.8 Hz), 6.72 (t, 1H, *J* = 7.5 Hz), 6.58 (d, 1H, *J* = 2.1 Hz), 6.35 (d, 1H, *J* = 7.8 Hz), 4.43 (d, 1H, *J* = 15.3 Hz), 4.36 (q, 2H, *J* = 12.6 Hz), 4.05 (m, 1H, *J* = 15.6 Hz), 3.97 (s, 1H), 3.79 (dt, 1H, *J* = 11.1, 6.9 Hz), 3.61 (d, 1H, *J* = 0.8 Hz), 3.50 (t, 1H, *J* = 10.4 Hz), 3.36 (dd, 1H, *J* = 9.0, 5.4 Hz), 3.22 (dd, 1H, *J* = 9.3, 3.9 Hz), 2.66-2.65 (m, 1H), 2.39 (s, 3H), 1.99 (dd, 1H, *J* = 11.8, 6.6 Hz), 1.60-1.53 (m, 10 H); **IR** (thin film, $cm^{-1}$) 3029.9 (w), 2922.0 (w), 2856.1 (w), 1739.1 (w), 1663.6 (w), 1598.9 (w), 1477.4 (w), 1453.5 (w), 1418.4 (m), 1350.1 (m), 1208.1 (m), 1162.3 (m), 1138.1 (m), 1090.9 (m), 1026.3 (m), 734.8 (s); **HRMS** (+APCI) calculated for $C_{37}H_{36}F_3N_2O_6S_2$ 725.1967, found 725.1963 $[M+H]^+$; and thermodynamic enol triflate **359**

as an amorphous white solid (4.0 g, 26%); $\mathbf{R_f}$ 0.53 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) δ 7.72 (d, 2H, *J* = 8.1 Hz), 7.39 (d, 2H, *J* = 8.0 Hz), 7.36-7.29 (m, 6H), 7.20-7.18 (m, 3H), 7.15 (t, 1H, *J* = 7.8 Hz), 7.11-7.07 (m, 2H), 6.76 (t, 1H, *J* = 7.5 Hz), 6.64 (d, 1H, *J* = 7.8 Hz), 4.58 (d, 1H, *J* = 15.3 Hz), 4.49 (q, 2H, *J* = 9.3 Hz), 4.34 (d, 1H, *J* = 11.9 Hz), 4.29 (d, 1H, *J* = 15.3 Hz), 4.17 (dd, 1H, *J* = 11.9, 2.7 Hz), 4.08 (s, 1H), 3.57 (dt, 1H, *J* = 10.8, 7.2 Hz), 3.31 (t, 1H, *J* = 10.4 Hz), 3.14-3.08 (m, 2H), 2.87-2.83 (m, 1H), 2.47 (s, 3H), 1.21 (dd, 1H, *J* = 12.0, 7.1 Hz), 1.10 (q, 1H, *J* = 10.9 Hz); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) 149.0, 144.4, 144.2, 138.4, 137.4, 132.2, 130.7, 130.2, 129.9, 129.3, 128.7, 128.7, 128.6, 128.3, 128.1, 128.1, 127.7, 125.1, 119.4, 118.4 (q, 1C, *J* = 318.5 Hz), 111.1, 73.5, 65.0, 64.4, 59.8, 54.9, 52.8, 47.7, 35.6, 32.3, 21.8; **IR** (thin film, $cm^{-1}$) 3030.0 (w), 2926.5 (w), 2861.7 (w), 1599.2 (m), 1478.4 (m), 1453.4 (m), 1415.4 (m), 1353.8 (m), 1212.3 (s), 1164.7 (s), 1138.9 (s), 1092.7 (m), 1069.4 (m); **HRMS** (+APCI) calculated for $C_{37}H_{36}F_3N_2O_6S_2$ 725.1967, found 725.1967 $[M+H]^+$.

**Synthesis of diol 370:**

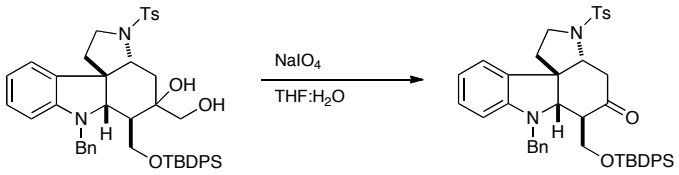



**341** **370**

A solution of osmium tetroxide (0.181 g, 0.714 mmol) in THF (1.0 mL) was added to a solution of tetracycle **341** (0.479 g, 0.649 mmol) and DMAP (0.174 g, 1.43 mmol) in THF (7.0 mL), and the resulting mixture was stirred for 4 hours. Methanol (10.0 mL) was added, and the solution was cooled to 0 °C. Sodium borohydride (0.491 g, 13.0 mmol) was added in portions, and the mixture was stirred at 0 °C for 10 minutes, warmed to

room temperature and stirred for 1.5 hours. The reaction was quenched by addition of $H_2O$ (10 mL) and EtOAc (30 mL). The resulting biphasic mixture was stirred vigorously for 15 minutes. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 x 30 mL). The organic extracts were combined, washed with brine (100 mL), dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (9:1 → 3:2 hexanes/EtOAc) afforded **370** as an amorphous white solid (0.34 g, 68%); $\mathbf{R_f}$ 0.44 (3:2 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) (1:1 mixture of diastereomers) δ 7.88 (d, 2H, *J* = 7.9 Hz), 7.80 (d, 2H, *J* = 8.0 Hz), 7.70-7.59 (m, 8H), 7.55 (d, 1H, *J* = 7.3 Hz), 7.54-7.33 (m, 17H), 7.16-7.02 (m, 8H), 6.85-6.77 (m, 6H), 6.46-6.40 (m, 2H), 4.04-3.84 (m, 8H), 3.82-3.70 (m, 4H), 3.60-3.42 (m, 8H), 3.31 (t, 1H, *J* = 10.5 Hz), 3.19 (t, 1H, *J* = 10.3 Hz), 3.05 (d, 1H, *J* = 9.0 Hz), 2.98 (dd, 1H, *J* = 12.6, 1.8 Hz), 2.92 (dd, 1H, *J* = 13.1, 2.5 Hz), 2.87 (d, 1H, *J* = 8.2 Hz), 2.58 (dd, 1H, *J* = 12.9, 2.5 Hz), 2.49-2.42 (m, 7H), 2.09-2.03 (m, 1H), 1.86 (t, 1H, *J* = 12.9 Hz), 1.83 (t, 1H, *J* = 12.6 Hz), 1.59 (dd, 1H, *J* = 11.1, 6.9 Hz), 1.50-1.46 (m, 1H), 1.26-1.18 (m, 1H), 1.05 (s, 9H), 1.03 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) (1:1 mixture of diastereomers) δ 149.2, 149.2, 143.8, 143.7, 138.2, 137.9, 135.8, 135.8, 135.7, 135.7, 133.4, 132.9, 132.3, 132.2, 132.1, 132.0, 131.8, 130.4, 130.3, 129.9, 129.8, 128.6, 128.5, 128.5, 128.4, 128.3, 128.2, 128.2, 128.2, 127.9, 127.4, 125.5, 125.3, 119.4, 119.3, 111.6, 110.4, 76.2, 74.2, 70.1, 66.8, 66.5, 66.0, 64.3, 63.6, 59.6, 58.8, 56.2, 56.2, 53.7, 52.7, 49.8, 49.6, 47.2, 46.7, 36.7, 36.5, 36.2, 34.0, 26.9, 26.9, 21.8, 21.7, 19.2, 19.1; **IR** (thin film, $cm^{-1}$) 3466.0 (br w), 2930.4 (w), 1599.5 (w), 1471.2 (w), 1332.9 (w), 1215.9 (w), 1160.6 (m), 1044.3 (m), 747.6 (s), 700.0 (s), 663.5 (s); **HRMS** (+ESI) calculated for $C_{46}H_{53}N_2O_5SSi$ 773.3444, found 773.3443 $[M+H]^+$.

**Synthesis of ketone 368:**

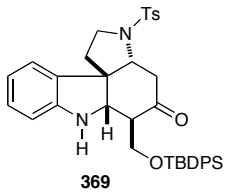



**370** **368**

Sodium periodate (0.187 g, 0.872 mmol) was added to a solution of diol **370** (0.169 g, 0.218 mmol) in THF:$H_2O$ (2:1, 4.4 mL), and the mixture was stirred for 18 hours. EtOAc (5 mL) was added, followed by saturated aqueous $NaHCO_3$/20% aqueous $Na_2SO_3$ (1:1, 10 mL). The resulting biphasic mixture was stirred vigorously for 15 minutes. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 x 10 mL). The organic extracts were combined, washed with brine (30 mL), dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (13:1 → 4:1 hexanes/EtOAc) afforded ketone **368** as an amorphous white solid (0.132 g, 81%); $\mathbf{R_f}$ 0.46 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) δ 7.64 (d, 2H, *J* = 8.2 Hz), 7.53-7.50 (m, 4H), 7.47-7.43 (m, 2H), 7.38-7.34 (m, 4H), 7.29-7.22 (m, 4H), 7.19-7.16 (m, 4H), 7.07-7.05 (dt, 1H, *J* = 7.8, 1.2 Hz), 6.71-6.69 (dt, 1H, *J* = 7.5, 1.2 Hz), 6.33 (d, 1H, *J* = 7.8 Hz), 4.38 (d, 1H, *J* = 15.3 Hz), 4.04 (d, 1H, *J* = 15.3 Hz), 3.71-3.63 (m, 3H), 3.58 (dd, 1H, *J* = 10.0, 6.4 Hz), 3.57-3.52 (m, 2H), 3.13 (dd, 1H, *J* = 18.6, 6.2 Hz), 2.85 (dd, 1H, *J* = 18.6, 12.2 Hz), 2.50 (t, 1H, *J* = 6.0 Hz), 2.40 (s, 3H), 1.96 (dd, 1H, *J* = 12.0, 6.8 Hz), 1.49-1.44 (q, 1H, *J* = 11.0 Hz), 0.96 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) δ 207.7, 150.1, 144.0, 137.6, 135.7, 135.7, 133.4, 133.1, 132.9, 130.2, 130.2, 130.1, 129.5, 128.8, 128.7, 128.1, 128.1, 127.8, 127.5, 127.5, 125.6, 118.8, 107.8, 67.5, 65.2, 57.9, 55.0, 53.7, 48.3, 48.0, 42.8, 36.1, 27.0, 21.8, 19.4; **IR** (thin film, $cm^{-1}$) 3050.0 (w), 2929.4 (w), 2856.8 (w), 1705.7 (m), 1599.5 (m), 1478.5 (m), 1350.9 (m), 1162.1 (s),

1092.0 (s), 700.6 (s), 732.7 (s), 665.1 (s); **HRMS** (+APCI) calculated for $C_{45}H_{49}N_2O_4SSi$ 741.3182, found 741.3184 $[M+H]^+$.

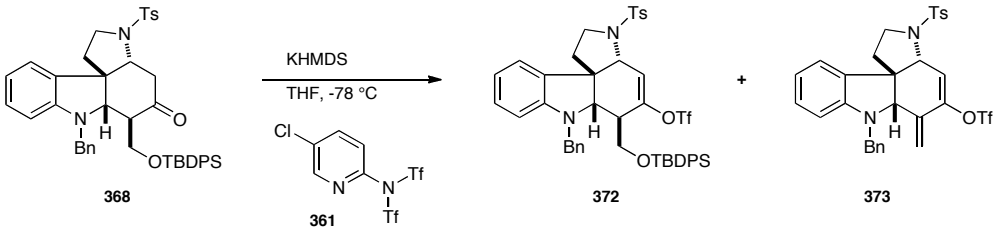
**Debenzylated ketone 369** was observed when the osmium mediated dihydroxylation of olefin **341** was carried out under catalytic conditions in the presence of stoichiometric $NaIO_4$ and 2,6-lutidine.




**369**

**$R_f$** 0.41 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) δ 7.71 (d, 2H, *J* = 8.1 Hz), 7.64 (d, 2H, *J* = 7.8, 0.6 Hz), 7.59 (d, 2H, *J* = 7.2, 0.6 Hz), 7.55 (d, 1H, *J* = 7.8 Hz), 7.47-7.44 (m, 2H), 7.41-7.37 (m, 4H), 7.34 (d, 2H, *J* = 8.2 Hz), 7.19-7.18 (t, 1H, *J* = 7.8 Hz), 6.88 (t, 1H, *J* = 7.5 Hz), 6.72 (d, 1H, *J* = 7.7 Hz), 4.76 (br s, 1H), 4.03 (dd, 1H, *J* = 10.6, 4.5 Hz), 3.83 (dd, 1H, *J* = 10.4, 9.2 Hz), 3.69 (dt, 1H, *J* = 10.9, 7.0 Hz), 3.55 (d, 1H, *J* = 6.3 Hz), 3.50 (t, 1H, *J* = 10.3 Hz), 3.22 (dd, 1H, *J* = 13.9, 3.9 Hz), 3.15 (dd, 1H, *J* = 13.6, 3.9 Hz), 2.93 (t, 1H, *J* = 13.7 Hz), 2.45 (s, 3H), 2.40-2.37 (m, 1H), 1.87 (dd, 1H, *J* = 12.0, 6.6 Hz), 1.54 (q, 1H, *J* = 11.0 Hz), 1.08 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) δ 206.6, 149.4, 144.2, 135.8, 135.7, 132.8, 132.7, 132.4, 130.3, 130.2, 130.2, 130.2, 129.3, 128.1, 128.1, 128.0, 125.6, 120.3, 112.1, 67.3, 64.2, 60.7, 55.9, 55.7, 48.1, 43.7, 35.3, 27.1, 21.8, 19.3; **IR** (thin film, $cm^{-1}$) 3368.0 (br, w), 3048.7 (w), 2929.3 (m), 2856.9 (w), 1710.1 (m), 1604.6 (w), 1464.5 (m), 1351.5 (m), 1164.4 (s), 1112.1 (s), 1091.3 (m), 1059.4 (m), 703.9 (s); **HRMS** (+ESI) calculated for $C_{38}H_{43}N_2O_4SSi$ 651.2713, found 651.2709 $[M+H]^+$.

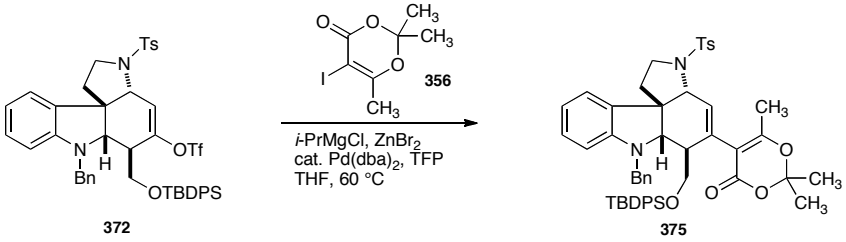
**Synthesis of kinetic enol triflate 372:**




A solution of ketone **368** (0.038 g, 0.051 mmol) in THF (0.45 mL) was added over 15 minutes to a solution of KHMDS (0.305 M in THF, 0.20 mL, 0.061 mmol) at -78 °C, and the resulting mixture was stirred for 30 minutes. A solution of triflating reagent **361** (0.028 g, 0.071 mmol) in THF (0.3 mL) was added over 5 minutes, and the resulting mixture was stirred at -78 °C for 5 hours. The reaction was quenched by addition of aqueous saturated $NaHCO_3$ (0.2 mL). $Et_2O$ (3 mL) was added and the crude reaction mixture washed with brine (2 x 1 mL), dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (9:1 hexanes/EtOAc,) afforded kinetic enol triflate **372** as an amorphous white solid (0.015 g, 33%); $\mathbf{R_f}$ 0.48 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) δ 7.63 (d, 2H, *J* = 8.2 Hz), 7.51 (d, 2H, *J* = 8.1, 1.5 Hz), 7.49 (dd, 2H, *J* = 8.0, 1.3 Hz), 7.46-7.42 (m, 2H), 7.38-7.32 (m, 4H), 7.30-7.22 (m, 6H), 7.14 (d, 2H, *J* = 7.8 Hz), 7.03 (dt, 1H, *J* = 7.7, 1.1 Hz), 6.70 (dt, 1H, *J* = 7.5, 0.8 Hz), 6.59 (d, 1H, *J* = 2.1 Hz), 6.31 (d, 1H, *J* = 7.8 Hz), 4.38 (d, 1H, *J* = 15.5 Hz), 4.10 (d, 1H, *J* = 15.6 Hz), 3.82 (s, 1H), 3.76 (dt, 1H, *J* = 10.8, 7.0 Hz), 3.63 (d, 1H, *J* = 1.3 Hz), 3.56 (dd, 1H, *J* = 10.2, 5.1 Hz), 3.48 (t, 1H, *J* = 10.2 Hz), 3.46-3.43 (d, 1H, *J* = 10.5, 6.3 Hz), 2.71 (t, 1H, *J* = 5.7 Hz), 2.38 (s, 3H), 2.00 (dd, 1H, *J* = 12.0, 6.6 Hz), 1.48 (q, 1H, *J* = 10.8 Hz), 0.94 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) δ 151.3, 150.1, 144.3, 137.8, 135.7, 135.6, 133.0, 132.7, 132.1, 131.0, 130.2, 130.2, 130.1, 128.8, 128.8, 128.3, 128.1, 128.1, 127.5, 127.4, 124.9, 121.1, 119.1, 118.5 (q, 1C, *J* = 320.3 Hz), 107.6; **IR**

(thin film, $cm^{-1}$) 2930.1, (w), 2857.9 (w), 1600.9 (w), 1477.0 (w), 1419.5 (w), 1350.3 (w), 1209.4 (m), 1164.4 (m), 1139.0 (m), 1110.5 (m), 733.8 (s), 700.5 (s), 608.2 (s); **HRMS** (+ESI) calculated for $C_{46}H_{47}F_3KN_2O_6S_2Si$ 911.2234, found 911.2236 $[M+K]^+$; and unsaturated kinetic enol triflate **373** as an amorphous white solid (5.3 mg, 17%); $\mathbf{R_f}$ 0.37 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) δ 7.72 (d, 2H, *J* = 7.8 Hz), 7.37 (d, 2H, *J* = 7.8 Hz), 7.35-7.24 (m, 6H), 7.06 (dd, 1H, *J* = 10.1, 5.3 Hz), 6.69 (t, 1H, *J* = 7.5 Hz), 6.47 (s, 1H), 6.37 (d, 1H, *J* = 8.0 Hz), 5.59 (s, 1H), 4.98 (s, 1H), 4.57 (d, 1H, *J* = 16.0 Hz), 4.03 (s, 1H), 3.99 (d, 1H, *J* = 15.9 Hz), 3.92 (dt, 1H, *J* = 10.8, 7.2 Hz), 3.57 (t, 1H, *J* = 10.8 Hz), 3.54 (d, 1H, *J* = 2.4 Hz), 2.45 (s, 3H), 2.18 (dd, 1H, *J* = 11.9, 6.8 Hz), 1.72 (q, 1H, *J* = 10.9 Hz); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) δ 150.3, 147.0, 144.6, 137.7, 133.4, 131.5, 130.5, 130.2, 129.1, 129.0, 128.4, 127.7, 127.5, 124.6, 121.3, 118.8, 118.6 (q, 1C, *J* = 319.8 Hz), 118.0, 107.0, 67.8, 61.5, 56.7, 48.6, 47.3, 34.5, 21.8; **HRMS** (+ESI) calculated for $C_{30}H_{28}F_3N_2O_5S$ 617.1392, found 617.1389 $[M+H]^+$.

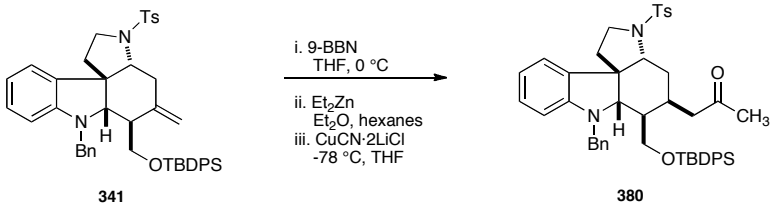
**Synthesis of coupling product 375:**




A solution of isopropyl magnesium chloride (0.028 mL, 0.056 mmol) was added over 5 minutes to a solution of **356** in THF (0.3 mL) at -30 °C, and the resulting mixture was stirred for 30 minutes. A solution of zinc bromide (0.012 mg, 0.054 mmol) in THF (0.5 mL) was added *via* cannula, and the resulting suspension was warmed to room temperature. A solution of kinetic enol triflate **372** (0.015 g, 0.017 mmol) in THF (0.2

mL) was added to a separate solution of $Pd(dba)_2$ (1.0 mg, 1.8 x $10^{-3}$ mmol) and TFP (1.0 mg, 4.3 x $10^{-3}$ mmol) in THF (0.2 mL), and this was immediately followed by addition of the zinc reagent solution *via* cannula. The resulting mixture was heated to 60°C for 1.5 hours, cooled to room temperature and quenched with brine (1.0 mL). The organic layer was separated, and the aqueous layer was extracted with ether (3 x 1.0 mL). The organic extracts were combined, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (9:1 hexanes/EtOAc) afforded compound **375** as an amorphous white solid (2.2 mg, 15%); $\mathbf{R_f}$ 0.19 (4:1 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) δ 7.65 (dd, 2H, *J* = 8.3, 1.8 Hz), 7.48 (dd, 2H, *J* = 8.0, 1.3 Hz), 7.43 (d, 2H, *J* = 7.8, 1.2 Hz), 7.41-7.38 (m, 1H), 7.36-7.33 (m, 1H), 7.30-7.17 (m, 10H), 7.16-7.13 (m, 2H), 6.91 (dt, 1H, *J* = 7.7, 1.2 Hz), 6.54 (dt, 1H, *J* = 7.4, 0.9 Hz), 6.32 (d, 1H, *J* = 2.7 Hz), 6.15 (d, 1H, *J* = 7.9 Hz), 4.36 (q, 2H, *J* = 17.1 Hz), 3.96 (dd, 1H, *J* = 10.4, 4.5 Hz), 3.79 (s, 1H), 3.78 (dt, 1H, *J* = 10.5, 7.2 Hz), 3.63 (d, 1H, *J* = 2.6 Hz), 3.35 (t, 1H, *J* = 10.2 Hz), 3.28 (t, 1H, *J* = 10.5 Hz), 2.76 (dd, 1H, *J* = 10.3, 4.4 Hz), 2.39 (s, 3H), 1.90 (dd, 1H, *J* = 12.0, 7.8 Hz), 1.61 (s, 3H), 1.60 (s, 3H), 1.35 (s, 3H), 1.14 (q, 1H, 10.8 Hz), 0.95 (s, 9H); **IR** (thin film, $cm^{-1}$) 2925.8 (m), 2855.2 (w), 1721.6 (s), 1601.6 (m), 1485.7 (m), 1389.7 (m), 1348.7 (s), 1269.4 (m), 1165.5 (s), 1110.7 (m), 1052.5 (m), 739.2 (m), 703.1 (m), 663.9 (m); **HRMS** (+ESI) calculated for $C_{52}H_{56}KN_2O_6SSi$ 903.3265, found 903.3259 $[M+K]^+$.

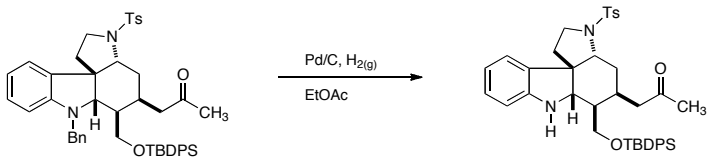
**Synthesis of ketone 380:**




A solution of tetracycle **341** (0.722 g, 0.977 mmol) in THF (5.1 mL) was cooled to 0 °C. 9-BBN (0.5 M in THF, 2.2 mL, 1.1 mmol) was added and the resulting solution was stirred at 0 °C for 42 hours. After removal of the volatiles *in vacuo* (0.1 mmHg, 25 °C, 1 hour), $Et_2O$ (5.5 mL) and $Et_2Zn$ (1 M in hexanes, 9.8 mL, 9.8 mmol) were added, and the resulting solution was stirred for 5 hours. The volatiles were removed *in vacuo* (0.1 mmHg, 25 °C, 1 hour), the grey-black residue was diluted with THF (6.9 mL), and the mixture was cooled to -78 °C. A freshly prepared solution of CuCN·2LiCl (1 M in THF, 9.8 mL, 9.8 mmol) was added over 30 minutes, and the mixture was stirred at -78 °C for 30 minutes. Acetyl chloride was added slowly over 30 minutes, and the resulting solution was warmed to -20 °C over 12 hours. The reaction was quenched with saturated aqueous $NH_4Cl$ (100 mL) containing aqueous $NH_3$ (1.5 mL, 30% in $H_2O$), and diluted with EtOAc (50 mL). The resulting biphasic mixture was stirred vigorously for 15 minutes. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 x 50.0 mL). The organic extracts were combined, washed with brine (150.0 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (9:1 hexanes/EtOAc) afforded ketone **380** as an amorphous white solid (0.443 g, 58%); $\mathbf{R_f}$ 0.50 (7:3 hexanes/EtOAc); $^1$**H NMR** ($CDCl_3$, 600 MHz) δ 7.61 (d, 2H, $J$ = 8.2 Hz), 7.56 (dd, 2H, $J$ = 8.0, 1.3 Hz), 7.49-7.44 (m, 3H), 7.40-7.36 (m, 3H), 7.30 (dd, 1H, $J$ = 7.3, 0.9 Hz), 7.27-7.19 (m, 7H), 7.13 (d, 2H, $J$ = 8.0 Hz), 7.02 (dt, 1H, $J$ = 7.7, 1.2 Hz),

6.57 (dt, 1H, *J* = 7.4, 0.7 Hz), 6.27 (d, 1H, *J* = 7.8 Hz), 4.50 (d, 1H, *J* = 16.3 Hz), 4.29 (d, 1H, *J* = 16.3 Hz), 3.67-3.61 (m, 2H), 3.37 (s, 1H), 3.29 (t, 1H, *J* = 10.4 Hz), 3.23 (dd, 1H, *J* = 10.5, 7.4 Hz), 2.95 (dd, 1H, *J* = 10.7, 7.7 Hz), 2.48-2.43 (m, 1H), 2.37 (s, 3H), 2.26-2.21 (m, 2H), 2.18-2.14 (m, 1H), 2.06-2.00 (m, 1H), 1.97 (s, 3H), 1.75-1.70 (m, 2H), 1.01 (q, 1H, *J* = 10.3 Hz), 0.97 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 207.3, 150.6, 143.8, 138.8, 135.6, 135.6, 133.4, 133.3, 132.4, 130.9, 130.1, 130.0, 129.9, 128.8, 128.7, 128.1, 128.0, 127.8, 127.1, 124.3, 116.7, 105.1, 69.0, 64.0, 59.3, 53.7, 47.7, 47.5, 43.5, 37.5, 30.5, 30.1, 30.1, 27.1, 21.7, 19.2; **IR** (thin film, $cm^{-1}$) 3049.8 (w), 2929.4 (w), 2856.7 (w), 1712.4 (m), 1599.5 (m), 1485.3 (m), 1347.5 (m), 1162.4 (s), 1104.8 (m), 1089.6 (m), 731.0 (s), 700.8 (s); **HRMS** (+ESI) calculated for $C_{48}H_{55}N_2O_4SSi$ 783.3652, found 783.3641 $[M+H]^+$.

**Synthesis of indoline 383:**

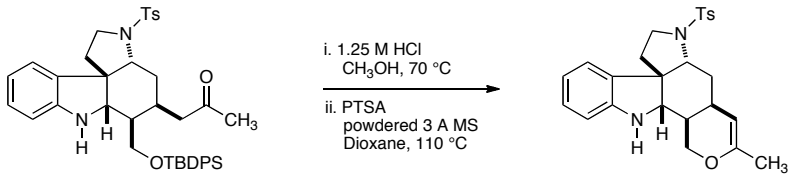



**380** **383**

Palladium on carbon (5% wt, 0.353 mg, 0.166 mmol) was added to a solution of ketone **380** (0.130 g, 0.166 mmol) in EtOAc (10.0 mL). The suspension was deoxygenated by argon sparge for 15 minutes. Subsequently hydrogen gas was bubbled through the mixture for 15 minutes. The suspension was stirred for 4 hours under a hydrogen atmosphere (1 atm). The suspension was filtered through celite, and the filter cake was washed with EtOAc (3 x 30 mL). The organic layer was concentrated *in vacuo*. Purification by chromatography on silica gel (17:3 → 4:1 hexanes/EtOAc) afforded

indoline **383** as an amorphous white solid (0.092 g, 80%); $\mathbf{R_f}$ 0.29 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) δ 7.74 (d, 2H, *J* = 8.2 Hz), 7.64-7.58 (m, 4H), 7.48-7.44 (m, 3H), 7.41-7.38 (m, 4H), 7.35 (d, 2H, *J* = 7.9 Hz), 7.11 (dt, 1H, *J* = 7.6, 1.2 Hz), 6.79 (dt, 1H, *J* = 7.5, 0.8 Hz), 6.64 (d, 1H, *J* = 7.7 Hz), 4.71 (br s, 1H), 3.62 (dd, 1H, *J* = 10.4, 4.9 Hz), 3.57 (dt, 1H, *J* = 10.8, 7.1 Hz), 3.50 (dd, 1H, *J* = 10.3, 8.5 Hz), 3.42 (t, 1H, *J* = 10.2 Hz), 3.33 (d, 1H, *J* = 7.6 Hz), 3.01 (dd, 1H, *J* = 12.5, 4.0 Hz), 2.46 (s, 3H), 2.45-2.40 (m, 1H), 2.27 (dd, 1H, *J* = 16.6, 6.0 Hz), 2.23 (dt, 1H, *J* = 13.5, 4.0 Hz), 2.17 (dd, 1H, *J* = 16.6, 8.4 Hz), 2.02 (s, 3H), 1.91 (dt, 1H, *J* = 12.9, 6.5 Hz), 1.80-1.75 (m, 2H), 1.50 (q, 1H, *J* = 10.8 Hz), 1.07 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) δ 206.9, 149.9, 143.9, 135.6, 135.6, 133.4, 132.9, 132.6, 131.1, 130.2, 130.2, 129.9, 128.4, 128.1, 128.1, 128.1, 125.3, 119.5, 111.2, 67.0, 66.8, 59.2, 55.7, 47.3, 44.6, 43.9, 36.0, 30.4, 30.4, 29.8, 27.1, 21.8, 19.2.

**Synthesis of pyran 377:**

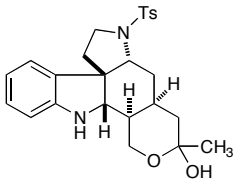



**383** **377**

A solution of indoline **383** (0.300 g, 0.433 mmol) in methanolic HCl (1.25 M, 12.0 mL) was heated at 70 °C for 16 hours. The mixture was cooled to room temperature and concentrated in *vacuo*. The crude mixture of acetals was dissolved in anhydrous dioxane (12.0 mL). PTSA (0.780 g, 0.453 mmol) was added, followed by activated powdered 3 Å molecular sieves (0.750 g). The flask was equipped with a reflux condenser and the suspension was heated at 110 °C for 2 hours. The mixture was cooled to reach room

temperature and diluted with aqueous saturated $NaHCO_3$ (12 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 x 12 mL). The organic extracts were combined, washed with brine (20 mL), dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (7:3 → 1:1 hexanes/EtOAc) afforded pyran **377** as an amorphous white solid (0.151 g, 80%); $\mathbf{R_f}$ 0.50 (1:1 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) δ 7.76 (d, 2H, *J* = 8.1 Hz), 7.47 (d, 1H, *J* = 7.4 Hz), 7.37 (d, 2H, *J* = 8.1 Hz), 7.09 (t, 1H, *J* = 7.6 Hz), 6.83 (t, 1H, *J* = 7.5 Hz), 6.71 (d, 1H, *J* = 7.8 Hz), 4.26 (s, 1H), 4.05-3.97 (m, 2H), 3.88 (dd, 1H, *J* = 11.2, 1.7 Hz), 3.54 (dt, 1H, *J* = 11.1, 6.9 Hz), 3.40 (t, 1H, *J* = 10.4 Hz), 3.33 (d, 1H, *J* = 8.3 Hz), 3.07 (dd, 1H, *J* = 12.6, 3.0 Hz), 2.67 (br s, 1H), 2.48 (s, 3H), 2.42 (dt, 1H, *J* = 12.9, 2.7 Hz), 1.99 (dt, 1H, *J* = 12.8, 4.5 Hz), 1.70 (s, 3H), 1.67 (dd, 1H, *J* = 11.8, 6.8 Hz), 1.47-1.40 (m, 2H); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) δ 152.0, 149.6, 143.9, 132.6, 131.2, 129.7, 128.2, 128.2, 125.6, 119.9, 111.7, 100.0, 67.3, 63.5, 58.7, 55.4, 47.5, 37.5, 35.8, 31.5, 30.8, 21.8, 20.0; **IR** (thin film, $cm^{-1}$) 3355.8 (w), 2923.1 (w), 2854.6 (w), 1675.5 (w), 1598.6 (w), 1462.0 (w), 1346.8 (w), 1327.1 (w), 1162.3 (s), 1091.3 (m); **HRMS** (+APCI) calculated for $C_{25}H_{29}N_2O_3S$ 437.1899, found 437.1895 $[M+H]^+$;

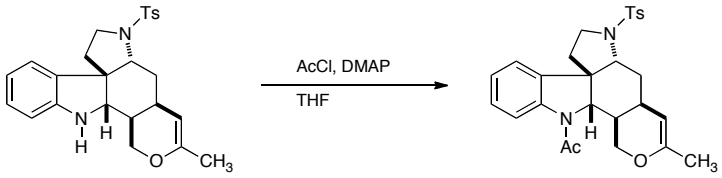
**Hemiacetal 384** was isolated in variable ratios upon treatment of compound **383** with 1.25 M HCl in methanol. Compound **384** was also subjected to PTSA and 3 Å podwered molecular sieves in refluxing dioxane to afford compound **377**.




**384**

**$R_f$** 0.27 (1:4 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) δ 7.74 (d, 2H, *J* = 7.9 Hz), 7.49 (d, 1H, *J* = 7.4 Hz), 7.38 (d, 2H, *J* = 7.9 Hz), 7.08 (t, 1H, *J* = 7.6 Hz), 6.81 (t, 1H, *J* = 7.4 Hz), 6.69 (d, 1H, *J* = 7.7 Hz), 4.05 (dd, 2H, *J* = 12.0, 2.4 Hz), 4.04 (br s, 1H), 3.57-3.50 (m, 2H), 3.46 (d, 1H, *J* = 9.4 Hz), 3.39 (t, 1H, *J* = 10.4 Hz), 3.06 (dd, 1H, *J* = 12.6, 2.4 Hz), 2.48 (s, 3H), 2.42 (d, 1H, *J* = 10.8 Hz), 2.31 (d, 1H, *J* = 13.3 Hz), 2.07 (br s, 1H), 2.00 (dt, 1H, *J* = 13.2, 4.4 Hz), 1.70 (dd, 1H, *J* = 11.7, 7.1 Hz), 1.57-1.50 (m, 2H), 1.45-1.40 (m, 4H), 1.26-1.24 (m, 1H); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) δ 149.1, 144.1, 132.8, 131.4, 129.9, 128.2, 128.1, 125.6, 119.9, 111.8, 95.9, 62.7, 61.4, 59.1, 55.9, 47.2, 38.0, 35.8, 35.7, 30.8, 30.5, 29.0, 21.8; **IR** (thin film, $cm^{-1}$) 3361.4 (br w), 3050.8 (w), 2933.0 (w), 1604.4 (w), 1461.6 (w), 1345.5 (w), 1329.8 (w), 1265.1 (w), 1159.9 (m), 1089.3 (m), 1031.8 (m), 731.2 (s), 701.6 (m), 665.7 (s), 606.8 (m); **HRMS** (+ESI) calculated for $C_{25}H_{31}N_2O_4S$ 455.2005, found 455.2001 $[M+H]^+$.

**Synthesis of acetamide 388:**

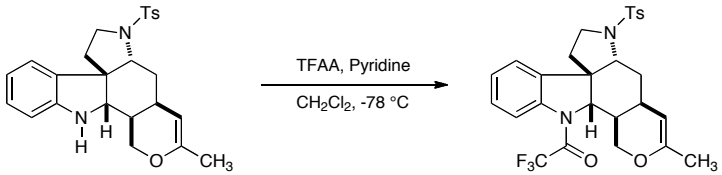



**377** **388**

Acetyl chloride (0.083 mL, 1.17 mmol) was added dropwise to a solution of pyran **377** (0.102 g, 0.233 mmol) and DMAP (0.130 g, 1.06 mmol) in THF (2.3 mL), and the resulting mixture was stirred for 1 hour. The reaction was quenched with saturated aqueous $NaHCO_3$ (3 mL). The resulting biphasic mixture was stirred vigorously for 15 minutes. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 x 3 mL). The organic extracts were combined, washed with brine (10 mL),

dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (3:2 → 1:1 hexanes/EtOAc) afforded acetamide **388** as an amorphous white solid (0.092 g, 82%); $\mathbf{R_f}$ 0.32 (3:7 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) (1:0.6 mixture of rotamers) δ 8.01 (d, 1H, *J* = 8.0 Hz), 7.78-7.73 (m, 3.2H), 7.63 (d, 0.6H, *J* = 7.4 Hz), 7.56 (d, 1H, *J* = 7.5 Hz), 7.43-7.36 (m, 3.2H), 7.29-7.26 (m, 1.6H), 7.16-7.10 (m, 2.2H), 4.71 (d, 0.6H, *J* = 8.5 Hz), 4.28 (s, 1H), 4.23-4.22 (m, 1.2H), 4.11 (dd, 1H, *J* = 11.5, 1.7 Hz), 4.03 (d, 1H, *J* = 8.6 Hz), 3.88 (d, 1H, *J* = 11.6 Hz), 3.77 (dd, 0.6H, *J* = 10.6, 1.5 Hz), 3.54-3.49 (m, 1.6H), 3.46-3.38 (m, 1.6H), 3.12 (dd, 1H, *J* = 12.7, 3.2 Hz), 3.07 (dd, 0.6H, *J* = 12.6, 2.9 Hz), 2.73 (br s, 1H), 2.66 (br s, 0.6H), 2.49 (s, 4.8H), 2.44 (dt, 1H, *J* = 13.2, 3.0 Hz), 2.41-2.35 (m, 2.4H), 2.29 (s, 3H), 1.99 (dt, 1H, *J* = 12.9, 4.5 Hz), 1.92 (dt, 0.6H, *J* = 12.9, 4.6 Hz), 1.78-1.71 (m, 1.6H), 1.67-1.59 (m, 3.2H), 1.53-1.43 (m, 3H); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) (1:0.6 mixture of rotamers) 168.6, 168.0, 153.1, 152.6, 144.3, 144.2, 141.5, 141.2, 136.7, 134.9, 132.5, 132.0, 129.9, 129.9, 128.5, 128.3, 128.2, 128.2, 126.3, 125.1, 125.0, 124.7, 120.2, 117.7, 99.8, 99.1, 67.4, 66.7, 65.7, 64.5, 58.6, 58.5, 54.9, 54.1, 47.1, 46.9, 37.1, 37.0, 35.8, 35.5, 32.2, 31.6, 30.2, 26.7, 23.4, 23.4, 21.8, 21.8, 20.2, 20.1; **IR** (thin film, $cm^{-1}$) 2922.2 (w), 1655.8 (s), 1597.6 (w), 1473.4 (m), 1461.7 (m), 1393.9 (m), 1349.9 (m), 1332.8 (w), 1163.1 (s), 1091.6 (m), 730.2 (m); **HRMS** (+APCI) calculated for $C_{27}H_{31}N_2O_4S$ 479.2005, found 479.1999 $[M+H]^+$.

**Synthesis of trifluoroacetamide 397:**

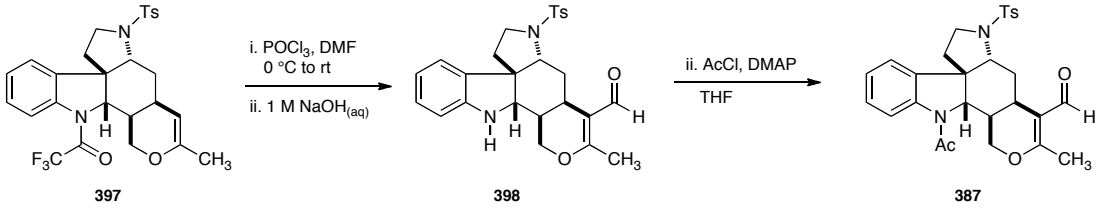



**377** **397**

A solution of pyran **377** (0.316 g, 0.724 mmol) in $CH_2Cl_2$ (7.0 mL) was cooled to -78 °C. Pyridine (0.18 mL, 2.17 mmol) was added, followed by dropwise addition of trifluoroacetic anhydride (0.11 mL, 0.80 mmol), and the resulting mixture was stirred at -78 °C for 30 minutes. The reaction was quenched with aqueous phosphate buffer (pH = 7.0, 10 mL). The resulting biphasic mixture was warmed to room temperature and stirred vigorously for 15 minutes. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 x 10 mL). The organic extracts were combined, washed with brine (20 mL), dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (17:3 hexanes/EtOAc) afforded trifluoroacetamide **397** as an amorphous white solid (0.367 g, 95%); $\mathbf{R_f}$ 0.50 (7:3 hexanes/EtOAc); **$^1$H NMR** ($CDCl_3$, 600 MHz) (1:0.3 mixture of rotamers) δ 7.95 (d, 1H, *J* = 7.9 Hz), 7.75 (d, 2.6H, *J* = 8.1 Hz), 7.67 (d, 1.3H, *J* = 7.3 Hz), 7.41-7.25 (m, 5.5H), 4.77 (d, 0.3H, *J* = 8.5 Hz), 4.37 (d, 1H, *J* = 8.1 Hz), 4.22 (s, 1.3H), 4.15 (d, 0.3 Hz, *J* = 10.8 Hz), 4.10 (d, 1H, *J* = 11.4 Hz), 3.84-3.81 (m, 1.3H), 3.52 (dt, 1.3 H, *J* = 10.8, 7.3 Hz), 3.47-3.38 (m, 1.3H), 3.13 (dd, 1H, *J* = 12.5, 3.1 Hz), 3.09 (d, 0.3H, *J* = 12.0 Hz), 2.77-2.68 (br s, 1.3H), 2.50 (, 3.9H), 2.44-2.42 (m, 1.3 H), 2.01 (dt, 1H, *J* = 12.9, 4.7 Hz), 1.95-1.88 (m, 0.3H), 1.77-1.70 (m, 3.9H), 1.68-1.48 (m, 3.9H); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) (1:0.3 mixture of rotamers) 154.7 (q, $^2J_{C\text{-}F}$ = 37.3 Hz, 1C), [153.1], 152.7, 144.4, 140.8, [138.5], [136.5], 135.5, 132.2, [131.8], 130.0, [129.9], 128.6, [128.2], 128.1, 127.0, [126.7], [126.1],

125.6, 121.1, [118.2], 116.2 (q, $^{1}J_{C\text{-}F}$ = 286.2 Hz, 1C), 99.0, [67.8], [67.1], 66.0, 66.0, [58.4], 58.2, 55.3, [53.8], [47.0], 46.7, 36.3, [36.1], [35.0], 34.8, 32.0, [31.7], 30.2, [29.9], 21.8, [20.1], 20.0; **IR** (thin film, $cm^{-1}$) 2922.7 (w), 2882.2 (w), 1690.6 (s), 1598.4 (w), 1475.0 (w), 1462.0 (w), 1428.6 (w), 1350.8 (w), 1331.8 (w), 1275.5 (w), 1207.0 (m), 1154.7 (s), 1091.7 (m); **HRMS** (+APCI) calculated for $C_{27}H_{28}F_3N_2O_4S$ 533.1722, found 533.1722 $[M+H]^+$.

**Synthesis of aldehyde 387:**

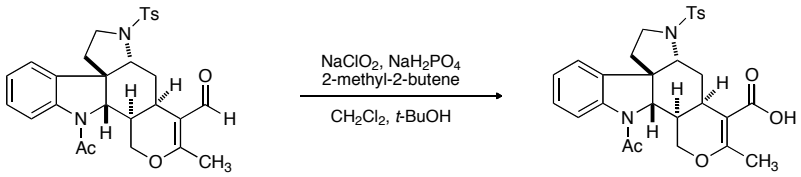



397 398 387

Phosphoryl chloride (0.38 mL, 4.13 mmol) was added dropwise to DMF (2.0 mL) at 0 °C, and the resulting mixture was stirred for 10 minutes. A solution of trifluoroacetamide **397** (0.366 g, 0.688 mmol) in DMF (4.0 mL) was added over 5 minutes to the Vilsmeier reagent solution, and the mixture was stirred at 0 °C for 30 minutes, warmed to room temperature and stirred for a further 30 minutes. The mixture was cooled to 0 °C and quenched with aqueous NaOH (3 M, 6 mL) warmed to room temperature and stirred for 1 hour. EtOAc (10 mL) was added, and the organic layer was separated. The aqueous layer was extracted with EtOAc (3 x 10 mL), and the organic extracts were combined, washed with $H_2O$ (2 x 40 mL), brine (40 mL), dried over $Na_2SO_4$, and concentrated *in vacuo*. The crude aldehyde **398** was dissolved in THF (7.0 mL). DMAP (0.092 g, 0.757 mmol) and acetyl chloride (0.25 mL, 0.35 mmol) were added, and the resulting suspension was stirred at room temperature for 1 hour. The

reaction was quenched with $H_2O$ (10 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 x 10 mL). The organic extracts were combined, washed with brine (30 mL), dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (1:1 → 1:9 hexanes/EtOAc) afforded aldehyde **387** as an amorphous white solid (0.250 g, 72%); **$^1$H NMR** ($CDCl_3$, 600 MHz) (1:0.4 mixture of rotamers) δ 9.81 (s, 0.4H), 9.79 (s, 1H), 8.05 (d, 0.4H, *J* = 8.0 Hz), 7.75-7.68 (m, 2.8H), 7.64 (d, 1H, *J* = 7.4 Hz), 7.54 (d, 0.4H, *J* = 7.4 Hz), 7.37 (d, 2.8H, *J* = 8.0 Hz), 7.30-7.27 (m, 1.4H), 7.18-7.07 (m, 2.4H), 4.50 (d, 1H, *J* = 5.0 Hz), 4.07-4.00 (m, 2.8H), 3.89 (d, 0.4H, *J* = 5.0 Hz), 3.60-3.51 (m1.4H), 3.48-3.44 (m, 1.4H), 3.05 (dd, 0.4H, *J* = 12.3, 4.9 Hz), 2.96 (dd, 1H, *J* = 12.3, 5.1 Hz), 2.89-2.70 (m, 1.8H), 2.66 (q, 1H, *J* = 5.7 Hz), 2.49 (d, 4.2H, *J* = 4.7 Hz), 2.39 (s, 3H), 2.26 (s, 1.2H), 2.24-2.19 (m, 4.2H), 2.16-2.07 (m, 1.4H), 1.91 (quintet, 0.4H, *J* = 5.1 Hz), 1.84 (quintet, 1H, *J* = 5.3 Hz), 1.74 (dd, 0.4H, *J* = 11.7, 6.7 Hz), 1.68 (dd, 1H, *J* = 12.0, 6.6 Hz), 1.60-1.49 (m, 1.4H); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) (1:0.6 mixture of rotamers) δ 188.5, 188.4, 171.8, 170.6, 168.2, 167.6, 144.0, 144.0, , 141.4, 140.6, 135.6, 133.7, 132.7, 132.5, 129.8, 129.7, 128.6, 128.5, 127.9, 127.9, 126.0, 124.9, 124.7, 124.6, 118.8, 117.0, 116.6, 116.1, 68.4, 67.9, 65.8, 64.4, 58.3, 57.9, 53.7, 52.5, 46.8, 46.7, 38.9, 38.0, 36.1, 35.8, 27.9, 27.7, 27.6, 27.4, 23.7, 23.5, 21.6, 21.6, 17.0, 16.9; **IR** (thin film, $cm^{-1}$) 2891.2 (w), 1649.1 (s), 1598.2 (m), 1475.9 (m), 1462.2 (w), 1392.4 (m), 1343.7 (m), 1161.6 (s), 906.0 (s); **HRMS** (+APCI) calculated for $C_{28}H_{31}N_2O_5S$ 507.1954, found 507.1942 $[M+H]^+$.

**Synthesis of acid 399:**

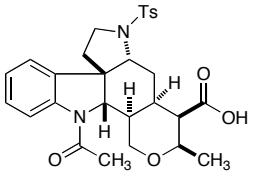



387 399

Aldehyde **387** (0.012 g, 0.024 mmol) was dissolved in a mixture of $CH_2Cl_2$ (0.20 mL) and *tert*-BuOH (0.80 mL). 2-Methyl-2-butene (0.45 mL) was added, and the resulting mixture was stirred for 5 minutes. A solution of $NaClO_2$ (0.080 g, 0.88 mmol) and $NaH_2PO_4$ (0.097 g, 0.70 mmol) in $H_2O$ (0.80 mL) was added, and the resulting mixture was stirred for 72 hour in the dark. The reaction was quenched with brine (2 mL). The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (3 x 1 mL). The organic extracts were combined, washed with brine (2 x 1 mL), dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (7:3 → 1:1 hexanes/EtOAc) afforded acid **399** as an amorphous white solid (6.9 mg, 55%); **$^1$H NMR** ($CDCl_3$, 600 MHz) (1:1.5 mixture of rotamers) δ $^1$H-NMR (600 MHz; $CDCl_3$): δ 8.06 (d, 1H, *J* = 8.0 Hz), 7.72-7.64 (m, 6.5H), 7.66 (d, 1H, *J* = 7.5 Hz), 7.41-7.34 (m, 5H), 7.31-7.28 (m, 2.5H), 7.16-7.13 (m, 4H), 4.53 (d, 1.5H, *J* = 4.9 Hz), 4.01-3.94 (m, 6H), 3.60-3.53 (m, 2.5H), 3.43-3.34 (m, 2.5H), 3.09-3.05 (m, 1H), 3.03 (dd, 1.5H, *J* = 12.3, 4.5 Hz), 2.83-2.80 (m, 2H), 2.72-2.66 (m, 3H), 2.47 (s, 4.5H), 2.45 (s, 3H), 2.41 (s, 4.5H), 2.27 (s, 3H), 2.25 (s, 4.5H), 2.24 (s, 3H), 2.21-2.15 (m, 2.5H), 1.95-1.90 (m, 1H), 1.90-1.84 (m, 1.5H), 1.71-1.62 (m, 2.5H), 1.52-1.45 (m, 2.5H); **$^{13}$C NMR** ($CDCl_3$, 150 MHz) (1:1.5 mixture of rotamers) δ 172.8, 172.5, 168.5, 168.5, 168.0, 167.5, 144.2, 144.2, 141.5, 140.9, 135.9, 134.1, 132.3, 132.0, 130.1, 130.1, 128.8, 128.7, 128.1, 128.1, 126.3, 125.2, 125.0, 124.8, 119.4, 116.3, 105.5, 105.0, 68.1, 67.5, 66.1, 64.9, 58.5, 58.4,

54.2, 52.8, 47.1, 46.9, 39.4, 38.8, 36.1, 36.0, 30.0, 29.1, 23.9, 23.6, 21.8, 21.8, 21.0, 20.7; **IR** (thin film, $cm^{-1}$) 2956.8 (s), 2925.1 (s), 1661.4 (s), 1477.1 (m), 1395.4 (m), 1597.2 (m), 1162.9 (s); **HRMS** (+APCI) calculated for $C_{28}H_{31}N_2O_4$ 523.1903, found 523.1891 $[M+H]^+$.

**Synthesis of Saturated Acid 401 (Tentative Structure):**

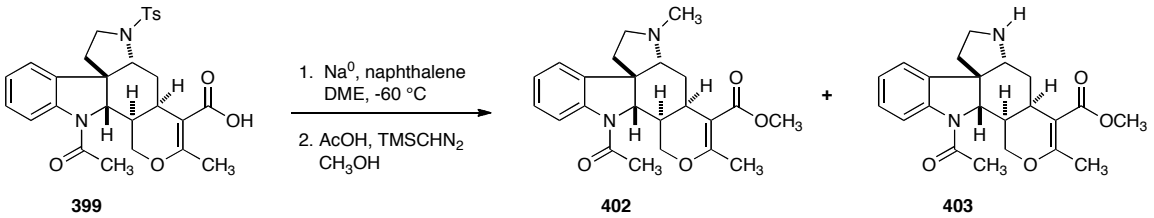



**401 (Tentative structure)**

Rhodium on silica (5% by weight, 28.0 mg, 0.014 mmol) was added to a solution of acid **399** (7.1 mg, 0.014 mmol) in EtOAc (1.5 mL). The mixture was subjected to an atmosphere of hydrogen gas (50 psi) for 24 hours using a Parr shaker hydrogenator. EtOAc (4 mL) was added and the mixture was stirred for 30 minutes. The suspension was filtered through celite, and the filter cake was washed with EtOAc (3 x 3 mL). The filtrate was concentrated *in vacuo*. Purification by chromatography on silica gel (7:3 → 1:1 hexanes/EtOAc) afforded compound **401** as an amorphous white solid (3.8 mg, 50%); $^1$H **NMR** ($CDCl_3$, 600 MHz) (1:1 mixture of rotamers) δ 8.13 (d, 1H, *J* = 8.0 H), 7.47- (d, 1H, *J* = 7.2 Hz), 7.37 (d, 1H, *J* = 7.4 Hz), 7.31 (t, 2H, *J* = 7.2Hz), 7.18 (d, 1H, *J* = 8.1 Hz), 7.16-7.11 (m, 2H), 4.65 (d, 1H, *J* = 3.6 Hz), 4.18 (dd, 1H, *J* = 10.5, 2.1 Hz), 4.11-4.07 (m, 2H), 4.02 (q, 2H, *J* = 9.5 Hz), 3.90 (q, 2H, *J* = 10.2 Hz), 3.84 (dd, 1H, *J* = 12.3, 5.4 Hz), 3.80 (dd, 1H, *J* = 12.2, 5.6 Hz), 3.49-3.42 (m, 2H), 2.99-2.94 (m, 2H), 2.70-2.67 (m, 1H), 2.59-2.56 (m, 1H), 2.47-2.41 (m, 4H), 2.41-2.34 (m, 4H), 2.20 (s, 6H), 2.12-

1.82 (m, 18H), 1.71-1.66 (m, 5H), 1.66-1.55 (m, 5H), 1.03-1.00 (m, 6H); **HRMS** (+ESI) calculated for $C_{28}H_{32}N_2NaO_6S$ 547.1879 $[M+Na]^+$, found 551.1879 $[M+4H+Na]^+$.

**Synthesis of amine 402:**

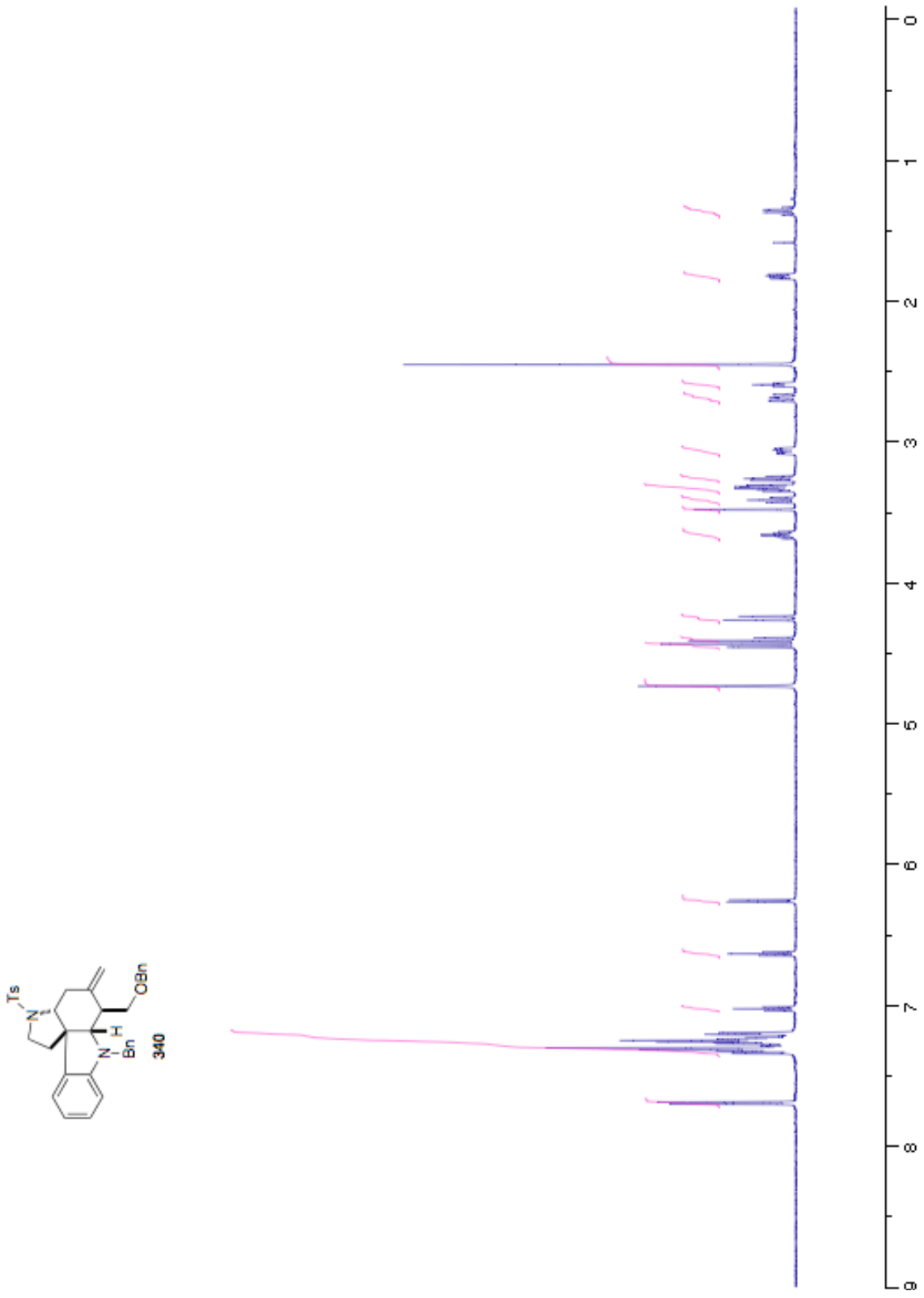



399 402 403

DME (4.4 mL) was added to a flask charged with naphthalene (0.728 g, 5.68 mmol) and sodium metal (0.106 g, 4.61 mmol). The resuling dark green mixture was stirred at r.t. for 1 h. In a separate flask, a solution of tosylamine **399** (0.014 g, 0.027 mmol) in DME (0.5 mL) was cooled to -60 °C. The sodium naphthalide solution (55 μL, 0.028 mmol) was added slowly by syringe until the clear starting material solution turned green. The reaction was quenched by addition of a solution of acetic acid/methanol (10:1, 0.3 mL). The resulting mixture was warmed to r.t. and concentrated *in vacuo*. The excess acetic acid was removed by repeated azotroping with toluene, and the crude reaction mixture was dissolved in methanol (0.45 mL). Excess $TMSCHN_2$ (2 M in $Et_2O$, 0.1 mL) was added and the mixture was stirred for 20 minutes. The reaction mixture was concentrated *in vacuo*. EtOAc (2.0 mL) was added, followed by aqueous saturated $NaHCO_3$, and the resulting biphasic mixture was stirred for 15 minutes. The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 x 1.0 mL). The organic extracts were combined, washed with brine (2.0 mL), dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo*. Purification by chromatography on silica gel (93:7 $CH_2Cl_2$/methanol) afforded amine **402** as a pale yellow oil (1.8 mg, 17%); **$^1$H NMR** ($CDCl_3$, 600 MHz) (1:1 mixture

of rotamers) δ 8.06 (d, 1H, *J* = 8.4 Hz), 7.80 (d, 1H, *J* = 7.2 Hz), 7.70 (d, 1H, *J* = 7.2 Hz), 7.25-7.20 (m, 2H), 7.10 (d, 1H, *J* = 7.8 Hz), 7.07-7.04 (m, 2H), 4.59 (d, 1H, *J* = 3.8 Hz), 4.17-4.15 (m, 1H), 4.09-4.02 (m, 4H), 3.67 (s, 3H), 3.66 (s, 3H), 3.28-3.23 (m, 2H), 2.76-2.72 (1H), 2.59-2.56 (m, 1H), 2.46-2.38 (m, 5H), 2.37-2.27 (m, 11H), 2.15 (s, 3H), 2.15 (s, 3H), 1.99-1.87 (m, 4H), 1.84-1.69 (m, 6H); **HRMS** (+ESI) calculated for $C_{23}H_{29}N_2O_4$ 397.2127, found 397.2120 $[M+H]^+$; and amine **403** as a pale yellow oil (1.5 mg, 15%); **$^1$H NMR** ($CDCl_3$, 600 MHz) (1:1 mixture of rotamers) δ 8.08 (d, 1H, *J* = 8.0 Hz), 7.62 (d, 1H, *J* = 7.5 Hz), 7.51 (d, 1H, *J* = 7.4 Hz), 7.25 (t, 2H, *J* = 7.8 Hz), 7.13 (d, 1H, *J* = 8.0 Hz), 7.08 (t, 2H, *J* = 7.5 Hz), 4.66 (d, 1H, *J* = 4.8 Hz), 4.11-4.01 (m, 5H), 3.68 (s, 3H), 3.64 (s, 3H), 3.29-3.20 (m, 4H), 3.14-3.09 (m, 2H), 2.80-2.78 (m, 1H), 2.67-2.64 (m, 1H), 2.44 (s, 3H), 2.35 (s, 3H), 2.18-2.13 (m, 6H), 2.00-1.76 (m, 10H); **HRMS** (+ESI) calculated for $C_{22}H_{27}N_2O_4$ 383.1971, found 383.1964 $[M+H]^+$.

## 3.6. NMR Spectra


Ts
N
N
H
Bn
OBn
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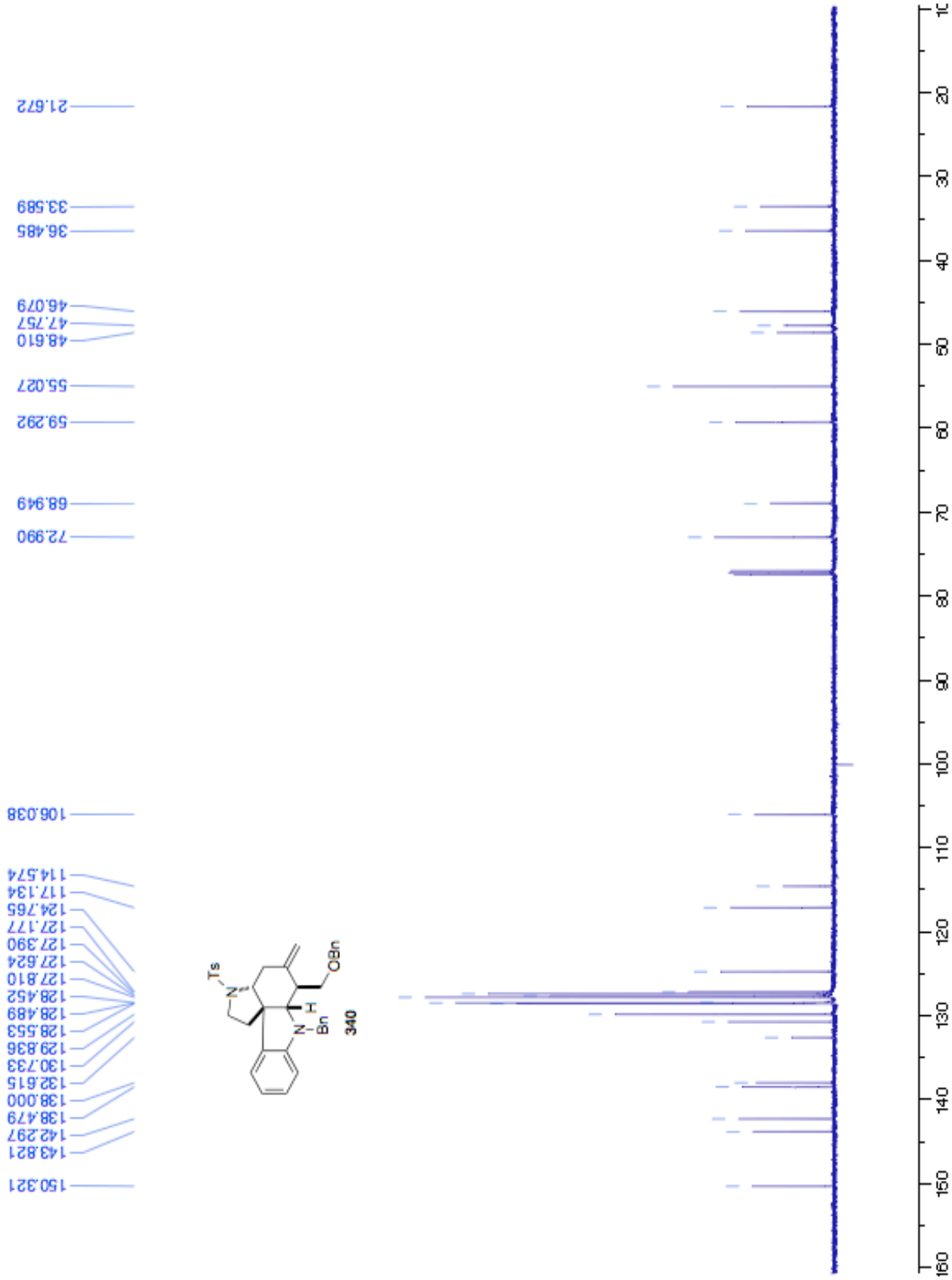
0
1
2
3
4
5
6
7
8
9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33.589
36.485
46.079
47.757
48.610
55.027
59.292
68.949
72.990
106.038
114.574
117.134
124.765
127.177
127.390
127.624
127.810
128.452
128.489
128.553
129.836
130.733
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138.000
138.479
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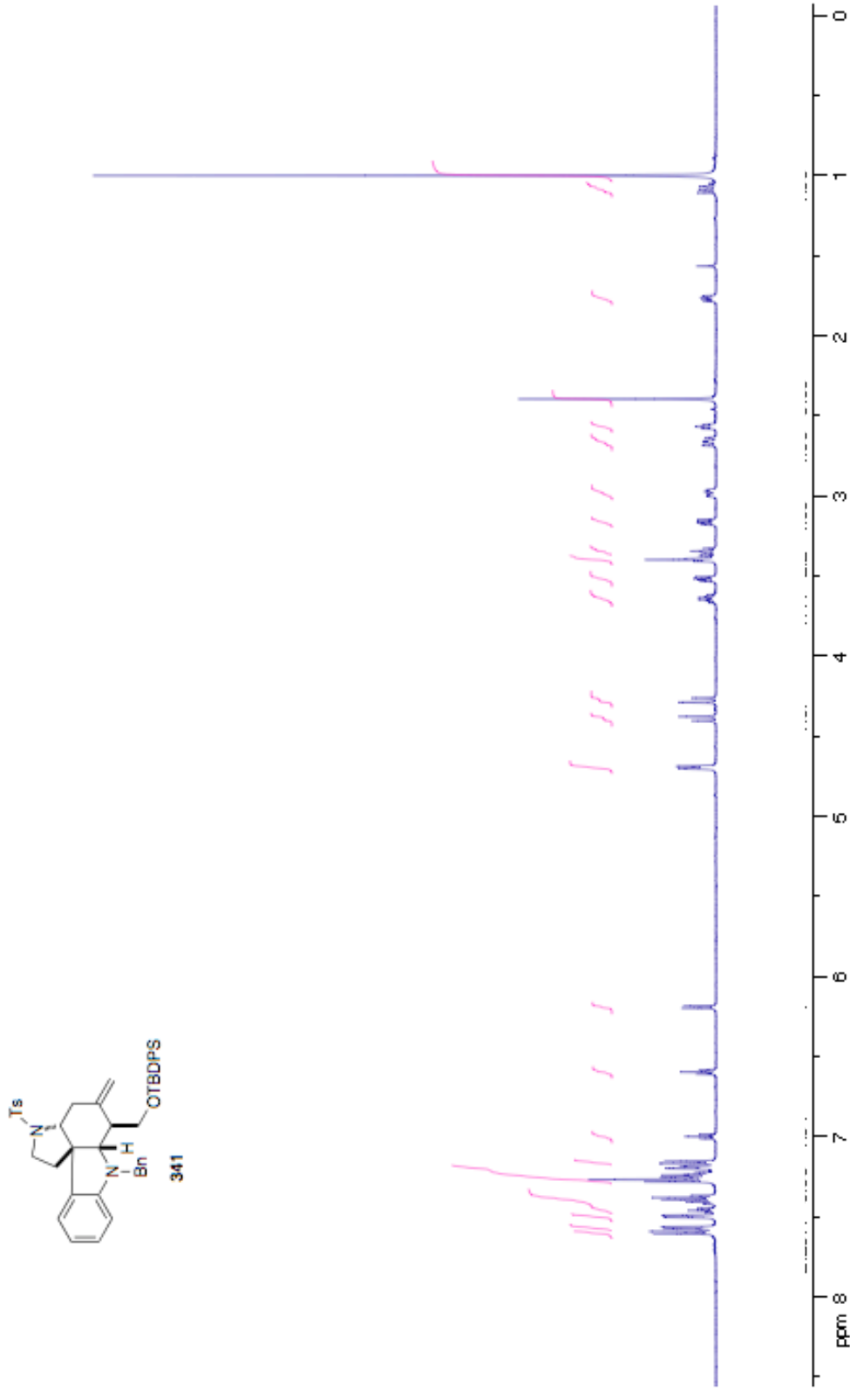
Ts
N
OBn
H
N
Bn
340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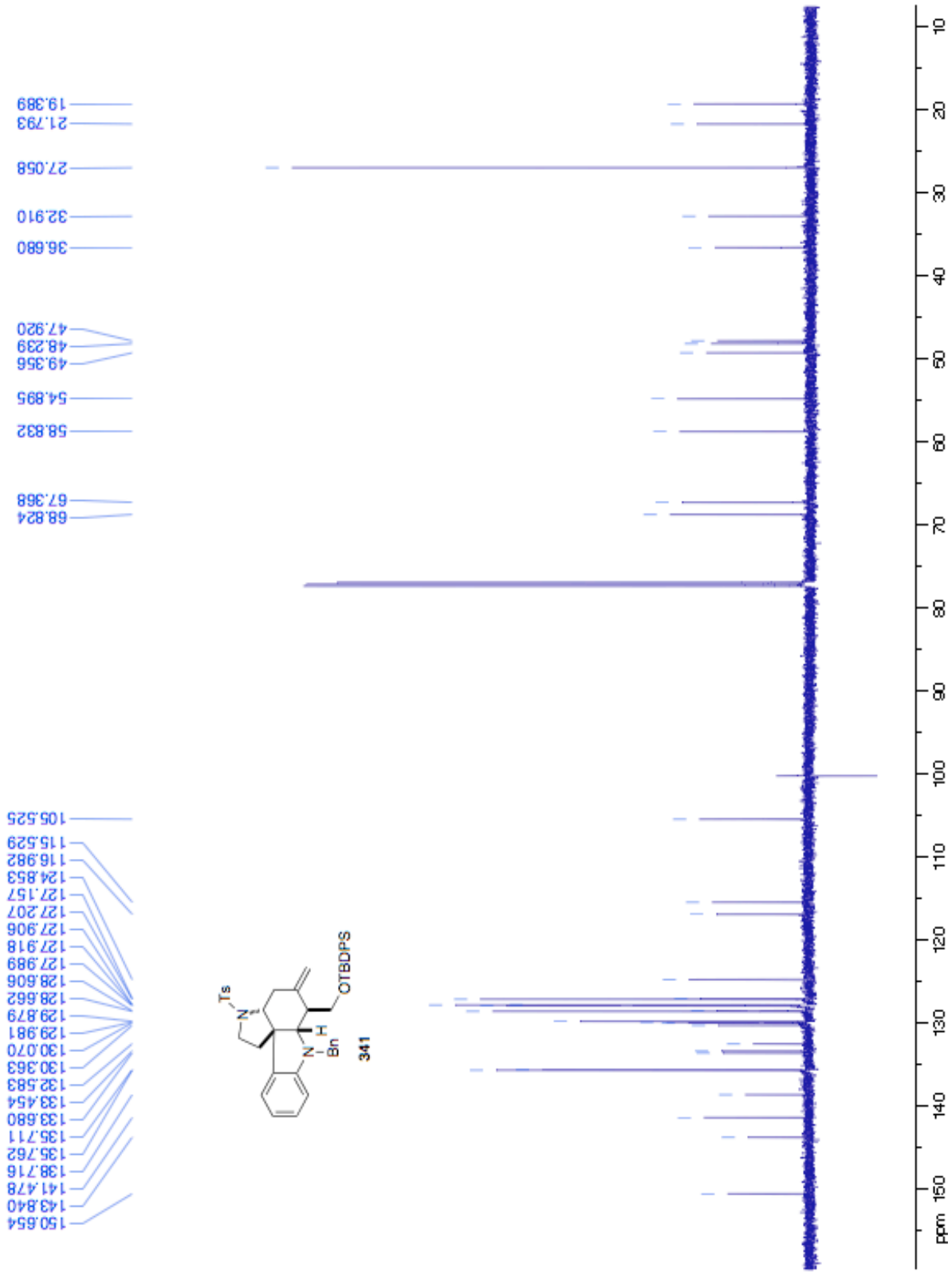
H
N
Bn
OTBDPS
341
ppm
0
1
2
3
4
5
6
7
8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27.058
32.910
36.680
47.920
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49.356
54.895
58.832
67.368
68.824
105.525
115.529
116.982
124.853
127.157
127.207
127.906
127.918
127.989
128.606
128.662
129.879
129.981
130.070
130.363
132.583
133.454
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141.478
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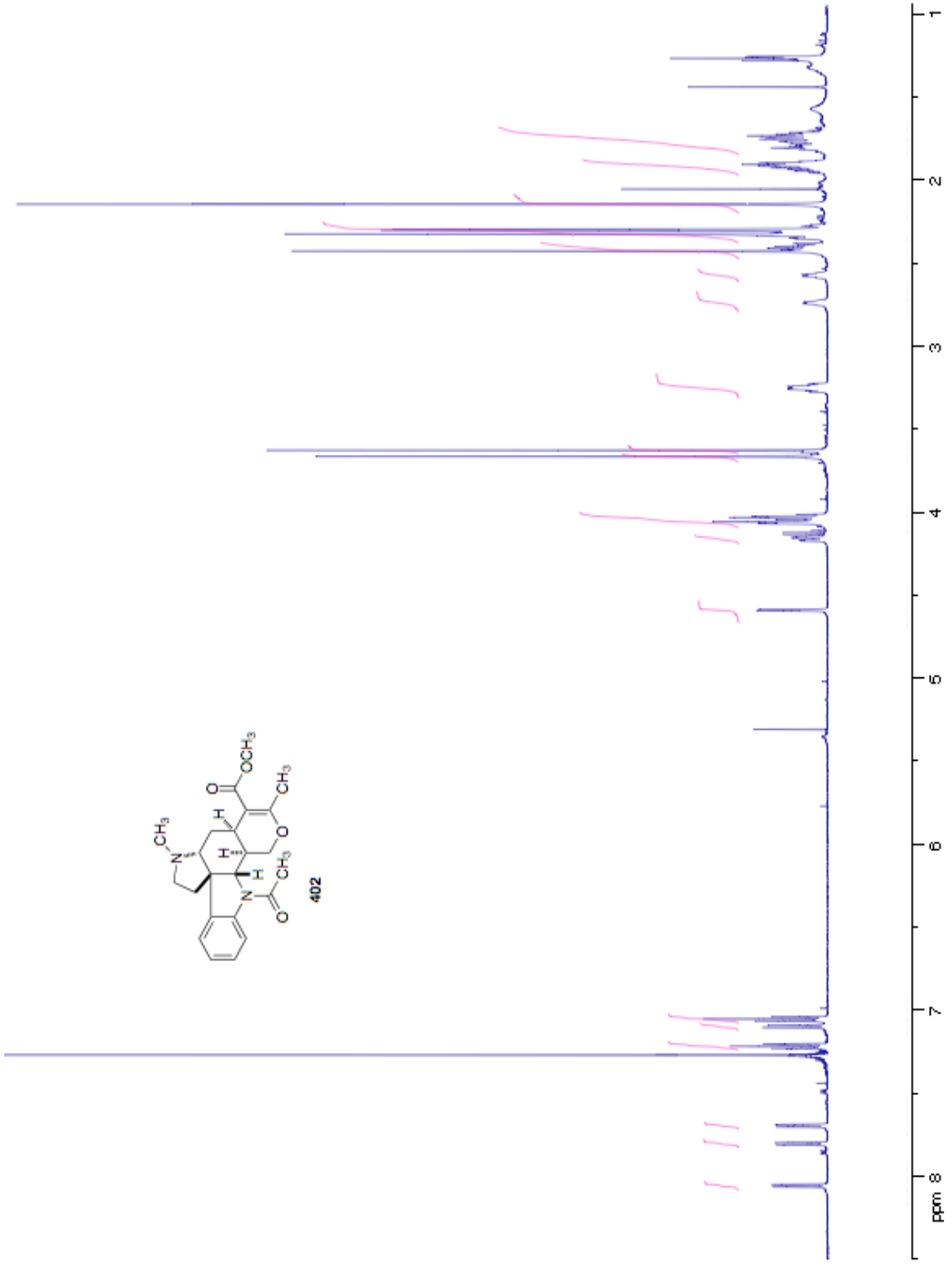
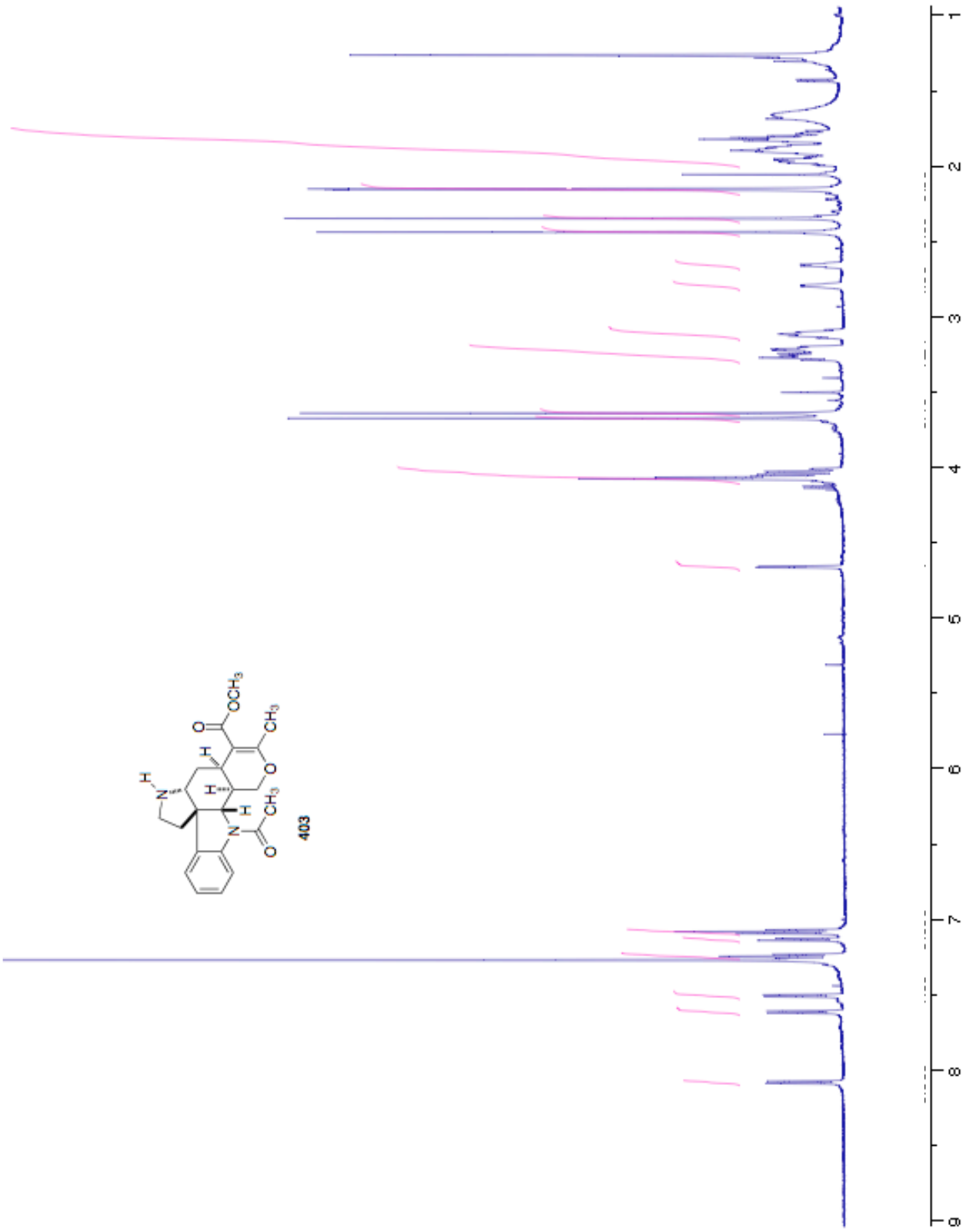
150.654
Ts
N
H
N
Bn
OTBDPS
341
ppm


ppm 8
7
6
5
4
3
2
1
402


403

# 4. References


1. Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schenker, K. *J. Am. Chem. Soc.* **1954,** *76*, 47449.
2. Josef, H. *Collect. Czech. Chem. Comm.* **2004,** *69*, 1681.
3. (a) Saxton, J. E., 1.1 Alkaloids of the Aspodospermine Group. In *The Alkaloids*, Cordell, G. A., Ed. Academic Press: San Diego, 1988; Vol. 51; (b) Saxton, J. E., 1.1 Synthesis of the Aspidosperma Alkaloids. In *The Alkaloids: Chemistry and Biology*, Cordell, G. A., Ed. Academic Press: San Diego, 1998; Vol. 50.
4. Rahman, A.-u.-. *Studies in Natural Product Chemistry*. series editor, eds:ELSEVIER SCIENCE B.V.: Amsterdam, 2002; Vol. 26.
5. (a) Rasonaivo, P.; Galeffi, G.; de Vicente, Y.; Nicoletti, M. *Rev. Latinoamer. Quim.* **1991,** *22*, 32; (b) Ramanitrahasimbola, D.; Rasoanaivo, P.; Ratsimamanga, S.; Vial, H. *Molecular and Biochemical parasitology* **2006,** *146*, 58; (c) Rasoanaivo, P.; Ratsimamanga-Urverg, S.; Milijaona, R.; Rafatro, H.; Rakoto-Ratsimamanga, A.; Galeffi, C.; Nicoletti, M. *Planta Med.* **1994,** *60*, 13.
6. Rasoanaivo, P.; Palazzino, G.; Nicoletti, M.; Galeffi, C. *Phytochemistry* **2001,** *56*, 863.
7. Martin, M.-T.; Rasoanaivo, P.; Palazzino, G.; Galeffi, C.; Nicoletti, M.; Trigalo, F.; Frappier, F. *Phytochemistry* **1999,** *51*, 479.
8. Caira, M. R.; Rasoanaivo, P. *Journal of Chemical Crystallography* **1995,** *25*, 725.
9. World Health Organization, World Malaria Report **2009**.
10. Henry, M.; Alibert, S.; Orlandi-Pradines, E.; Bogreau, H.; Fusai, T.; Rogier, C.; Barbe, J.; Pradines, B. *Current Drug Targets* **2006,** *7*, 935.
11. Hayeshi, R.; Masimirembwa, C.; Mukanganyama, S.; Ungell, A.-L. B. *European Journal of Pharmaceutical Sciences* **2006,** *29*, 70.
12. (a) Howard, E. M.; Zhang, H.; Roepe, P. D. *Membrane Biology* **2002,** *190*, 1; (b) Zhang, H.; Paguio, M.; Roepe, P. D. *Biochemistry* **2004,** *43*, 8290.
13. Trigalo, F.; Joyeau, R.; Pham, V. C.; Youte, J. J.; Rasoanaivoa, P.; Frappier, F. *Tetrahedron* **2004**, 5471.
14. Harley-Mason, J.; Waterfield, W. R. *Chemistry and Industry* **1960**, 1477.
15. van Tamelen, E. E.; Dolby, L. J.; Lawton, R. G. *Tetrahedron Lett.* **1960,** *19*, 30.
16. Büchi, G.; Matsumoto, K. E.; Nishimura, H. *J. Am. Chem. Soc.* **1971,** *93*, 3299.
17. Ando, M.; Büchi, G.; Ohnuma, T. *J. Am. Chem. Soc.* **1975,** *97*, 6880.
18. Turet, L.; Markó, I. E.; Tinant, B.; Declercq, J.-P.; Touillaux, R. *Tetrahedron Lett.* **2002,** *43*, 6591.
19. Heurex, N.; Wouters, J.; Marko, I. E. *Organic Letters* **2005,** *7*, 5245.
20. He, F.; Bo, Y.; Altom, J. D.; Corey, E. J. *J. Am. Chem. Soc.* **1999,** *121*.
21. Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004,** *126*, 10558.
22. (a) Akiyama, T.; Morita, H.; Fuchibe, K. *J. Am. Chem. Soc.* **2006,** *128*, 13070; (b) Akiyama, T.; Morita, H.; Itoh, J.; Fuchibe, K. *Org. Lett.* **2005,** *7*, 2583; (c) Itoh, J.; Fuchibe, K.; Akiyama, T. *Angew. Chem. Int. Ed.* **2006,** *45*, 4796.
23. (a) Lee, T. V.; Richardson, K. A.; Taylor, D. A. *Tetrahedron Letters* **1986,** *27*, 5021; (b) Lee, T. V.; Boucher, R. J.; Porter, J. R.; Taylor, D. A. *Tetrahedron* **1988,** *44*, 4233; (c) Lee, T. V.; Boucher, R. J.; Rockell, C. J. M. *Tetrahedron Lett.* **1988,** *29*, 689.

24. Itoh, K.; Yogo, T.; Ishii, Y. *Chem. Lett.* **1977**, 103.
25. Ni, Z.-J.; Luh, T.-Y. *Organic Syntheses* **1998,** *Coll. Vol. 9*, 727.
26. Guziec, F. S.; Luzzio, F. A. *Synthesis* **1980**, 691.
27. Hu, T.; Panek, J. S. *J. Org. Chem.* **1999,** *64*, 3000.
28. Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994,** *35*, 8019.
29. Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983,** *48*, 4155.
30. (a) Lee, T. V.; Channon, J. A.; Cregg, C.; Porter, J. R.; Roden, F. S.; Yeoh, H. T.-L. *Tetrahedron* **1989,** *45*, 5877; (b) Lee, T. V.; Porter, J. R.; Roden, F. S. *Tetrahedron Lett.* **1988,** *29*, 5009; (c) Mickelson, T. J.; Koviach, J. L.; Forsyth, C. J. *J. Org. Chem.* **1996,** *61*, 9617; (d) Narayanan, B. A.; Bunnelle, W. H. *Tetrahedron Lett.* **1987,** *28*, 6261.
31. (a) Kiyooka, S.-i.; Shirouchi, M. *J. Org. Chem.* **1992,** *57*, 1; (b) Kiyooka, S.-i.; Shirouchi, M.; Kaneko, Y. *Tetrahedron Lett.* **1993,** *34*, 1491; (c) Kiyooka, S.-i.; Suzuki, K.; Shirouchi, M.; Kaneko, Y.; Tanimori, S. *Tetrahedron Lett.* **1993,** *34*, 5729; (d) Kopecky, D. J.; Rychnovsky, S. D. *J. Org. Chem.* **2000,** *65*, 191; (e) Kopecky, D. J.; Rychnovsky, S. D. *Organic Syntheses* **2003,** *80*, 177.
32. (a) Jung, J.-W.; Shin, D.-Y.; Seo, S.-Y.; Kim, S.-H.; Paek, S.-M.; Jung, J.-K.; Suh, Y.-G. *Tetrahedron Lett.* **2005,** *46*, 573; (b) Suh, Y.-G.; Kim, S.-H.; Jung, J.-K.; Shin, D.-Y. *Tetrahedron Lett.* **2002,** *43*, 3165; (c) Suh, Y.-G.; Shin, D.-Y.; Jung, J.-K.; Kim, S.-H. *Chem. Comm.* **2002**, 1064.
33. Terada, M.; Machioka, K.; Sorimachi, K. *Angew. Chem. Int. Ed.* **2006,** *45*, 2254.
34. Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2004,** *126*, 11804.
35. Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004,** *126*, 5356.
36. (a) Klausen, R. S.; Jacobsen, E. N. *Org. Lett.* **2009,** *11*, 887; (b) Menche, D.; Hassfeld, J.; Li, J.; Menche, G.; Ritter, A.; Rudolph, S. *Org. Lett.* **2006,** *8*, 741; (c) Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007,** *129*, 13404; (d) Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002,** *124*, 10012.
37. Danheiser, R. L.; Miller, R. F.; Brisbois, R. G. *Organic Syntheses* **1998,** *Coll. Vol. 9*, 197.
38. (a) Amat, M.; Lozano, O.; Escolano, C.; Molins, E.; Bosch, J. *J. Org. Chem.* **2007,** *72*, 4431; (b) Amat, M.; Santos, M. M. M.; Gómez, A. M.; Jokic, D.; Molins, E.; Bosch, J. *Org. Lett.* **2007**, 2907.
39. Yong Qin, H. S., Ju Yang, Wei Chen *Org. Lett.* **2006,** *8*, 6011.
40. (a) Sole, N.; Torres, J. L.; Anton, J. M. G.; Valencia, G.; Reig, F. *Tetrahedron* **1986,** *42*, 193; (b) Carpino, L. A.; El-Faham, A. *J. Org. Chem.* **1995,** *60*, 3561; (c) König, W.; Geiger, R. *Chem. Ber.* **1970,** *103*, 788; (d) Mahmoud, K. A.; Long, Y.-T.; Schatte, G.; Kraazt, H.-B. *Eur. J. Inorg. Chem.* **2005**, 173.
41. (a) Dong, Q.; Anderson, C. E.; Cuifolini, M. A. *Tetrahedron Lett.* **1995,** *36*, 5681; (b) Eckert, H.; listl, M.; Ugi, I. *Angew. Chem. Int. Ed. Engl* **1978,** *17*, 361.
42. Ryoichi Kuwano, M. K., Koji Sato, Takashi Ito, Kohei Kaneda, Yoshihiko Ito *Tetrahedron: Asymmetry* **2006,** *17*, 521.
43. Nakashima, D.; Yamamoto, H. *Journal of the American Chemical Society* **2006,** *128*, 9626.
44. Kiso, Y.; Inai, M.; Kitagawa, K.; Akita, T. *Chem. Lett.* **1983**, 739.
45. Tanner, D.; Somfai, P. *Tetrahedron* **1988,** *44*, 613.
46. (a) Shelkov, R.; Nahmany, M.; Melman, A. *J. Org. Chem.* **2002,** *67*, 8975; (b) Shelkov, R.; Nahmany, M.; Melman, A. *Org. Biomol. Chem.* **2004,** *2*, 397.

47. (a) Dobarro, A.; Velasco, D. *Tetrahedron* **1996,** *52*, 13733; (b) Hintermann, T.; Seebach, D. *Helv. Chim. Acta* **1998,** *81*, 2093.
48. Sames, D.; Liu, Y.; DeYoung, L.; Polt, R. *J. Org. Chem.* **1995,** *60*, 2153.
49. (a) Heathcock, C. H.; Blumenkopf, T. A.; Smith, K. M. *J. Org. Chem.* **1989,** *54*, 1548; (b) Ji, S.; Gortler, L. B.; Waring, A.; Battisti, A.; Bank, S.; Closson, W. D.; Wriede, P. *J. Am. Chem. Soc.* **1967,** *89*, 5311; (c) Katoh, T.; Itoh, E.; Yoshino, T.; Terashima, S. *Tetrahedron Lett.* **1966,** *37*, 3471; (d) McIntosh, J. M.; Matassa, L. C. *J. Org. Chem.* **1988,** *53*, 4452.
50. Rose, M. D.; Cassidy, M. P.; Rashatasakhon, P.; Padwa, A. *J. Org. Chem.* **2007,** *72*, 538.
51. (a) Cardillo, G.; Gentilucci, L.; Gianotti, M.; Perciaccante, R.; Tolomelli, A. *J. Org. Chem.* **2001,** *66*, 8657; (b) Danilin, A. A.; Purygin, P. P.; Makarova, N. V.; Zemtsova, M. N.; Moiseev, I. K. *Russian J. Org. Chem.* **2001,** *37*, 56; (c) Hellou, J.; Bérubé, G.; Newlands, M. J.; Fallis, A. G.; Gabe, E. J. *Can. J. Chem.* **1988,** *66*, 439; (d) Lehnert, W. *Tetrahedron Lett.* **1970,** *54*, 4723; (e) Lehnert, W. *Tetrahedron* **1973,** *29*, 635; (f) Mangelinckx, S.; Vermaut, B.; Verhé, R.; Kimpe, N. D. *Synlett* **2008,** *17*, 2697; (g) Renzetti, A.; Dardennes, E.; Fontana, A.; Maria, P. D.; Sapi, J.; Gérard, S. *J. Org. Chem.* **2008,** *73*; (h) Zhu, Q.; Qiao, L.; Wu, Y.; Wu, Y.-L. *J. Org. Chem.* **2001,** *66*, 2692.
52. Delgado, R.; Blakey, S. B. *Eur. J. Org. Chem.* **2009**, 1506.
53. (a) Baxter, J.; Mata, E. G.; Thomas, E. J. *Tetrahedron* **1998,** *54*, 14359; (b) Piers, E.; Chong, J. M.; Morton, H. E. *Tetrahedron Lett.* **1989,** *45*, 363.
54. Inokuchi, E.; Narumi, T.; Niida, A.; Kobayashi, K.; Tomita, K.; Oishi, S.; Ohno, H.; Fujii, N. *J. Org. Chem.* **2008,** *73*, 3942.
55. (a) Bal, B. S.; Childers, W. E.; Pinnick, H. W. *Tetrahedron Lett.* **1981,** *37*, 2091; (b) Dalcanale, E.; Montanari, F. *J. Org. Chem.* **1986,** *51*, 567.
56. Duchêne, A.; Abarbri, M.; Parrain, J.-L.; Kitamura, M.; Noyori, R. *Synlett* **1994**, 524.
57. Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983,** *24*, 391.
58. (a) Liu, X.; Ready, J. M. *Tetrahedron* **2008,** *64*, 6955; (b) Zhang, D.; Ready, J. M. *J. Am. Chem. Soc.* **2007,** *129*, 12088.
59. (a) Magnus, P.; Giles, M.; Bonnert, R.; Kim, C. S.; McQuire, L.; Merritt, A.; Vicker, N. *J. Am. Chem. Soc.* **1992,** *114*, 4403; (b) Magnus, P.; Katoh, T.; Matthews, I. R.; Huffman, J. C. *J. Am. Chem. Soc.* **1989,** *111*, 6707; (c) Magnus, P.; Mendoza, J. S.; Stamford, A.; Ladlow, M.; Willis, P. *J. Am. Chem. Soc.* **1992,** *114*.
60. (a) Goti, A.; Romani, M. *Tetrahedron Lett.* **1994,** *35*, 6567; (b) Maruyama, K.; Kusukawa, T.; Huguchi, Y.; Nishinaga, A. *Chem. Lett.* **1991**, 1093; (c) Yamaguchi, J.-i.; Takeda, T. *Chem. Lett.* **1992**, 1933.
61. Dounay, A. B.; Humphreys, P. G.; Overman, L. E.; Wrobleski, A. D. *J. Am. Chem. Soc.* **2008,** *130*, 5368.
62. McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983,** *24*.
63. (a) Zorn, N.; Lett, R. *Tetrahedron Lett.* **2006,** *47*, 4331; (b) Bunlaksananusorn, T.; Knochel, P. *J. Org. Chem.* **2004,** *69*, 4595.
64. (a) d'Angelo, J. *Tetrahedron* **1976,** *32*, 2979; (b) Xie, L.; Isenberger, K. M.; Held, G.; Dahl, L. M. *J. Org. Chem.* **1997,** *62*, 7526.
65. (a) Iwaoka, T.; Murohashi, T.; Katagiri, N.; Sato, M.; Kaneko, C. *J. Chem. Soc. Perkin Trans. 1* **1992**, 1393; (b) Thibonnet, J.; Vu, V. A.; Bérillon, L.; Knochel, P.

*Tetrahedron* **2002,** *58*, 4787; (c) Vu, V. A.; Bérillon, L.; Knochel, P. *Tetrahedron Lett.* **2001,** *42*, 6847; (d) Wang, X.-j.; Sun, X.; Zhang, L.; Xu, Y.; Krishnamurthy, D.; Senanayake, C. H. *Org. Lett* **2006,** *8*, 305.
66. (a) Hupe, E.; Calaza, M. I.; Knochel, P. *Tetrahedron Lett.* **2001,** *42*, 8829; (b) Hupe, E.; Calaza, M. I.; Knochel, P. *Chem. Eur. J.* **2003,** *9*, 2789.
67. Peterli-Roth, P.; Maguire, M. P.; León, E.; Rapoport, H. *J. Org. Chem.* **1994,** *59*, 4186.
68. Ramesh, N. G.; Balasubramanian, K. K. *Tetrahedron Lett.* **1991,** *31*, 3875.
69. Samuel, A. P. S.; Xu, J.; Raymond, K. N. *Inorg. Chem.* **2009,** *48*, 687.
70. Sharma, G. V. M.; Ilangovan, A.; Lavanya, B. *Synth. Comm.* **2000,** *30*, 397.
71. Corey, E. J.; Gilman, N. W.; Ganem, B. E. *J. Am. Chem. Soc.* **1968,** *90*, 5616.
72. Harding, K. E.; May, L. M.; Dick, K. F. *J. Org. Chem.* **1975,** *40*, 1664.
73. Mannam, S.; Sekar, G. *Tetrahedron Lett.* **2008,** *49*, 1083.
74. Shimokawa, J.; Ishiwata, T.; Shirai, K.; Koshino, H.; Tanatani, A.; Nakata, T.; Hashimoto, Y.; Nagasawa, K. *Chem. Eur. J.* **2005,** *11*, 6878.
75. (a) Bellur, E.; Freifeld, I.; Böttcher, D.; Bornscheuer, U. T.; Langer, P. *Tetrahedron* **2006,** *62*, 7132; (b) Blouin, M.; Béland, M.-C.; Bressard, P. *J. Org. Chem.* **1990,** *55*, 1466; (c) Juhász, L.; Szilágyi, L.; Antus, S.; Visy, J.; Zsila, F.; Simonyo, M. *Tetrahedron* **2002,** *58*, 4261; (d) Schatz, P. F.; Ralph, J.; Lu, F.; Guzei, I. A.; Buzel, M. *Org. Biomol. Chem.* **2006,** *4*, 2801; (e) Pohmakotr, M.; Issaree, A.; Sampaongoen, L.; Tuchinda, P.; Reutrakul, V. *Tetrahedron Lett.* **2003,** *44*, 7937.
76. (a) Bartlett, P. A.; Meadows, J. D.; Ottow, E. *J. Am. Chem. Soc.* **1984,** *106*, 5304; (b) Brandänge, S.; Färnbäck, M.; Leijonmarck, H.; Sundin, A. *J. Am. Chem. Soc.* **2003,** *125*, 11942; (c) Honda, T.; Satoh, A.; Yamada, T.; Hayakawa, T.; Kanai, K. *J. Chem. Soc. Perkin Trans. 1* **1998**, 397; (d) Kametani, T.; Katoh, T.; Fujio, J.; Nogiwa, I.; Tsubuki, M.; Honda, T. *J. Org. Chem.* **1988,** *53*, 1982; (e) Kametani, T.; Katoh, T.; Tsubuki, M.; Honda, T. *J. Am. Chem. Soc.* **1986,** *108*, 7055; (f) Lee, J. Y.; Kim, B. H. *Tetrahedron* **1996,** *52*, 571.
77. (a) Donohoe, T. J.; House, D. *J. Org. Chem.* **2002,** *67*, 5015; (b) Vincent, S. P.; Sinaÿ, P.; al., e. *Chem. Eur. J.* **2007,** *13*, 1471.
78. Ankner, T.; Hilmersson, G. *Org. Lett* **2009,** *11*, 503.