



# Synthesis of a poison frog bioactive alkaloids

Sara Mazeh

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## **THÈSE**

Pour obtenir le grade de

### **DOCTEUR DE LA COMMUNAUTÉ UNIVERSITÉ GRENOBLE ALPES**

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Présentée par

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préparée au sein du **Laboratoire Département de Pharmaco  
chimie Moléculaire**  
dans l'**École Doctorale Chimie et Sciences du Vivant**

### **Synthèse d'alcaloïdes bioactifs issus de batracien**

### **Synthesis of a poison frog bioactive alkaloids**

Thèse soutenue publiquement le **9 décembre 2019**,  
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Dedicated to my parents,  
this simply wouldn't exist without you.

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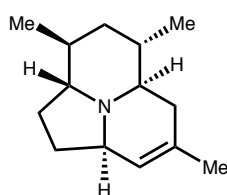
## ABBREVIATIONS – ACRONYMS

AD	Alzheimer's Disease
AIBN	azobis( <i>isobutyronitrile</i> )
aq.	aqueous
AZADO	2-Azaadamantane- <i>N</i> -oxyl
Boc	<i>tert</i> butoxycarbonyl
BPS	<i>tert</i> butyldiphenylsilyl
cat.	catalytic
CSA	camphorsulfonic acid
Cys	cysteine
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
ESI	electrospray ionization
equiv	equivalent
GTP	guanosine-5'-triphosphate
HMPA	hexamethylphosphoramide
HRMS	high-resolution mass spectrometry
IR	infrared
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
M	metal

MS	mass spectrometry
MeOH <sub>NH3</sub>	methanol saturated with ammonia
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
Nu	nucleophile
Pd/C	palladium on charcoal
Ph	phenyl
ppm	parts per million
PTSA	<i>para</i> -toluenesulphonic acid
RCM	ring-closing metathesis
RT	room temperature
TBAF	tetrabutylammonium fluoride
TBDMS, TBS	<i>tert</i> -butyldimethylsilyl
TCCA	trichloroisocyanuric acid
TCDI	1,1'-thiocarbonyldiimidazole
TFA	trifluoroacetic acid
Tf	trifluoromethanesulfonyl (triflate)
THF	tetrahydrofuran
TMS	trimethylsilyl
TST	temporary silyl tether
TLC	thin-layer chromatography
UV	ultraviolet
v/v	volume per volume

# GENERAL INTRODUCTION

This thesis details the synthetic journey toward alkaloid (–)-205B which was isolated from the skin of *Dendrobatidae* neotropical frog (*Figure 1*). In addition to the challenging 8b-azaacenaphthylene ring system rarely encountered in the structure of natural products and the presence of 5 stereogenic carbons, our effort was stimulated by its promising biological activity. This target compound is expected to display a selective activity for the inhibition of specific type of neuronal receptors which are recognized to be involved in the starting point of Alzheimer's disease (AD). Thus, selective inhibitors of these receptors can be considered as potential therapeutic agents for this neurodegenerative disease.

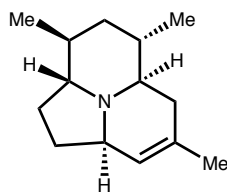


*Figure 1: Alkaloid (–)-205B*

On this basis, this manuscript is divided into four principal parts:

- The first chapters are devoted to highlight the importance of the targeted alkaloid; both from a synthetic and biological aspect.
- The following chapter will cover a brief description of the previously reported syntheses.
- A main chapter will detail our successful multi-step synthesis of this alkaloid based on the difficulties faced in a previous approach, whereupon a new strategy was explored.
- Finally, all the experimental procedures and characterization data of the synthesized molecules will be provided in the experimental part.

Cette thèse décrit le détail du travail effectué conduisant à la synthèse de l'alcaloïde (-)-205B (*Figure 1*). Celui-ci a été isolé en très faible quantité d'extraits de peau de grenouilles de la famille des *Dendrobatidae*. En plus de son système tricyclique de type 8b-azaacenaphthylene peu fréquemment rencontré dans la structure des produits naturels et de la présence de 5 centres asymétriques, l'intérêt de ce travail est également dû à l'activité biologique prometteuse de ce composé. En effet, cet alcaloïde est suspecté d'être un inhibiteur sélectif d'un certain type de récepteur neuronal qui a récemment été identifié comme un point de départ de la maladie d'Alzheimer. Ainsi, tout inhibiteur sélectif de ces récepteurs peut être considéré comme un agent thérapeutique potentiel de cette maladie neurodégénérative.



*Figure 1: Alcaloïde (-)-205B*

Ce manuscrit est ainsi divisé en quatre parties principales:

- Les premiers chapitres ont pour but de montrer l'importance de cet alcaloïde cible, aussi bien d'un point de vu synthétique que biologique.
- Le chapitre suivant permettra de décrire brièvement les précédentes approches publiées dans la littérature.
- Le chapitre principal présentera en détail les différentes étapes de notre approche synthétique et particulièrement montrera les solutions développées afin de résoudre les difficultés rencontrées lors de notre première stratégie.
- Enfin, la partie expérimentale donnera les modes opératoires et décrira les caractéristiques spectrales de chaque molécule synthétisée.



CHAPTER I: FROM NATURAL PRODUCTS  
TO ALKALOID (–)-205B

## I. Overview of Natural Products

By natural products, we mean molecules of nature. Nature is extremely generous in offering mankind a pool of unique and diverse products inspiring novel discoveries in the field of medicine and life-saving therapies. With the recent technological advances, a New Golden Era of natural product-based drugs is dawning. Natural products possess enormous structural and chemical diversity of molecules having tremendous impact in the drug discovery field for the treatment of the most challenging diseases. The curiosity of chemists and biologists impels them to discover the reason behind the nature for all the medicines offered to human.

The record of these bioactive natural products has been incredible for their medicinal impact. Plant-based drug discovery is as old as the mankind itself. The essential need of human for healthcare prompted him to explore the surrounding nature. All the story begins with the traditions of yesterday being transformed by scientists to the drugs of tomorrow. Herewith, nature's cures are passing from one generation to another with the addition of the solid scientific foundations.

Traditional Chinese and Indian Medicine are the most ancient of all the medicinal traditions and undoubtedly, they spread all over the world. Examples for the Indian and Chinese medicinal herbs are; *Rheum palmatum*, *Panax ginseng*, *Cenetella asiatica*, *Santalum album*, *Ephedra sinica*, etc..<sup>1</sup> Besides, the ancient Egyptian medicine epitomized in the known 'Ebers Papyrus'<sup>2</sup> is dated about 1550 BC. It includes about 700 medicinal compounds mainly of vegetal sources.

Many plants were recorded in the early years for their biological properties that open promising avenues to treat many diseases. Within the 18<sup>th</sup>–19<sup>th</sup> century, a method to extract, purify and isolate these biological active compounds from the plants was developed in order to elucidate their structure. We owe the first breakthrough in this realm to Friedrich Serturnen who was able to isolate the first well-known drug, Morphine, from *Papaver somniferum* in 1806 that is used as narcotic and analgesic.<sup>3</sup> Moreover, this plant was found to be a valuable source for other medicinally used alkaloids including antitussive codeine, spasmolytic papaverine, and several derived semi-synthetic drugs such as

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<sup>1</sup> Gurib-Fakim, A. *Molecular Aspects of Medicine* **2006**, 27, 1-93.

<sup>2</sup> Aboelsoud, N. H. *J. Med. Plant. Res.* **2010**, 4, 82-86.

<sup>3</sup> Kong, J. M.; Goh, N. K.; Chia, L. S.; Chia T. F. *Acta Pharmacologica Sinica* **2003**, 24, 7-21.

oxycodone, buprenorphine and naltrexone.<sup>4</sup> After this date, more and more herbal medicines were discovered such as, Quinine, atropine, Caffeine, Coine, Emetine, strychnine, Tubocurarine and Acetylsalicylic acid (Aspirin).

About the quarter of all the European Medical Agency (EMA) approved drugs are plant based with well-known drugs.<sup>5</sup> Also, according to the World Health Organization; 80% of the world's population rely on derivatives extracted from plants in their medicine.<sup>6</sup>

The discovery of bioactive natural products is not only to maintain human health, but also to fight plant viral diseases that affect the yield and the quality of the crops. This was studied by Q. Wang, A. Lu & Z. Wang who discover the alkaloid Gramine (Figure 2) and its analogues as a novel agent against plant virus.<sup>7</sup>

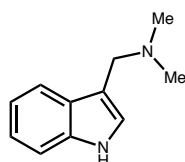


Figure 2: Gramine

On the other hand, an array of natural products bearing interesting pharmacological properties are known in the literature to be of diverse non-vegetal sources. Fungi have a clear track record for the diverse bioactive natural products they possess. 75% of the studied polypore fungi possess antimicrobial activity and many others have shown other biological activities such as antiviral, cytotoxic, cardiovascular, anti-inflammatory, anti-cancer activities. In 1953, a glycopeptide antibiotic, Vancomycin, was isolated from *Amycolatopsis orientalis* by Edmund Kornfeld which was approved by FDA in 1958 and reported to be effective against severe infections.<sup>8</sup> Also, ganoderic acid  $\beta$ , isolated from *Ganoderma lucidum*, was proved to have anti-HIV protease activity.<sup>9</sup> (Figure 3)

<sup>4</sup> Wijekoon, C. P.; Facchini, P. J. *Plant J* **2012**, *69*, 1052-1063.

<sup>5</sup> Patridge, E.; Gareiss, P.; Kinch, M. S.; Hoyer, D. *Drug Discovery Today* **2016**, *21*, 204-207.

<sup>6</sup> (a) Nirmal, S. A.; Pal, S. C.; Otimenyin, S.; Aye, T.; Elachouri, M.; Kundu, S. K.; Thandavarayan, R. A.; Mandal, S. C. "Contribution of Herbal Products in Global Market" *The Pharma Review* **2013**. (b) Ekor M. *Front. Pharmacol.* **2014**, *4*, 1-10.

<sup>7</sup> Lu, A.; Wang, T.; Hui, H.; Wei, X.; Cui, W.; Zhou, C.; Li, H.; Wang, Z.; Guo, J.; Ma, D.; Wang, Q. *J. Agric. Food. Chem.* **2019**, *67*, 2148-2156.

<sup>8</sup> (a) Butler, M. S. *J. Nat. Prod.* **2004**, *67*, 2141-2153. (b) Dewick, P.M. *Medicinal Natural Products: A Biosynthetic Approach*, 2nd ed.; John Wiley and Son: West Sussex, UK **2002**; p.520.

<sup>9</sup> Min, B.; Nakamura, N.; Miyashiro, H.; Bae, K.; Hattori, M. *Chem. Pharm. Bull.* **1998**, *46*, 1607-1612.

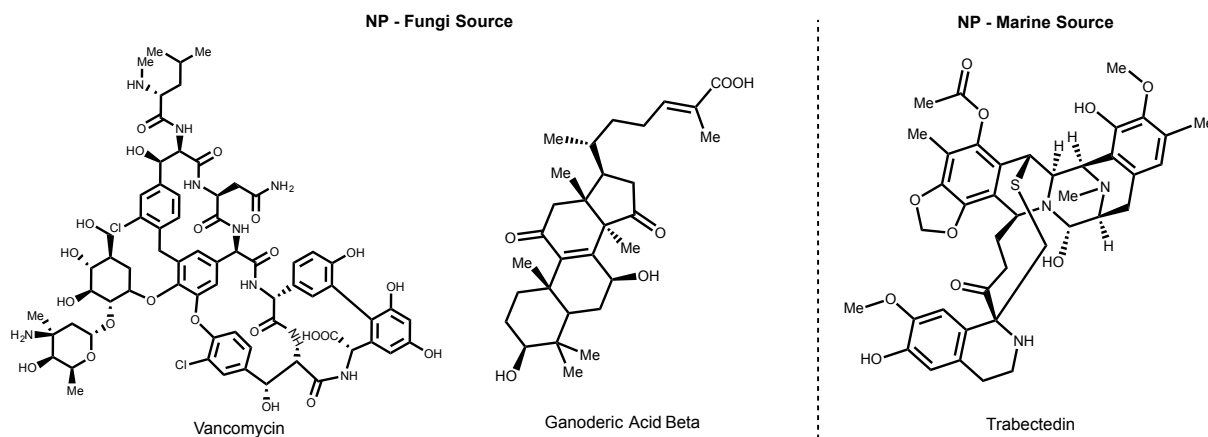


Figure 3: Bioactive Natural Products from Diverse Sources

Furthermore, exploration the marine source for more medicinal products was highlighted in the past 40 years where thousands of bioactive natural products were isolated. In October 2007, the European Union approved the first marine anticancer drug the Trabectedin which was isolated from the ascidian *Ecteinascidia turbinata* (Figure 3).<sup>10,11</sup> Bacteria also contributes highly to medicine through providing a wide range of antibiotics, antitumor agents, immunomodulators and enzyme inhibitors.<sup>12</sup>

## II. Introduction to Alkaloids

Between 1983 and 1994, 39% of the approved drugs were originated from natural products, and according to Cragg *et al.*, 60–80% of the anticancer and antibacterial medicines were natural products–based.<sup>13</sup> The interest in nature as a source of more challenging therapeutic agents continues to highlight the importance of plant secondary metabolite either as drug or drug precursors. The biodiversity of nature is progressing from time to time to provide a wide array of these secondary metabolites.

Plants usually produce a wide variety of molecules divided between primary and secondary metabolites. Primary metabolites are those of intrinsic function integrating directly in the essential roles for survival as growth, development and reproduction. They are composed of the core building block

<sup>10</sup> Mayer, A. M. S.; Glaser, K. B.; Cuevas, C.; Jacobs, R. S.; Kem, W.; Little, R. D.; McIntosh, J. M.; Newman, D. J.; Potts, B. C.; Shuster, D. E. *Trends Pharm. Sci.* **2010**, *31*, 255-265.

<sup>11</sup> (a) Rinehart, K. L.; Holt, T. G.; Fregeau, N. L.; Stroh, J. G.; Keifer, P. A.; Sun, F.; Li, L. H.; Martin, D. G. *J. Org. Chem.* **1990**, *55*, 4512-451. (b) Wright, A. E.; Forleo, D. A.; Gunawardana, G. P.; Gunasekera, S. P.; Koehn, F. E.; McConnell, O. J. *J. Org. Chem.* **1990**, *55*, 4508-4512.

<sup>12</sup> Sekurova, O. N.; Schneider, O.; Zotchev, S. B. *Microbial Biotechnology* **2019**, *0*, 1-17.

<sup>13</sup> Gragg, G. M.; Newman, D. J.; Snader, K. M. *J. Nat. Prod.* **1997**, *60*, 52-60.

molecules such as sugars, nucleic acids, fatty acids and amino acids that are the raw materials for the synthesis of the major macromolecules within the body (protein, carbohydrates, DNA, RNA and lipids). Whereas secondary metabolites are believed to act as additives that have no relation with survival, but with protection and species interaction.

As mentioned before, a wide array of secondary metabolites is produced by plants where about 100,000 metabolites have been detected to date according to *Afendi* Study.<sup>14</sup> They are categorized based on their carbon skeletal structure and functional groups into alkaloids, terpenes, steroids, polyketides, peptides and porphyrins. Many of these metabolites were proved to be of highly significant pharmaceutical properties (*Table 1*). The biogenesis of these secondary metabolites is highlighted in *Figure 4*.

Alkaloids are basic nitrogenous secondary metabolites, where their name come out from their alkaline chemical structure. They were known in ancient time by the easiness of their extraction from plants and the powerful and deadly effect they possess. They were found to be diverse in their structures where more than 3000 alkaloids were detected in about 4000 plant species. All are of amino acids' precursors.<sup>15</sup>

The role of these alkaloids in plants is believed to be related to their protection and defense against predators; including herbivores and pathogens. These low molecular mass secondary metabolites are released and activated under diverse stressors to exhibit their defense activity. For example, it was shown that aporphine alkaloid save the tulip tree from parasitic mushrooms.<sup>16</sup>

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<sup>14</sup> Afendi, F. M.; Okada, T.; Yamazaki, A.; Hirai-Morita, A.; Nakamura, Y.; Nakamura, K.; Ikeda, S.; Takahashi, H.; Altaf-Ul-Amin, M.; Darusman, L. K.; Saito, K.; Kanaya, S. *Plant Cell Physiology* **2012**, *53*, 1-12.

<sup>15</sup> Kumar, V.; Wani, S. H.; Suprasanna, P.; Tran, L. P. *Salinity Responses & Tolerance in Plants* **2018**, *2*.

<sup>16</sup> Nissar, A. R.; Sudarshana, M. S.; Smitha, N.; Guru, C. *World Journal of Pharmaceutical Research* **2014**, *3*, 731-741.

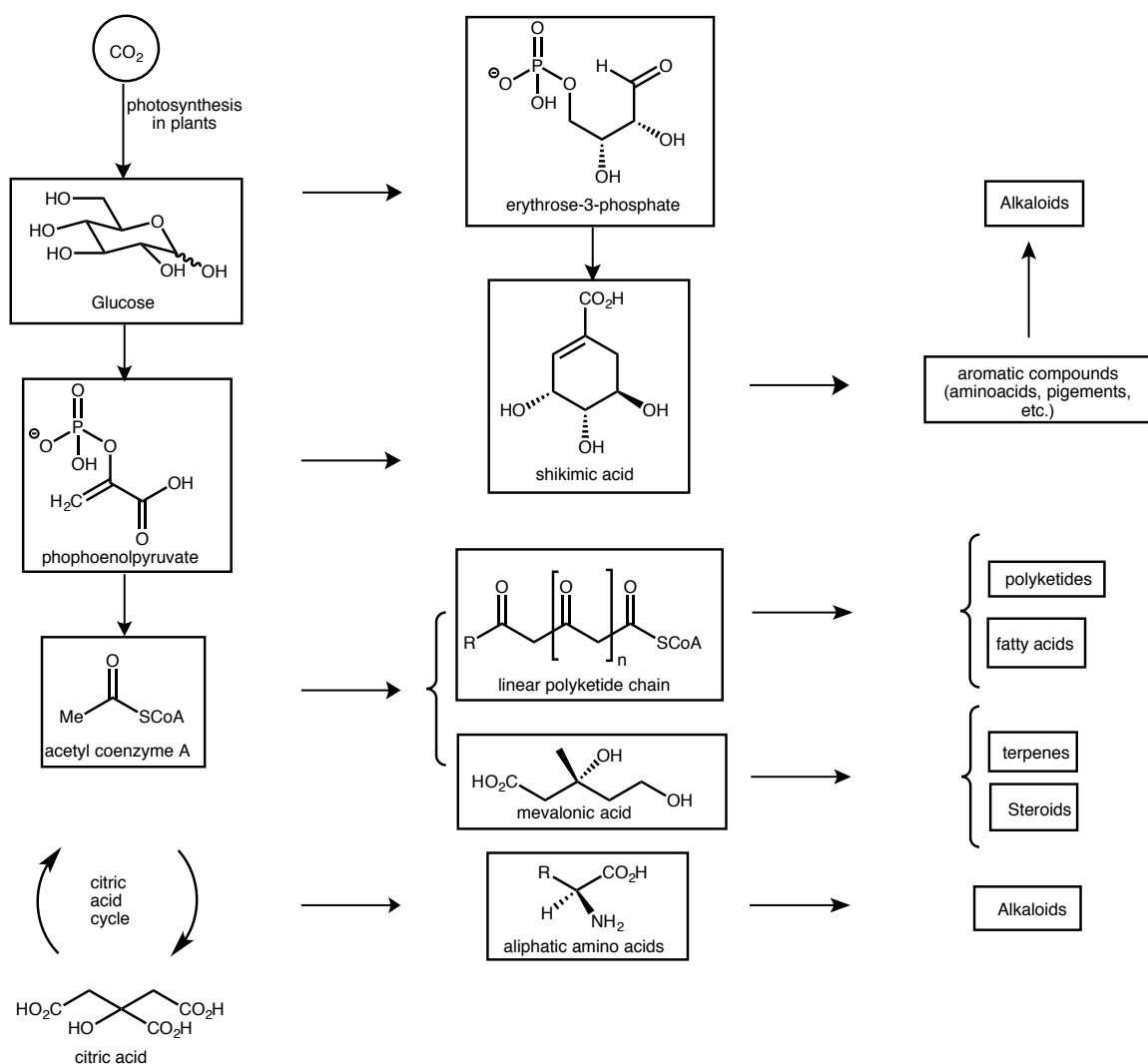


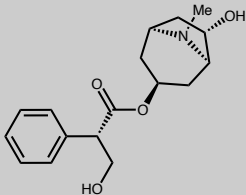
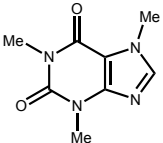
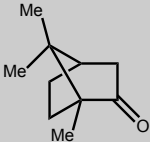
Figure 4: Biogenesis of secondary metabolites

Many of these naturally occurring alkaloids possess potent pharmacological activity and some show interesting use in modern medicine. To illustrate, Atropine which is an alkaloid existing in various plants of the family *Solanaceae* such as belladonna, Datura, henbane and mandrake, is widely used as antidote to nerve gas poisoning. Moreover, Caffeine is known in modern medicine as central nerve system stimulant and Quinine for its antipyretic, analgesic and most importantly for its antimalarial property. More interestingly, some natural products show an inhibiting activity against more challenging diseases. Vinblastine and Vincristine, isolated from *Catharanthus roseus* plants, are used

for cancer therapy by inhibiting the hydrolysis of guanosine-5'-triphosphate (GTP) and thus inhibiting cell division at metaphase level and promoting cell death.<sup>17</sup>

The first synthesized alkaloid is the piperidine alkaloid coniine by Ladenburg in 1886,<sup>18</sup> which was first extracted from poison hemlock (*Conium Maculatum*) in 1826 by Giseke.<sup>19</sup> This alkaloid was proven to be extremely toxic where it was the reason behind the death of Socrates. It causes paralysis of motor nerve endings by blocking the nicotinic receptors on the post-synaptic membrane of the neuromuscular junction, followed by death due to cessation of breath.<sup>20</sup>

As for the more challenging diseases; Galantamine which is a naturally occurring plant tertiary alkaloid was approved to treat mild to moderate Alzheimer's Disease (AD) and various other memory impairments. It can be provided by extraction from several plants but also through synthesis. It has been considered due to its specific, reversible and competitive inhibition properties of acetylcholinesterase (AChE) and being an allosteric modulator of nAChRs.

Secondary Metabolite Drug	Structure	Plant Source	Biological Activity
Anisodamine		<i>Anisodus tanguticus</i>	Anticholinergic, circulatory shock
Caffeine		<i>Coffea arabica</i>	CNS and metabolic stimulant
Camphor		<i>Cinnamomum camphora</i>	Cough, neurodermatitis, fungal infections

<sup>17</sup> Thirumaran, R.; Prendergast, G. C.; Gilman, P. B. *Cancer Immunotherapy "Cytotoxic Chemotherapy in Clinical Treatment of Cancer chapter 7"* **2007**, 101-116.

<sup>18</sup> Ladenburg A. *Berichte der Deutschen Chemischen Gesellschaft* **1886**, 19, 439-441.

<sup>19</sup> Giseke A.L. *Archiv des Apotheker-Vereins im nördlich Deutschland* **1826**, 20, 97–111.

<sup>20</sup> Hotti, H.; Rischer, H. *Molecules* **2017**, 22, 1-23.

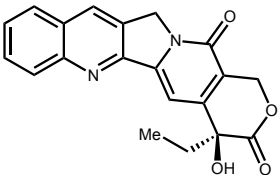
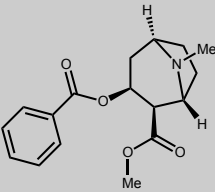
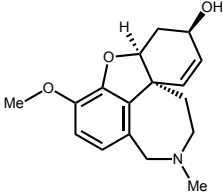
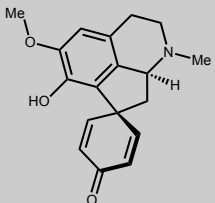
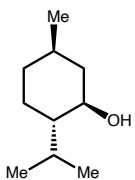
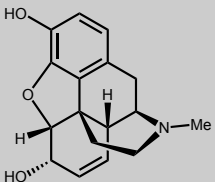
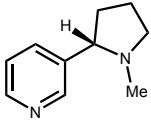
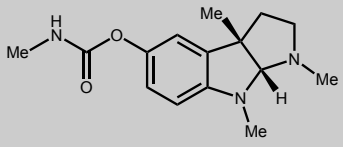
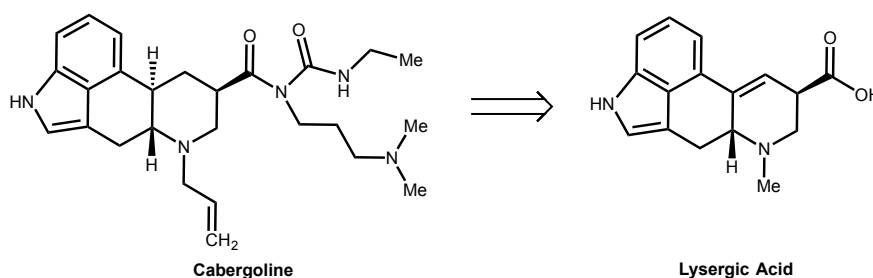
Camptothecin		<i>Camptotheca acuminata</i>	Anticancer
Cocaine		<i>Erythroxylum coca</i>	Local anaesthetic
Galantamine		<i>Galanthus caucasicus</i>	Alzheimer's disease, memory impairment
Glaziovine		<i>Ocotea glaziovii</i>	antidepressant
Menthol		<i>Mentha species</i>	Rubefacient
Morphine		<i>Papaver somniferum</i>	Analgesic, antitussive
Nicotine		<i>Nicotiana tabacum</i>	Insecticide
Physostigmine (Eserine)		<i>Physostigma venenosum</i>	Glaucoma, Alzheimer's disease

Table 1: Plants Secondary metabolites used in modern therapeutics



The vogue of natural products discovery is increasing as they are not only proven to be an invaluable resource of novel drugs but also, they can be used as inspiration and blueprints for the fashioning of non-natural molecules of pharmaceutical value. Between 1981 and 2002, natural product analogues–based drugs proved to be 65% in the field of antihypertension and 70% as antimigraine out of the synthetic new chemical entities.<sup>21</sup> The history of medicine is full of remarkable examples of how the natural products have impacted the field of biology and drug discovery. An example of drug agent inspired from natural products is Cabergoline, analogue of the natural ergot alkaloids, which was approved for the treatment of Parkinson's disease (*Figure 5*).<sup>22</sup> These natural ergot alkaloids were the raw materials for a lot of key synthetic intermediates that led to drug discovery.<sup>23</sup> Moreover, *cocaine* was the inspiration for the synthesis of a wide range of anesthetic drugs such as procaine, bupivacaine, eucaine, etc. which were proved to be less toxic than cocaine.<sup>24</sup>



*Figure 5: Cabergoline as Drug Agent*

### III. Amphibians as a Source of Bioactive Alkaloids

Although poisons are most widely known to be found in plants as a defense against herbivores, but later some studies have investigated the chemistry of poisons in animals' skin and microorganisms leading to the development of new therapeutic agents. Several studies had discussed the potential pharmaceutical significance of products derived from amphibian skin secretions ranging from amines, peptides, proteins, steroids and alkaloids.<sup>25</sup> These secretions were used as a poison defensive weapon against predators, and some of these compounds were found to exhibit considerable

<sup>21</sup> Newman, D. J.; Gragg, G. M.; Snader, K. M. *J. Nat. Prod.* **2003**, *66*, 1022-1037.

<sup>22</sup> Wilson, R. M.; Danishefsky, S. J. *J. Org. Chem.* **2006**, *71*, 8329-8351.

<sup>23</sup> Liu, H.; Jia, Y. *Nat. Prod. Rep.* **2017**, *34*, 411-432.

<sup>24</sup> Ruetsch, Y. A.; Boni, T.; Borgeat, A. *Current Topics in Medicinal Chemistry* **2001**, *1*, 175-182.

<sup>25</sup> (a) Lazarus, L. H.; Bryant, S. D.; Attila, M.; Salvadori, S. *Environ. Health Perspect.* **1994**, *102*, 648-654. (b) Sullivan, J. P.; Decker, M. W.; Brioni, J. D.; Donnelly-Roberts, D.; Anderson, D. J.; Bannon, A. W.; Kang, C. H.; Adams, P.; Piattoni-Kaplan, M.; Buckley, M. J. *J. Pharmacol. Exp. Ther.* **1994**, *271*, 624-631.

analgesic, cardiostimulant, antimicrobial, antifungal, antimalarial, antiasthma, anticancer, or antibacterial activity, etc..<sup>26</sup>

Tempone had studied the activity of the amphibian secretions for the treatment of not well studied infectious diseases. It was found that *Chaunus ictericus* secretions possess high fungistatic activity, and the *Phyllomedusa distincta* secretions present anti-Toxoplasma activity. Also, it was reported for the first time an antileishmanial activity for the secretions of *Siphonops annulatus*.<sup>27</sup>

Alkaloids are not only limited to plants but also generated or accumulated by other living organisms: frogs, ants, bacteria, fungi, beetles, mammals and spiders. 50% of the known antibiotics nowadays are isolated from *Streptomyces*, the most productive genus of Actinomycete (class of marine bacteria).<sup>28</sup>

In the past three decades, the John Daly group reported the detection and characterization of about 800 alkaloids from amphibian sources. Their structures were either determined by NMR analysis or required additional confirmation based on the mass spectra analysis. These biologically active lipid-soluble alkaloids are distributed among different classes; samandarines, batrachotoxins, histrionicotoxins, epibatidine, pumiliotoxins, diverse array of izidines (pyrrolizidines, lehmizidines, indolizidines, quinolizidines), epiquinamide, piperidines, gephyrotoxins, quinolines and coccinelline-like tricyclics. Whereas, some of the extracted alkaloids remained unclassified as their structures have remained unknown due to their limited abundance.<sup>29</sup> These noxious alkaloids were found to be stored in the granular skin glands of the amphibians, and they can be either of endogenic or exogenic origin.

Even though, some studies showed that amphibians serve as an indirect source of some natural alkaloids through their diet on alkaloid-containing plants.<sup>30</sup> Dendrobatidae, a subgroup of the poison dart frogs allocated in South and Central America, are characterized by their designs and hues that

<sup>26</sup> Gomes, A.; Giri, B.; Saha, A.; Mishra, R.; Dasgupta, S. C.; Debnath, A.; Gomes, A. *Indian Journal of Experimental Biology* **2007**, *45*, 579-593.

<sup>27</sup> Gustavo Tempone, A.; de Souza Carvalho Melhem, M.; Oliveira Prado, F.; Motoie, G.; Mitsuyoshi Hiramoto, R.; Maria Antoniazzi, M.; Fernando Baptista Haddad, C.; Jared, C. *Letters in Drug Design & Discovery* **2007**, *4*, 67-73.

<sup>28</sup> Zotchev, S. B. *Advances in Botanical Research* **2013**, *68*, 301-333.

<sup>29</sup> Daly, J. W.; Spande, T. F.; Garraffo, H. M. *J. Nat. Prod.* **2005**, *68*, 1556-1575.

<sup>30</sup> Plant Toxins (Part of the Toxinology book series) **2015**, 1-15.

are deliberately ostentatious to ward off potential predators, a tactic called aposematic coloration.<sup>31</sup> The skin of these frogs is a stock of toxic plant alkaloids originating from their feeding on arthropods which in turn fed on plants. The enthusiasm to study profoundly the secretions from the subgroup skin came out initially because Indians on the Pacific coast of Colombia used the alkaloids extracted from the skin of *Phylllobates* to poison their blow-darts and directly killing or paralyzing their preys.<sup>32</sup> This points out that these extracts can be of remarkable biological activity targeting the central nervous system.

Batrachotoxins (BTX), the most effective neurotoxic and cardiotoxic steroidal alkaloid, is secreted by the most toxic genus of the dart frogs, *Phylllobates*, and also detected in the feathers and skin of birds. This neurotoxin alkaloid (BTX) drastically alters the properties of the voltage-gated sodium channel once bind. Accordingly, this binding causes the irreversible and permanent opening of these channels due to conformational change, leading to change in membrane potential. Death can result due to muscular and respiratory paralysis.<sup>33</sup> Also several classes of frog skin alkaloids; pseudophrynaminol, pyrrolidines, spiropyrrolizidines and piperidines, were proved to be potent blockers of nicotinic channels.<sup>34</sup> Whereas epibatidine, discovered by John Daly, was demonstrated to act as an agonist on the nicotinic receptors and then proved to be analgesic 200 times more powerful than morphine.<sup>35</sup> But it is no longer been considered for a potential therapeutic uses due to its toxicity.

Nevertheless, these frogs accumulate also bioactive amino acids that were proved to affect the GTPase activity of G proteins that are involved in signal transduction.<sup>36</sup>

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<sup>31</sup> Caldwell, J. P. *J. Zool.* **1996**, *240*, 75-101.

<sup>32</sup> Daly, J. W. *Journal of Medicinal Chemistry* **2003**, *46*, 445-452.

<sup>33</sup> Wang, S. Y.; Mitchell, J.; Tikhonov, D. B.; Zhorov, B. S.; Wang, G. K. *Mol. Pharmacol.* **2006**, *69*, 788-795.

<sup>34</sup> (a) Badio, B.; Garraffo, H. M.; Padgett, W. L.; Greig, N. H.; Daly, J. W. *Biochem. Pharmacol.* **1997**, *53*, 671-676. (b) Daly, J. W.; Nishizawa, Y.; Edwards, M. W.; Waters, J. A.; Aronstam, R. S.; *Neurochem. Res.* **1991**, *16*, 489-500. (c) Badio, B.; Shi, D.; Shin, Y.; Hutchinson, K. D.; Padgett, W. L.; Daly, J. W. *Biochem. Pharmacol.* **1996**, *52*, 933-939.

<sup>35</sup> Badio, B.; Garraffo, H. M.; Spande, T. F.; Daly, J. W. *Med. Chem. Res.* **1994**, *4*, 440-448.

<sup>36</sup> Moni, R. W.; Romero, F. S.; Daly, J. W. *Cell. Mol. Neurobiol.* **1995**, *15*, 465-493.

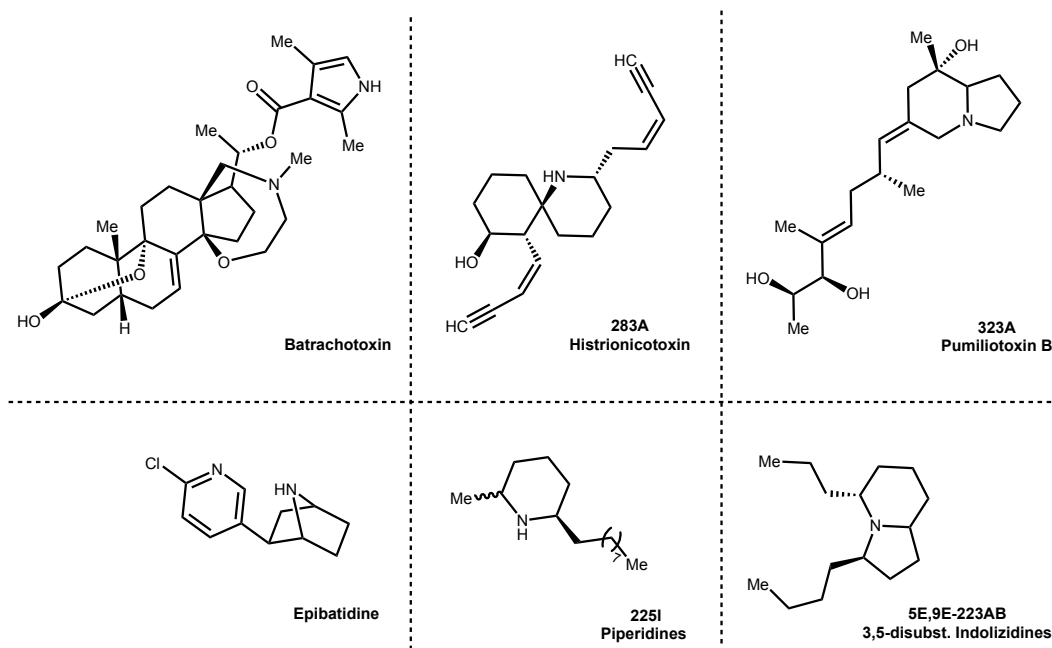


Figure 6: Alkaloids isolated from amphibians

Reliance only on nature to broaden the scope of these valuable bioactive natural products is hazardous. Sometimes, their isolation lead to change of the biological activity. In addition, the stock of products in the skin of these animals can change over time especially with the alteration of the ecosystem that impact directly the biodiversity. On the other hand, some of the natural products found in the skin of the poison dart frogs or other amphibians remain with unknown structure and biological activity due to the limited distribution of these compounds. Subsequently, the chemical synthesis of these natural products can stand in for their supply and thus for their biological evaluation as a way to avoid their isolation.

Synthetic chemistry has never been and never will be solely concerned with the challenges it offers while targeting complex structures. Thanks to synthetic organic chemistry, the library of compounds available today has helped in nurturing drug discovery research field, in addition to developing everyday materials due to the other interesting properties they possess. Every year brings its bounty. The work presented in this thesis is another collaborative record that can be added to the vast number of syntheses seeking to better understand other fields through the construction of natural products.

## IV. Alkaloid (–)-205B

The structure of the alkaloid (–)-205B, that belong to coccinelline-like tricyclics, was first reported in 1987 as diastereoisomers<sup>37</sup> but extensive FTIR, NMR and HRMS analysis were required to confirm the relative stereochemical configuration.<sup>38</sup> This alkaloid, isolated from *Dendrobates pumilio*,<sup>37,38</sup> has a unique tricyclic structure of 8b-azaacenaphthylene with five stereocenters. No other alkaloids from amphibian skin is known to belong to this group. Notably, skins of 3620 frogs were required to deliver only 13 mg of (–)-205B.

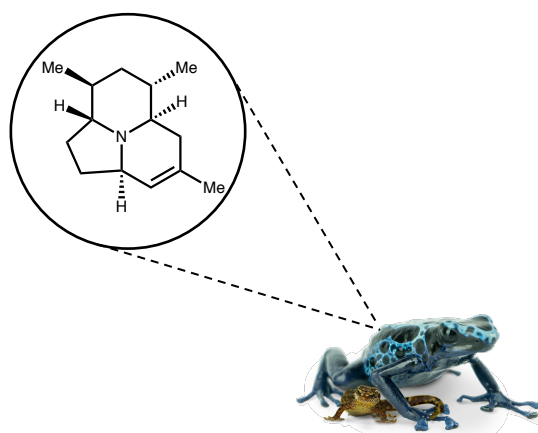


Figure 7: Alkaloid (–)-205B – *Dendrobates Pumilio*

The synthetic efforts covered in this thesis were embarked upon not just for their opportunity as challenging and intriguing targets but also for their relevance to other fields. Promising selective activity against central nervous system motivated the pursuit of these neurotoxic frog's alkaloids extract. More interestingly, their potential to impact neurodegenerative disease has inspired our work specifically toward the alkaloid (–)-205B. This is fully discussed in the following chapter.

<sup>37</sup> Tokuyama, T.; Nishimori, N.; Shimada, A.; Edwards, M. W.; Daly, J. W. *Tetrahedron* **1987**, *43*, 643-652.

<sup>38</sup> Tokuyama, T.; Garraffo, H. M.; Spande, T. F.; Daly, J. W. *Anal. Asoc. Quim. Argentina* **1998**, *86*, 291-298.

## CHAPTER II: BIOLOGICAL ASPECTS OF (–)- 205B

## I. Mode of Biological Activity of Alkaloids

Alkaloids are widely distributed in plants, bacteria, marine animals, fungi, arthropods, amphibians, algae, also in birds and mammals. It seems that their presence is fundamental for the protection of the living organism, opposing the previous beliefs considering them as waste products. Although alkaloids accumulated in the skin of animals were proved to serve as neurotoxin such as the Dendrobatid frog's alkaloids, they can also act as therapeutic agent if they are supplied in lower doses. In such case, their poisonous effects are avoided and converted into interesting pharmacological activities such reducing blood pressure, killing tumor cells and relieving pain.<sup>39</sup>

For providing wide array of synthetic pharmacological active analogues of the interesting bioactive natural alkaloids, understanding the detailed mechanism of their mode of action is essential. The ability of alkaloids to defend plants or animals indicates that they interfere with important molecular and cellular targets in the predators such as ion channels, receptors, signal transduction, biomembrane, DNA, Endoplasmic Reticulum and Golgi.<sup>39</sup>

During their evolution, the structure of alkaloids is shaped in a way that they mimic endogenous substances such as neurotransmitter in their structure and thus they are able to bind to neuroreceptors. This stands for addressing alkaloids as "*neurotransmitter analogs*"<sup>40</sup> especially that both alkaloids and neurotransmitters are derived from amino acids.

Neurotransmitters are endogenous substances that act as chemical messenger to transmit signal between neurons or between neuron and muscle. The electric signal that travel throughout the neuron is converted into a chemical one in the axon by allowing the vesicles–containing neurotransmitters to fuse with presynaptic membrane thus releasing the neurotransmitters into the synapse. The communication occurs across the synapse where the neurotransmitters bind to receptors on the postsynaptic neuron, thus stimulating the latter by mediating either inhibitory, excitatory or modulatory effect.

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<sup>39</sup> Fattorusso, E.; Tagliatela-Scafati, O. "Modern Alkaloids: Structure, Isolation, Synthesis and Biology", WILEY-VCH, chapter 1, **2007**.

<sup>40</sup> Patrick, G.L. "An Introduction to Medicinal Chemistry", II Edition, Oxford Press, **2001**.



Figure 8: Neurotransmitters across synapse

## II. Nicotinic Acetylcholine Receptors

### i. From Structure to Function

Acetylcholine receptors are integral membrane proteins that are induced by a neurotransmitter. They are considered cholinergic receptors as they selectively bind to acetylcholine neurotransmitter. They are divided into two major subtypes; the metabotropic muscarinic receptors and the ionotropic nicotinic receptors where both of them can be activated by the endogenous acetylcholine ligand. The difference is manifested in the fact that nicotinic receptors bind also to nicotine agonist whereas the muscarinic respond to muscarine.<sup>41</sup>

Nicotinic acetylcholine receptors belong to a large family of ligand-gated ion channels known as ionotropic receptors. These receptors were shown to be involved in cognitive functions such as learning, comprehension, attention and memory. They can be found throughout the central and peripheral nervous system (neuronal-type nicotinic receptors) that are implicated in the fast-synaptic transmission, and at the skeletal neuromuscular junction (muscle-type nicotinic receptors) which are involved in neuromuscular transmission.

They are of molecular mass of 290 kDa having their own basic pentameric structure that made up of five subunits symmetrically surrounding the central pore (*Figure 9B*).<sup>42</sup> Each subunit shares a common motif: a large extracellular amino-terminal domain, three hydrophobic transmembrane segments (referred ad M1–M3), a large intracellular loop of amino acid sequences, and a 4<sup>th</sup> C-terminal

<sup>41</sup> (a) Dale, P.; Augustine, G. J.; Fitzpatrick, D.; Hall, W. C.; LaMantia, A.; McNamara, J. O.; White, L. E. *Neuroscience* (4th ed.) **2008**, 122-126. (b) Siegel, G. J.; Agranoff, B. W.; Fisher, S. K.; Albers, R. W.; Uhler, M. D., *Basic Neurochemistry: molecular, Cellular and Medical Aspects* (8<sup>th</sup> ed.) **1999**. (c) Itier, V.; Bertrand, D. *FEBS Letters*. **2001**, 504, 118-25.

<sup>42</sup> Unwin, N. *Journal of Molecular Biology* **2005**, 346, 967-89.



hydrophobic transmembrane domain (M4) (Figure 9A). To date, 17 nAChR subunits are described in the literature and they are distributed between neuronal and muscular nAChR. Neuronal nAChR can be found as homomeric or heteromeric assembly of 12 subunits ( $\alpha_2$ – $\alpha_{10}$  and  $\beta_2$ – $\beta_4$ ) whereas the muscle-type are a combination of these 5 different subunits ( $\alpha_1$ ,  $\beta_1$ ,  $\delta$ ,  $\gamma$ ,  $\epsilon$ ). The Cys–Cys pair is necessary for agonist binding and it is designated to distinguish  $\alpha$  subunits from the other subunits.

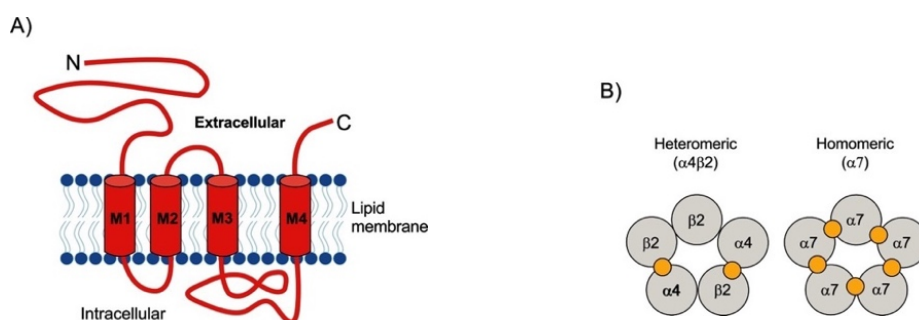


Figure 9: Diagrammatic representation of the nAChR ion-channel pentamers

The biological function of these receptors is about translating the chemical binding to neurotransmitters into a change in the subunits' conformation leading to the pore opening allowing the flow of cations. The net positive charge flow is inward resulting in the generation of electric signal that will be transmitted throughout the cell leading to cellular response. The neuronal nAChRs agonists are nicotine, epibatidine and choline. Whereas binding to antagonists, such as mecamylamine, dihydro- $\beta$ -erythroidine and hexamethonium, will inhibit this opening and thus inhibiting the transmission of signals. (Figure 10)

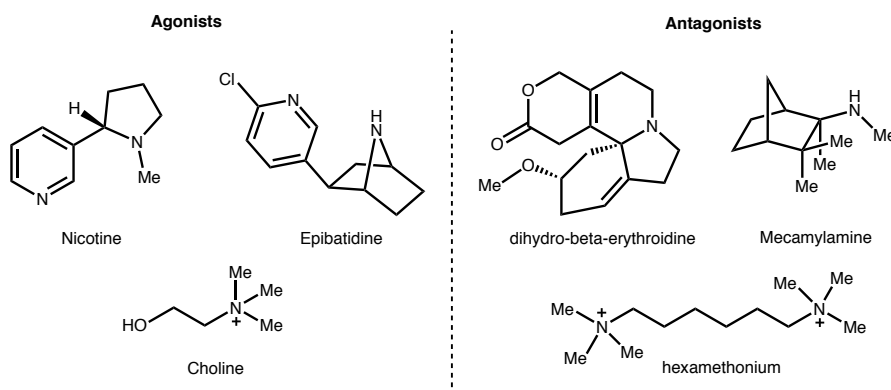


Figure 10: Neuronal nAChRs agonists and antagonists

## ii. Frog Skin Alkaloids: Pharmacological Activity on nAChR Subtypes

Dendrobatid frogs are known for the storage of biologically active alkaloids in their skin that have direct relation with nicotinic AChRs such as the agonist, Epibatidine. After isolation and structure elucidation of a group of alkaloids, their effect on nAChRs was examined by *Tsuneki et al.*<sup>43</sup> It was found that the 5,8-disubstituted indolizidinone (–)-235B' acts as a non-competitive inhibitor of  $\alpha_4\beta_2$  receptor and (–)-223A exhibit blocking effect on both  $\alpha_4\beta_2$  and  $\alpha_7$  receptors. Whereas the (–)-1-epi-207I and the unnatural alkaloid (+)-205B were described as antagonists inhibiting selectively the  $\alpha_7$  nAChR (Figure 11). (+)-205B was listed among the potential therapeutic agents targeting Schizophrenia disease.<sup>44</sup> To broaden this scope, syntheses of various alkaloids belonging to this family were reported by Toyooka *et al*/ permitting further pharmacological studies due to their low abundance or being unnatural.<sup>45</sup>

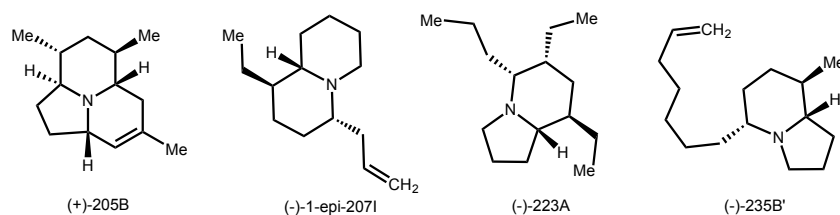


Figure 11: Selective activity of Dendrobatid frog's alkaloids and analogues on nAChR

Therefore, the biological activity associated with these alkaloids have stimulated research in several synthetic groups to provide alkaloids with unknown biological activity. A significant attention was given to the alkaloid of interest, (–)-205B, that might have selective activity on the  $\alpha_7$  nAChR as either agonist or antagonist.

## iii. nAChRs – Neurodegenerative Diseases Affinity

For more than 20 years, the neuronal nAChRs have been the target for drug discovery for several neurodegenerative diseases, with a special focus on the  $(\alpha_4)_2(\beta_2)_3$  and  $(\alpha_7)_5$  receptors as they are the most expressed in the central nervous system.

<sup>43</sup> Tsuneki et al., *Molecular Pharmacology*, **2004**, 66, 1061-1069.

<sup>44</sup> Arneric, S. P.; Holladay, M.; Williams, M. *Biomedical Pharmacology* **2007**, 74, 1092-1101.

<sup>45</sup> Toyooka, N.; Tsuneki, H.; Kobayashi, S.; Dejun, Z.; Kawasaki, M.; Kimura, I.; Sasaoka, T.; Nemoto, H. *Current Chemical Biology* **2007**, 1, 97-114.

Freedman *et al*/had studied potential new candidates as therapeutic agents for Schizophrenia.<sup>46</sup> It was noted that schizophrenic people have reduced level of  $\alpha_4\beta_2$  and  $\alpha_7$  subunits receptors. This might explain the relation of high level of smoking in people with schizophrenia where tobacco is considered as an external source for nicotine that will regulate the number of binding sites on the cell surface. More rewarding, a lot of efforts had been done by SIBIA (Salk Institute Biomedical Industry Association), in particular by R.J. Reynolds and Abbott, for the discovery of nAChR agonists as a potential treatment of pain, Schizophrenia and Alzheimer's disease (AD) (Figure 12).<sup>44</sup>

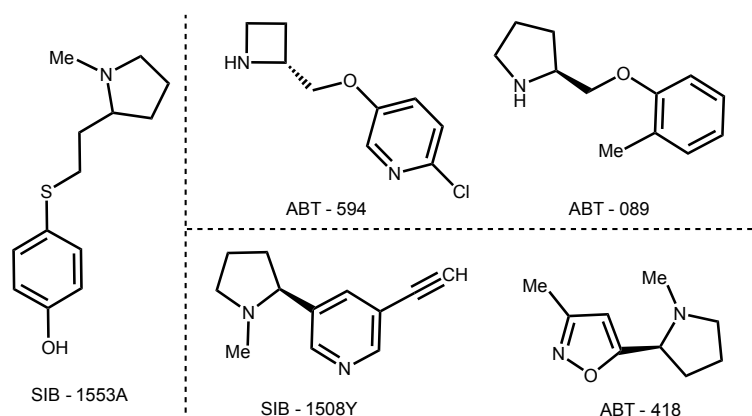


Figure 12: early discovered nAChRs agonists as potential therapeutic agent

Recently several studies have linked specifically the  $\alpha_7$  nAChR to neurodegenerative diseases, thus targeting this receptor may be a potential approach for developing a new medication.<sup>47</sup> AD has been considered as a challenging disease to treat. It is one of the common dementias suffered by aged people and its therapy is still very limited. On-going developments in biological research had opened the way for proposing agonists and antagonists as therapeutic agents for such disease. In the 90s, several inhibitors for acetylcholinesterase were approved for the treatment of mild to moderate AD. Later on, more attention was given for the development of  $\alpha_7$  nAChRs agonists as anti-AD agents, where some represent a promising potential candidate for the treatment of AD.<sup>48</sup> (Figure 13)

<sup>46</sup> Martin, L.F.; Kem, W.R.; Freedman, R. *Psychopharmacology* **2004**, *174*, 54-64.

<sup>47</sup> (a) Ma, K. G.; Qian, Y. H. *Neuropeptides* **2019**, *73*, 96-106. (b) Godyń, J.; Jończyk, J.; Panek, D.; Malawska, B. *Pharmacol Rep* **2016**, *68*, 127-138.

<sup>48</sup> (a) Bitner, R. S.; Bunnelle, W. H.; Decker, M. W.; Drescher, K. U.; Kohlhaas, K. L.; Markosyan, S.; Marsh, K. C.; Nikkel, A. L.; Browman, K.; Radek, R.; Anderson, D. J.; Buccafusco, J.; Gopalakrishnan, M. *J. Pharmacol. Exp. Ther.* **2010**, *334*, 875-886. (b) Kem WR. *Behav. Brain Res.* **2000**, *11*, 169-181. (c) Prickaerts, J.; van Goethem, N. P.; Chesworth, R.; Shapiro, G.; Boess, F. G.; Methfessel, C.; Reneerkens, O. A. H.; Flood, D. G.; Hilt, D.; Gawryl, M.; Bertrand, S.; Bertrand, D.; König, G. *Neuropharmacology* **2012**, *62*, 1099-1110. (d) Callahan, P. M.; Bertrand, D.; Bertrand, S.; Plagenhoef, M. R.; Terry, A. V. *Neuropharmacology* **2017**, *117*, 422-433.

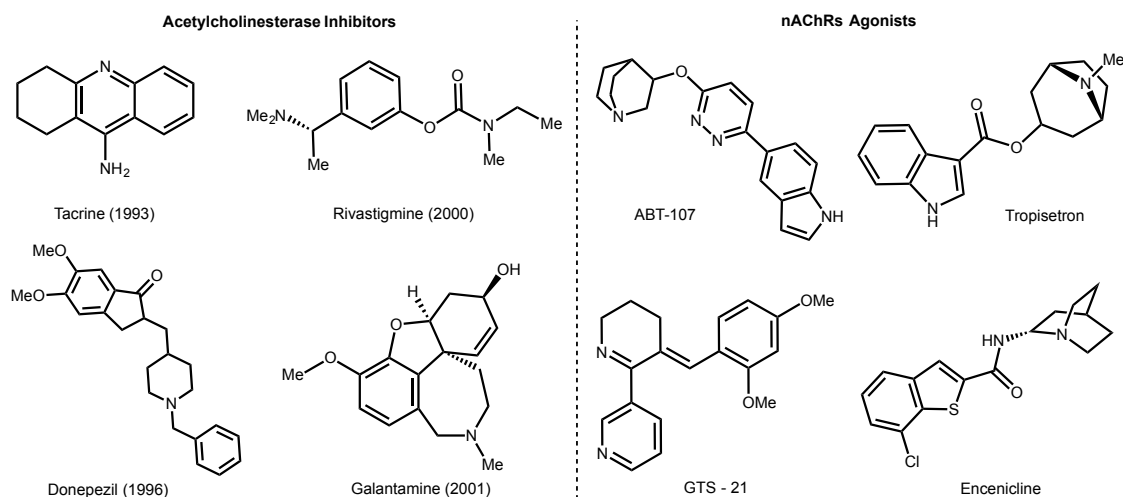


Figure 13: Therapeutic Agents for AD

#### iv. Therapeutic Potential of (–)-205B Targeting Alzheimer's disease

Alzheimer's disease (AD) is a neurodegenerative disease described for the first time in 1907 by Alois Alzheimer, and it is characterized by irreversible brain damage that causes dementia.<sup>49</sup> It shows loss of neurons in the brain especially in the cortex. Although the causes of this disease are still ambiguous and debated, it is known that building up amyloid plaques (consist of amyloid beta protein) and neurofibrillary tangles (composed of tau protein) are the two hallmarks characterizing AD and help in its progression. In addition, most neuroscientists believe that this disease begins when amyloid beta starts to accumulate.

Amyloid plaques are accumulation of amyloid beta (A $\beta$ ) peptides that are normally formed in the brain after the secretase-catalyzed cleavage of the amyloid precursor protein (APP). APP is found at the surface of every neuron. Its primary biological function is not fairly known though more evidences have confirmed the integration of APP in key events of neuronal development. It is implicated in the synapse's formation and neuroplasticity.<sup>50</sup> APP can be sectioned either in amyloidogenic or in non-amyloidogenic pathway. The non-amyloidogenic pathway consists of cleaving the APP by the  $\alpha$ -secretase releasing the soluble APP $\alpha$  oligomers extracellularly that are cleaned away in the body. These fragments are considered to be of neurotrophic and neuroprotective properties.<sup>51</sup> A second

<sup>49</sup> Hippus, H.; Neundörfer, G. *Dialogues Clin. Neurosci.* **2003**, *5*, 101-108.

<sup>50</sup> (a) Turner, P. R.; Kate O'Connor, K.; Tate, W. P.; Abraham, W. C. *Progress in Neurobiology* **2003**, *70*, 1-32. (b) Priller, C.; Bauer, T.; Mitteregger, G.; Krebs, B.; Kretschmar, H. A.; Herms, J. *J. Neurosci.* **2006**, *26*, 7212-7221. (c) Sosa, L. J.; Cáceres, A.; Dupraz, S.; Oksdath, M.; Quiroga, S.; Lorenzo, A. *J Neurochem* **2017**, *143*, 11-29.

<sup>51</sup> Carrillo-Mora, P.; Rogelio Luna, R.; Colín-Barenque, L. *Oxidative Medicine and Cellular Longevity* **2014**.

cleavage is due to the  $\delta$ -secretase found at the plasma membrane releasing the APP intracellular C-terminal domain (AICD) in the cell and the soluble peptide p3 out of the cell. Whereas in the amyloidogenic pathway, the APP is first cleaved by the  $\beta$ -secretase releasing the soluble APP fragment  $\beta$  (sAPP $\beta$ ) followed by the  $\delta$ -secretase to give the AICD intracellularly leaving behind the A $\beta$  peptides monomers out the neurons that are normally degraded by specific enzymes and metabolized by microglia (Figure 14). These peptides have the capacity to interact with similar molecules to self-assemble into insoluble fibrils, which in turn bond with other fibrils to form amyloid sheets. Their molecular conformation makes them strongly resistant to degradation by proteolytic enzymes. The deposition of these A $\beta$  peptides extracellularly is a characteristic of several neurodegenerative diseases; Alzheimer's disease and Down's syndrome.

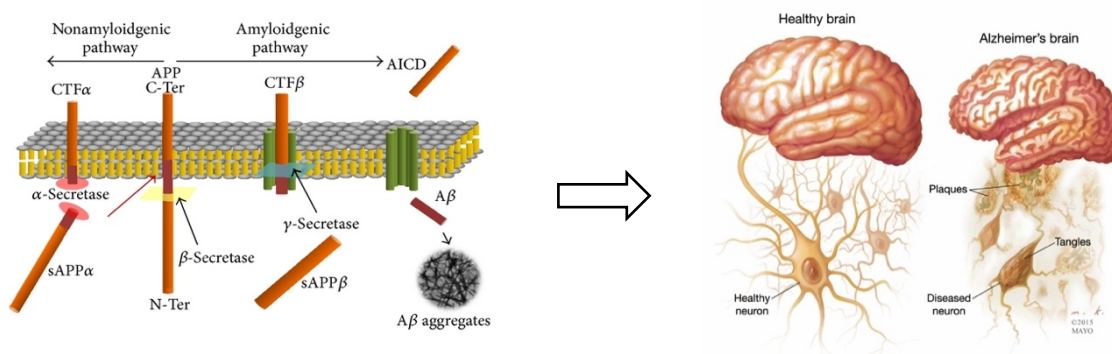


Figure 14: Formation of Amyloid Plaque –AD Brain

Even though most studies focus on the neurotoxic effects of these A $\beta$  peptides causing the neurodegeneration in AD, it was proved that they are of important physiological role. At low concentration, these peptides are found in their monomer soluble form that are proved to exhibit neuroprotective properties. Several studies supported the participation of A $\beta$  in the synaptic activity, memory formation and neuronal cell growth and survival.<sup>52</sup> Moreover, there is evidences indicating that they are of properties conferring species survival such as the anti-microbial and anti-cancer properties.<sup>53</sup> However, the A $\beta$  peptides become pathological only when its production and degradation are imbalanced, thus the effect of these peptides is concentration-dependent. Once the amyloid beta protein is no longer regulated, this led to the overproduction of these sticky peptides

<sup>52</sup> Bishop, G. M.; Robinson, S. R. *Drugs Aging* **2004**, *21*, 621-630.

<sup>53</sup> (a) Pearson, H. A.; Peers, C. J. *Physiol* **2006**, 5-10. (b) Brothers, H. M.; Gosztyla, M. L.; Robinson, S. R. *Frontiers in Aging Neuroscience*, **2018**, *10*.

that will aggregate over time leading to the formation of the indissoluble fibrils and then creating the senile plaques. Consequently, these A $\beta$  peptides become of neurotoxic properties leading to synaptic dysfunction, loss of connection between nerve cells, memory impair and structural damage of the brain. This consolidates the idea of targeting A $\beta$  deposition rather than A $\beta$  production for treating AD.

The amyloid plaques are observed initially in the cortex, secondly in the hippocampus and then it reaches the whole brain. These amyloid plaques will lead later to the formation of neurofibrillary tangles causing eventually cell death.

The brain of AD patients shows a decrease in the  $\alpha_7$  nAChRs.<sup>54</sup> The high affinity of this receptor to A $\beta$  proteins lead to the formation of  $\alpha_7$  nAChRs–A $\beta$  complex thus increasing the concentration of A $\beta$  in the synapse resulting in the formation of plaques and thus leading to the impairment of the signal transmission and neuronal dysfunction. Sequentially, the  $\alpha_7$  nAChRs play a key role in AD pathology.

As a way for treating AD, at what point ideally should neuroscientists intervene to treat this disease? A lot of studies had addressed either the  $\beta$  secretase to modify its production or the enzyme responsible for its degradation. Others focus on keeping amyloid plaques from reaching the tipping point and triggering the cascade.

Drug discovery is largely focused on the development of active agents toward the reduction of A $\beta$  peptide accumulation. The  $\alpha_7$  nAChRs should be the target to prevent the complexation with the peptides. Thus, the use of  $\alpha_7$  nAChR agonist or antagonist can be a possible therapeutic approach for AD as it will compete with  $\alpha_7$  nAChR–A $\beta$  interaction. It is also believed that A $\beta$  peptides also interact with other subtypes of nAChRs contributing in AD pathology that could be targeted for the AD therapy.<sup>55</sup>

There are many examples in the literature of  $\alpha_7$  nAChR agonists that exhibit neuroprotective effect.<sup>44,56</sup> Nicotine has induction effect on these receptors with clearance of these plaques and this justifies the

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<sup>54</sup> Wu, J.; Ishikawa, M.; Zhang, J.; Hashimoto, K. *Int. J. Alzheimers Dis*, **2010**.

<sup>55</sup> Lombardo, S.; Maskos, U. *Neuropharmacology* **2015**, *96 (Pt B)*, 255-262.

<sup>56</sup> Bertrand, D.; Lee, C. L.; Flood, D.; Marger, F.; Donnelly-Roberts, D. *Pharmacol. Rev.* **2015**, *67*, 1025-1073.

fact that tobacco smokers are found with less possibility to have AD. But the toxic side effects of nicotine and its addiction property can't be discarded. However, Cotinine was found to be an interesting molecule to be studied for the AD treatment. It is a nicotine metabolite that was found to improve memory and attention with none of the toxic and addictive effects of nicotine.<sup>57</sup> It was proved to decrease the concentration of the A $\beta$  peptides once treated to mouse model of AD.<sup>58</sup> Also, it was reported that 2-[2-(4-bromophenyl)-2-oxoethyl]-1-methyl pyridinium, S 24795, is a partial agonist selectively acting on the  $\alpha_7$  nAChR and proved to decrease the  $\alpha_7$  nAChR–A $\beta$  complexes (Figure 15).<sup>59</sup>

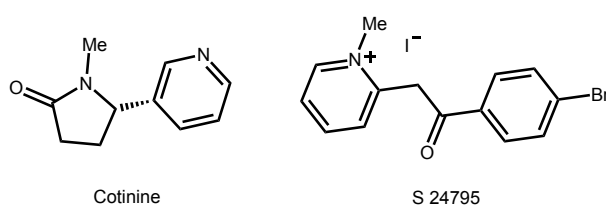


Figure 15: partial agonist for  $\alpha_7$  nAChR

Antagonists to  $\alpha_7$  nAChR have been far less evaluated. Methyllaconitine (MLA); an alkaloid isolated from Delphinium plant species, and  $\alpha$ -bungarotoxin; a polypeptide found in the venom of Taiwanese banded krait snake, are the principal examples.

Recently, another point of view has been reported in the literature. Most recent studies have suggested that the internalization of the A $\beta$  peptide inside the neurons is the earliest marker in AD patients as it is detected before the extracellular senile plaque deposition.<sup>47a</sup> Nonetheless, it was proposed that it might be also the inducing signal for the extracellular A $\beta$  peptide accumulation. These intracellular A $\beta$  proteins were found to affect the synaptic plasticity leading to the axon degradation and eventually cell death. It has been reported that  $\alpha_7$  nAChRs are integrated in this internalization phenomena. Thus again, targeting  $\alpha_7$  nAChRs with either agonist or antagonist can mediate AD therapy by reducing or preventing this internalization.

<sup>57</sup> Hatsukami, D. K.; Grillo, M.; Pentel, P. R.; Oncken, C.; Bliss, R. *Pharmacology Biochemistry and Behavior* **1997**, *57*, 643-650.

<sup>58</sup> Echeverría, P. C.; Forafonov, F.; Pandey, D. P.; Mühlebach, G.; Picard, D. *BioData Mining* **2011**, *4*, 15.

<sup>59</sup> Feuerbach, D.; Lingenhoehl, K.; Olpe, H. R.; Vassout, A.; Gentsch, C.; Chaperon, F.; Nozulak, J.; Enz, A.; Bilbe, G.; McAllister, K.; Hoyer, D.; *Neuropharmacology* **2009**, *56*, 254-263.

Seeking other neurodegenerative diseases, people with Down's Syndrome are also faced to AD-like neuropathology (their brain develop same changes as AD people) in their third decade. The presence of an extra copy of the gene for the amyloid precursor protein (APP) on the chromosome 21 results in the acceleration of the amyloid plaque deposition in their brain.<sup>60</sup> Consequently, any  $\alpha_7$  nAChR agonists might intervene in the binding between A $\beta$  and  $\alpha_7$  nAChR and thus preventing or slowing the cascade that lead to the deposition of amyloid plaques. In such case, this can prevent progressive dementia and improve memory and cognition in people with Down's Syndrome.

On the whole, our interest toward the alkaloid (-)-205B is driven first by the fact that the natural form belongs to the blow-dart poison used by Colombian Indians to paralyze their preys. Furthermore, the possibility that it might act selectively on  $\alpha_7$  nAChR arises the expectation to interfere with neurodegenerative diseases involving aggregation of amyloid beta peptide such as Alzheimer's disease.

Due to the scarcity of this natural product, we decided to embark in the chemical total synthesis of this alkaloid. As an extension of this work, biological evaluation will then be performed in collaboration with biological teams allowing to assess its selective activity toward  $\alpha_7$  nAChR and its ability to modulate the toxicity of A $\beta$  peptides.

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<sup>60</sup> Wisniewski, K. E.; Wisniewski, H. M.; Wen, G. Y. *Ann. Neurol.* **1985**, *17*, 278-282.

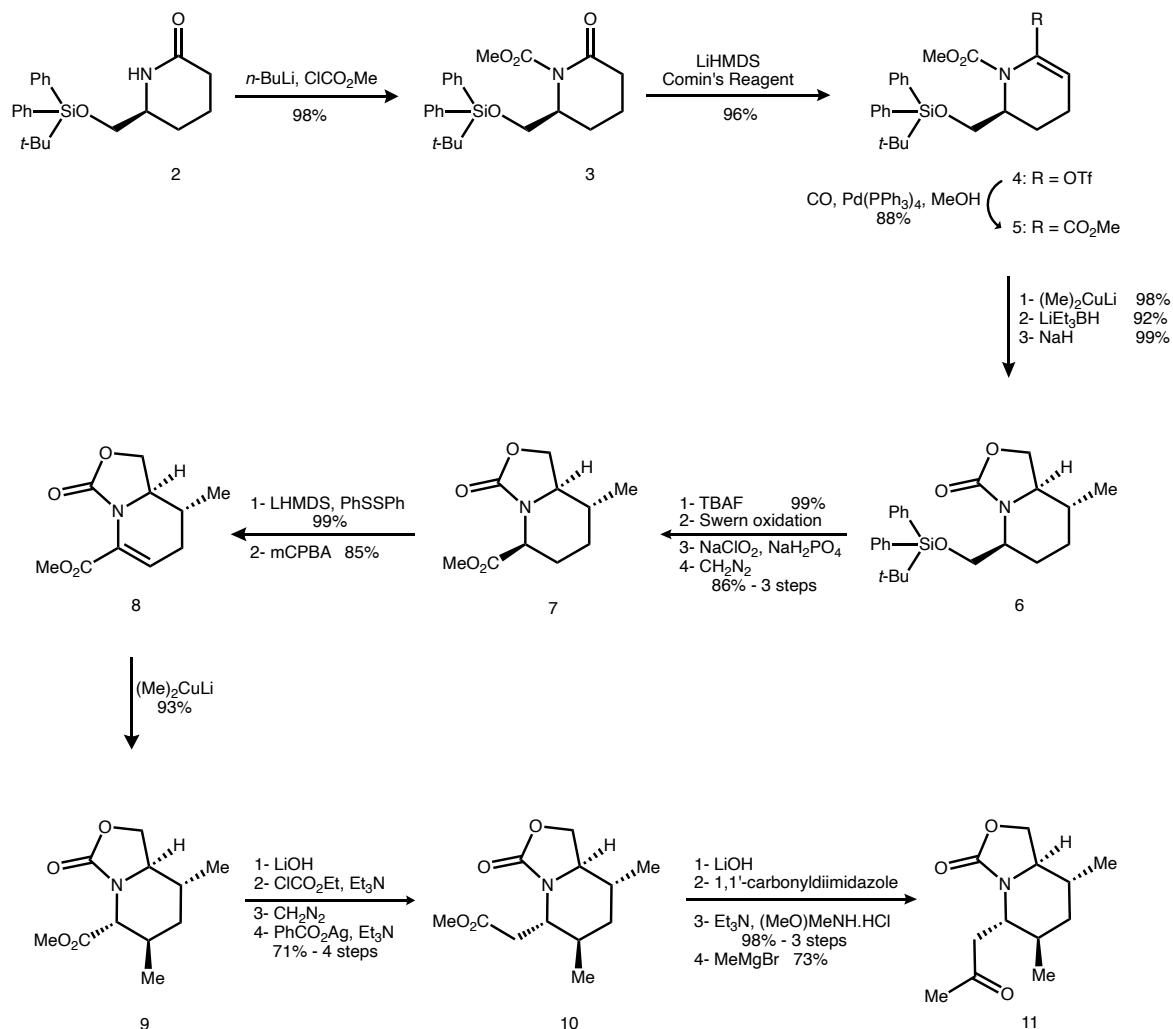


# CHAPTER III: REPORTED SYNTHESSES OF (–)- 205B

The challenged structure of alkaloid **1** coupled with its biological interest prompted several research groups to find out a synthetic approach for this natural product. But till now, its pharmacological properties are not reported yet probably because of its limited abundance.

## I. Toyooka Synthesis

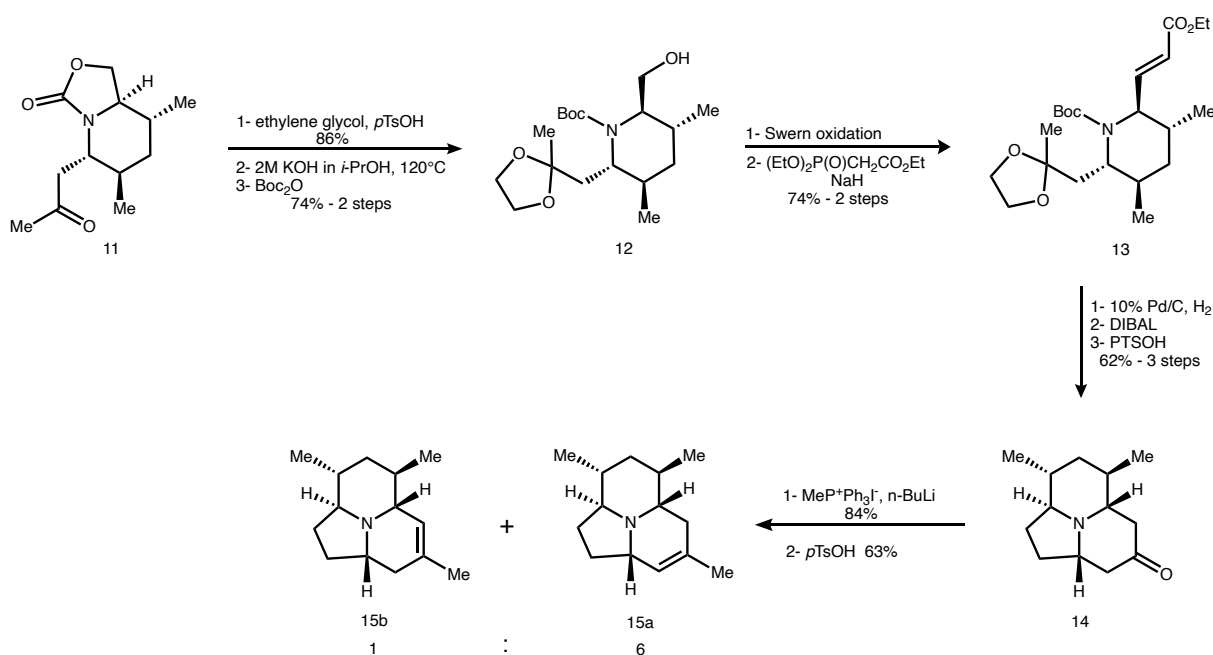
The first enantioselective total synthesis of this structurally unique 205B alkaloid was realized by Toyooka and Nemoto that led to the unnatural antipode **15a**.<sup>61</sup> However, this work had allowed to establish the absolute configuration of the natural product. The synthesis commenced with the enaminoester **5** that was synthesized from the commercially available lactam **2** in 3 steps.



Scheme 1: Synthesis of methyl ketone **11**

<sup>61</sup> Toyooka, N.; Fukutome, A.; Shinoda, H.; Nemoto, H. *Angew Chem Int Ed* **2003**, *42*, 3808-3810. See also: Toyooka, N.; Fukutome, A.; Shinoda, H.; Nemoto, H. *Tetrahedron* **2004**, *60*, 6197-6216.

Upon the steric and stereoelectronic effects, treating the enaminoester **5** with Gilman reagent allowed the axial attack of the methyl group forming the methylated product as a single stereoisomer. The N-methoxy carbonyl group is believed to direct this addition by freezing the ring conformation with the methyl silyloxy substituent in an axial orientation owing to 1,3-allylic strain. After the reduction of the ester group, the oxazolidinone ring **6** was constructed in basic medium. The carbamate intermediate **7** was furnished through a series of deprotection, oxidation and esterification. This intermediate **7** was subjected to oxidative elimination protocol. The second stereoselective key step was the Michael reaction that afforded again only the desired isomer **9** favoring the axial position of the methyl group due to stereoelectronic effect. Then the latter intermediate **9** is homologated by 4 steps to intermediate **10** via Arndt-Eistert sequence. Transformation of ester **10** to methyl ketone **11** was done via the Weinreb's amide.



Scheme 2: Completion of Toyooka synthesis of (+)-205B

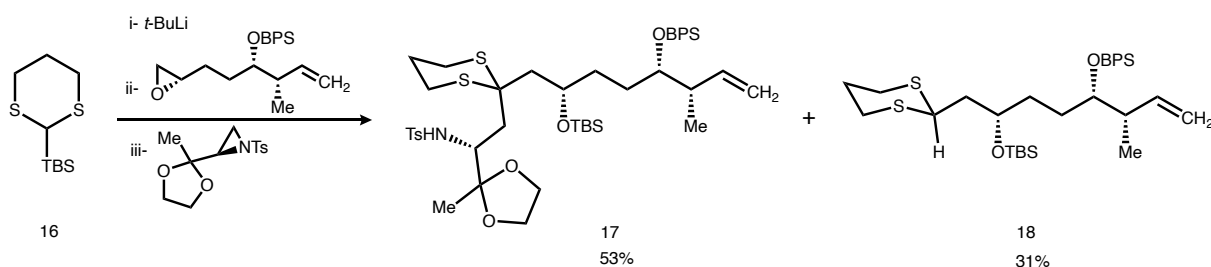
The corresponding ketone **11** formed from the ester group is then protected as acetal, followed by hydrolysis of the oxazolidinone ring and amine-Boc protection (**12**). Simple Swern oxidation and Horner-Wadsworth-Emmons olefination yielded piperidine **13**. The tricyclic core of the target product was constructed via intramolecular Mannich-type cyclization affording the ketone intermediate **14**. Finally, the alkaloid (+)-205B **15a** was obtained after Wittig olefination forming the exo-alkene followed

by the regioselective acid-catalyzed isomerization revealing that the desired isomer **15a** is lower in energy than the other isomer **15b** (6:1 ratio respectively).

This synthesis is characterized by the elegant control of the stereochemistry and the efficient formation of the tricyclic framework. However, due to several transformation of functional groups, the main drawback of this sequence is the length of the synthesis (30 steps).

## II. Smith Synthesis

Soon after, Smith and Kim accomplished in 2005 the first total synthesis of the alkaloid (-)-205B in 27 steps.<sup>62</sup> He exploited more the “Umpolung” chemistry of silyl 1,3-dithianes **16** that was introduced by Corey and Seebach in 1965,<sup>63</sup> where a chiral epoxide (prepared in 9 steps from commercial compounds) and chiral *N*-Ts aziridine (prepared in 4 steps from serine derivative) were used as electrophiles to access to the 1,5-amino alcohol **17** through Brook rearrangement. (Scheme 3)



Scheme 3 : Synthesis of intermediate 17

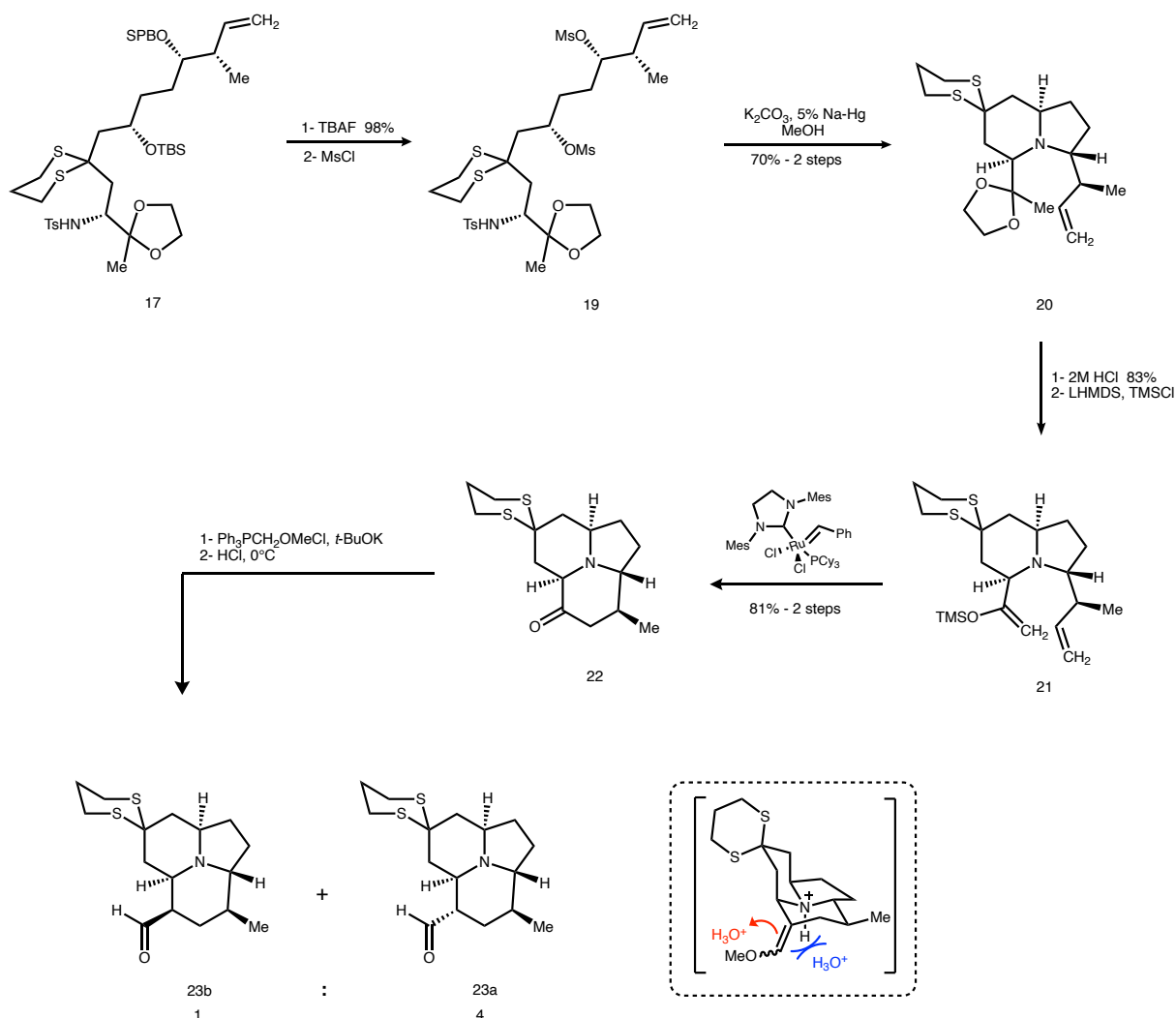
Treating the tosylated amine with Na-amalgam led to the sequential nitrogen deprotection and cyclization through a double displacement of the corresponding bimesylated diols **19** allowing the construction of the indolizidinone ring **20**. Unmasking the embedded ketone as acetal followed by the formation of the corresponding silyl enol ether **21** led to the 8b-azaacenaphthylene tricyclic ring **22** via ring closing metathesis.

The next mission was the challenging stereoselective installation of the axial methyl group. After several experimentation, this was achieved by Wittig olefination followed by acid hydrolysis resulting in the formation of the desired axial aldehyde as the major isomer **23a** (4:1 ratio). Electrostatic repulsion

<sup>62</sup> (a) Smith, A. B., III; Kim, D.-S. *Org. Lett.* **2005**, *7*, 3247-3250. (b) Smith, A. B., III; Kim, D.-S. *J. Org. Chem.* **2006**, *71*, 2547-2557.

<sup>63</sup> (a) Corey, E. J.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 1075. (b) Seebach, D.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 231.

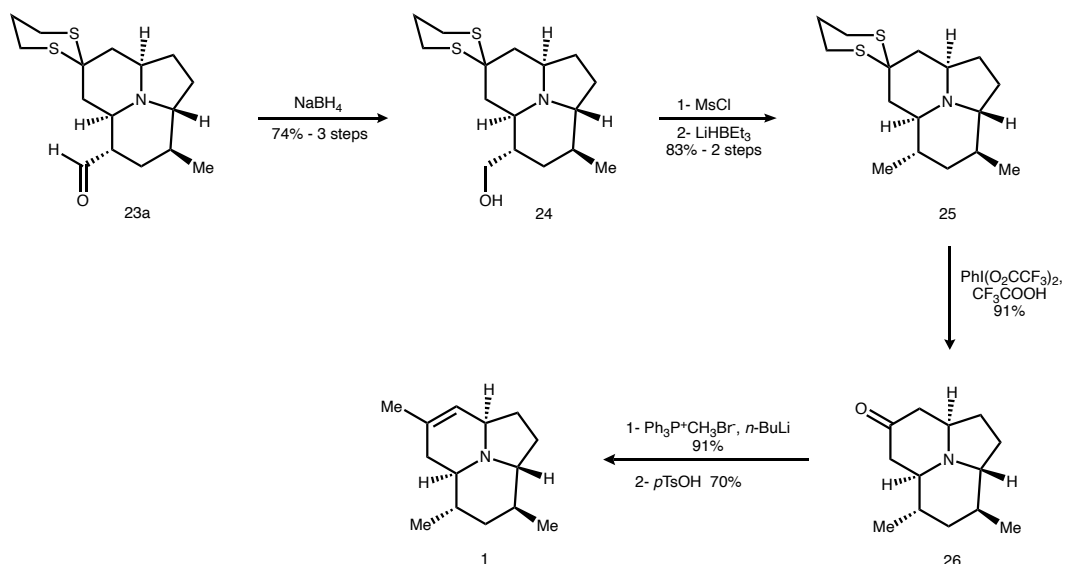
favors the equatorial approach of the proton, where the repulsion between the protonated amine and the upcoming axial hydronium ion disfavors this delivery. (*Scheme 3*)



*Scheme 4: Synthesis of intermediate 23a*

The desired methyl group **25** was formed by successive reductions followed by applying the Stork protocol to remove the dithiane producing the ketone **26**. The last step to furnish the alkaloid **1** was same as Toyooka's comprising of methylenation and isomerization. (*Scheme 5*)

This synthetic pathway is distinguished by the efficient linchpin coupling strategy developed by Smith. However, this approach is accomplished in 27 steps to reach the final product starting from commercially available starting materials. In addition, it presents the difficulty of introducing the axial oriented methyl substituent.



Scheme 5: Completion of Smith Synthesis

### III. Comins Synthesis

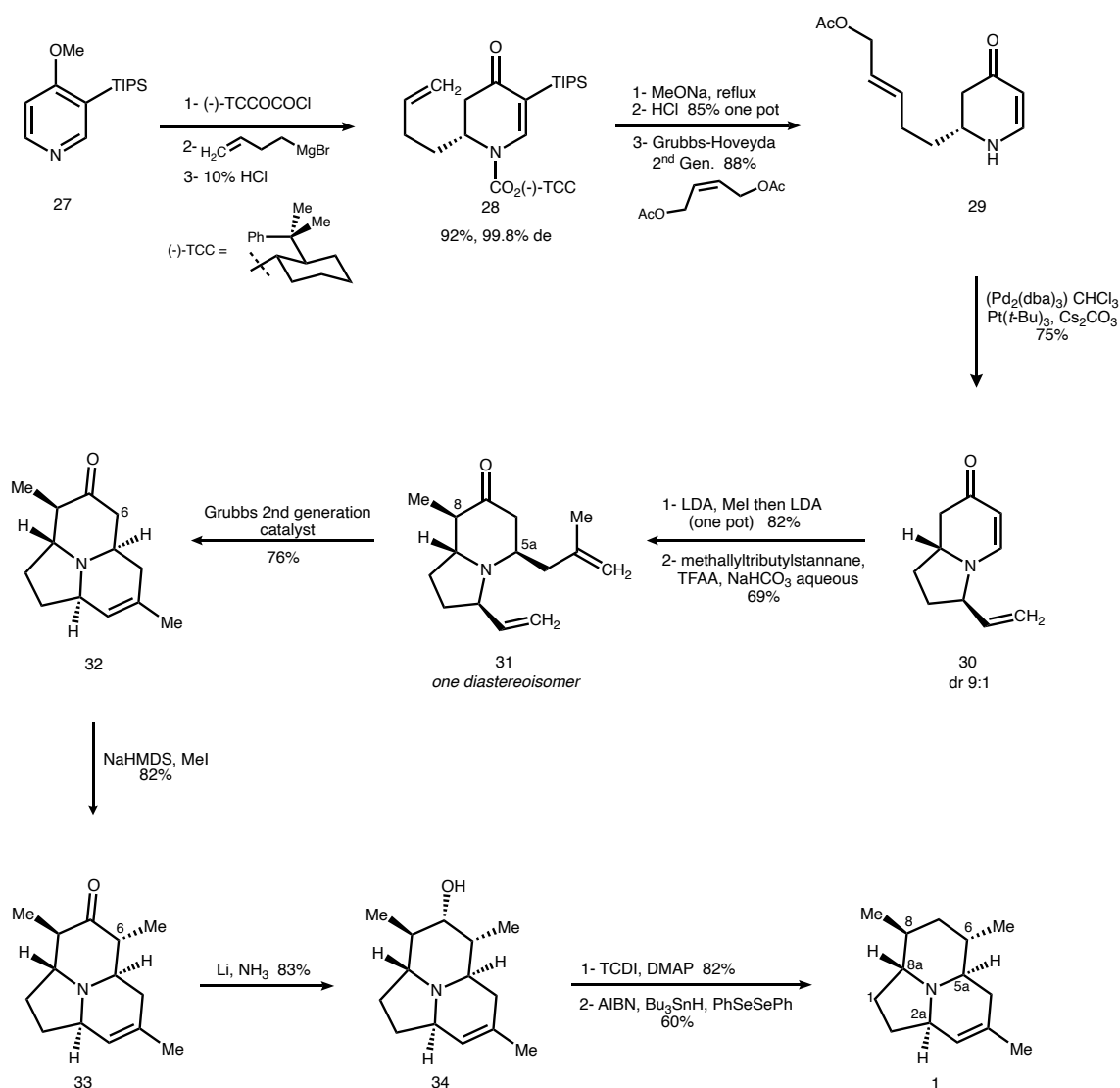
In 2011, another concise and highly stereocontrolled total synthesis of this alkaloid was reported by Comins and Tsukanov (*Scheme 6*).<sup>64</sup> The synthesis started with the enantiopure dihydropyridone **28** that was prepared according to the author developed asymmetric addition of Grignard reagent on the in situ formed chiral *N*-acylpyridinium salt of 4-methoxy-3-(triisopropylsilyl)pyridine **27**.<sup>65</sup> This dihydropyridone **28** undergoes deprotection followed by cross metathesis with (*Z*)-but-2-ene-1,4-diyl acetate using the Grubbs-Hoveyda 2<sup>nd</sup> generation catalyst forming the pyridone **29**. Then the indolizidone ring **30** was constructed utilizing the intramolecular Tsuji-Trost allylic amination in a highly optimized conditions for high diastereoselective outcome (minor isomer not shown).

The stereoselective introduction of the equatorial methyl group at C<sub>8</sub> was achieved by a direct alkylation that leads to the expected methylated product in a fairly low diastereomeric ratio. Fortunately, only the desired isomer could be obtained by careful kinetic protonation of the enolate of the methylated mixture. After extensive experimentation, the axial 5a-methyl group was introduced by

<sup>64</sup> (a) Tsukanov, S. V.; Comins, D. L. *Angew. Chem. Int. Ed.* **2011**, *50*, 8626-8628. (b) Tsukanov, S. V.; Comins, D. L. *J. Org. Chem.* **2014**, *79*, 9074-9085.

<sup>65</sup> (a) Comins, D. L.; Chen, X.; Morgan, L. A. *J. Org. Chem.* **1997**, *62*, 7435-7438. (b) Comins, D. L.; Joseph, S. P.; Goehring, R. R. *J. Am. Chem. Soc.* **1994**, *116*, 4719-4728.

conjugate addition of methallyl tributystannane to the enone activated by the trifluoroacetic anhydride followed by aqueous hydrolysis of the vinyl acetate intermediate.



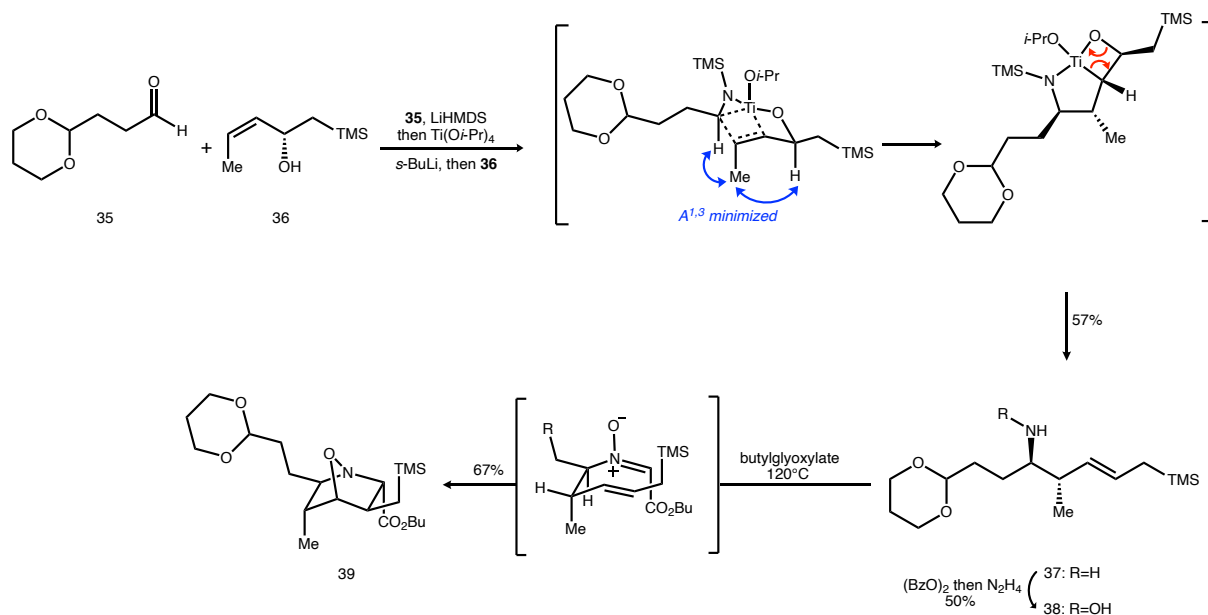
*Scheme 6: Comins Synthesis of (-)-205B*

Introducing the axial C<sub>6</sub>-methyl group as a single stereoisomer was achieved with the rigid tricyclic ring system **32** in hand, otherwise a mixture of inseparable diastereoisomers was obtained if methylation was done on the indolizidinone **31**. Thereby, the ring closing metathesis of **31** was conducted using Grubbs second-generation catalyst followed by stereoselective enolate alkylation to introduce the axial methyl group at C<sub>6</sub> to afford the tricyclic intermediate **33**. Reductive cleavage of the ketone was accomplished through a three-step protocol. Birch reduction of the ketone generated only the equatorial alcohol **34** which was reduced through a modified Barton-McCombie strategy using PhSeH as the hydrogen donor to give the targeted natural product **1**.

This approach is characterized by its limited number of steps (15 steps from the commercially available 4-methoxy pyridine). However, it has shown the difficulty of introducing the methyl substituents in high stereoselectivity and the challenging Barton-McCombie deoxygenation.

## IV. Micalizio Synthesis

Another asymmetric synthesis of the alkaloid (–)-205B was proposed by Micalizio and Yang in 2012 involving 2 stereoselective methods: the Ti-mediated reductive cross-coupling and a stereoselective intramolecular [3+2] cycloaddition.<sup>66</sup> The cross coupling reaction between aldehyde **35** and allylic alcohol **36**, prepared in 2 steps from commercially available ethyl TMS acetate, was done via the intermediacy of the TMS-imine obtained by the reaction of the aldehyde **35** with the excess of LiHMDS. The stereocontrol is believed to result from the boat-like transition state geometry avoiding the 1,3-allylic strain, followed by syn elimination of the oxatitanacyclobutane intermediate allowing the formation of the intermediate **37**. (*Scheme 7*)



*Scheme 7: Synthesis of Intermediate 39*

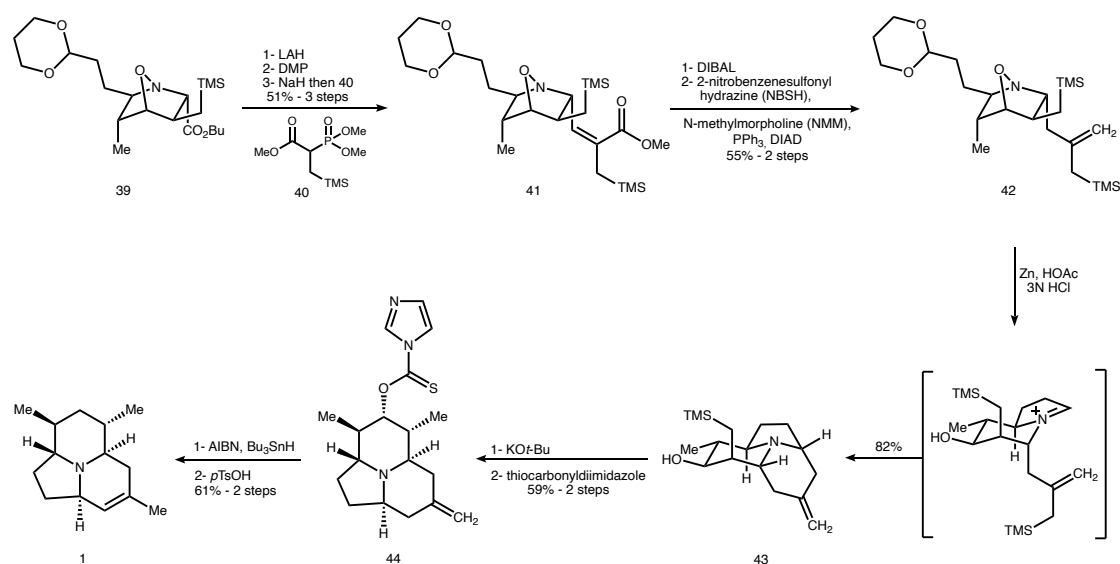
Oxidation of the primary amine followed by the highly stereoselective intramolecular [3+2] cycloaddition upon heating with butylglyoxylate afforded the piperidine intermediate **39** (*Scheme 7*).

<sup>66</sup> Yang, D.; Micalizio, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 15237-15240.



The latter step proceeds through the generation of the nitron intermediate by the condensation of hydroxyl amine with butylglyoxylate, which in turn undergoes direct [3+2] cycloaddition.

After functional group transformation and Horner-Emmons reaction, the corresponding olefin **41** was converted to the *exo*-allylic silane **42** by sequential reduction and Myers deoxygenation.<sup>67</sup> The next key step was the one pot acid-induced aza-Sakurai reaction. It was performed by unmasking the embedded aldehyde and reductive cleavage of the N–O bond that lead to the formation of the iminium intermediate delivering the tricyclic product **43**. Finally, the alkaloid **1** was formed after a sequence of proto-desilylation, deoxygenation and isomerization steps. (*Scheme 8*)



*Scheme 8: Completion of Micalizio Synthesis*

This synthetic pathway was realized in 15 steps with 0.7% overall yield and it is mainly characterized with the high control over the stereogenic centers.

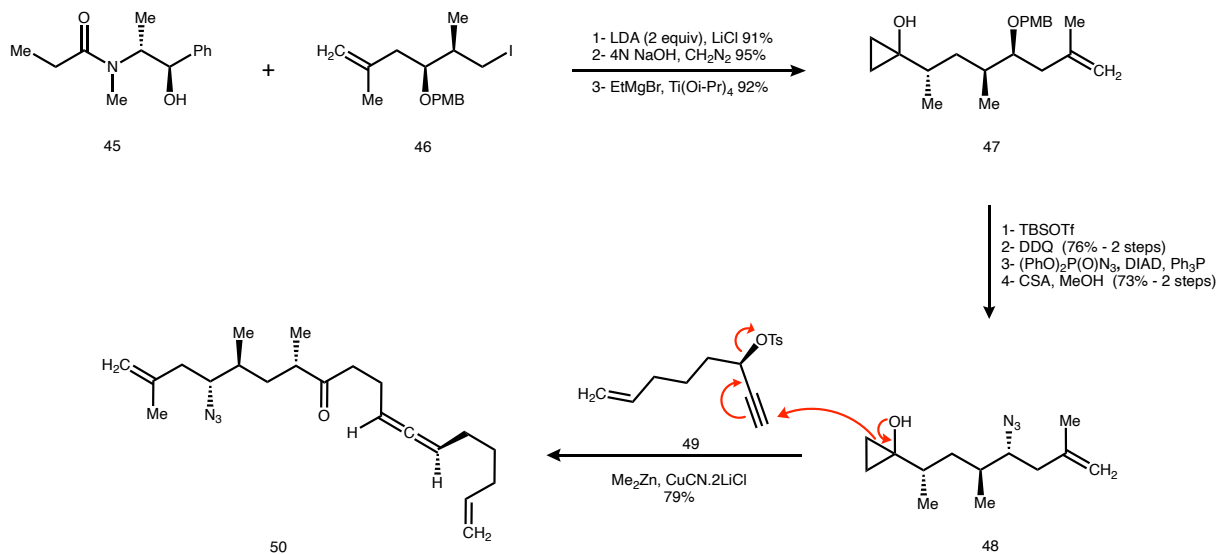
## V. Cha Synthesis

Lastly in 2015, Cha and Rao<sup>68</sup> provided another synthetic approach for this alkaloid. It is based on an anti-S<sub>N</sub>2' alkylation, an electrophilic allene cyclization and a ring closing metathesis for the endocyclic double bond formation in **1** (*Scheme 10*).

<sup>67</sup> (a) Myers, A. G.; Zheng, B. *Tetrahedron Lett.* **1996**, *37*, 4841-484. (b) Myers, A. G.; Movassaghi, M.; Zheng, B. *J. Am. Chem. Soc.* **1997**, *119*, 8572-8573.

<sup>68</sup> Rao, N. N.; Cha, J. K. *J. Am. Chem. Soc.* **2015**, *137*, 2243-2246.

The cyclopropanol **47** was first prepared in 3 steps including Myers' asymmetric alkylation<sup>69</sup> and Kulinkovich cyclopropanation<sup>70</sup> from the commercially available pseudo-ephedrine derivative **45** and the iodide **46** (prepared from the corresponding diol<sup>71</sup>). Following the stereoselective substitution with azide, the formed cyclopropanol **48** was used as homoenolate precursor which undergoes an anti-S<sub>N</sub>2' reaction with the chiral propargylic tosylate **49** affording the intermediate **50**. The tosylate partner **49** is accessible in 9 steps from diethyl *L*-tartrate.<sup>72</sup>

Scheme 9: Synthesis of Intermediate **50**

Staudinger reduction of the azide led to in situ formation of the corresponding cyclic imine **51**. The stereoselective formation of 2,6-trans-piperidine **52** was challenging as to provide the hydride from the back-face despite of the steric hindrance. Moreover, the applied condition should avoid the epimerization of the  $\alpha$ -chiral center through the formation of enamine. After extensive experimentation, this stereoselective reduction was achieved by using LAH in Et<sub>2</sub>O to give a 15:1 mixture in favor of the desired isomer **52** as a consequence of the stereoelectronic requirements on the preferred conformation depicted in *Scheme 10*. It is worthy to note that this high selectivity is observed only when using Et<sub>2</sub>O as solvent. No further investigation was performed to elucidate the

<sup>69</sup> (a) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496. (b) Myers, A. G.; Yang, B. H. *Org. Synth.* **2000**, *77*, 22.

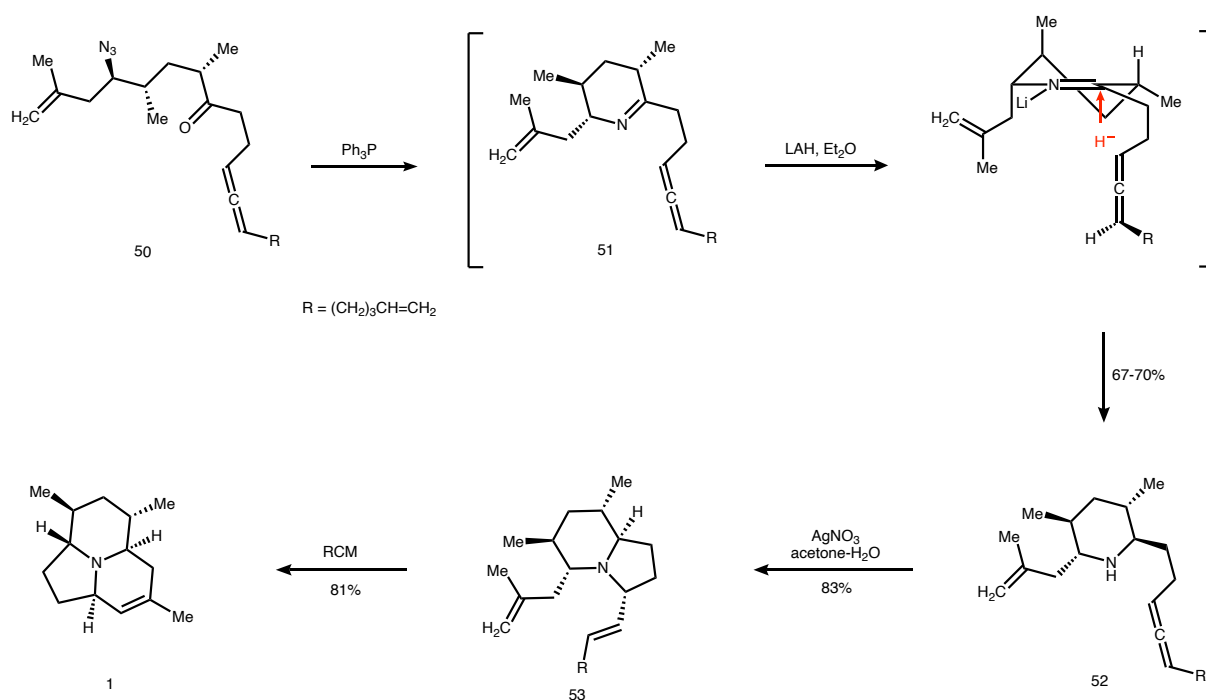
<sup>70</sup> (a) Kulinkovich, O. G.; de Meijere, A. *Chem. Rev.* **2000**, *100*, 2789. (b) Kulinkovich, O. G. *Chem. Rev.* **2003**, *103*, 2597.

(c) Cha, J. K.; Kulinkovich, O. G. *Org. React.* **2012**, *77*, 1.

<sup>71</sup> (a) Stefan, E.; Taylor, R. E. *Org. Lett.* **2012**, *14*, 3490. (b) Alegret, C.; Santacana, F.; Riera, A. *J. Org. Chem.* **2007**, *72*, 7688.

<sup>72</sup> (a) Mukai, C.; Sonobe, H.; Kim, J. S.; Hanaoka, M. *J. Org. Chem.* **2000**, *65*, 6654-6659. (b) Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **1987**, *52*, 3337-3342.

principle importance of this solvent that could favor the appropriate conformation for unidentified reasons.



*Scheme 10: Completion of Cha Synthesis*

Stereoselective cyclization of the amino allene **52** involving chiral transfer from the enantiopure allene to form 3,5-cis indolizidinone **53** was promoted by silver. Finally, the desired alkaloid **1** was achieved through RCM allowing the formation of the endocyclic olefin.

Up to date, it seems that this synthesis (*Scheme 10*) is the shortest where it was accomplished in 12 steps. However, the preparation of reagents **46** and **49** requires an additional 7 and 9 steps respectively, rendering this sequence of 28 steps at least.

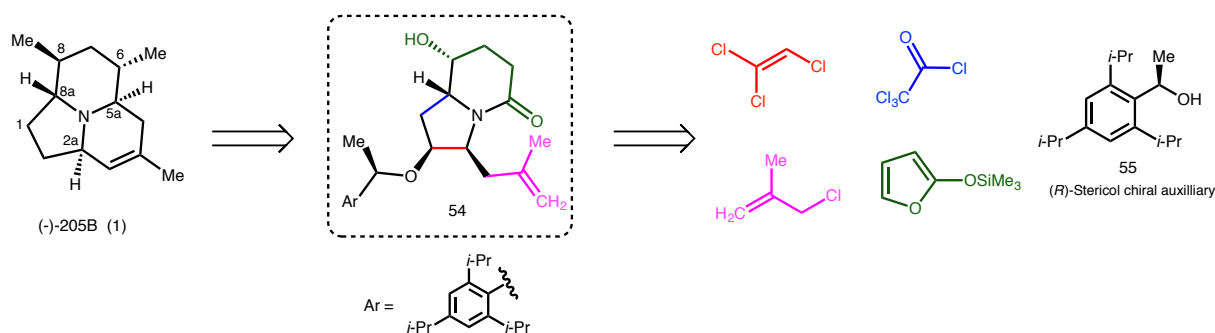
# CHAPTER IV: START OF THE JOURNEY TOWARD (–)-205B

With this overview of the reported syntheses of the chiral alkaloid 205B in the literature, our research study has been directed for the development of another synthetic approach targeting this natural products (-)-205B (**1**). Accordingly, the intended biological studies of **1** will allow revealing its pharmacological properties.

## I. Retrosynthetic Strategy of Alkaloid (-)-205B

The synthesis, started some years ago, is based on the powerful strategy developed by Greene *et al.*<sup>73</sup> leading to the chiral pyrrolidinone through a highly stereoselective [2+2] cycloaddition of dichloroketene and a chiral enol ether. This strategy highlights the remarkable ability of the easily available chiral alcohol **55** (Stericol) as an external chiral inductor.<sup>74</sup> In addition, several readily accessible commercial building blocks were the starting point of the highly stereoselective formation of an advanced intermediate, indolizidinone **54**. (*Scheme 11*)

Despite of the elegant synthetic strategy developed so far to reach **54**, the alkaloid of interest **1** remained difficult to access due to faced constraints in the subsequent steps. Driven by these chemical difficulties and by the final goal regarding the biological evaluations, a new chemistry was then explored as an entry to the target compound **1**.



*Scheme 11: Retrosynthetic Strategy of (-)-205B*

The strategy detailed in this chapter for the synthesis of intermediate **54** was reproduced during this work on large scale and being applied in its chiral version.

<sup>73</sup> Deprés, J.; Delair, P.; Poisson, J.; Kanazawa, A.; Greene, A. E. *Acc. Chem. Res.* **2016**, *49*, 252-261.

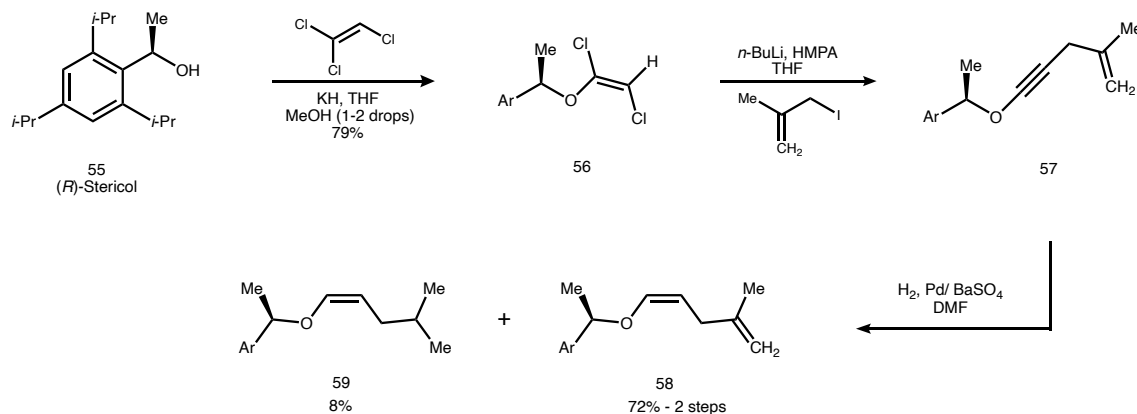
<sup>74</sup> Delair, P.; Kanazawa, A. M.; de Azevedo, M. B. M.; Greene, A. E. *Tetrahedron Asymmetry*, **1996**, *7*, 2707-2710.

## II. Synthesis of Indolizidinone Intermediate

Application of this strategy to the synthesis of the non-chiral pool 205B alkaloid led to the publication of the “first trial” approach which will be described briefly in this section.<sup>75</sup> The correct absolute stereochemistry responsible for the formation of (-)-205B is displayed in the schemes of this chapter, however the results of this first approach were obtained as racemic.

### i. Synthesis of Enol Ether

On the basis of precedent work for the formation of the chiral pyrrolidinone intermediate,<sup>76</sup> the synthesis commenced by the successive deprotonation of the inductor, ( $\pm$ )-Stericol **55**, with potassium hydride. Thereafter, the alcoholate ion attack the dichloroethyne, formed in situ by the deprotonation–elimination of trichloro ethylene. Addition of 1–2 drops of MeOH speeds up the reaction as it increases the concentration of the base in the reaction mixture. The corresponding dichloroenol ether **56** was isolated in 79% yield after purification.



*Scheme 12: Synthesis of Enol Ether 58*

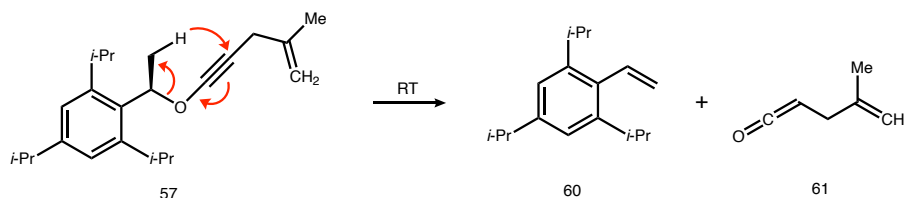
The enol ether **56** was transformed to ynoenol ether **57** by treating it with 2 equiv of *n*-BuLi and allyl iodide. The mechanism of this step consists of syn elimination of HCl forming the corresponding chloro-alkyne followed by lithium–halogen exchange to form the acetylide ion that is responsible for the S<sub>N</sub>2 substitution with the methyl allyl iodide.<sup>77</sup> The formed ynoenol ether **57** was observed to be thermally unstable generating variable amount of styrene derivative **60** along with the ketene **61** which

<sup>75</sup> Kamath, A.; Fabritius, C.; Philouze, C.; Delair, P. *Org. Biomol. Chem.* **2015**, *13*, 9834-9843.

<sup>76</sup> Roche, C.; Kadlečíková, K.; Veyron, A.; Delair, P.; Philouze, C.; Greene, A. E. *J. Org. Chem.* **2005**, *70*, 8352-8363.

<sup>77</sup> Darses, B.; Milet, A.; Philouze, C.; Greene, A.; Poisson, J. F. *Org. Lett.* **2008**, *10*, 4445-4447.

was not identified nor any other subsequent byproducts according to the following proposed mechanism (*Scheme 13*).<sup>78</sup> Isolation of this ynol ether **57** could be possible only by keeping the temperature as close to 0°C as possible during the work-up procedure and was used for the next step without any further purification.

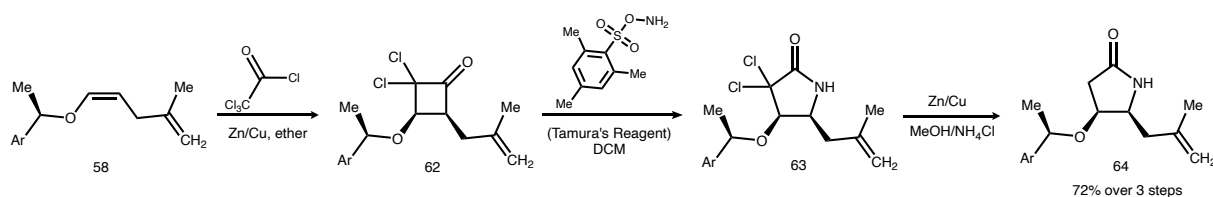


*Scheme 13: Decomposition of Ynol Ether 57*

Hydrogenation of the alkyne **57** to cis alkene **58** was achieved with Rosenmund catalyst in presence of ethylene diamine and 1-hexene that prevent the over reduction of the alkenes especially the terminal one. Nevertheless with all these precautions, 8% of the dihydroenol ether **59** was formed (identified from <sup>1</sup>H NMR of crude material). (*Scheme 12*)

## ii. Formation of Lactam Intermediate

The enol ether **58** was then transformed to lactam **64** by a highly stereoselective [2+2] cycloaddition with ketene forming first the cyclobutanone **62**, followed by Beckman rearrangement for ring expansion to the corresponding dichlorolactam **63**. In both reactions, regioselectivity and stereoselectivity are of great importance and fully controlled. Zn-mediated reductive dehalogenation then gave the chiral lactam **64** that was isolated in 72% yield from enol ether **58**.<sup>75</sup> (*Scheme 14*)



*Scheme 14: Synthesis of Lactam Intermediate 64*

The first key reaction in this pathway is the thermal [2+2] cycloaddition between the enol ether **58** and the dichloro-ketene. This ketene is generated in situ by dehalogenation of the trichloroacetyl

<sup>78</sup> Ramasheshan, M. L.L.; MaGee, D. I. *Tetrahedron* **1993**, *49*, 2159-2168.

chloride upon treating it with activated zinc.<sup>79</sup> The reaction proceeds smoothly forming a single regioisomer of the expected cyclobutanone **62** with high diastereomeric excess (95:5).

In the conventional knowledge; thermal [2+2] cycloaddition forming cyclobutanes are thermally symmetric forbidden but photochemically allowed based on the  $\text{HOMO}_{\text{alkene}}$  and  $\text{LUMO}_{\text{ketene}}$  interaction.<sup>80</sup> In contradiction, ketene-alkene thermal cycloadditions are orbital-symmetry allowed which it is analyzed by the concerted  $[\pi 2_s + \pi 2_a]$  reaction mechanism.<sup>81</sup> The ketene approaches antarafacially that is geometrically favored as they are linear and sterically less encumbered than alkene. (Figure 16)

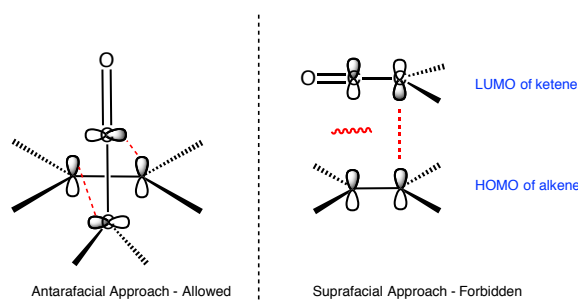


Figure 16: Possible mechanisms of [2+2] cycloaddition

More precisely, the reaction is now described, according to Burke's suggestion<sup>82</sup>, to proceed through a concerted non-synchronous process which follows  $[\pi 2_s + (\pi 2_s + \pi 2_s)]$  mechanism<sup>83</sup> which is illustrated in Figure 17. This mechanism counts for the non-synchronous formation of the bonds giving rise to partial separation of charges.

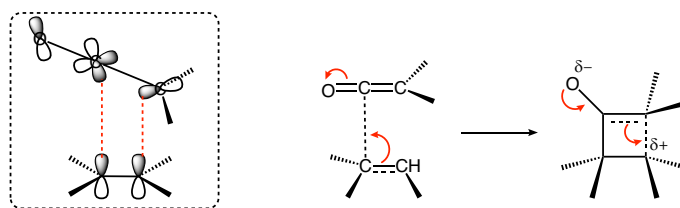


Figure 17: orbital interaction –  $\pi$  electron movements associated with  $[\pi 2_s + (\pi 2_s + \pi 2_s)]$  mechanism

The [2+2] cycloaddition reactions are known to proceed with high degree of regioselectivity and stereoselectivity. The high degree of regiocontrol observed when non-symmetrical alkenes are used

<sup>79</sup> Brady, W. T. *Tetrahedron* **1981**, *37*, 2949-2966.

<sup>80</sup> Woodward, R. B.; Hoffman, R. *Angew. Chem. Int. Ed., Engl.* **1969**, *8*, 781.

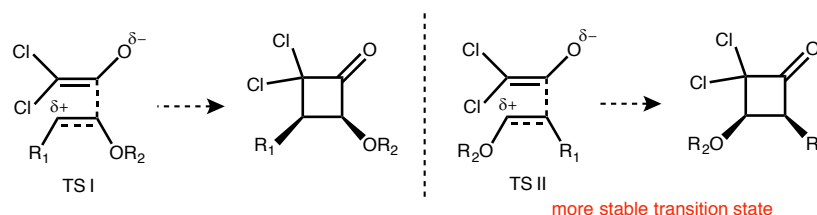
<sup>81</sup> Woodward, A. B.; Hoffmann, R. "The Conservation of Orbital Symmetry", Verlag-Chemie, Academic Press, Weinheim, **1970**, p 68.

<sup>82</sup> Burke, L.A. *J. Org. Chem.* **1985**, *50*, 3149-3155.

<sup>83</sup> Valenti, E.; Pericas, M. A.; Moyano, A. *J. Org. Chem.* **1990**, *55*, 3582-3593.



as a consequence of electronic effects in the transition state. Due to the non-synchronous mechanism of this reaction, the partial positive charge should be located on the carbon with richer electron environment. *Figure 18* shows the 2 possible transition states through which this reaction could pass taking into account its concerted non-synchronous type. Transition state II is of lower energy as the electron deficiency on the carbon is much more compensated by the alkoxy group due to its electron donating property.



*Figure 18: 2 possible transition states of [2+2] cycloaddition*

Regarding the diastereospecificity, the stereochemistry of the alkene is retained in the final cyclobutanone product. On the other hand, appending the (*R*)-Stericol alcohol to the alkene had induced facial selectivity, where the diastereoselectivity of this reaction is believed to be induced by this external chiral auxiliary group. According to a previously reported synthesis, theoretical calculations showed that one conformer of enol ether is greatly favored over the other.<sup>84</sup> This lowest energy conformation had a face of the olefin blocked by one of the isopropyl groups thus orienting the approach of the ketene mainly from the other face.

Cyclobutanones are useful intermediates that possess synthetic interest as it undergoes facile ring expansions in order to relieve ring strain.<sup>85</sup> Later on, Baeyer–Villiger oxidation, Beckman rearrangement and pinacol-type rearrangement conditions were more developed that give rise to lactones, lactams and cyclopentanones derivatives respectively.

Lactam **64** represents a key intermediate in this synthetic pathway that is obtained through Beckman rearrangement. This ring expansion is fulfilled by treating the cyclobutanone with the synthesized Tamura's reagent (*O*-mesitylenesulphonylhydroxylamine, MSH) with high degree of regioselectivity

<sup>84</sup> Roche, C.; Greene, A. E.; Delair, P. *Org Lett.* **2003**, *10*, 1741-1744.

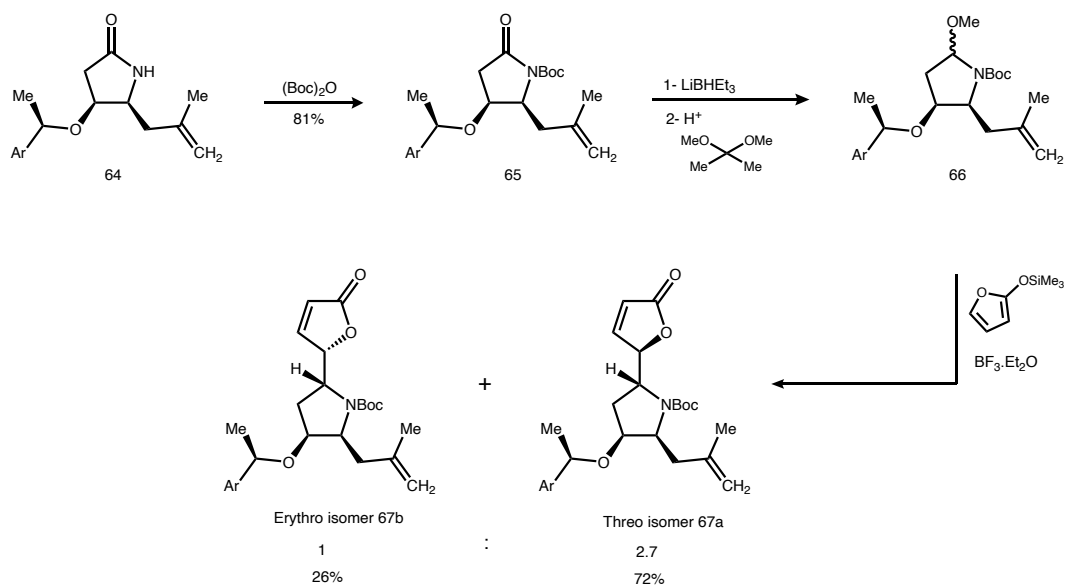
<sup>85</sup> (a) Canales, E.; Corey, E. J. *J. Am. Chem. Soc.* **2007**, *129*, 12686-12687. (b) Miesch, M.; Wendling, F. *Eur. J. Org. Chem.* **2000**, 3381-3392. (c) Conia, J. M.; Robson, M. J. *Angew. Chem. Int. Ed.* **1975**, *14*, 473-485.

and stereospecificity.<sup>86</sup> The electronic effect is responsible for this region-control where the presence of the 2 chlorine atoms at  $\alpha$ -position decrease electron density on the adjacent bond.<sup>87</sup> Thus, directing the regioselectivity through reducing the migration aptitude of the adjacent C–C bond results in only one isomer of the lactam **63**. The anionotropic nature of this rearrangement ensures the stereo-integrity of the migrating chiral center. Both cyclobutanone **62** and dichlorolactam **63** are susceptible to degradation over silica gel thus no purifications were attempted.

### iii. Formation of Indolizidinone

Construction of the indolizidinone ring **54** was planned to be formed through intramolecular cyclization of the amine with a butenolide group, which in turn is synthesized from pyrrolidinone **64** via vinylogous Mannich reaction.

This synthesis started with the protection of the lactam **64** with Boc group that was performed in 81% yield. The formed Boc-lactam **65** was subjected to partial reduction followed by conversion of hydroxyl into methoxy group forming the hemiaminal derivative **66**. The second key step of this strategy was the vinylogous Mannich reaction that control the stereochemistry of 2 chiral centers. (*Scheme 15*)



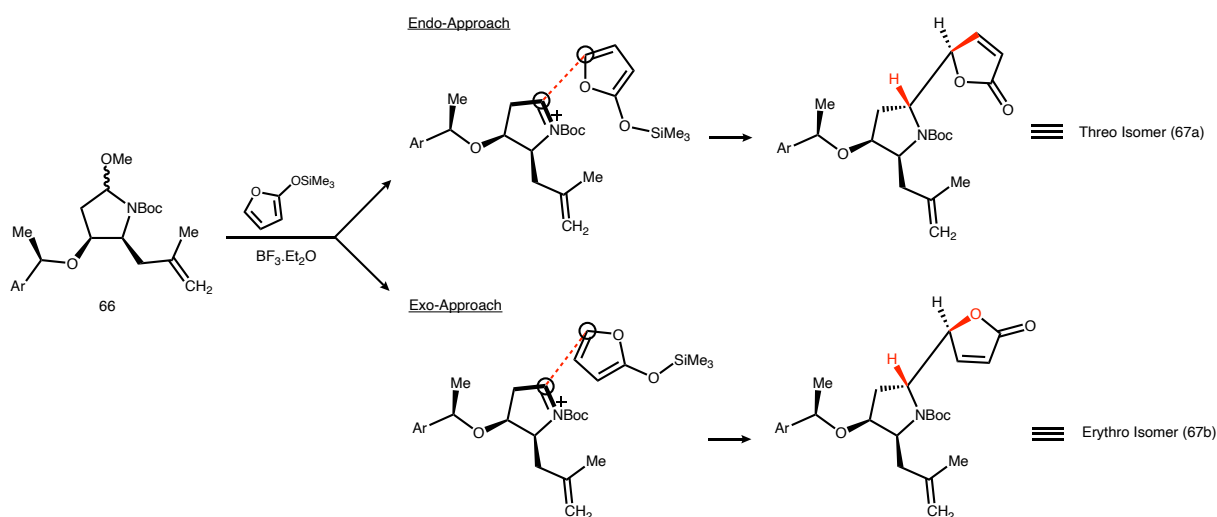
*Scheme 15: Synthesis of Butenolide Intermediate 67a*

<sup>86</sup> (a) Tamura, Y.; Minamikawa, J.; Ikeda, M. *Synthesis* **1977**, 1-17. (b) Bartman, W.; Beck, G.; Knolle, J.; Rupp, R. H. *Tetrahedron Lett.* **1982**, 23, 3647. (c) Chalker, J. M.; Gunnoo, S. B.; Boutureira, O.; Gerstberger, S. C.; Fernández-González, M.; Bernardes, G. J. L.; Griffin, L.; Hailu, H.; Schofield, C. J.; Davis, B. G. *Chem. Sci.* **2011**, 2, 1666-1676. (d) Xu, S.; Unabara, D.; Uemura, D.; Arimoto, H. *Chem. Asian J.* **2014**, 9, 367-375.

<sup>87</sup> Luh, T.-Y.; Chow, H.-F.; Leung, W. Y.; Tam, S. W. *Tetrahedron* **1985**, 41, 519-525.

It was observed that treating the hemiaminal **66** with silyloxyfuran and Lewis acid resulted in the formation of only 2 diastereoisomers out of the possible 4. This selectivity is sterically controlled where the 2 substituents on the in situ generated cyclic iminium intermediate block the front face and direct the approach of the silyloxyfuran only from the least sterically hindered face.

The butenolide is formed by the addition of the silyloxyfuran on the formed iminium ion under the effect of Lewis acid. According to Martin's ab-initio calculations, the lowest energy transition state adopts a preferential *endo* Diels-Alder like approach which is favored either by cumulative steric interactions or by stabilizing stereoelectronic factors.<sup>88</sup> Such approach led to the formation of the *threo* adduct **67a** majorly. (Scheme 16)



Scheme 16: 2 Approaches of Vinylogous Mannich Reaction

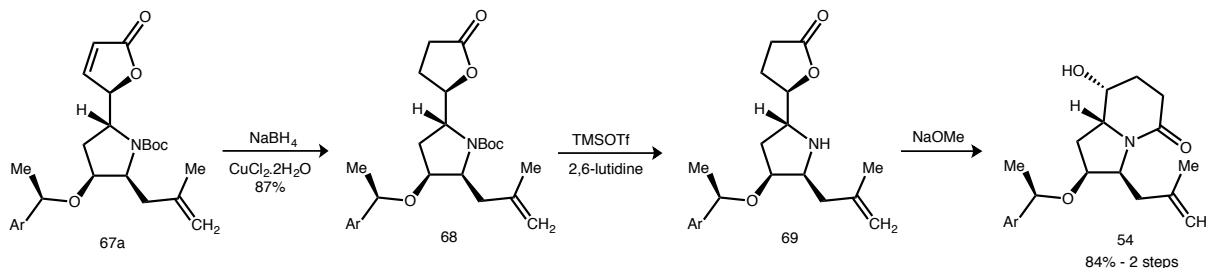
With great satisfaction, it was noticed that these transformations are highly efficient allowing the isolation of 72% of the major *threo* isomer **67a** from the corresponding lactam-Boc **65** for this 3 steps–sequence. Minor isomer **67b** was also isolated in 26% yield.

For the formation of the target indolizidinone **54**, the conjugated double bond was reduced chemoselectively in the presence of the terminal olefinic group. This was achieved by using  $\text{NaBH}_4$  in MeOH in the presence of  $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$  which furnish pure lactone **68** in 87%.<sup>89</sup> The next challenging step was the selective deprotection of Boc group in the presence of the acid-sensitive

<sup>88</sup> Bur, S. K.; Martin, S. *Org. Lett.* **2000**, *2*, 3445-3447.

<sup>89</sup> (a) Dankwardt, S. M.; Dankwardt, J. W.; Schlessinger, R. H. *Tetrahedron Lett.* **1998**, *39*, 4971-4974. (b) Gemal, A. L.; Luche, J-M. *J. Am. Chem. Soc.* **1981**, *103*, 5454-5459.

chiral inductor, which was overcome by using bulky electrophile such as TMSOTf in the presence of 2,6-lutidine generating the amino lactone **69**. The basic intramolecular cyclization of the butenolide **69** afforded the indolizidinone **54** in 84% over 2 steps. (*Scheme 17*)

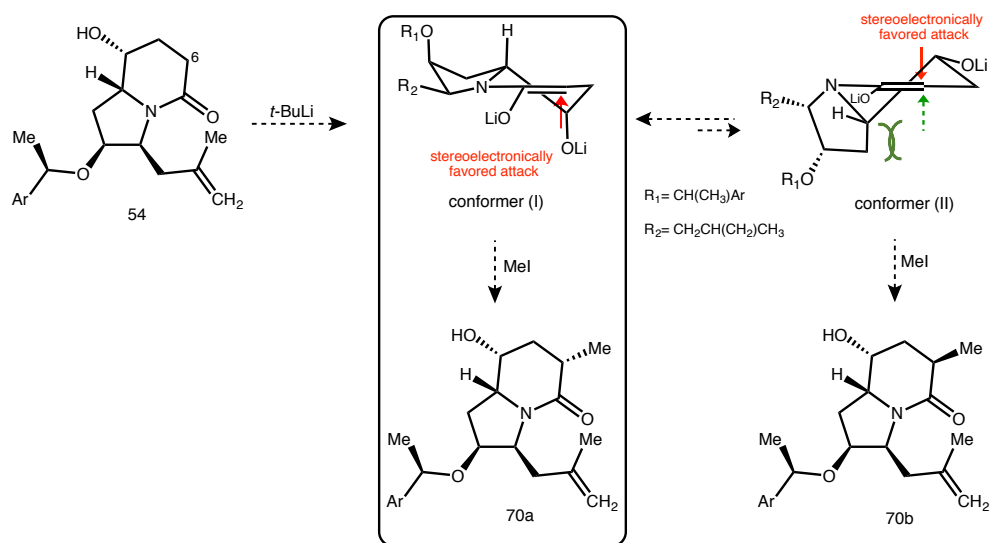


*Scheme 17: Synthesis of Indolizidinone Intermediate*

### III. Toward (-)-205B: “Unsuccessful Approach”

#### i. Installation of the C<sub>6</sub>-axial methyl group

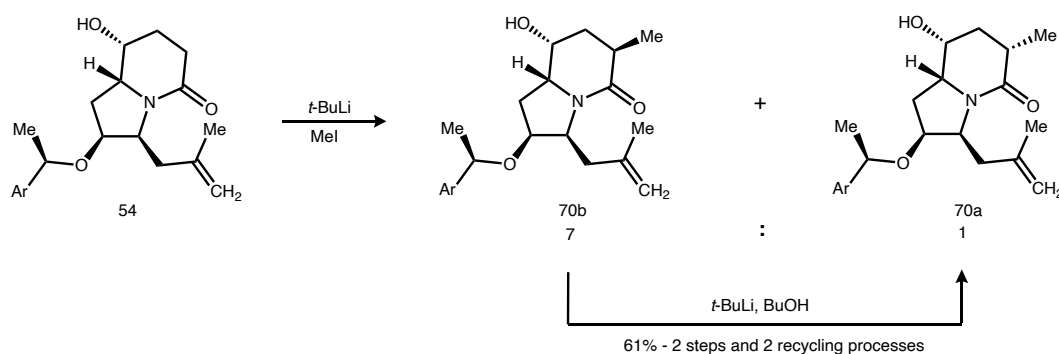
In this approach, the C<sub>6</sub>-methyl group was introduced in a classical way by alkylation of the enolate with methyl iodide. It was expected that the equilibrium between the 2 conformations of the generated enolate is shifted to favor conformer (I). Thus, the axial position of the methyl group could be directed by the stereoelectronic effect. Also, by analogy of the previous vinylogous Mannich reaction, this attack direction could be also supported by the steric hindrance requirements where the substituents of the 5-membered ring would favor the introduction of the electrophile as desired. (*Scheme 18*)



*Scheme 18: Stereochemical outcome of the alkylation step*

However, treatment of lactam **54** with an excess of *t*BuLi in THF at  $-78^{\circ}\text{C}$  followed by the addition of MeI afforded methylated products in favor of the unexpected isomer **70b** in 7:1 ratio. This stereochemical outcome is better explained through either the convex/concave nature of this bicyclic framework or the conformer (II) where the steric and the stereoelectronic arguments would disfavor an endo-bicyclic approach of methyl iodide.

So, in order to attain the desired diastereoisomer **70a**, the methylated lactam **70b** had to be epimerized. Thus, after extensive experimentation, the isolated major isomer **70b** was subjected to deprotonation–protonation that yielded only a 1:1 epimeric mixture of the 2 diastereoisomers. It was necessary to perform 2 recycling of such process to obtain the pure desired methylated indolizidinone **70a** in 61% yield.<sup>75</sup> (*Scheme 19*)

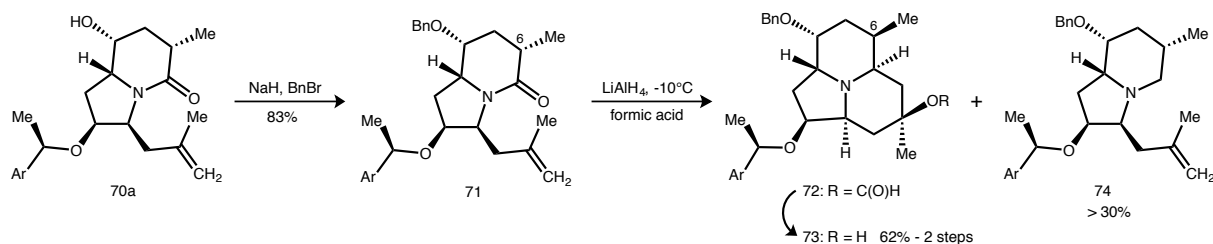


*Scheme 19: First Difficulty encountered in the previous approach*

## ii. Construction of the Tricyclic Core of the Target Product

After protection of the hydroxyl group of **70a** as benzyl ether **71**, the tricyclic product **72** was constructed through an aza–Prins cyclization.<sup>75,90</sup> After extended experimentation, the lactam **71** was reduced partially using LAH at low temperature followed by aza–Prins cyclization upon iminium formation by formic acid. Despite the mild conditions ( $-10^{\circ}\text{C}$ ), partial reduction was accompanied with the unavoidable formation of the over-reduced product **74** where ~30% was detected. After saponification of the resulting formate, tertiary alcohol **73** was obtained in 62% over 2 steps. (*Scheme 20*)

<sup>90</sup> Reddy, B. V. S.; Nair, P. N.; Antony, A.; Lalli, C.; Grée, R. *Eur. J. Org. Chem.* **2017**, 1805-1819.



Scheme 20: Formation of the tricyclic intermediate 73

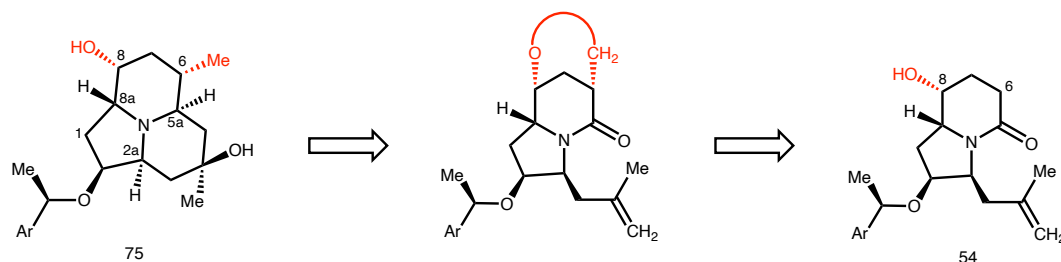
However, upon structural determination through X-ray analysis, it was surprisingly discovered that the C<sub>6</sub> chiral center was totally epimerized. It was surprising to note that the imine–enamine equilibrium proceeded rapidly resulting in the formation of the more stable configuration of the product where the axial methyl group shifts totally to the equatorial position (as shown in **72**).

This unexpected easy epimerization compromised strongly this synthetic approach which was complicated also by the difficult control of the partial reduction and the unfavorable stereochemical outcome of the alkylation reaction. Therefore, a new approach should be explored allowing to reach the target alkaloid, (-)-205B.

# CHAPTER V: ALTERNATIVE STRATEGY DEVELOPMENT

## I. Basics of the New Approach

Based on the difficult installation of the C<sub>6</sub>-axial methyl group by standard methylation method,<sup>75</sup> a new strategy was suggested ensuring a stereo-directed alkylation. This methodology is based on linking C<sub>6</sub> to the C<sub>8</sub>-hydroxyl group of the indolizidinone intermediate **54** by a transient cycle. In such way, a methyl-equivalent group is forced to be introduced at C<sub>6</sub> with same stereochemistry as the C<sub>8</sub>-hydroxyl group which was identified by X-ray analysis to be of axial position<sup>75</sup> (*Scheme 21*). This transient additional cycle should implicate certain conditions. First, it should be introduced easily and should be stable enough towards the subsequent steps for the construction the 8b-azaacenaphthylene ring system. Finally, it should be easily cleaved and be able to release the expected methyl group.



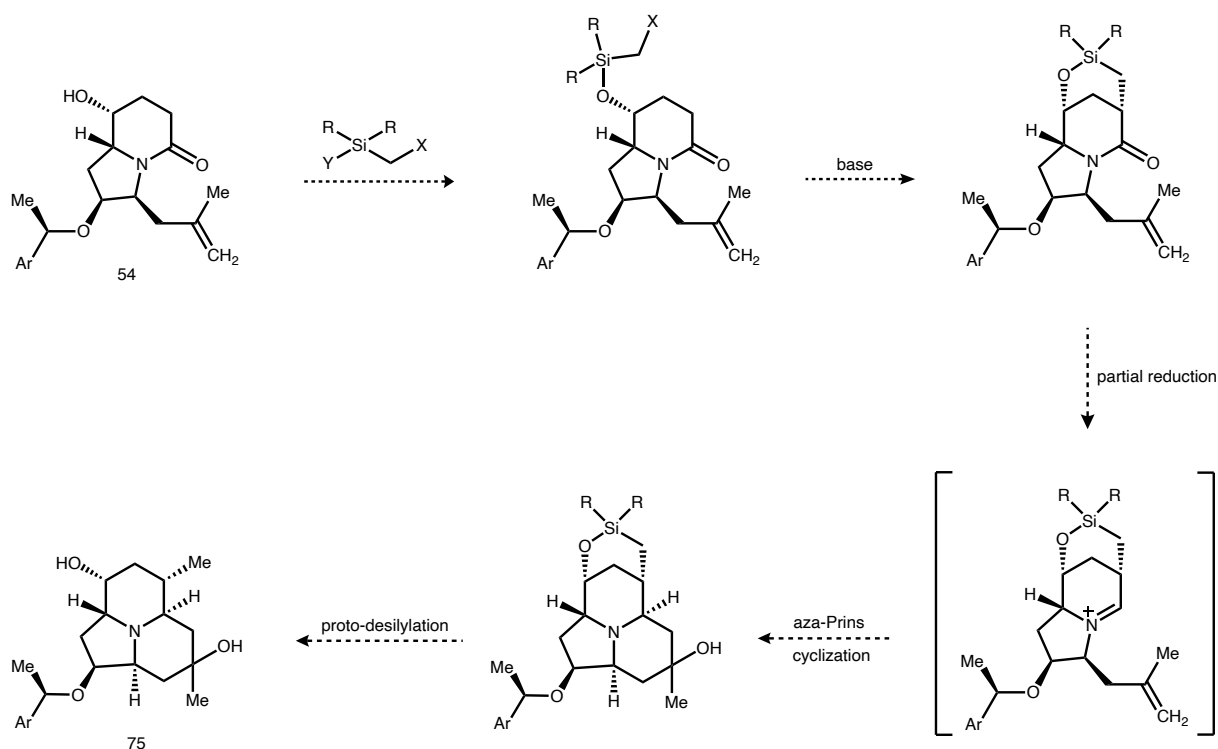
*Scheme 21: Retrosynthetic Strategy of New Approach*

Silicon protecting groups are widely used in modern organic synthesis as they are adaptable to a variety of reaction conditions and their high affinity for fluorine permits their deprotection smoothly.<sup>91</sup> Thereafter, the simplest way to introduce the desired cycle is by temporary silicon tether (TST) where it can be easily and smoothly introduced to the secondary hydroxyl group and allow the formation of the 6-membered silyl ring by nucleophilic displacement. In addition, upon the aza-Prins cyclization, the presence of this transient cycle will prevent the formation of a double bond at the bridgehead of a bridged ring system, according to Bredt's rule.<sup>92</sup> Consequently, upon subjecting the lactam to a reducing agent leading to the imine, enamine will not be formed avoiding the possible C<sub>6</sub> epimerization. This silyl cycle can finally release the hydroxyl and methyl group by the known proto-desilylation. (*Scheme 22*)

<sup>91</sup> Kocienski, P. J. *Protecting Groups*, 3<sup>rd</sup> Ed., G. Thieme: Stuttgart **1994**.

<sup>92</sup> (a) *The Merck Index*, 9<sup>th</sup> ed.; Merck & Co., Inc.: Rahway, NJ, 1976, p. ONR-14. (b) Bredt, J.; Houben, J. O. S.; Levy, P. *Ber. Dtsch. Chem. Ges.* **1902**, *35*, 1286-1292. (c) Bredt, J. Thouet, H.; Schmitz, J. *Justus Liebigs Ann. Chem.* **1924**, *437*, 1-13. (d) Fawcett, F.S. *Chem. Rev.* **1950**, *47*, 219. (e) Köbrich, G. *Angew. Chem. Int. Ed., Engl.* **1973**, *12*, 464. (f) Buchanan, G. L. *Chem. Soc. Rev.* **1974**, *3*, 41-43.





Scheme 22: General Strategy of New Approach

## II. Temporary Silicon-Tethered Chemistry

Silicon tethers are widely used due to their ease of preparation, their stability and adaptability toward wide array of reaction conditions and their selective and ease of de-functionalization to afford the desired product. The most common employed TSTs are illustrated by medium-sized silicon cycles either as disiloxane, siloxane or silane linker (*Figure 19*). Tethering two partners through a silyl link renders the reaction to run in an intramolecular version implicating several advantages over their intermolecular counterparts. These links are proved to influence the rate of the reaction which run also with higher regio- and stereoselectivity as these tethers constrain the transition states thus having fewer degrees of freedom. They, in turn, work as an important synthon due to their considerable potential for further transformations into various intermediates in synthesis through reactions like proto-desilylation, Fleming–Tamao oxidation, silane-group transfer or transmetallation. This strategy is valuable as it is employed in the synthesis of wide range of natural products.<sup>93</sup>

<sup>93</sup> Čusak, A. *Chemistry* **2012**, *18*, 5800-5824.

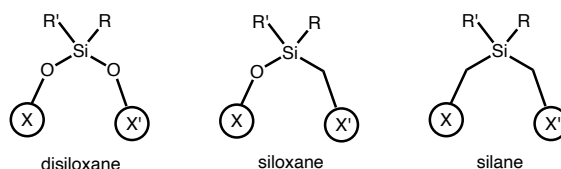


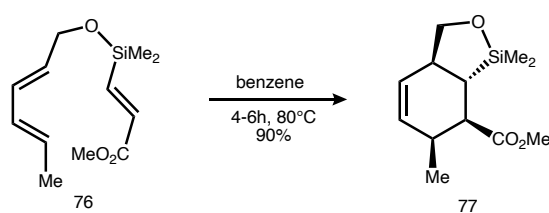
Figure 19: Common Silicon Tethers

This chemistry was initially introduced in the 80s by Nishiyama and Stork, where silyl tethers were applied for the synthesis of 1,3-diols from allylic alcohol based on radical cyclization.<sup>94</sup> Later, these tethers were used for wider applications that are beneficial in organic chemistry and have been reviewed periodically.<sup>95</sup> Due to the importance of this subject and in order to give a brief overview of some of the TST applications, selected interesting transformations are highlighted in the following paragraph.

## i. Diels–Alder Reaction

The synthetic utility of TST methodology was exhibited by Stork in Diels–Alder chemistry allowing the access of *endo* product **77** displaying high regio- and stereoselectivity.<sup>96</sup> Targeting the alkaloid (–)-Calyciphylline **80**, Smith<sup>97</sup> had also integrated these tethers upon intramolecular Diels–Alder reaction for high diastereoselective outcome. This synthetic strategy was responsible for the introduction of 4 stereogenic centers of the final natural alkaloid. It was achieved using a Lewis acid that promote the *endo* approach allowing the formation of the desired isomer in high diastereoselectivity through the proposed transition state **81**. (Scheme 23)

Stork (1992):



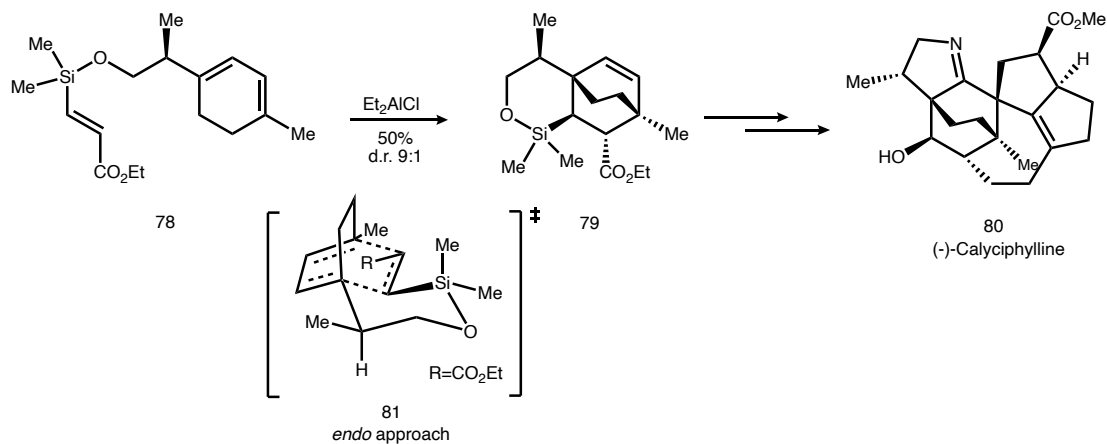
<sup>94</sup> (a) H. Nishiyama, T. Kitajima, M. Matsumoto, K. Itoh *J. Org. Chem.* **1984**, *49*, 2298-2300. (b) G. Stork, M. Kahn, *J. Am. Chem. Soc.* **1985**, *107*, 500-501.

<sup>95</sup>(a) Bols, M.; Skrydstrup, T. *Chem Rev* **1995**, *95*, 1253-1277. (b) Fensterbank, L.; Malacria, M.; Sieburth, S. M. N. *Synthesis* **1997**, *1997*, 813-854. (c) Gauthier, D. R.; Zandi, K. S.; Shea, K. J. *Tetrahedron* **1998**, *54*, 2289-2338. (d) Bracegirdle, S.; Anderson, E. A. *Chem Soc Rev* **2010**, *39*, 4114-4129.

<sup>96</sup> Stork, G.; Chan, T. Y.; Breault, G. A. *J. Am. Chem. Soc.* **1992**, *114*, 7578-7579.

<sup>97</sup> Shvartsbart, A.; Smith, A. B. *J. Am. Chem. Soc.* **2015**, *137*, 3510-3519.

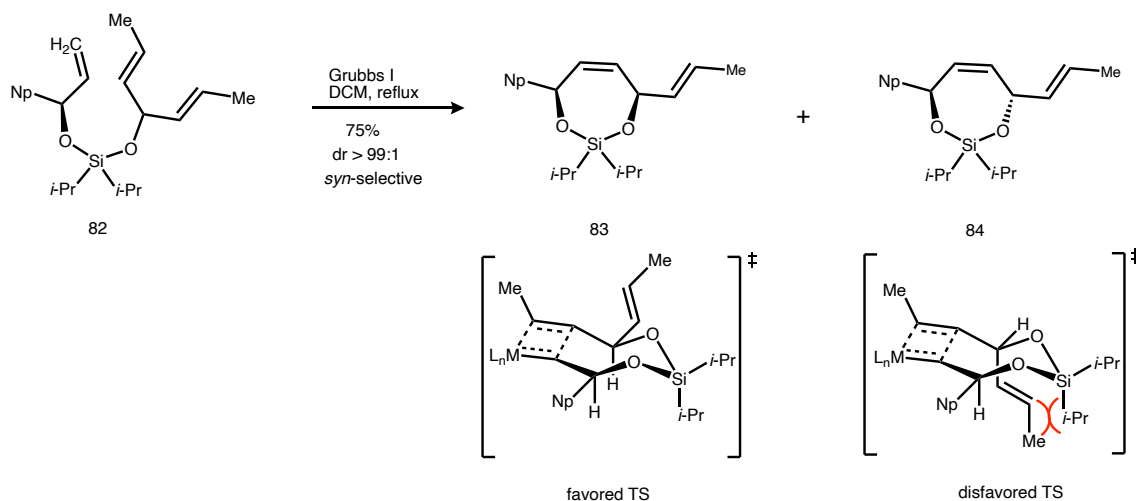
Smith (2015):



Scheme 23: TST-based Diels Alder Reaction

## ii. Alkene Metathesis

Applications of this TST strategy were further extended for RCM which showed an improved difference in their efficiency and selectivity compared to untethered cross metathesis. The selectivity has been manifested by the formation of the *Z*-alkene as an alternative to the usual *E*-alkene geometry for conventional cross metathesis as a consequence of the cycle constraint.



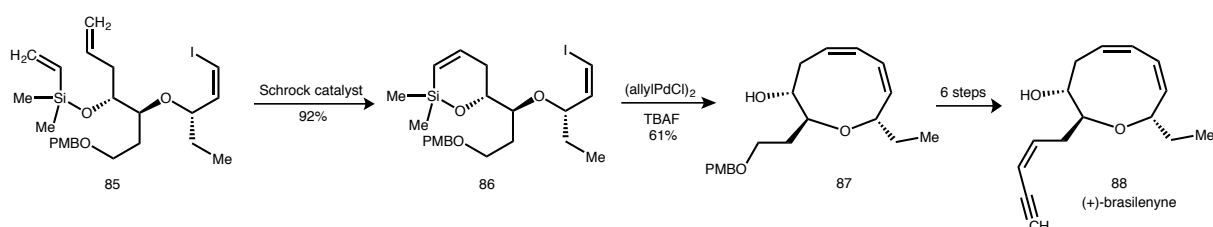
Scheme 24: TST application in Metathesis (1,4-stereocontrol)

Asymmetric RCM being induced by TST was studied by Evans *et al.*<sup>98</sup> on wide variety of substrates. In this strategy, one of the tethered components of **82** should be derived from a prochiral alcohol. Thereby, a considerable diastereoselectivity was observed in the 1,4-silaketal products (**83** and **84**) upon the RCM where chirality transfer occurs within the chiral allylic ether **82**. A newly stereogenic center has been introduced as a consequence of the steric interactions in the transition state. Thus, it

<sup>98</sup> P. A. Evans; B. Cui; G. P. Buffone *Angew. Chem. Int. Ed.* **2003**, *42*, 1734-1737.

is notable that having bulky substituents on silicon is necessary to afford diastereoselectivity as high as 99:1 (*Scheme 24*).

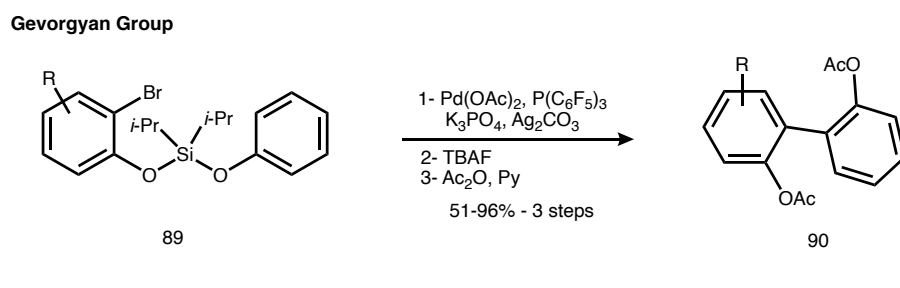
Interestingly, this TST-RCM strategy was proved to be valuable in the total synthesis of natural products. In 2002, an elegant synthesis of (+)-brasilenyne **88** was reported by Denmark *et al.* highlighting the importance of integrating this strategy to reach the target product.<sup>99</sup> A tandem TST-RCM/Hiyama cross-coupling was developed to access the 9-membered ring **87**. The TST-RCM product **86** was showed to be the ideal substrate for the further functionalization through an intramolecular Hiyama cross-coupling. (*Scheme 25*)



*Scheme 25: TST-RCM applied in natural products synthesis*

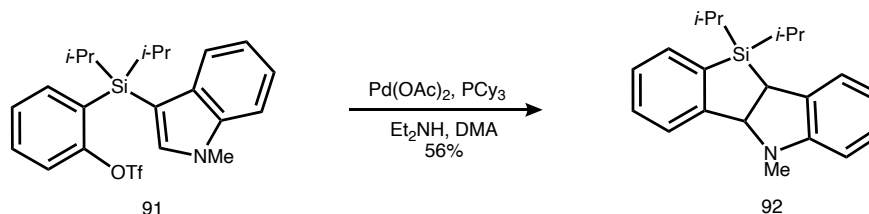
### iii. C-H functionalization

Employment of silyl tethers for intramolecular C-H bond activation had given significant attention due to its beneficial use in organic synthesis. The silicon tethered chemistry had been investigated in this arena by both the Hiyama and Gevorgyan groups for the formation of silicon-bridged biaryls (*Scheme 26*).<sup>100</sup> It is notable that the silyl group can be further functionalized either by oxidation or proto-desilylation.



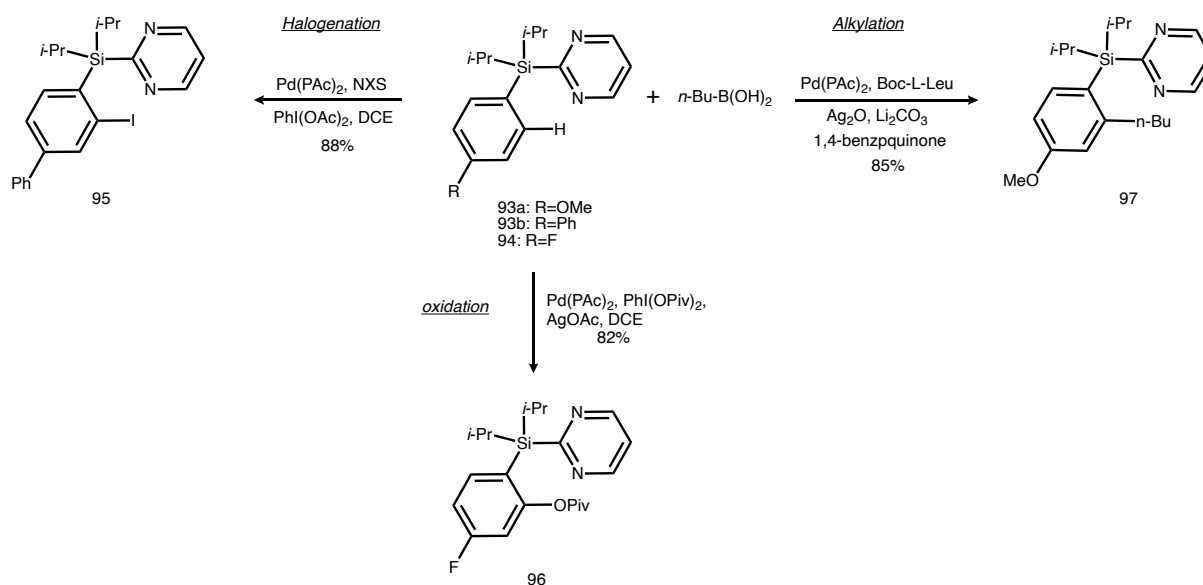
<sup>99</sup> Denmark, S. E.; Yang, S. M. *J. Am. Chem. Soc.*, **2002**, *124*, 15196-15197.

<sup>100</sup> (a) Shimizu, M.; Mochida, K.; Hiyama, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 9760-9764. (b) Huang, C.; Gevorgyan, V. *Org. Lett.* **2010**, *12*, 2442-2445.

**Hiyama Group**


Scheme 26: Silicon Tethers in C–H activation

On the other hand, recent studies have provided the access for a wide range of functionalized organic molecules through the efficient construction C–C, C–X, C–O and C–B bonds by C–H activation.<sup>101</sup> In this category, the silyl tethers is used to link a directing group that can be either nitrogen- or oxygen-based in order to control the regioselectivity mainly through proximity. The scope of this methodology had been applied for C–H alkenylation, alkylation, arylation, acylation and halogenation of phenols and anilines which are difficult to be achieved in intermolecular conditions. Some examples are highlighted in *Scheme 27*.



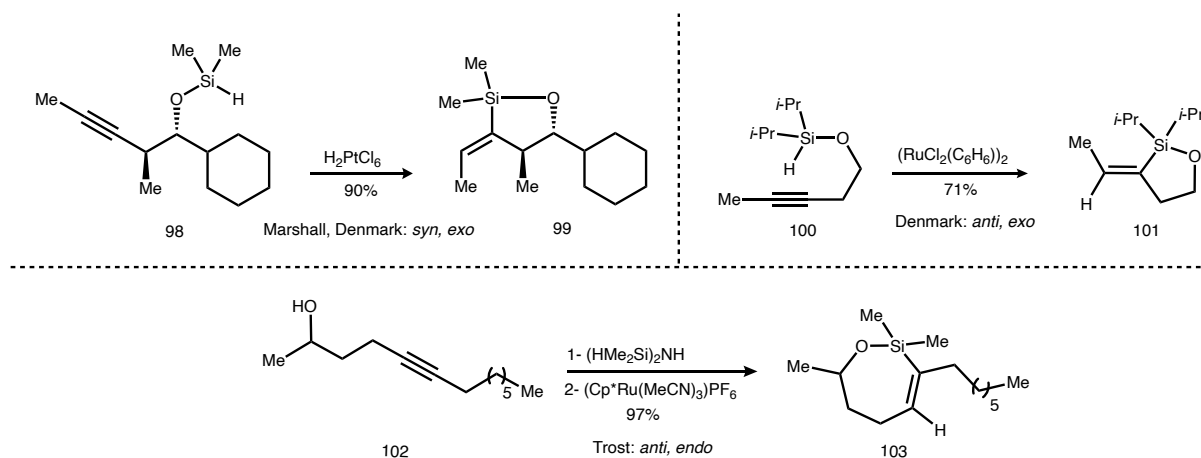
Scheme 27: TST directed C–H activation

#### iv. Hydrosilylation and Carbosilylation

TSTs have also seen well developed applications in unsaturated systems. Alkyne–hydrosilylations are challenging as they require the control over both the regioselectivity and the stereoselectivity. Several groups have developed hydrosilylation's catalysts that provide access to a wide range of

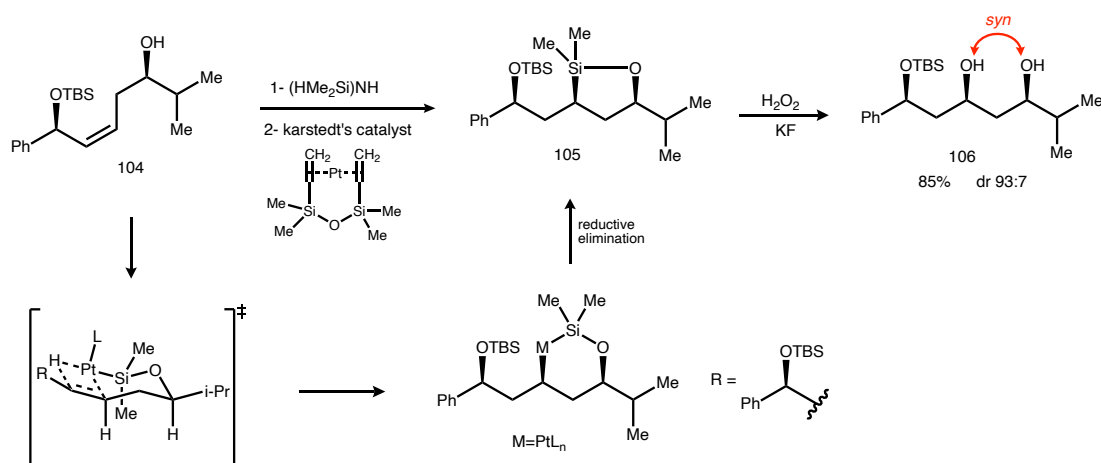
<sup>101</sup> (a) Parasram M.; Gevorgyan V. *Acc. Chem. Res.* **2017**, *50*, 2038-2053. (b) Usman, M.; Zhang, X.W.; Liu, W.B. *Synthesis* **2019**, *51*, 1529-1544.

complementary selectivity of vinyl silane products which seems to be dependent on the used catalyst and the silicon substituents (*Scheme 28*).<sup>102</sup>



*Scheme 28: TST-based Hydrosilylation of Alkynes*

Applying this strategy to alkenes is more interesting as it will lead to the installation of new stereocenters. The chair-like transition state with the olefin being in a pseudo-equatorial position is expected to be responsible for the stereocontrol allowing the formation of a product **105** with high level of stereoinduction (*Scheme 30A*).<sup>103</sup>

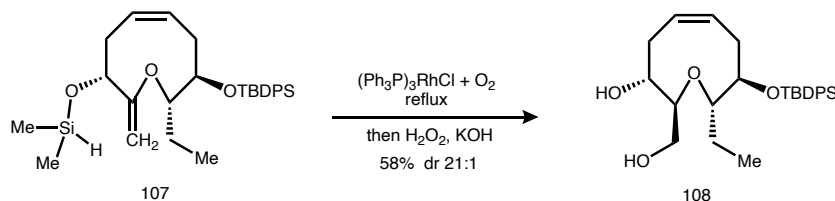


*Scheme 29: TST-based Hydrosilylation of Alkenes*

<sup>102</sup> (a) Tamao, K.; Maeda, K.; Tanaka, T.; Ito, Y. *Tetrahedron Lett.* **1988**, *29*, 6955-6956. (b) Marshall, J. A.; Yanik, M. M. *Org. Lett.*, **2000**, *2*, 2173-2175. (c) Denmark, S. E.; Pan, W. T. *Org. Lett.*, **2001**, *3*, 61-64. (d) Denmark, S. E.; Pan, W. T. *Org. Lett.*, **2003**, *5*, 1119-1122. (e) Denmark, S. E.; Pan, W. T. *Org. Lett.*, **2002**, *4*, 4163-4166. (f) Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc.*, **2003**, *125*, 30-31.

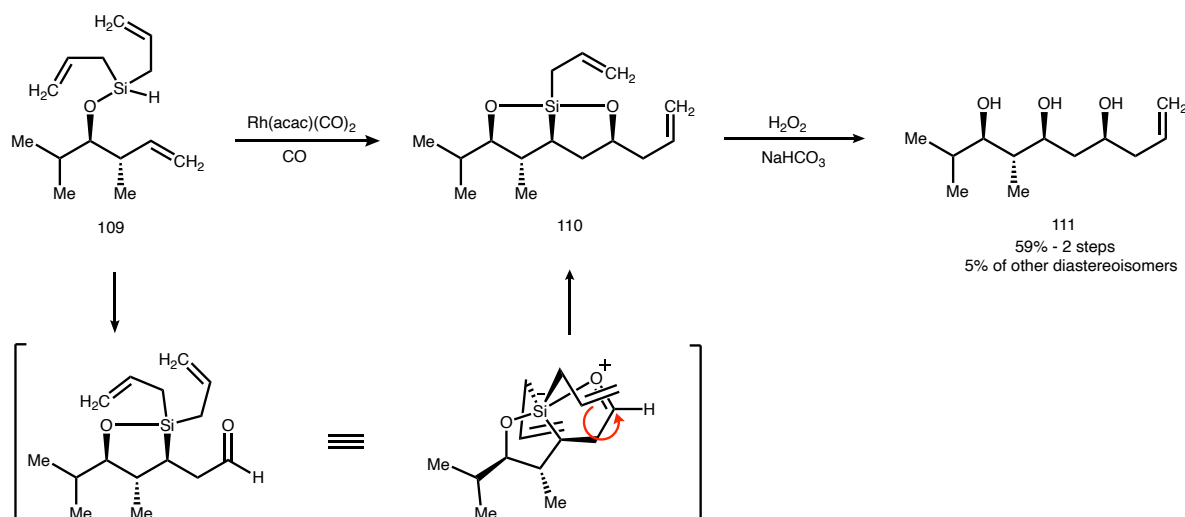
<sup>103</sup> Li, F. Z.; Roush, W. R. *Org. Lett.* **2009**, *11*, 2932-2935.

As an application of the intramolecular alkene-hydrosilylation strategy, a new chiral center was efficiently introduced en route to the synthesis of (+)-obtusenyne **108**, a medium ring oxacycle.<sup>104</sup> (Scheme 30B)



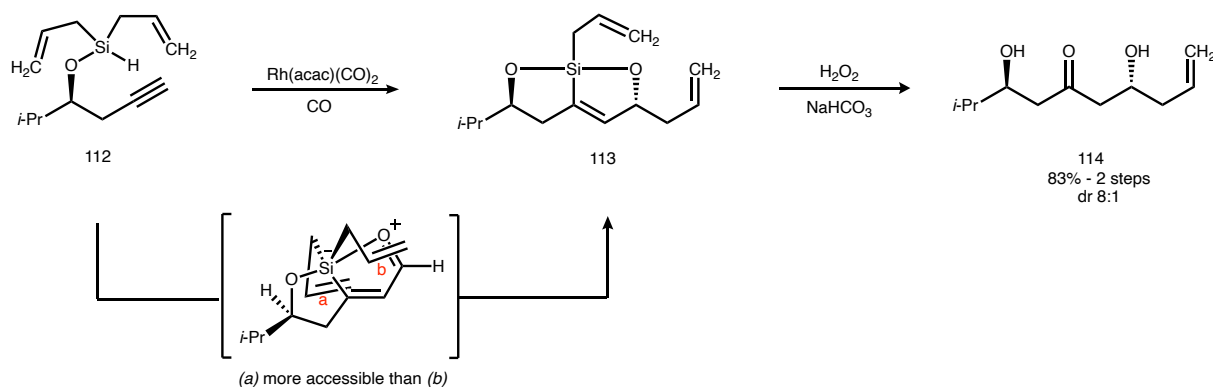
Scheme 30: TST-based Hydrosilylation of Alkenes

As an extension of hydrosilylation, TST carbosilylation seems to be more complex as it will result in the formation of at least one C–C bond. Recently, Leighton and co-workers had elevated this chemistry to the “one pot” stereoselective carbosilylation–allylation tandem reaction. It could be either applied to alkenyl or alkynyl substrates, and thus resulting in syn or anti 1,5–diols respectively (Scheme 31).<sup>105</sup> The observed diastereoselectivity of **110** arises as a result of the preferential attack of the allyl group that lies in closer proximity to the activated aldehyde. Whereas the 1,5–stereoinduction observed in **113** from alkynyl substrates is sterically directed with the transfer of the back-allyl group from the least hindered face.



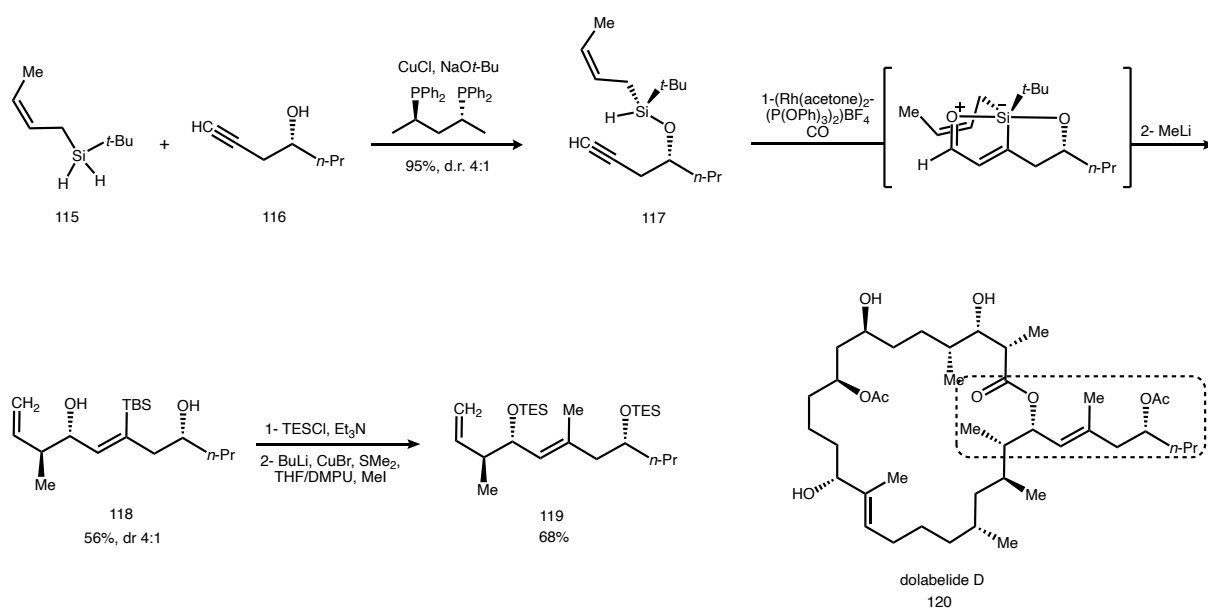
<sup>104</sup> (a) Mak, S. Y. F.; Curtis, N. R.; Payne, A. N.; Congreve, M. S.; Wildsmith, A. J.; Francis, C. L.; Davies, J. E.; Pascu, S. I.; Burton, J. W. Holmes, A. B. *Chem. Eur. J.* **2008**, *14*, 2867-2885. (b) Burton, J. W.; Anderson, E. A.; O'Sullivan, P. T.; Collins, I.; Davies, J. E.; Bond, A. D.; Feeder, N.; Holmes, A. B. *Org. Biomol. Chem.* **2008**, *6*, 693-702.

<sup>105</sup> (a) Zacuto, M. J.; Leighton, J. L. *J. Am. Chem. Soc.* **2000**, *122*, 8587-8588. (b) O'Malley, S. J.; Leighton, J. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 2915-2917.



Scheme 31: Tandem Carbosilylation – Allylation

Worthwhile, tether-controlled asymmetric stereoinduction can be achieved by utilizing chiral TST where it can control the diastereoselectivity of the silylformylation/allylation reaction.<sup>106</sup> This is demonstrated in the total synthesis of the polyketide dolabelide D **120**, where syn 1,5–stereocontrol was achieved as a result of the chiral TST **117** (Scheme 32).



Scheme 32: TST-based Synthesis of Dolabelide D

## v. Silicon–Tethered Nucleophilic Addition Reactions

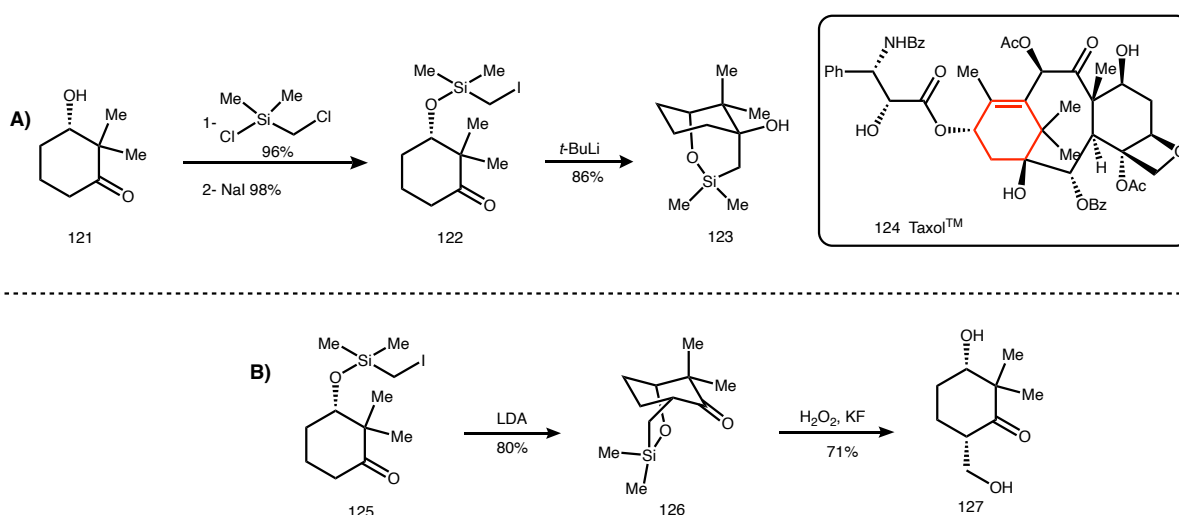
TST have been applied for the formation of a chiral tertiary alcohol via the nucleophilic addition to a ketone based on chirality transfer within the molecule. In the intermolecular fashion, the stereochemical outcome of this kind of addition is directed by steric hindrance and/or stereoelectronic effects. In consequence, a low to moderate diastereoselectivity will be obtained.

<sup>106</sup> (a) Schmidt, D. R.; O'Malle, S. J.; Leighton, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 1190-1191. (b) Park, P. K.; O'Malley, S. J.; Schmidt, D. R.; Leighton, J. L. *J. Am. Chem. Soc.* **2006**, *128*, 2796-2797.



However, engaging silyl tethers will lead to the enhancement of the stereoselectivity and orient such addition regardless of the other impactful factors. Nakada *et al.* had applied this protocol in a study toward the total synthesis of Taxol where chirality transfer was realized from silyl ether **122** to the bicyclic tertiary alcohol **123**.<sup>107</sup>

On the other hand, it was noticed that upon using LDA as the base resulted in a stereoselective intramolecular alkylation upon reversing the polarity leading to the chiral diol **127** after tamao oxidation. To the best of our knowledge, this is the only reported result of such kind of stereoselective alkylation through a silyl linkage.



Scheme 33: Chiral Transfer upon TST – Nucleophilic Addition

### III. Retrosynthetic Analysis of New Strategy

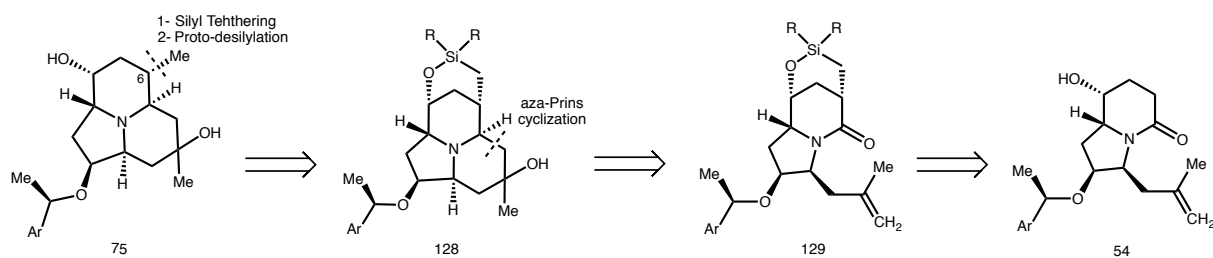
Inspired by the chemistry introduced by Nakada,<sup>107</sup> we think whether this methodology would be applicable on our substrate for an introduction of the C<sub>6</sub>-axial methyl group. This stereoselective reaction could be directed by the C<sub>8</sub>-hydroxyl group occupying an axial position.

Retrosynthetically speaking, the C<sub>6</sub>-axial methyl group (**75**) would be installed by the known protodesilylation of the silyl moiety after the construction of the polycyclic scaffold **128**. This polycyclic structure **128** would be achieved via the aza-Prins cyclization of the lactam **129**. Finally, the first key intermediate **129** would be synthesized by tethering the indolizidinone intermediate **54** by the appropriate silyl reagent followed by intramolecular alkylation.

<sup>107</sup> Iwamoto, M.; Miyano, M.; Utsugi, M.; Kawada, H.; Nakada, M. *Tetrahedron Letters* **2004**, 45, 8647-8651.

Detailed synthesis will be discussed in the following section according to this general scheme.

(Scheme 34)



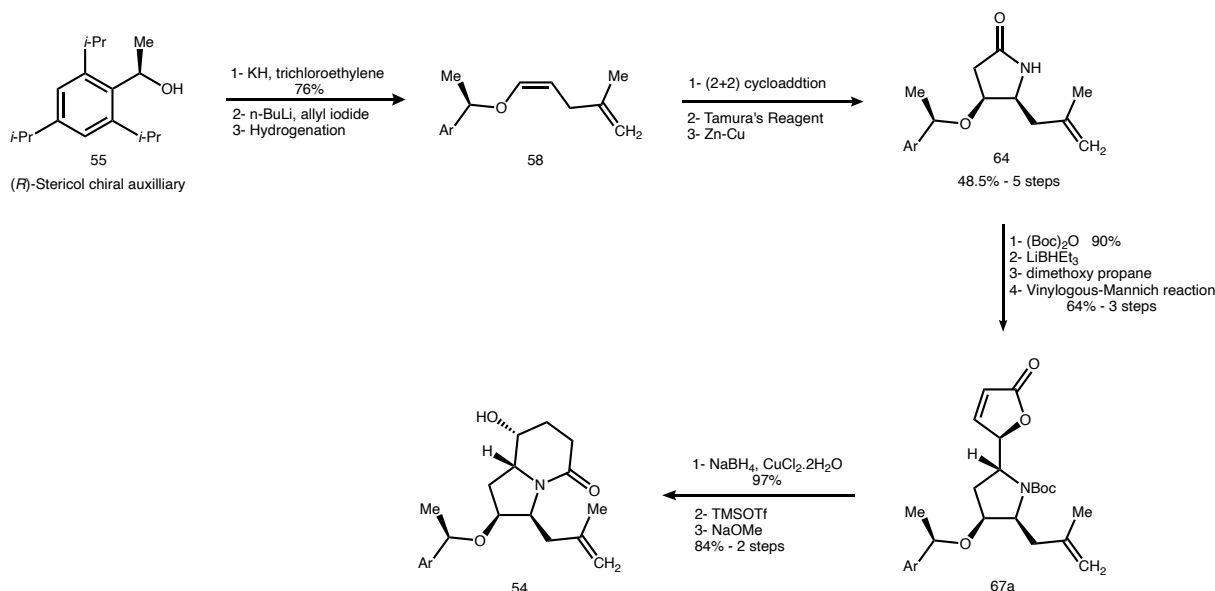
Scheme 34: Retrosynthetic Analysis of New Approach

# CHAPTER VI: ACHIEVEMENT OF TOTAL SYNTHESIS OF (–)-205B

As discussed in the previous chapter, the aim of our work is the development of a new approach for the synthesis of the natural alkaloid, (-)-205B.

## I. Synthesis of the First Advanced Intermediate

Following the previously published procedure,<sup>75</sup> the first advanced intermediate **54** was synthesized in an *optically active* form. The first consideration in this synthetic approach of the natural alkaloid (-)-205B was the choice of the enantiomer of the external inductor in order to obtain the desired absolute configuration of the final alkaloid. Based on previous syntheses,<sup>108</sup> it was defined that the *R* enantiomer **55** is the effective chiral controller for the introduction of such stereochemistry.



Scheme 35: Synthesis of Indolizidinone Intermediate 45

Subsequently, the synthesis started with (*R*)-Stericol **55** that allows the isolation of the lactam intermediate **64** through the asymmetric ketene-alkene **58** cycloaddition, ring expansion through Beckman rearrangement and dechlorination. In turn, the indolizidinone **54** was synthesized via a vinylogous Mannich reaction, followed by reduction and intramolecular lactamization. It is worthy to note the robustness of this synthetic route by the fact that 5.3 g of the intermediate **54** was isolated

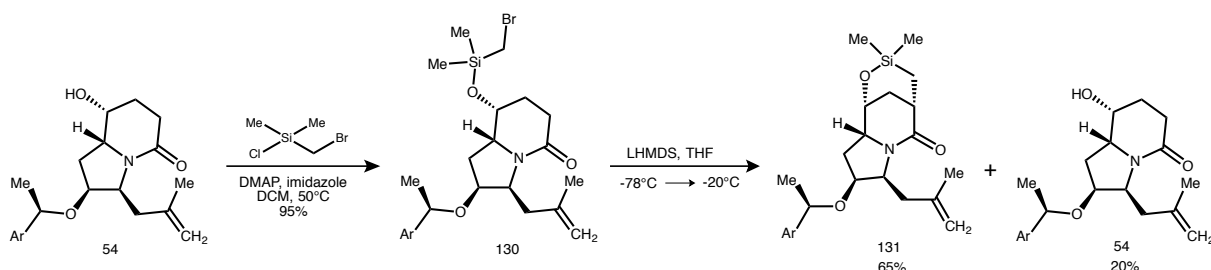
<sup>108</sup> (a) de Azevedo, M. B. M.; Greene, A. E. *J. Org. Chem.* **1995**, *60*, 4940-4942. (b) Kanazawa, A.; Delair, P.; Pourashraf, M.; Greene, A. E. *J. Chem. Soc., Perkin Trans. I* **1997**, 1911-1912. (c) Nebois, P.; Greene, A. E. *J. Org. Chem.* **1996**, *61*, 5210-5211. (d) Kanazawa, A.; Gillet, S.; Delair, P.; Greene, A. E. *J. Org. Chem.* **1998**, *63*, 4660-4663. (e) Delair, P.; Brot, E.; Kanazawa, A.; Greene, A. E. *J. Org. Chem.* **1999**, *64*, 1383.

starting from 16.7 g of the (*R*)-Stericol alcohol **55**, indicating the high efficiency of this pathway (17.3% yield over 13 steps  $\Rightarrow$  87%/step). (*Scheme 35*)

## II. Formation of Silyl Tether

Looking up for the development of a novel methodology for controlling the stereoselective installation of the C<sub>6</sub>-axial methyl group with enough stability to avoid epimerization upon the ensuing steps, we have great hope with the methodology investigated by Nakada based on silicon tethered chemistry.<sup>107</sup> Therefore, the first step to explore will be the silyl ether linkage of the secondary hydroxyl group with the appropriate silyl reagent followed by intramolecular alkylation of the lactam's enolate.

Our initial attempts for the formation of this TST relied on the commercial chloro(bromomethyl)dimethylsilane. It was observed that the rate of the silylation step is quite slow probably because the substrate **54** is sterically hindered. Thus, unusual heating was necessary to take the reaction to completion affording the protected alcohol **130** in 95% yield.<sup>109</sup> After several experiments, it was discovered that subjecting the lactam to LHMDS allowed the formation of the corresponding enolate which in turn undergoes nucleophilic substitution with the expected transfer of chirality. Upon this basic condition, the desired cyclic silyl ether **131** was obtained at best in 65%. Unfortunately, basic hydrolysis of Si-O bond had occurred in variable and unavoidable amount forming back the intermediate **54**.



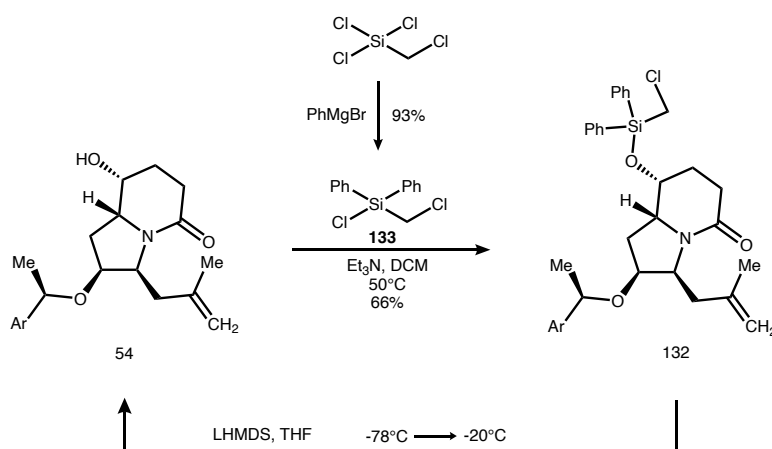
*Scheme 36: Formation of dimethyl-TST*

Knowing that the silicon's substituents can alter the steric and electronic characteristics of the alcohol protecting group contributing to their relative stability,<sup>110</sup> we embarked this sequence with bulkier silyl reagents expecting that it will ensure the required basic stability of the corresponding silyl ether.

<sup>109</sup> Wee, A. G. H.; Fan, G.; Bayirinoba, H. M. *J. Org. Chem.* **2009**, *74*, 8261-8271.

<sup>110</sup> Nelson, T. D.; Crouch R. D. *Synthesis*, **1996**, 1031-1069.

In order to reach a more stable silyl ether derivative, chloro(chloromethyl)diphenylsilane **133** was first considered due to its readily accessibility in spite of the fact that diphenyl substituted silyl reagents are not particularly known to form silyl ether with very high stability toward basic hydrolysis. Silane **133** was prepared through a Grignard addition of phenyl magnesium bromide solution on the trichloro(chloromethyl)silane in 93% yield.<sup>111</sup> Silylation ran smoothly yielding 66% of the protected alcohol **132** whereas it was noticed that this silyl ether is so sensitive to basic treatment. The output of the cyclization condition is the Si-O bond cleavage exclusively with 0% of the desired silyl tethered intermediate. (*Scheme 37*)



*Scheme 37: Trial with Chloro(chloromethyl)diphenylsilane*

Protection of alcohols by TIPS group is known for their stability against basic treatment.<sup>110,112</sup> Thus, substituting the 2 groups on silicon with isopropyl can stand for improving the hydrolytic stability of the silylated alcohol. This corresponding silyl reagent, chloro(chloromethyl)diisopropylsilane **134**, is not commercial and partially described in the literature. The preparation of this silyl reagent was done according to Gevorgyan procedure who described the iodo derivative.<sup>113</sup> The commercially available chlorodiisopropylsilane undergo nucleophilic substitution with chloromethyl lithium generated in situ which is followed by an oxidative chlorination. The volatile silyl reagent **134** was prepared with enough purity to be used without any further purification in a yield range from 85 to 94%.

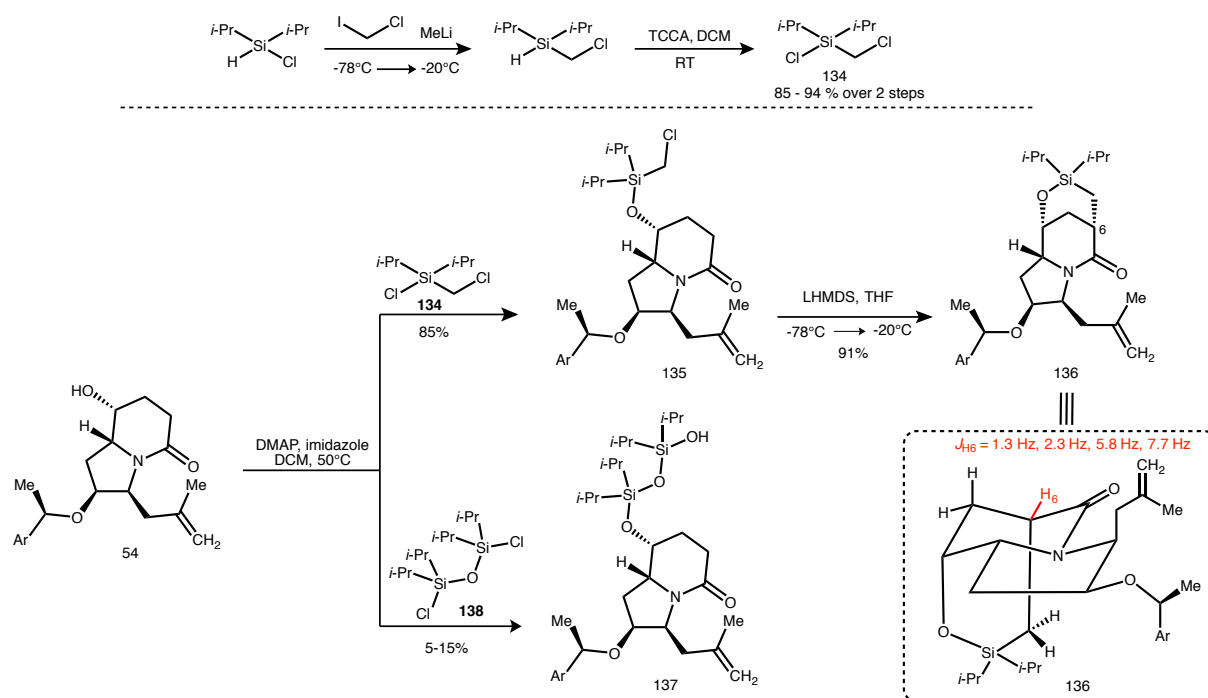
Silylation of the secondary hydroxyl **54** using the prepared silyl reagent **134** afforded the corresponding silylated indolizidinone **135** in 85% yield. As a side product, the disiloxane **137** was

<sup>111</sup> Allen, J. M.; Aprahamian, S. L.; Sans, E. A.; Shechter, H. *J Org Chem* **2002**, *67*, 3561-74.

<sup>112</sup> (a) Protecting Groups. Kunz, H.; Waldman, H. *Comprehensive Organic Synthesis* Trost, B. M.; Fleming, I. Eds.; Pergamon Press: Oxford **1991**, *6*, 631. (b) Rücker, C. *Chem. Rev.* **1995**, *95*, 1009-1064.

<sup>113</sup> Parasram, M.; Iaroshenko, V. O.; Gevorgyan, V. *J. Am. Chem. Soc.* **2014**, *136*, 17926-17929.

also isolated in a range of 5–15% depending on the quality of the used silyl reagent. The plausible explanation for the formation of this product **137** is due to the slow hydrolysis of the commercial diisopropylchlorosilane upon standing forming the corresponding dihydrodisiloxane. Upon the preparation of the silyl reagent, this dihydrodisiloxane is then oxidized to the dichlorodisiloxane **138** by TCCA.



Scheme 38: Synthesis of diisopropyl-TST

With great satisfaction, exposing the lactam **135** to basic conditions (LHMDS) allowed the intramolecular cyclization **136** to run in 91% yield with no trace of Si–O hydrolysis. In order to get experimental evidence of the stereochemistry of the newly formed stereogenic center at C<sub>6</sub> of **136**, coupling constants relative to H<sub>6</sub> were extracted. Due to the bicyclic nature of the silyloxy bridge, it was expected that this proton occupies an equatorial position. The four  $J$  values of H<sub>6</sub> were found to be all below 10 Hz indicating the occupancy of an equatorial position.<sup>114</sup> As predicted, exploiting the silicon tethered chemistry in our synthesis allowed the smooth successful installation of the C<sub>6</sub>–“methyl group equivalent” axially.

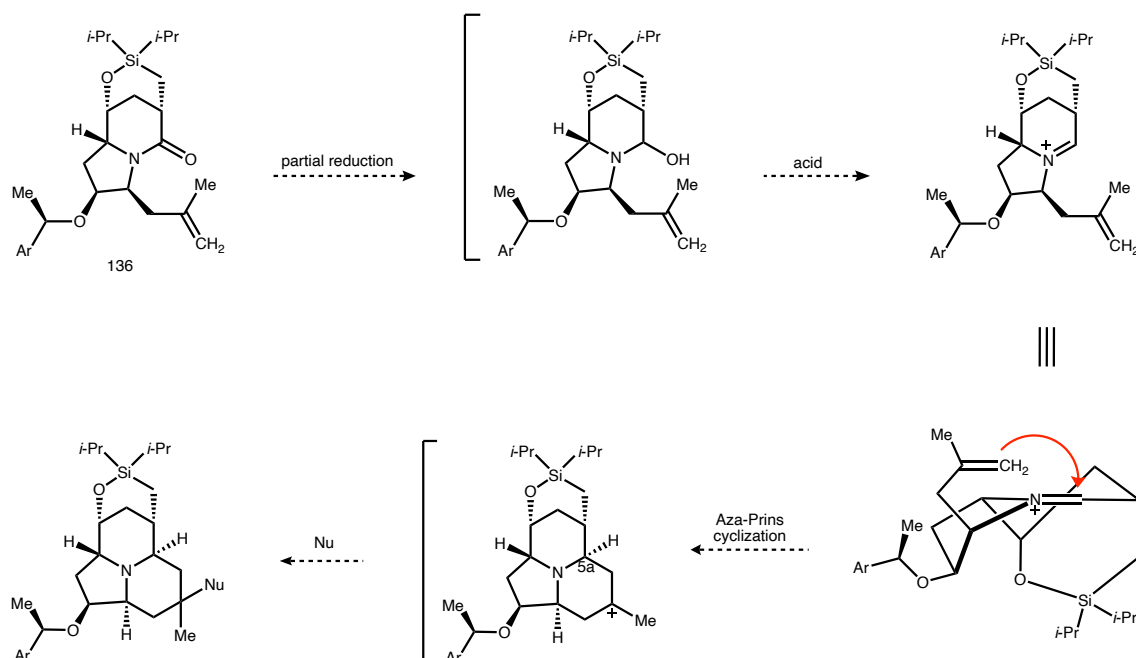
It is worthy to note that this result is, to the best of our knowledge, the second example of a stereoselective intramolecular alkylation reaction induced through a silyl link. Due to the high stability

<sup>114</sup> (a) Karplus, M. *J. Chem. Phys.* **1959**, *30*, 11-15. (b) Karplus, M. *J. Am. Chem. Soc.* **1963**, *85*, 2870-2871.

of this linker toward basic hydrolysis, this strategy argues well for the development of a more general new chiral transfer methodology through silyl tethers. Work is currently in progress in the laboratory in order to define the scope and limitation of this chiral transfer methodology.

### III. Construction of the 8b-azaacenaphthylene ring

With the tethered lactam **136** in hand, construction of the tricyclic core via reduction–cyclization sequence was planned to be done right after. A range of reduction conditions were studied in order to find the best fit to chemoselectively reduce lactam keeping the terminal double bond intact, and significantly limiting the over-reduction of lactam forming the corresponding tertiary amine. According to a rational explanation for the mechanism of this ring formation; the subsequent addition of acid triggers the formation of the reactive iminium intermediate that is stereospecifically attacked by the olefin moiety through the known aza–Prins reaction. The rigidity of the polycyclic iminium intermediate and the spatial orientation of the double bond favors the frontal attack on the iminium allowing the formation of the desired stereochemistry at C<sub>5a</sub>. The formed tertiary carbocation is neutralized by a nucleophile affording the tricyclic product. (*Scheme 39*)



*Scheme 39: Mechanistic representation for the reduction–cyclization sequence*

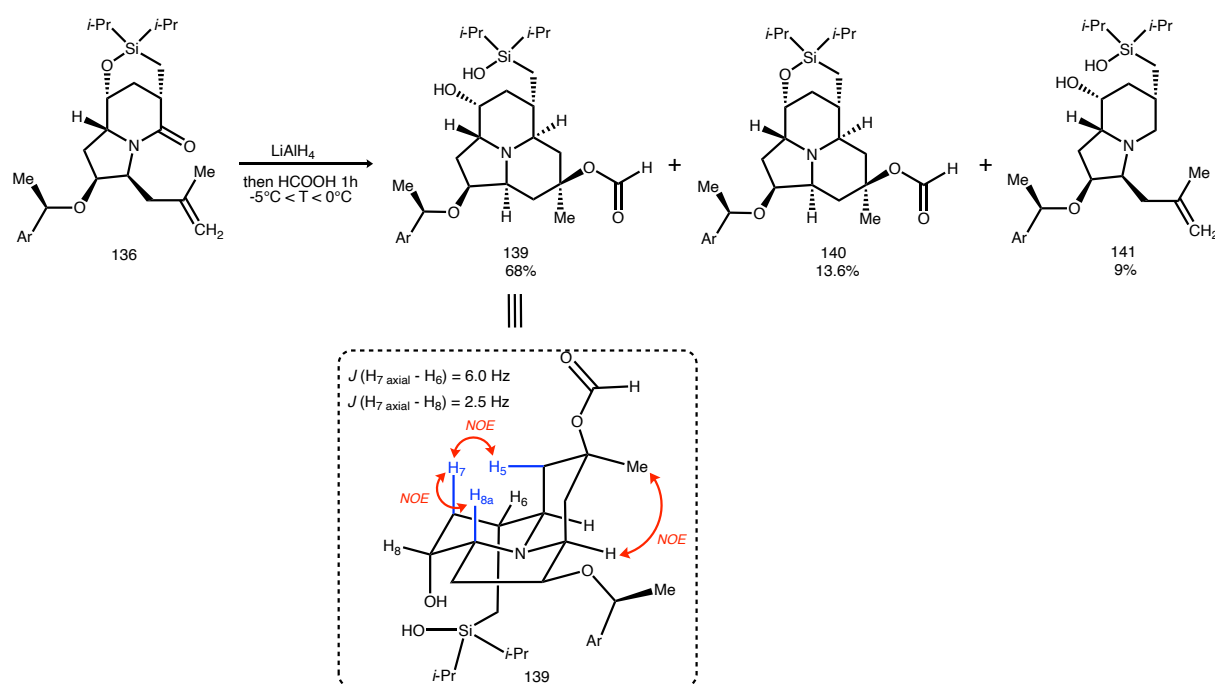
Following the previous approach,<sup>75</sup> the lactam **136** was partially reduced using LiAlH<sub>4</sub> (commercial standardized ethereal solution) at low temperature to avoid the formation of tertiary amine as much as possible followed by the addition of formic acid. Surprisingly, this condition led to the isolation of 2



cyclized products as it was observed that acidic medium provokes the partial hydrolysis of Si-O bond. Accordingly, both hydrolyzed **139** and unhydrolyzed **140** silyl ether were isolated in 68% and 13.6% respectively. Regarding the problem of the complete reduction of lactam, we were pleased to find out that the tertiary amine **141** was obtained only in 9%. (*Scheme 40*)

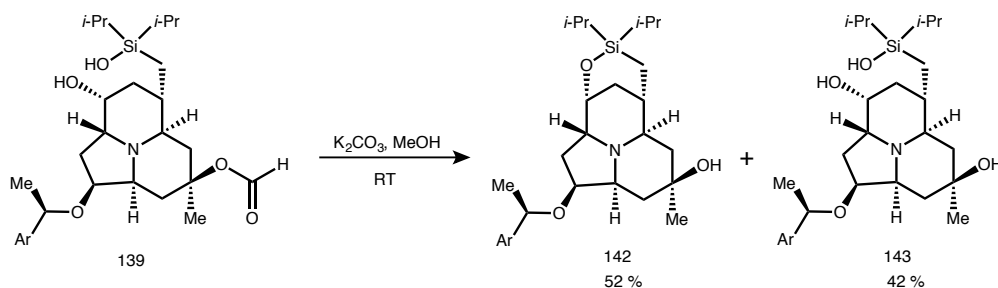
Foreseeing that the presence of TST would avoid the reversible imine–enamine equilibrium and thereby preventing the epimerization of the C<sub>6</sub> stereogenic center, the unexpected hydrolysis of the silyl ether linker weakens this anticipation. Therefore, the stereochemical integrity of the C<sub>6</sub> chiral center of the tricyclic intermediate **139** was again evaluated. It should be proved that the hydrolysis of the silyl ether ring had occurred after the tricyclic ring system construction.

Once again, H<sub>6</sub> is expected to occupy an equatorial position in the chair conformation confirmed by the observed NOE signals between the axial protons; H<sub>7</sub>, H<sub>8a</sub> and H<sub>5</sub>. Then, the *J* values extracted for the axial H<sub>7</sub> are all below 10 Hz (except for the <sup>2</sup>*J*) which is consistent to the fact that both H<sub>6</sub> and H<sub>8</sub> occupy an equatorial position. Fortunately, this 3–steps sequence is an efficient and effective track for the optimization of the previous approach and introduction of the desired stereochemistry. In addition, this NOE experiment (CDCl<sub>3</sub>, 500 MHz) performed for the formate **139** had verified the other stereochemistries so far introduced and allowed the determination of the inconsequential stereochemistry of C<sub>4</sub>.



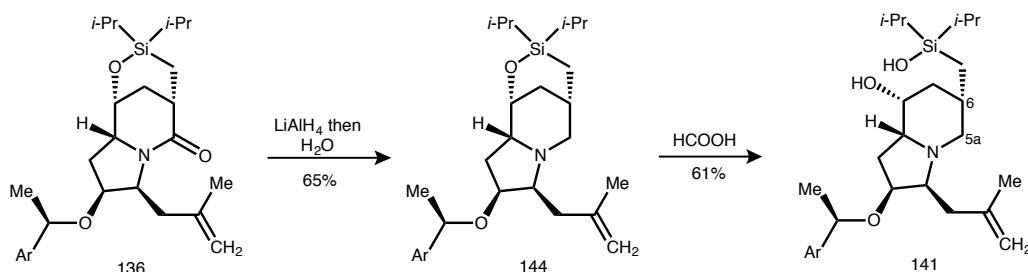
*Scheme 40: LAH-based reduction and Aza-Prins Cyclization*

Saponification of the untethered tricyclic formate **139** led to the corresponding tertiary alcohol. As noticed that Si-O bond is favored in basic medium, saponification furnished 2 products; cyclized **142** and uncyclized **143** in approximately 5:4 ratio (*Scheme 41*). This result can stand for another evidence that no epimerization occurred at the C<sub>6</sub> chiral center upon the previous step.



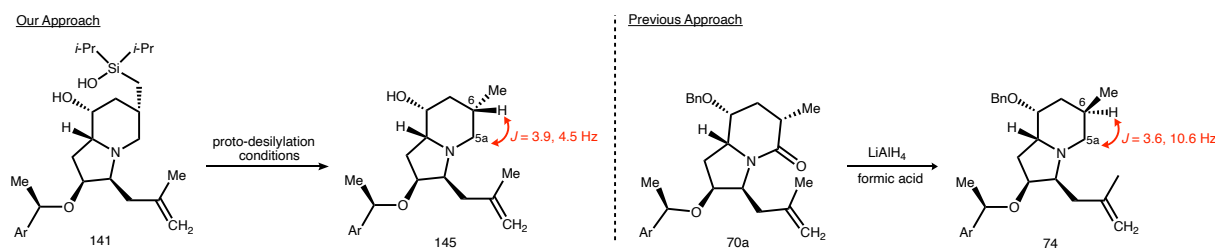
*Scheme 41: Saponification of formate 139*

For the identification of the over-reduction ratio upon this step, isolation of the bicyclic tertiary amines was planned. Lactam **136** was subjected to 3 equiv of  $LiAlH_4$  at RT resulting in the formation of the expected tertiary amine **144**. Acid treatment led to the complete hydrolysis of the silyl ether linker forming the untethered tertiary amine **141** (*Scheme 42*). Again, the H<sub>6</sub> stereochemistry of **141** was confirmed by the coupling constant correlating it with axial H<sub>5a</sub> ( $J_{H5a} = 3.5, 11.3$  Hz).



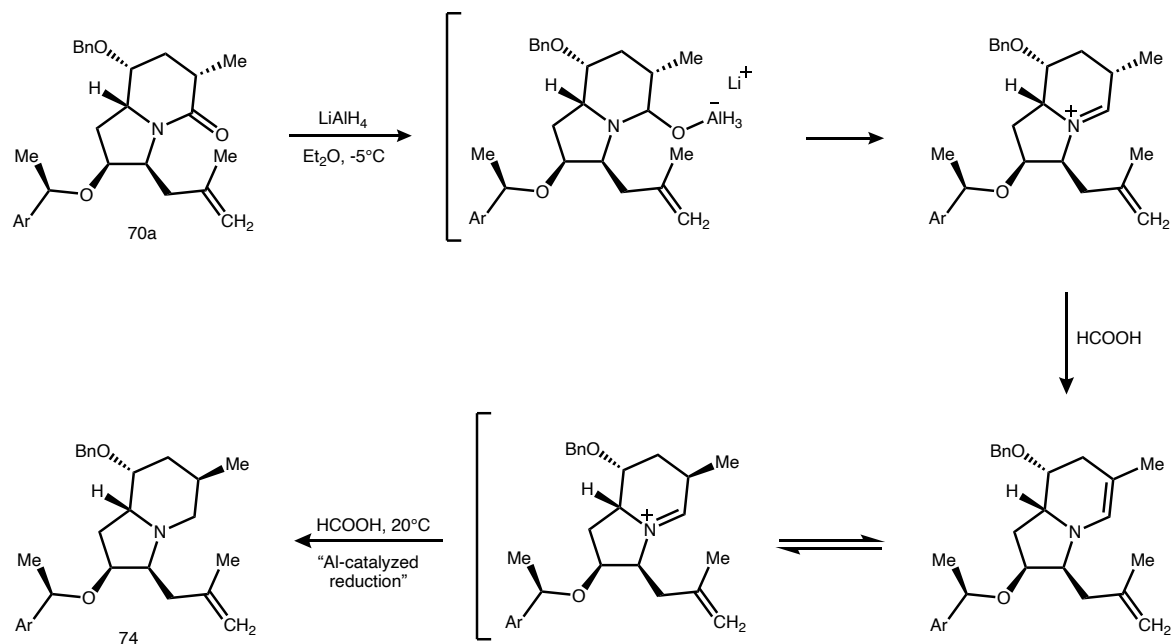
*Scheme 42: Over-reduction of Lactam 136*

At this stage, an intriguing observation has to be mentioned. By comparing the over-reduced amine **145** obtained by the proto-desilylation of the silylated amine **141** (see next part for the conditions) with the previously isolated one **74**, it was noticed that H<sub>5a</sub> (azaacenaphthylene numbering conserved for clarity) has different coupling constants with the surrounding protons (*Scheme 43*). Contrary to what was published previously,<sup>75</sup> the coupling constant of H<sub>5a</sub> in **74** (10.6 Hz) infers that H<sub>6</sub> more probably occupies an axial position.



Scheme 43: 2 epimers of the over-reduced product (145 and 74)

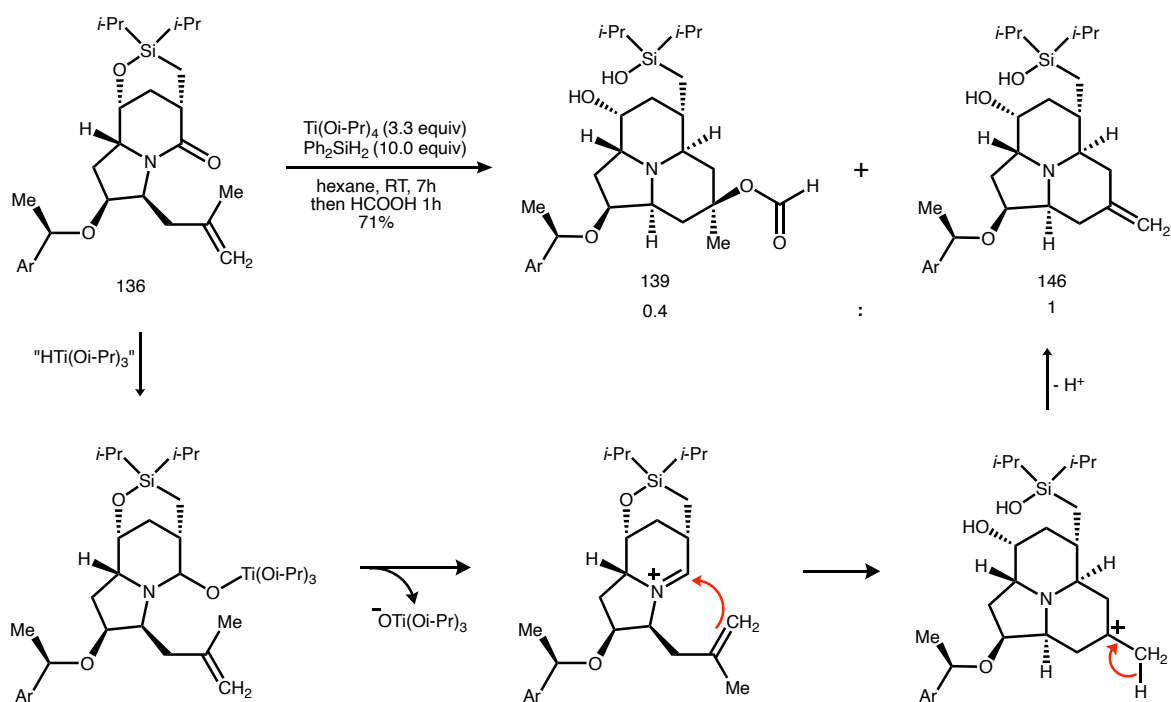
As a consequence, the epimerization of the C<sub>6</sub> chiral center (compound **74**) observed in the previous approach occurred even before the over-reduction step. In these conditions, epimerization of the iminium through the enamine is very unlikely in an aprotic solvent with even excess of hydride source (2 equiv. of LAH were used). If epimerization occurs after the addition of formic acid, this implies that quenching the excess of LAH with formic acid led to the formation of an enough reducing agent toward iminium ion allowing the formation of the over-reduced product (*Scheme 44*). This assumption is further supported by the fact that formic acid can be used as a reducing agent for enamines at elevated temperature (100°C).<sup>115</sup> However, enamine reduction forming amine **74** had occurred at ambient temperature, so does aluminum catalyze this reduction step in the presence of formic acid? No further experiments were performed in order to get more evidences on this puzzling observation. At this stage, we can say that the order of the elementary steps of this cascade is not well defined yet.


 Scheme 44: Suggested mechanism for the formation of amine **74**

<sup>115</sup> (a) Leonard, N. J.; Sauers, R. R. *J Am Chem Soc* **1957**, *79*, 6210-6214. (b) Nilsson, A.; Carlson, R. *Acta Chemica Scandinavica, Series B: Organic Chemistry and Biochemistry* **1985**, *B39*, 187-90.

On the other hand, it was further noticed that cyclization based on LAH reducing agent was irreproducible once the scale is increased as the corresponding over-reduced product **141** was isolated in at least 30%. Subsequently, our attention was turned from a too highly reactive reducing reagents to avoid as much as possible the over-reduction to uncyclized tertiary amine **141**.

The titanium tetrakisopropoxide/diphenylsilane reducing agent system, introduced by Buchwald,<sup>116</sup> was described in the literature to effectively allow the transformation of amide to aldehyde under mild conditions passing through the enamine intermediate. Treating our lactam **136** with this hydride source followed by the addition of formic acid resulted in the formation of a mixture of tricyclic systems; the olefinic product **146** as the major and the hydrolyzed formate **139** (Scheme 45).



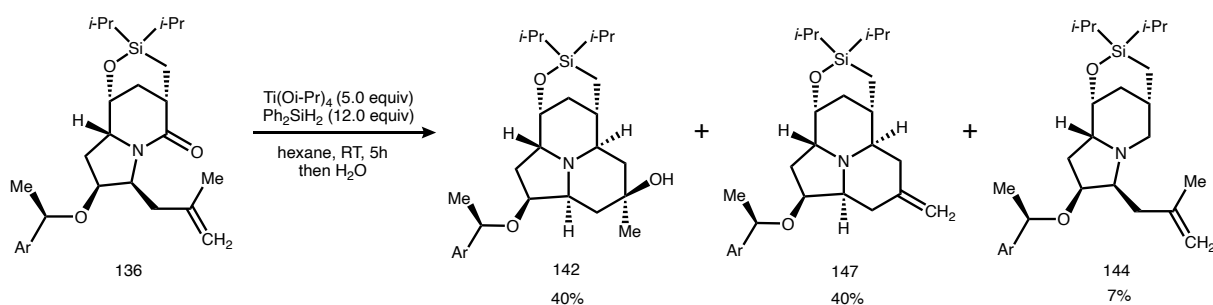
Scheme 45: Buchwald's Conditions – Formic acid

It is proposed that the active reducing agent in this system being the titanium hydride-like complex that is formed as a result of the titanium tetrakisopropoxide catalyst and the silane. Lactam is then inserted into this complex, and the titanium alkoxide intermediate is formed after the hydride transfer. Acidic elimination of titanium oxide allows the formation of the iminium intermediate that is attacked with the double bond, as described before. According to our results, it was hypothesized that the olefinic product **146** would be the result of the early generation of the iminium intermediate through

<sup>116</sup> (a) Bower, S.; Kreutzer, K. A.; Buchwald, S. L.; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1515-1516. (b) Jakubec, P.; Hawkins, A.; Felzmann, W.; Dixon, D. J. *J. Am. Chem. Soc.* **2012**, *134*, 17482-17485.

the departure of triisopropyltitanate as an enough leaving group, followed by the aza-Prins cyclization leading to the generation of the tertiary carbocation. Due to the absence of any efficient nucleophile in the reaction mixture at that stage (solvent is hexane), the carbocation is quenched by proton elimination.

To verify this expectation, the lactam **136** was subjected to the same reduction conditions but with no acid quenching. A 1:1 mixture of tertiary alcohol **142** and terminal double bond **147** was obtained with 7% of the tertiary amine **144** (*Scheme 46*). Therefore, probably the acidity of titanium provokes the earlier iminium formation. Despite that these conditions seems to strongly favor the formation of cyclized products with acceptable low percentage of over-reduced product, the presence of the double bond at early stage of the synthetic pathway is however undesirable as the subsequent planned steps included hydrogenation of a terminal double bond to install the remaining methyl group. Depending on this result, a potentially less Lewis acidic reducing agent system should be applied as a way to avoid this earlier cyclization.



*Scheme 46: Buchwald's Conditions – No Formic acid*

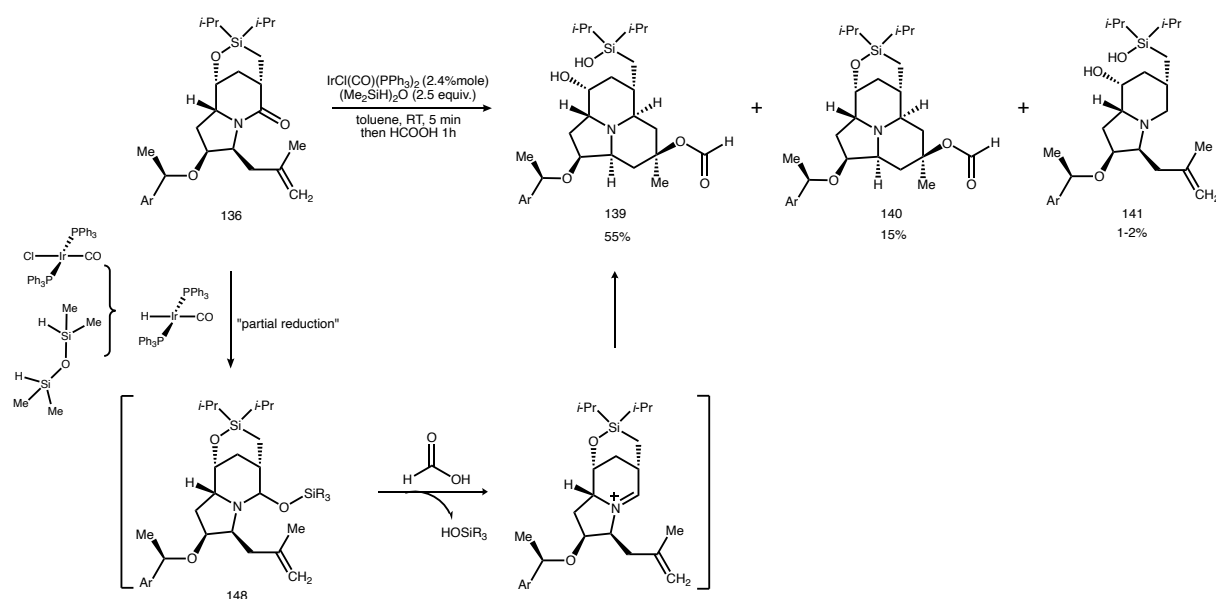
Recently, Dixon has developed a new system for the reductive-nitro Mannich cyclization cascade<sup>117</sup> as well as other amide reductive functionalization<sup>118</sup> that could be the answer for the required reactivity for our substrate. This system is based on the iridium(I) –tetramethyldisiloxane (TMDS) couple ensuring the partial reduction of lactam. In this case, the species resulting from the hydride addition is believed to exist in the reaction mixture as the corresponding silyloxy intermediate **148**, stable enough not to spontaneously generate the iminium intermediate until the addition of formic acid driving the followed cyclization. In our case, a mixture of cyclized products **139** and **140** were isolated in 55% and 15%

<sup>117</sup> Gregory, A. W.; Chambers, A.; Hawkins, A.; Jakubec, P.; Dixon, D. J. *Chem. Eur. J.* **2015**, *21*, 111-114.

<sup>118</sup> (a) Arriba, À. L. F.; Lenci, E.; Sonawane, M.; Formery, O.; Dixon, D. J. *Angew. Chem. Int. Ed.* **2017**, *56*, 3655-3659. (b) Xie, L.-G.; Dixon, D. J. *Chem. Sci.* **2017**, *8*, 7492-7497. (c) Gabriel, P.; Gregory, A. W.; Dixon, D. J. *Org. Lett.* **2019**, *21*, 6658-6662. (d) Xie, L.-G.; Dixon, D. J. *Nat. Comm.* **2018**, *9*, 2841.

respectively differing only by the partial hydrolysis of the silyl ether linkage. The noteworthy result of these conditions is that the over-reduction of lactam can be controlled where the ratio of the tertiary amine **141** was drastically diminished to 1–2% (*Scheme 47*).

Further in the synthesis, this mixture of formates **139** and **140** was used unpurified without any consequences, even if it made the NMR analysis of the crude more complicated. However, analytical samples of **139** and **140** were obtained by silica gel chromatography allowing full characterization for each compound.



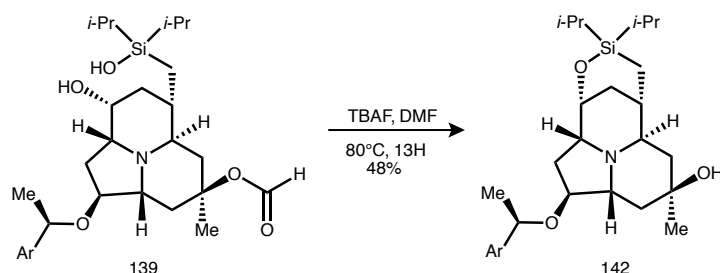
*Scheme 47: Dixon's partial reduction and aza-Prins Cyclization*

This Aza-Prins reaction is expected to proceed through a plausible mechanism shown in *Scheme 47*. Vaska's complex  $\text{IrCl}(\text{CO})(\text{PPh}_3)_2$  catalyzes efficiently the hydride transfer from the silane through an iridium hydride-like complex to reduce partially the lactam **136** forming the silyloxy intermediate. This silyloxy intermediate is believed to be enough stable in the reaction medium preventing the formation of the corresponding iminium and thus the possibility of over-reduction. The addition of the acid triggers the elimination of silanol forming the iminium intermediate, followed by the aza-Prins cyclization that lead to the construction of the tricyclic core of the natural product. The generated carbocation is then trapped by the formate ion.

## IV. Unmasking of C<sub>6</sub>–axial methyl group

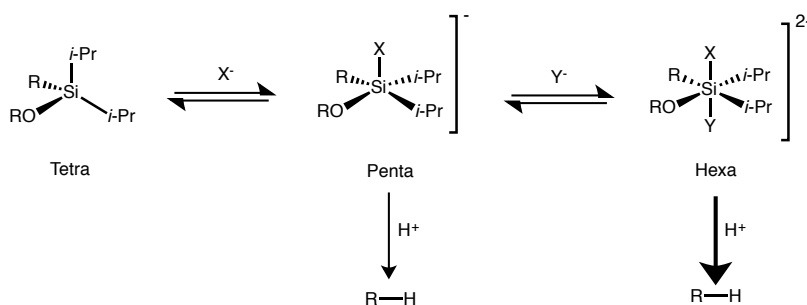
To release the C<sub>6</sub>–axial methyl group embedded in the structure of **139**, the unactivated C(sp<sup>3</sup>)–SiR(*i*-Pr)<sub>2</sub> was subjected to the known proto-desilylation.<sup>119</sup> In order to define the best optimized conditions for a mild and efficient proto-desilylation reaction, a range of conditions were studied.

Fluoride-induced desilylation of intermediate **139** with 10 equiv. of TBAF,<sup>120</sup> either as hydrated solid or as THF solution, resulted only in re-cyclization of the silyl ether and formate saponification forming the tethered tertiary alcohol intermediate **142** as the only isolated product (*Scheme 48*). It is tenable that the increased steric congestion around silicon disfavors the attack by the fluoride ion and thus prohibiting the activation of the silicon carbon bond toward cleavage.



*Scheme 48: Unsuccessful fluoride-induced protodesilylation*

For non-activated alkyl silanes, these reactions are likely needed to proceed through a penta- or hexacoordinated siliconate. The excess of electron density is distributed on the alkyl groups surrounding the silicon and thus increasing the tendency of the Si–C bond toward electrophilic cleavage.<sup>121</sup>



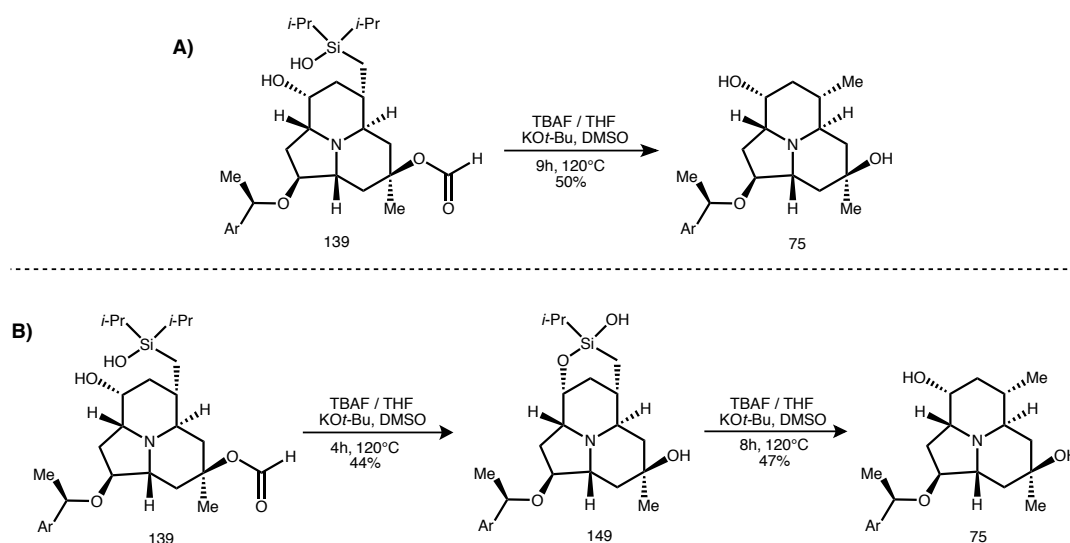
*Scheme 49: Si–C Cleavage via hypercoordinated species*

<sup>119</sup> (a) Hudrlík, P.; Hudrlík, A.; Kulkarni, A. *J. Am. Chem. Soc.* **1982**, *104*, 6809. (b) Hudrlík, P.; Holmes, P.; Hudrlík, A. *Tetrahedron Lett.* **1988**, *29*, 6395. (c) Hudrlík, P.; Gebreselassie, P.; Tafesse, L.; Hudrlík, A. *Tetrahedron Lett.* **2003**, *44*, 3409. (d) Landais, Y.; Mahieux, C. *Tetrahedron Lett.* **2005**, *46*, 675. (e) Stork, G.; Sofia, M. J. *J. Am. Chem. Soc.* **1986**, *108*, 6826.

<sup>120</sup> (a) Heitzman, C. L.; Lambert, W. T.; Mertz, E.; Shotwell, J. B.; Tinsley, J. M.; Va, P.; Roush, W. R. *Org. Lett.* **2005**, *7*, 2405-2408. (b) Smith, J.; Kamath, A.; Greene, A. E.; Delair, P. *Synlett* **2014**, *25*, 209-212.

<sup>121</sup> Tamao, K. *Proc. Jpn. Acad., Ser. B* **2008**, *84*, 123-133.

According to Woerpel, proto-desilylation of a bulky substituents—silyl moiety is effective with KO(*t*Bu) and *n*-Bu<sub>4</sub>NF in a mixture of DMSO:THF (4:1) at 120°C.<sup>122</sup> Treating our silylated substrate **139** with the described conditions for 9 hours yielded the desired product **75** in 50% (*Scheme 50A*). The presence of the *tert*butoxide seems to increase the electron density where silicon carbon bond is indeed highly more activated toward cleavage. The major unsolvable restriction of these conditions was the cleavage of the chiral auxiliary group in variable and unavoidable amount leaving behind the (*R*)-Stericol **55**. Extra addition of 5% of water to the reaction mixture led to the failure of the reaction. It seems that the proton source is internally from the TBAF solution that contains certain percentage of water.



*Scheme 50: KO(*t*-Bu) and TBAF-based proto-desilylation*

In an attempt to know the most susceptible bonds to be cleaved first, early quenching of the reaction was done (after 4h). It was noticed that this reaction passes through the intermediate **149** where desilylation of an isopropyl group occurs first while restoring the silyl-ether link and promoting saponification in basic medium (*Scheme 50B*).

Throughout the several optimization trials, it was observed that the reaction does not work with moderately aged bottle of TBAF/THF solution, and even sometimes with freshly new bottle. This behavior was related to the effect of the water percentage in TBAF solution on the desilylation reaction.

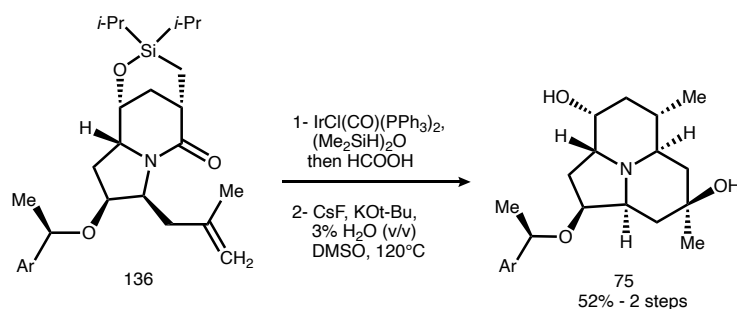
<sup>122</sup> (a) Clark, T.B.; Woerpel, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 9522-9523. (b) Nevarez, Z.; Woerpel, K. A. *Org. Lett.* **2007**, *9*, 3773-3776. (c) Anderson, L. L.; Woerpel, K. A. *Org. Lett.* **2009**, *11*, 425-428.



Vaghefi *et al.* noted that too wet TBAF is the reason behind the failure of desilylation reactions where they recommend not using a TBAF solution exceeding 5% water content.<sup>123</sup>

For the control of the water content in every reaction, we have subrogated the fluoride source with cesium fluoride accompanied with the addition of 3% water (v/v) in DMSO. These conditions appeared to us as the most practicable and reproducible reaction conditions so far studied.

For synthetic purpose, it was reasonable to think that running proto-desilylation of both formates **139** and **140** separately is not necessary and that the crude product of the aza-Prins reaction (*see Scheme 47*) could be used unpurified for this proto-desilylation step. Thus, the corresponding 2 steps–4 transformations cascade yielded the advanced alcohol intermediate **75** in 52% yield (*Scheme 51*).

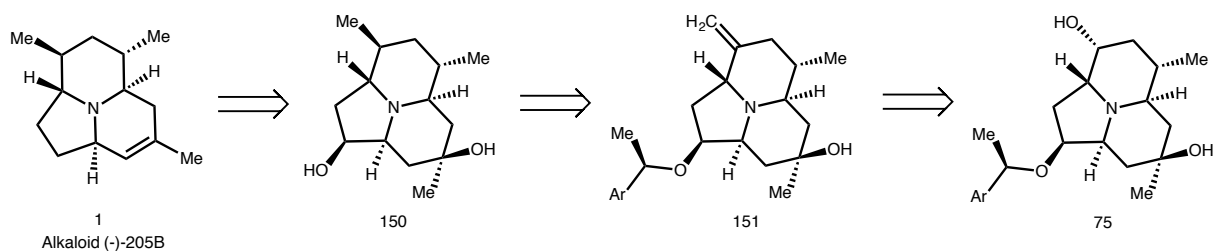


*Scheme 51: Aza-Prins cyclisation – protodesilylation sequence*

## V. Toward Alkaloid (–)-205B Retrosynthetically

Once the C<sub>6</sub>–axial methyl group is successfully installed, our attention was focused toward the final part of the synthetic pathway. The target alkaloid **1** was planned to be synthesized via the tricyclic intermediate **150** by sequential deoxygenation and regioselective dehydration forming the internal double bond. This advanced intermediate **150** can be obtained by the stereoselective hydrogenation affording the equatorial methyl group followed by chiral auxiliary group cleavage. The exomethylene group (**151**) in turn can be prepared from the secondary hydroxyl group (**75**) by the standard oxidation–methylenation sequence. (*Scheme 52*)

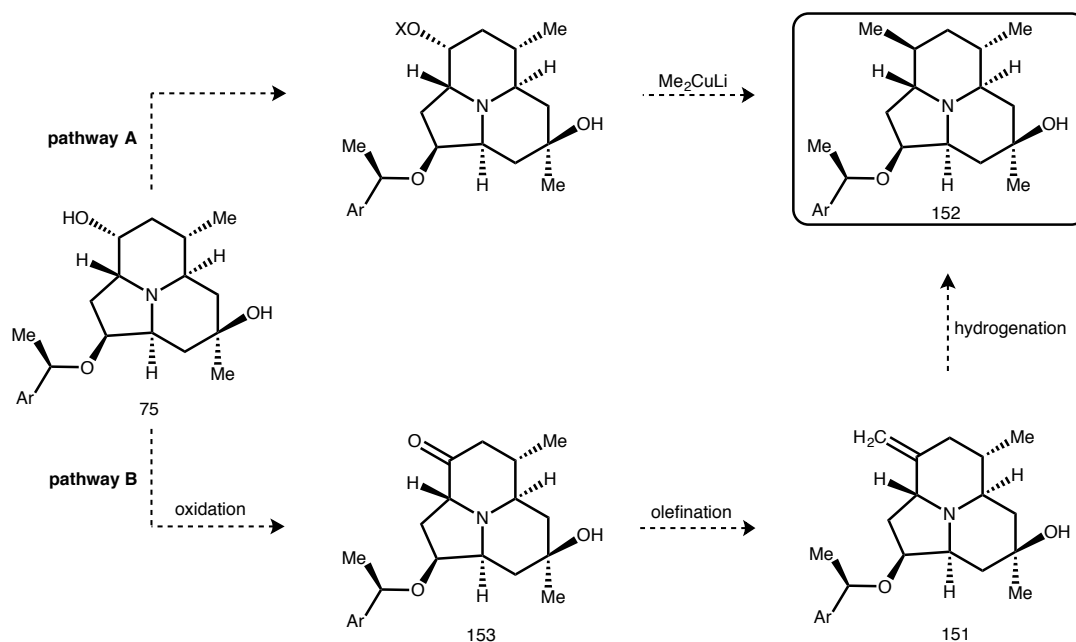
<sup>123</sup> Hogrefe, R. I.; McCaffrey, A. P.; Borozdina, L. U.; McCampbell, E. S.; Vaghefi, M. M. *Nucleic Acids Research* **1993**, *21*, 4739-4741.



Scheme 52 : Retrosynthetic Strategy of alkaloid (-)-205B

## VI. Formation of C<sub>8</sub>–equatorial methyl group

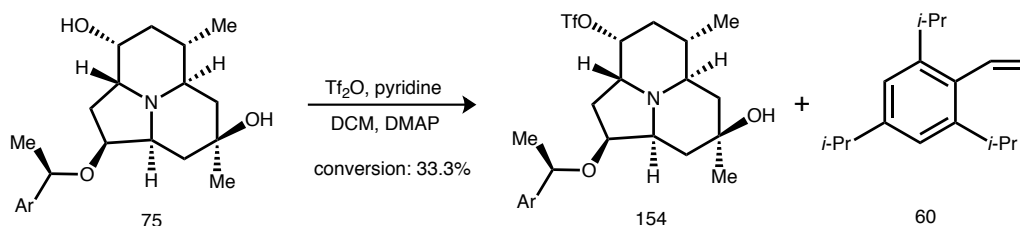
With the requisite 8b-azaacenaphthylene ring system **75** in hand, the next step is the conversion of the secondary axial hydroxyl group at C<sub>8</sub> to equatorial methyl group **152**. There is 2 plausible pathways for such transformation (*Scheme 53*); either by the 2 steps–conversion to a good leaving group followed by substitution with Gilman reagent (pathway A) or the 3 steps–oxidation, olefination and hydrogenation – with the equatorial methyl group being the major epimer according to Smith work<sup>62</sup> (pathway B).

Scheme 53: 2 pathways for the formation of C<sub>8</sub>–equatorial methyl group

### i. The 2–Steps Approach

Having to convert the hydroxy group into good leaving group, we have started by the attempt to produce the triflated alcohol **154**. Unfortunately, we faced to the low conversion of the starting alcohol **75** yielding at best 1:2 mixture of the triflate derivative **154** and alcohol **75** respectively. Along with

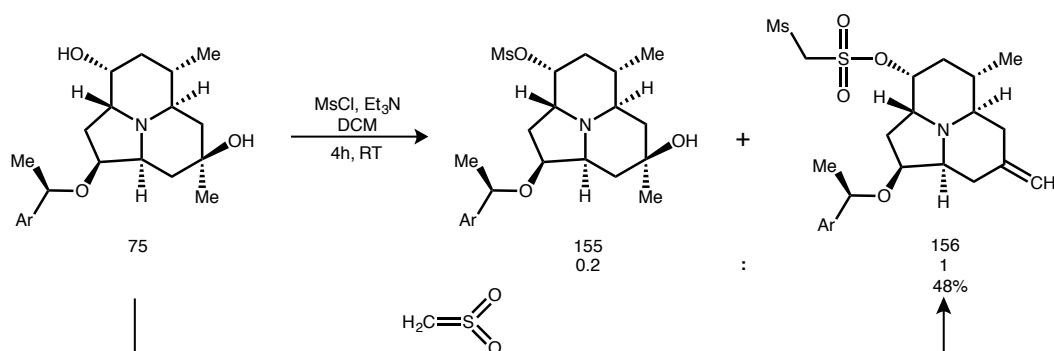
the variable formation of the styrene derivative **60** probably because of the medium acidity or the high electrophilicity of the reagent triggering this benzyl ether cleavage. (Scheme 54)



Scheme 54: Triflation of alcohol 75

So, our focus was then directed toward the formation of the mesylated product **155**. Using triethylamine as the base yielded a 0.2:1 mixture of the mesylated product **155** and the terminal olefin **156** respectively, from which olefin **156** was isolated in 48% (Scheme 55). This result was not surprising as these conditions were described in the literature to be an efficient method for the conversion of tertiary alcohol into olefin.<sup>124</sup> The strong base is responsible for the formation of the sulfene which is more reactive than MsCl thus reacting with tertiary alcohol allowing the formation of the kinetic olefin **156**. As an attempt to slow down the formation of sulfene, reaction was carried out at 0°C for 1h. However, the ratio was only improved at best 0.36:1 of the desired mesylated product **155** and byproduct **156** respectively.

Even not expected, the adduct **156** is probably produced due to the reaction of the alcohol function with (methylsulfonyl)-methanesulfonate which is formed in situ based on sulfene intermediate. This kind of adducts has been scarcely reported in the literature.<sup>125</sup>

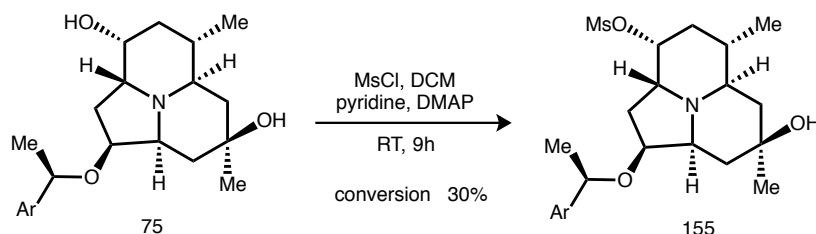


Scheme 55: Mesylation using triethylamine as base

<sup>124</sup> Yadav, J. S.; Mysorekar, S. V. *Synthetic Communications* **1989**, 19, 1057-1060.

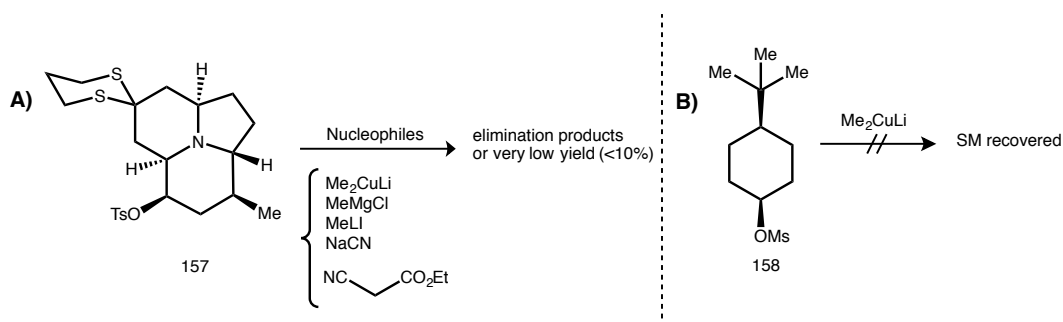
<sup>125</sup> (a) Ciabattini, J.; Cabell, M. *Tetrahedron Letters* **1968**, 2693-2696. (b) Shealy, Y. F.; Krauth, C. A.; Laster, W. R. *Journal of Medicinal Chemistry* **1984**, 27, 664-670.

Considering weaker base such as pyridine had solved the elimination problem, but the conversion of this reaction was low (30%) (*Scheme 56*). Prolonging the reaction time led to the deviation of the desired pathway allowing the formation of byproducts that are expected to correspond for the elimination of the mesylated group at RT.



*Scheme 56: Mesylation using pyridine as base*

To our knowledge, elimination reaction could be faster than the desired substitution with cyclohexyl carbocation. This was also mentioned by Smith for the substitution of the tosylate derivative **157** with a wide variety of nucleophiles that led majorly for the elimination product (*Scheme 57A*).<sup>62</sup> Furthermore, displacing the derived mesylate in a model compound **158** with the organocuprate nucleophile furnished the starting material (*Scheme 57B*), emphasizing more on the difficulty of the formation of the desired equatorial methyl group through this approach. Due to all the encountered difficulties within this pathway and having to undergo substitution on a six membered ring let us look further for other more promising approach for such transformation.



*Scheme 57: Difficulties of substitution of activated cyclohexyl alcohol*

## ii. The 3–Steps Approach

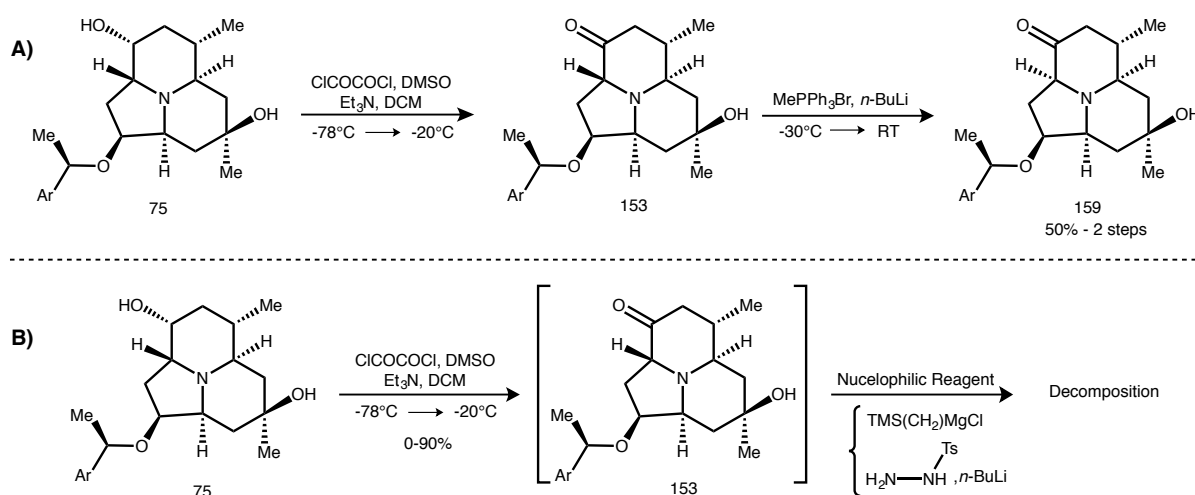
a. Formation of the exomethylene product

Our initial attempt to transform the secondary alcohol **75** into the corresponding ketone **153** under Swern oxidation conditions was proved to be troublesome. This reaction yielded unstable enolisable

ketone that was difficult to handle and store even with the precautions to keep it always at low temperature. During manipulation, TLC analysis indicated the consumption of the starting material **75**, however NMR spectra of isolated products were most often complex. Even under less electrophilic oxidation conditions such as Dess-Martin periodinane, the ketone was not stable enough to be isolated.

Despite of this fact, ketone **153** was obtained only once allowing basic analytical characterization ( $^1\text{H}$  NMR and mass spectroscopy). Upon treating a well isolated ketone **153** with Wittig reagent at  $-30^\circ\text{C}$  without any delay, the epimerized ketone **159** was isolated in 50% yield according to the first spectral analysis (*Scheme 58A*). In a sharp contrast, this epimerized ketone **159** seems to be more stable than our desired ketone **153** as it was purifiable over silica gel, easier to be handled and stored for several weeks without any noticed decomposition.

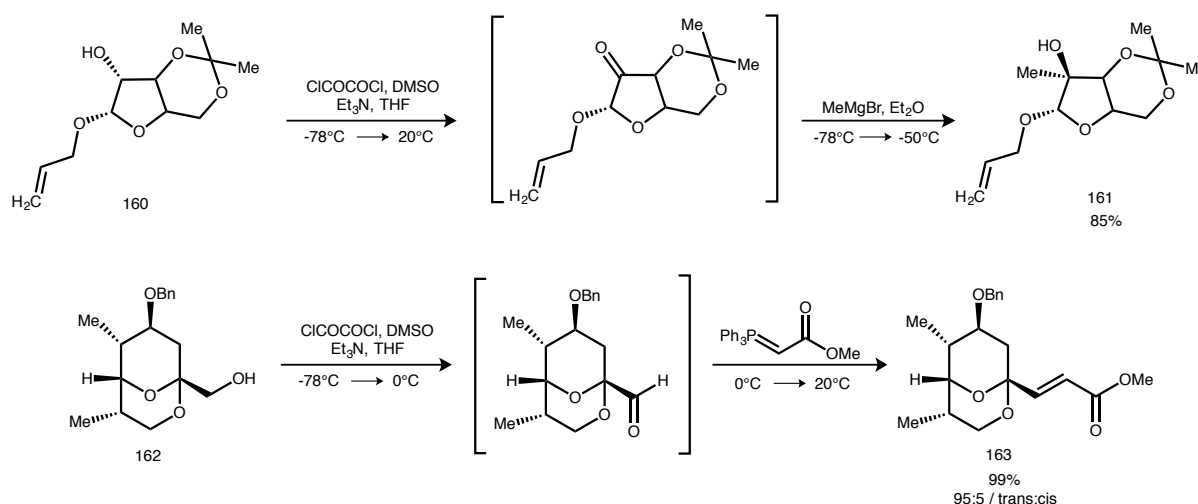
Because this encountered difficulty might be due to possible intrinsic instability of ketone **153**, we attempted to test its reactivity. The isolated crude “expected ketone” was subjected to nucleophilic addition (Grignard and Shapiro reagents) immediately. Unfortunately, no expected products were detected (*Scheme 58B*). This allowed us to infer that the formed amino ketone **153** might face total decomposition upon the oxidation work-up.



*Scheme 58: Swern Oxidation – Nucleophilic Addition sequence*

After these extensive trials for running oxidation that led most of the case to the isolation of unidentified materials, we came across an approach developed by Ireland who tackle with the same behavior with

a series of ketones.<sup>126</sup> In this study, it was highlighted the difficulty of isolating ketones bearing electronegative substituents as they would be prone to hydration and/or decomposition. This problem of the high reactivity of the carbonyl compounds was overpassed by the direct addition of the subsequent reagent to the crude of Swern oxidation mixture with no isolation of ketone (*Scheme 59*). This one pot strategy seems to be promising for the isolation of our desired olefin intermediate **151**.



*Scheme 59: One pot of Swern Oxidation – Nucleophilic Addition (Ireland Research)*

Considering that Swern oxidation was effective and that previous difficulties came out from the isolation of the ketone **153**, we wondered if a one pot–two steps procedure could be more rewarding. In addition, to avoid the possible epimerization of the expected ketone **153** by strong basic nucleophile, we considered a methylenation agent mild enough to be used with epimerizable ketone. We have considered Julia-Kocienski olefination as an efficient tool for the generation of alkene via the reaction of metallated heteroaryl sulfone with carbonyl compound. Recently, a new Julia reagent was described by Aissa that could fill our requirements; the TBT sulfone.<sup>127</sup> Moreover, the derived metallated TBT sulfone was proved to be the more resistant to self-condensation under basic conditions.<sup>128</sup>

In this case, the direct addition of the premetallated TBT sulfone to the Swern oxidation mixture, once consumed all the starting alcohol, could overcome the previous difficulty. The first trial was carried out with THF being the solvent of both Swern oxidation and Wittig olefination (*Scheme 60A*). To our

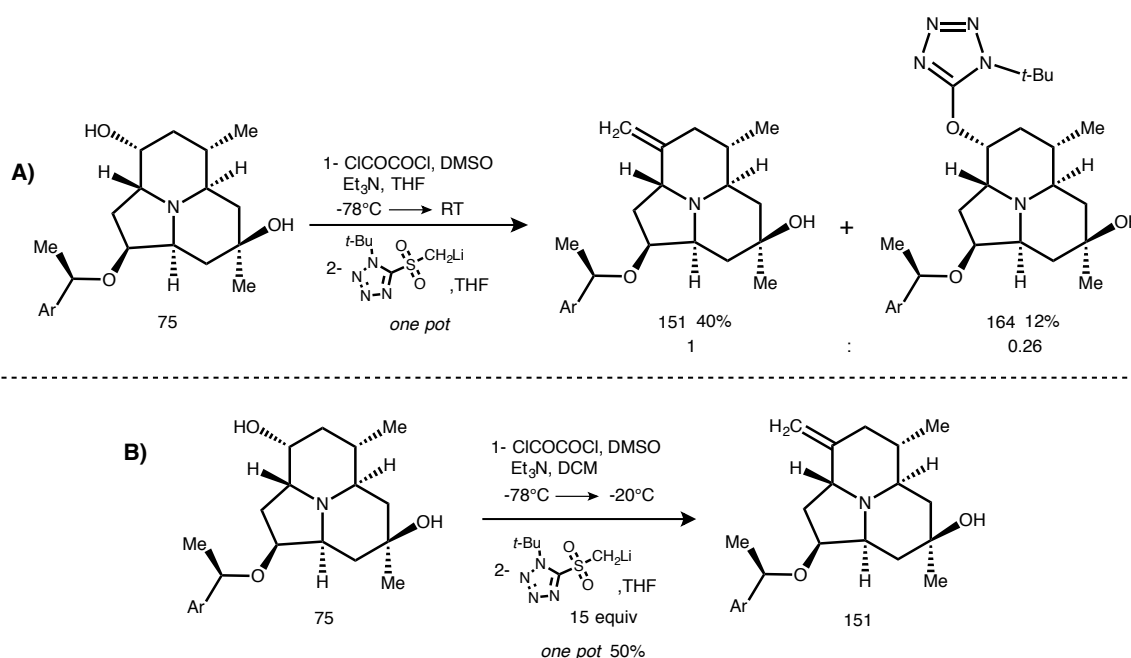
<sup>126</sup> Ireland, R. E.; Norbeck, D. W. *J. Org. Chem.* **1985**, *50*, 2198-2200.

<sup>127</sup> Aissa, C. *J. Org. Chem.* **2006**, *71*, 360-363.

<sup>128</sup> Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563-2585.

great satisfaction, the alkene **151** was isolated for the first time in 40% yield. However, we faced to the incompleteness of the Swern oxidation in THF in spite of the several attempts. The remained alcohol **75** in basic medium reacts with the excess of TBTSO<sub>2</sub>Me forming the intermediate **164** in 0.26:1 ratio with respect to the alkene **151** and was isolated in 12% yield.

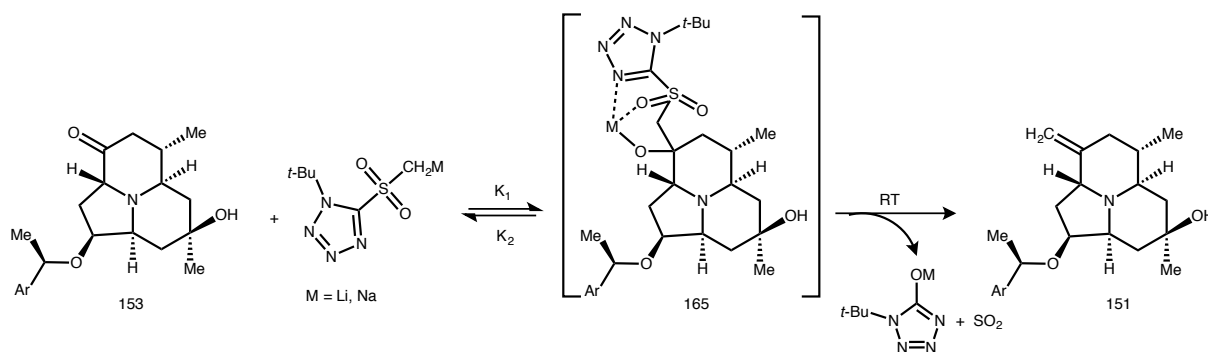
As the usual solvent of Swern oxidation is DCM, this one pot procedure was then tried using this solvent. Unfortunately, this solvent-change had affected the olefination step resulting in the formation of unidentified byproducts with alkene **151** as minor product. Therefore, after the complete formation of the ketone **153** in DCM (as noticed by TLC analysis), it was decided to perform solvent exchange (DCM to THF) followed by the addition of an excess of the freshly prepared solution of the premetallated sulfone in THF (*Scheme 60B*).<sup>129</sup> To our great satisfaction, this one pot reaction led only to the formation of the expected alkene **151** in 50% yield. As an attempt to improve the yield, Barbier-type procedure was applied where also 50% yield of the alkene **151** was obtained. However, it is important to note the irreproducibility of these conditions once the scale was increased.



*Scheme 60: One pot of Swern Oxidation – Julia Olefination*

<sup>129</sup> Zaed, A. M.; Sutherland, A. *Org. Biomol. Chem.* **2010**, *8*, 4394-4399.

This olefination termed as “modified Julia reaction” was first described by Sylvestre Julia and co-workers<sup>130</sup> and then modified by Kociensky.<sup>131</sup> The mechanism is known to involve nucleophilic addition of the metallated sulfone on the carbonyl compound, followed by the irreversible Smiles rearrangement within the alkoxide intermediate.<sup>132</sup> In our case, we had faced to the reversibility of the initial addition of the metallated sulfone to our ketone. Thus, the efficiency of the formation of the olefin will depend on the position of the first equilibrium (*Scheme 61*).



*Scheme 61: Julia-Kociensky Olefination Mechanism*

Knowing that Smiles rearrangement requires RT to occur, quenching the reaction at  $-60^{\circ}\text{C}$  allowed the isolation of the hydroxy sulfone derived from the intermediate **165** in 48% yield. Much to our surprise, subjecting this hydroxy sulfone to basic medium resulted in the formation of 1:0.25 mixture of the ketone **153** and the alkene **151** indicating that the equilibrium is in favor of the starting materials. It was observed that the counter ion ( $\text{Li}^+$  or  $\text{Na}^+$ ) has no influence on the position of the equilibrium. Thus, to favor the formation of the alkene **151**, a high concentration of metallated TBT sulfone is required in order to shift the equilibrium forward and allowing the rearrangement to occur.

Due to the demand of the high equivalence of this expensive sulfone, olefination was attempted with 1-phenyl-1H-tetrazol-5-yl (PT) sulfone.<sup>133</sup> This sulfone was considered as it was reported that simple alkyl PT sulfone metallates added irreversibly to aldehyde.<sup>128</sup> But, no improvement in the yield was detected.

<sup>130</sup> (a) Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Tetrahedron Lett.* **1991**, 32, 1175-1178. (b) Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Bull. Soc. Chim. Fr.* **1993**, 130, 336. (c) Baudin, J. B.; Hareau, G.; Julia, S. A.; Loene, R.; Ruel, O. *Bull. Soc. Chim. Fr.* **1993**, 130, 856.

<sup>131</sup> (a) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morely, A. *Synlett* **1998**, 26-28. (b) Kocienski, P. J.; Bell, A.; Blakemore, P. R. *Synlett* **2000**, 365.

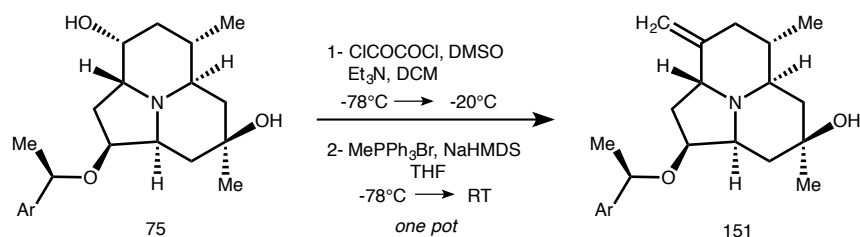
<sup>132</sup> Aïssa, C. *Eur. J. Org. Chem.* **2009**, 1831-1844.

<sup>133</sup> Pospíšil, J.; Sato, H. *J. Org. Chem.* **2011**, 76, 2269-2272.



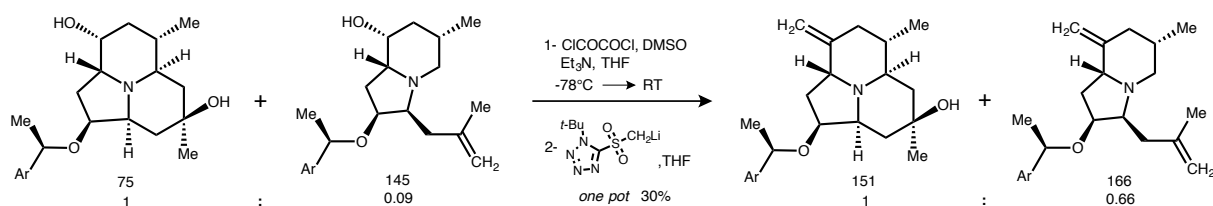
In order to bypass this unfavorable reversible step, we re-considered the Wittig reagent due to its expected higher nucleophilicity. Treating the unisolated ketone with the corresponding phosphonium salt with NaHMDS as a base at  $-78^{\circ}\text{C}$  (avoiding ketone epimerization) allowed the production of 40% of the olefin **151** (*Scheme 62*). The same irreproducibility problem was encountered with these conditions.

*Note:* Due to the partial stability of the alkene, it was subjected to pseudo-purification over silica gel. Thus, the yield provided is estimated from the NMR of the alkene that is contaminated with Wittig reagent.



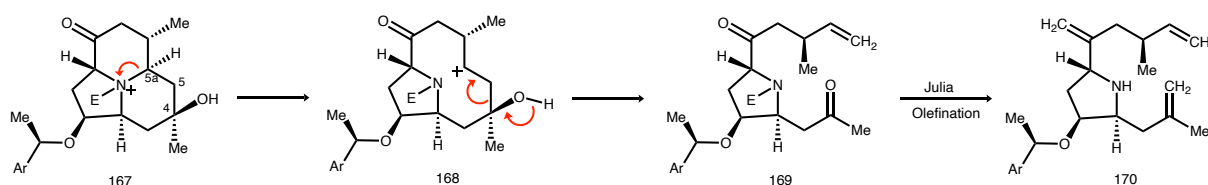
*Scheme 62: One pot of Swern Oxidation – Wittig Olefination*

At this stage, several observations seemed to say that amino-ketone **153** could be more stable than expected so far and that the in situ formation of this ketone did not solve the problem completely. For example, running the same one pot reaction starting with a 1:0.09 mixture of alcohol **75** and over reduced alcohol **145**, led to the isolation of a mixture of the corresponding alkenes **151** and **166** in a ratio of 1:0.66 respectively (*Scheme 63*). This can be a hint for the difference in stability of the 2 corresponding ketones indicating that the tricyclic ketone **153** is still subjected to decomposition even without isolation. In addition, the previous successful isolation of ketone **153** (with well analyzed NMR) upon subjecting the hydroxy sulfone-derived intermediate **165** to Smiles rearrangement's condition indicates that the instability of the ketone is still negotiable.



*Scheme 63: One Pot of Swern Oxidation – Julia Olefination*

On the other hand, the isolation of the byproduct **170** after this one pot–2 steps transformation allowed us to hypothesize that earlier observed decomposition of the tertiary amino ketone might be due to Grob–type fragmentation triggered by an electrophilic activation during the Swern oxidation (*Scheme 64*). This kind of fragmentation is observed at this stage probably because the ketone might weaken the C–N bond increasing its susceptibility for cleavage. This fragmentation is known to mainly proceed through a concerted mechanism for which the orbitals should obey conformational requirements where anti-periplanarity alignment is required for maximum orbital overlap, but some stepwise Grob like fragmentation are also reported in the literature.<sup>134</sup> In our case, as the lone pair of the oxygen, the  $\sigma$ -bond C<sub>4</sub>–C<sub>5</sub> and the  $\sigma$ -bond C<sub>5a</sub>–N are not parallel to each other, we expect that fragmentation occur in stepwise manner triggered by an electrophile species (E) during the Swern oxidation (*Scheme 64*).

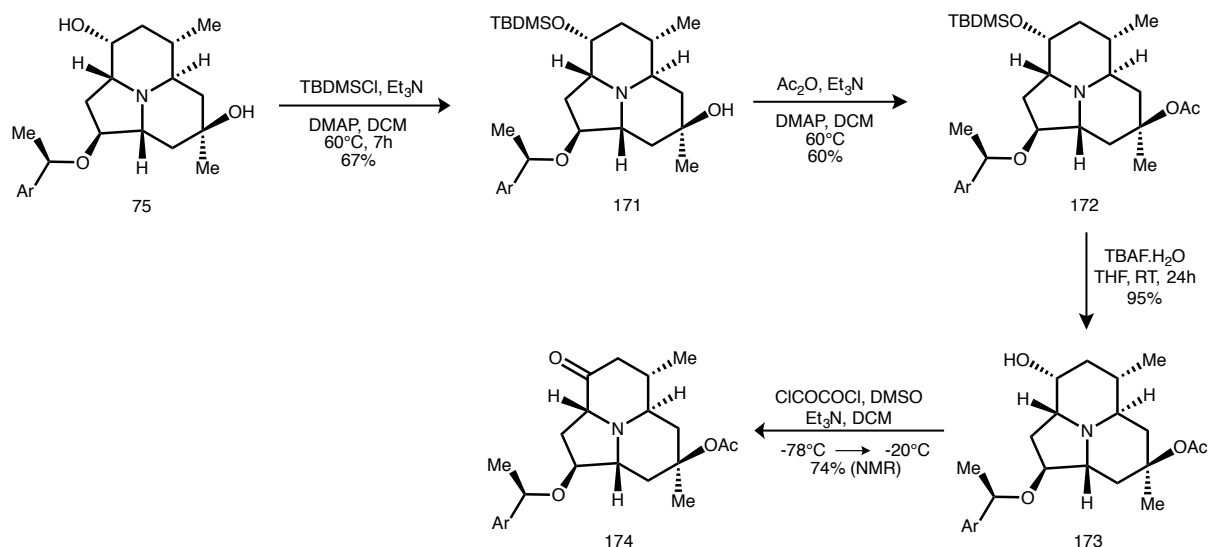


*Scheme 64: Grob–type Fragmentation*

Also, an indirect support to this expectation is the fact that Smith had characterized amino ketone-like substrate **22** in his synthetic approach without any mention to particular degradation.<sup>62</sup> Noteworthy, no tertiary hydroxyl group is present in his structure that could be engaged in a fragmentation process. To confirm this assumption, Swern oxidation was ran on the acylated compound **173** which was prepared by a conventional protection-acylation-deprotection sequence from **75** (*Scheme 65*). Thanks to our expectation, ketone's stability improvement was observed where it was isolated in 74% yield (estimated from the NMR). This acylated amino ketone **174** was easier to handle and can be stored for several days but purification remains impossible. We expect that the stability might be further improved with other protecting groups. But for our synthetic purpose, this solution does not seem to be the best compromised due to the additional steps.

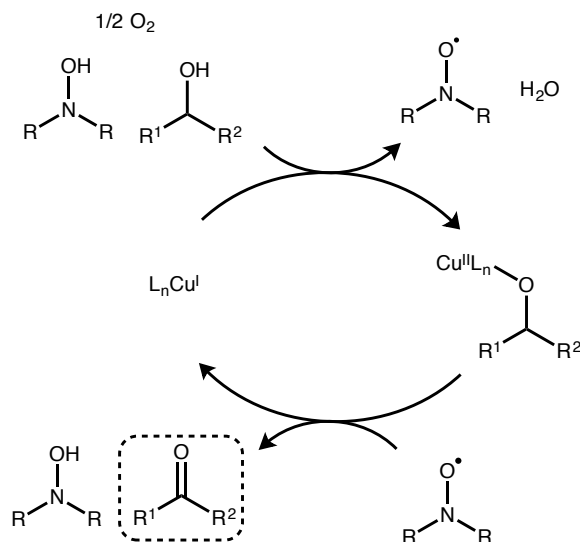
<sup>134</sup> (a) Gleiter, R.; Stohrer, A. D.; Hoffmann, R. *Helvetica Chimica Acta* **1972**, *55*, 893-906. (b) Prantz, K.; Mulzer, J. *Chem. Rev.* **2010**, *110*, 3741-3766.

# ACHIEVEMENT OF TOTAL SYNTHESIS OF (-)-205B



Scheme 65: Swern Oxidation of Acylated Compound 173

This challenging oxidation of amino alcohol into amino carbonyl compounds was reported in the literature to be very difficult without the protection of the amine group.<sup>135</sup> This can emphasize that ketone's behavior is a reflection of the basicity and the conformation of the fixed nitrogen lone pair that interacts with the oxidant. To answer to this limitation, Iwabuchi<sup>136</sup> had developed a new mild direct route for this transformation that is based on nitroxyl radical/copper catalytic system with oxygen being the oxidant. A simplified mechanism of this reaction is given in Scheme 66.<sup>137</sup>



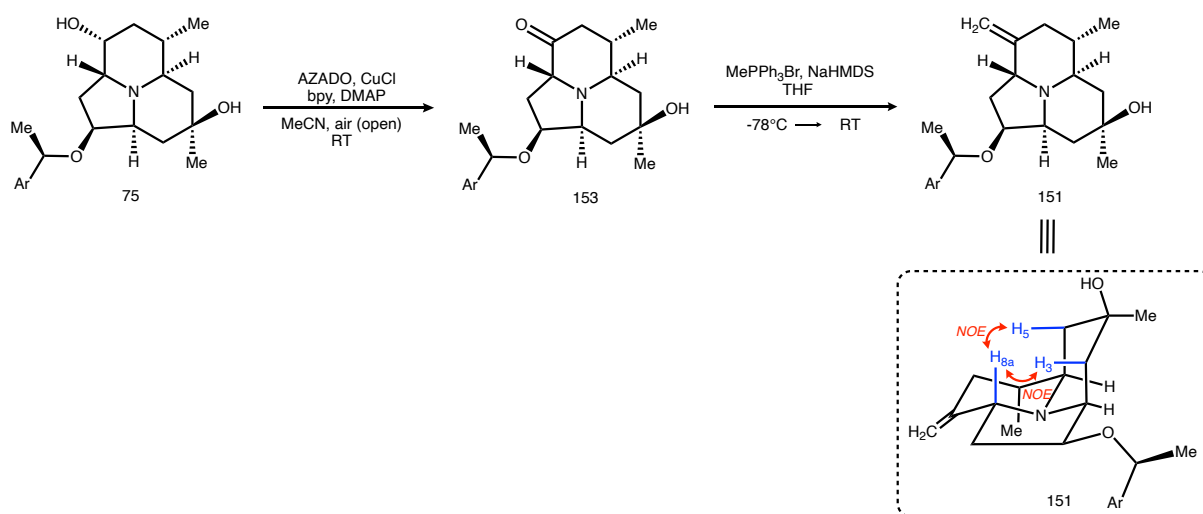
Scheme 66: AZADO oxidation mechanism

<sup>135</sup> (a) Geoghegan, K.; Evans, P. J. *Org. Chem.* **2013**, *78*, 3410-3415. (b) Lin, H. Y.; Causey, R.; Garcia, G. E.; Snider, B. B. *J. Org. Chem.* **2012**, *77*, 7143-7156. (c) Becker, M. H.; Chua, P.; Downham, R.; Douglas, C. J.; Garg, N. K.; Hiebert, S.; Jaroch, S.; Matsouka, R. T.; Middleton, J. A.; Ng, F. W.; Overman, L. E. *J. Am. Chem. Soc.* **2007**, *129*, 11987-12002.

<sup>136</sup> Sasano, Y.; Nagasawa, S.; Yamazaki, M.; Shibuya, M.; Park, J.; Iwabuchi, Y. *Angew. Chem. Int. Ed.* **2014**, *53*, 3236-3240.

<sup>137</sup> Hoover, J. M.; Ryland, B. L.; Stahl, S. S. *J. Am. Chem. Soc.* **2013**, *135*, 2357-2367.

Applying these conditions to our amino alcohol **75** led to the clean isolation of the ketone **153** and then used later for the Wittig olefination step without any further purification. Again, due to the partial stability of the alkene over silica, the crude was subjected to pseudo-purification allowing the isolation of alkene being contaminated with some Wittig reagent (45% yield estimated from NMR). Therefore, after the wide optimization conditions trials, it was found that AZADO oxidation followed by Wittig olefination are the best fit conditions for the reproducible production of the desired alkene **151** (*Scheme 67*).



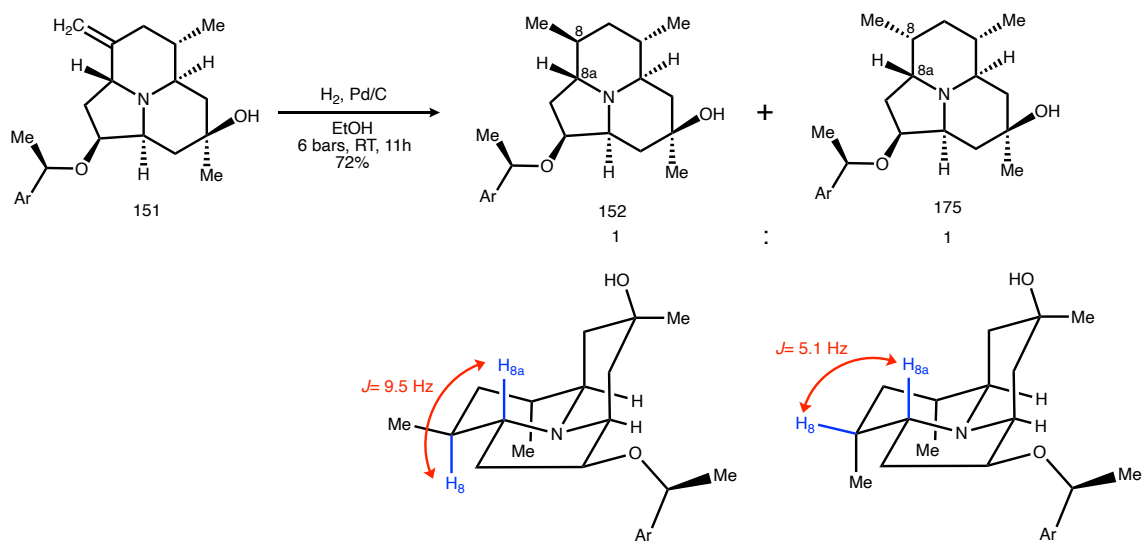
*Scheme 67: AZADO oxidation – Wittig Olefination*

The NOE experiment ( $\text{CDCl}_3$ , 500 MHz) was performed on the alkene intermediate **151** to confirm that no epimerization occurs upon methylenation. The space correlations between the axials;  $\text{H}_5\text{--H}_{8a}$  and  $\text{H}_3\text{--H}_{8a}$  emphasize the integrity of  $\text{C}_{8a}$  stereochemistry.

## b. Hydrogenation

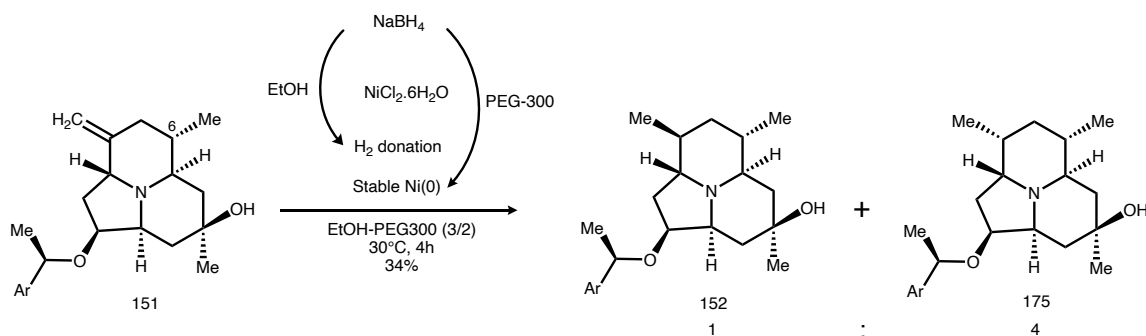
Affording the equatorial methyl group at  $\text{C}_8$  was first planned by subjecting the exocyclic alkene **151** to hydrogenation under standard pressure. As described by Smith on a related structure,<sup>62</sup> hydrogenation was expected to occur through the most accessible face leading to isomer **152**. However, hydrogenation at normal pressure and temperature was not efficient enough to reduce the double bond. Thus, the hydrogenation was attempted at higher pressure—6 bars (*Scheme 68*). The NMR analysis showed that hydrogenation proceeded with poor selectivity producing an inseparable equimolar mixture of both epimers (**152** and **175**). Differentiation between both isomers is based on the coupling constant

correlating  $H_{8a}$  with  $H_8$ . In the desired isomer **152**, axial-axial interaction lead to have higher  $J$  coupling constant ( $\sim 10$  Hz).



*Scheme 68: High Pressure Hydrogenation*

Taking the advantage of avoiding hydrogen gas manipulation, affording the alkane was sought by  $\text{NaBH}_4$ – $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$  mixture system according to a recently described procedure.<sup>138</sup> Reduction of alkenes **151** are catalyzed by the in situ generated  $\text{Ni}(0)$  nanoparticles, where PEG-300 ensures their stabilization. In these conditions, a 4:1 mixture of isomers was obtained (*Scheme 69*). However, spectral analysis showed that the major isomer would be of axial methyl group (**175**). The high diastereofacial selectivity is believed to be controlled by the steric hindrance where  $\text{C}_6$  axial methyl group could direct the approach of the catalyst which seems not to favor the desired equatorial methyl position **152**.



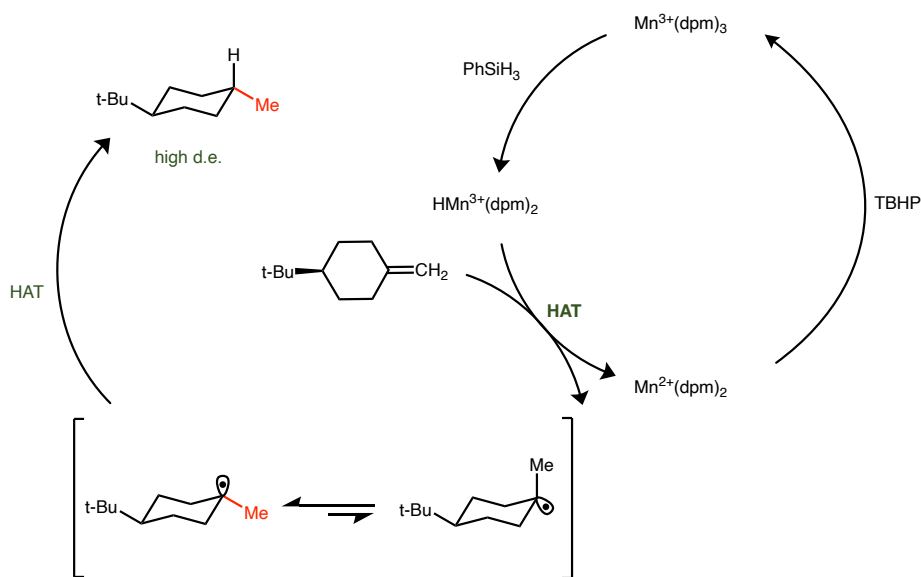
*Scheme 69:  $\text{Ni}(0)$  NPs catalyzed Reduction of Methylene*

Thus, hydrogenation of the exomethylene using common standard methods yielded at best 1:1 mixture of both isomers. This behavior is in a sharp contrast to the case described by Smith and could be the

<sup>138</sup> Li, K.; Liu, C.; Wang, K.; Ren, Y.; Li, F. *RSC Adv.* **2018**, *8*, 7761-7764.

result of the presence of the axial methyl group at C<sub>6</sub> which was absent in *Smith's* case. This methyl group could bring enough steric hindrance to reduce the rate of the axial hydrogen delivery due to the 1,3-diaxial interaction. Thus, having control over the stereochemistry is challenging as to deliver the hydrogen axially without any intrinsic steric bias of the substrate in order to get the expected methyl group equatorially. Therefore, it is prerequisite to afford a hydrogenation transfer favoring the thermodynamic orientation of this methyl group.

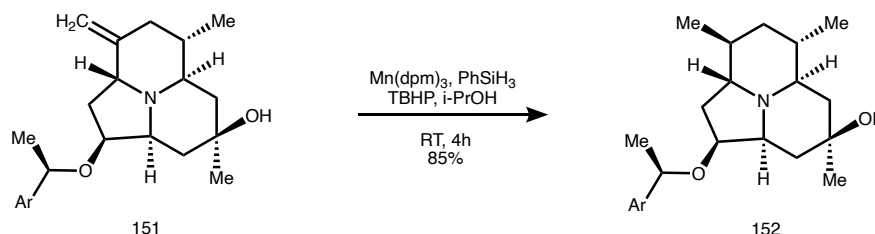
Quite recently, Shenvi and co-workers had reported a procedure to afford the thermodynamically favored configuration selectively under mild reaction conditions and with lower substrate–reagent steric interaction directivity (*Scheme 70*).<sup>139</sup> This stereoselective hydrogenation proceeds through the generation of a tertiary carbon radical via the hydrogen atom transfer (HAT) from an in situ formed metal hydride to an alkene. The resulting tertiary radical is then trapped by a second HAT. As the stereochemical integrity of the tertiary radical is not defined, this second HAT will favor the formation of the more stable isomer. The active species of this transformation “HMn(dpm)<sub>2</sub>” is formed as an effect of the reducing agent PhSiH<sub>3</sub> on the Mn<sup>3+</sup> catalyst provided. In addition, the *tert*butyl hydroperoxide (TBHP) is added as a re-oxidant to turn over the manganese catalyst from Mn<sup>2+</sup> to Mn<sup>3+</sup>. This scenario seems to be well suited to our desired stereoselective delivery of hydrogens favoring the thermodynamically isomer **151**.



*Scheme 70: HAT Reduction of Alkene*

<sup>139</sup> (a) Iwasaki, K.; Wan, K. K.; Oppedisano, A.; Crossley, S. W. M.; Shenvi, R. A. *J. Am. Chem. Soc.* **2014**, *136*, 1300-1303. (b) Obradors, C.; Martinez, R. M.; Shenvi, R. A. *J. Am. Chem. Soc.* **2016**, *138*, 4962-4971.

With great satisfaction, subjecting our alkene **151** to HAT hydrogenation allowed the isolation of the desired isomer **152** in 85% yield as one diastereoisomer, where the other isomer was not detected on the NMR of the crude material (*Scheme 71*).



*Scheme 71: HAT Reduction of Alkene 151*

## VII. Completion of Total Synthesis of (-)-205B

With the tricyclic product **152** in hand with full stereochemistry being introduced, the next step was the cleavage of the chiral auxiliary group. As expected, treatment of a DCM solution of **152** with TFA at 0°C afforded the diol **150** in 75% yield (*Scheme 72*).

The following considered task was the deoxygenation of the secondary hydroxyl group. The standard Barton-McCombie procedure consists of converting the hydroxyl to xanthate followed by radical tin-based mechanism for the reduction step.<sup>140</sup> However, organotin compounds are known for their bad smell, difficulty to be chromatographically separated and their toxicity which is not applicable for expected biological active compounds. For these reasons, organotin reducing agents should be avoided. A lot of research efforts had been done to find suitable organosilanes as alternatives for the hydrogen donor. The used organosilane should be of Si-H bond weak enough to expedite the hydrogen atom abstraction rate. It was found that tris(trimethylsilyl)silane have a high hydrogen donation ability,<sup>141</sup> also it is not toxic and very unpolar thus can be separated easily by purification.

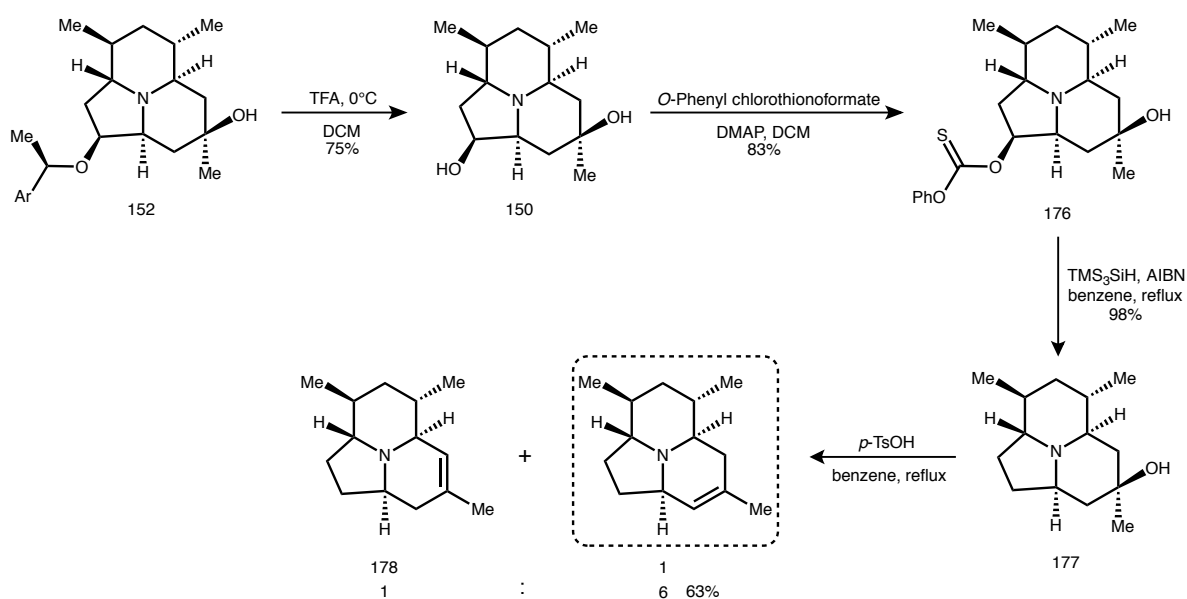
The Barton-McCombie sequence was achieved by first acylating the secondary alcohol **150** with phenyl thionochloroformate catalyzed by DMAP. The *O*-phenyl thionocarbonate **176** was isolated in 83% yield. Much to our delight, this thionocarbonate was reduced by TMS<sub>3</sub>SiH in the presence of

<sup>140</sup> (a) McCombie, S. W.; Motherwell, W. B.; Tozer, M. J. *Organic Reactions* **2012**, *77*, 161-591. (b) Majid, M.; Bakhtiari, A.; Faghihi, Z. *Curr. Org. Synth.* **2014**, *11*, 787-823. (c) Baguley, P. A.; Walton, J. C. *Angew. Chem. Int. Ed.* **1998**, *37*, 3072-3082.

<sup>141</sup> (a) Chatgililoglu, C.; Ferreri, C. *Res. Chem. Intermed.* **1993**, *19*, 755-775. (b) Chatgililoglu, C.; Ferreri, C.; Landais, Y.; Timokhin, V. *I. Chem. Rev.*, **2018**, *118*, 6516-6572.

AIBN as the radical initiator to give the deoxygenated product **177** in almost quantitative yield following a published procedure.<sup>142</sup> (*Scheme 72*)

Targeting the final alkaloid (-)-205B, the tertiary alcohol **177** should be dehydrated chemoselectively. According to Toyooka's work,<sup>61</sup> dehydration was done using PTSA in refluxing benzene allowing the formation of a 6:1 mixture of both isomers **1** and **178**, from which the desired internal olefin **1** was isolated in 63% yield (*Scheme 72*).



*Scheme 72: Toward Alkaloid (-)-205B*

In comparison with the analytical data provided in the literature for the alkaloid (-)-205B **1**, our data perfectly match for the <sup>1</sup>H, <sup>13</sup>C NMR, IR and mass spectroscopy (HRMS). (*Table 2*)

Regarding the optical rotation, the reported value [ $\alpha$ ]<sub>D</sub><sup>20</sup> is -8.3 (c 0.12, CHCl<sub>3</sub>). However, the measured optical rotation for our synthesized alkaloid is +2.6 (c 0.31, CHCl<sub>3</sub>). We attribute this difference to impurities that might present in our substrate affecting the measurement. Further purification is under progress.

<sup>142</sup> Kraft, P.; Weymuth, C.; Nussbaumer, C. *Eur. J. Org. Chem.* **2006**, 1403-1412.



Comparison of the Characterization Data with Literature			
$^{13}\text{C}$ NMR <sup>62</sup>		$^1\text{H}$ NMR <sup>62</sup>	
$\text{C}_6\text{D}_6$		$\text{C}_6\text{D}_6$	
Found, 125 MHz	Reference, 125 MHz	Found, 500 MHz	Reference, 500 MHz
129.9	129.9	5.17 (br s, 1H)	5.19 (br s, 1H)
126.8	126.9	3.89 (br s, 1H)	3.87 (br s, 1H)
61.0	61.0	2.97 (ddd, $J = 1.2$	2.95 (dd, $J = 11.5, 4.6$
59.0	59.0	4.7, 11.6 Hz, 1H)	Hz, 1H)
57.0	57.0	2.15 (ddd, $J = 5.2,$	2.15 (dd, $J = 9.8, 5.2$
36.4	36.4	9.9, 9.9 Hz, 1H)	Hz, 1H)
33.3	33.4	1.96–2.09 (m, 2H)	2.06 (app t, $J = 14.3$
33.1	33.2		Hz, 1H)
30.1	30.2		2.02–1.95 (m, 1H)
29.2	29.2	1.80 (dddd, $J = 1.6,$	1.84–1.79 (m, 1H)
28.7	28.7	5.1, 8.7, 10.7 Hz, 1H)	
24.2	24.2	1.59 (s, 3H)	1.59 (s, 3H)
20.8	20.8	1.53–1.60 (m, 1H)	1.60–1.53 (m, 1H)
19.4	19.4	1.20–1.40 (m, 6H)	1.39–1.21(m, 6H)
		1.30 (d, $J = 7.1$ Hz,	1.29 (d, $J = 7.1$ Hz,
		3H)	3H)
		0.81 (d, $J = 6.5$ Hz,	0.81 (d, $J = 6.6$ Hz,
		3H)	3H)
IR ( $\text{cm}^{-1}$ ) <sup>62</sup>			
Found		Reference	
2955		2959	
2925		2924	

ACHIEVEMENT OF TOTAL SYNTHESIS OF (-)-205B

2852	2841
1658	1655
1459	1458
1376	1376
	1170
Optical Rotation	
Found	Reference
$[\alpha]^{20}_D = +2.6$ (c 0.31, CHCl <sub>3</sub> )	$[\alpha]^{20}_D = -8.3$ (c 0.12, CHCl <sub>3</sub> ) <sup>62</sup>
	$[\alpha]^{20}_D = -8.6$ (c 0.45, CHCl <sub>3</sub> ) <sup>64</sup>
	$[\alpha]^{20}_D = -8.0$ (c 0.10, CHCl <sub>3</sub> ) <sup>66</sup>
	$[\alpha]^{20}_D = -8.1$ (c 0.8, CHCl <sub>3</sub> ) <sup>68</sup>
HRMS Found for C <sub>14</sub> H <sub>23</sub> N <sup>64</sup>	
Found	Reference
206.19045 (MH) <sup>+</sup>	206.1903 (MH <sup>+</sup> )

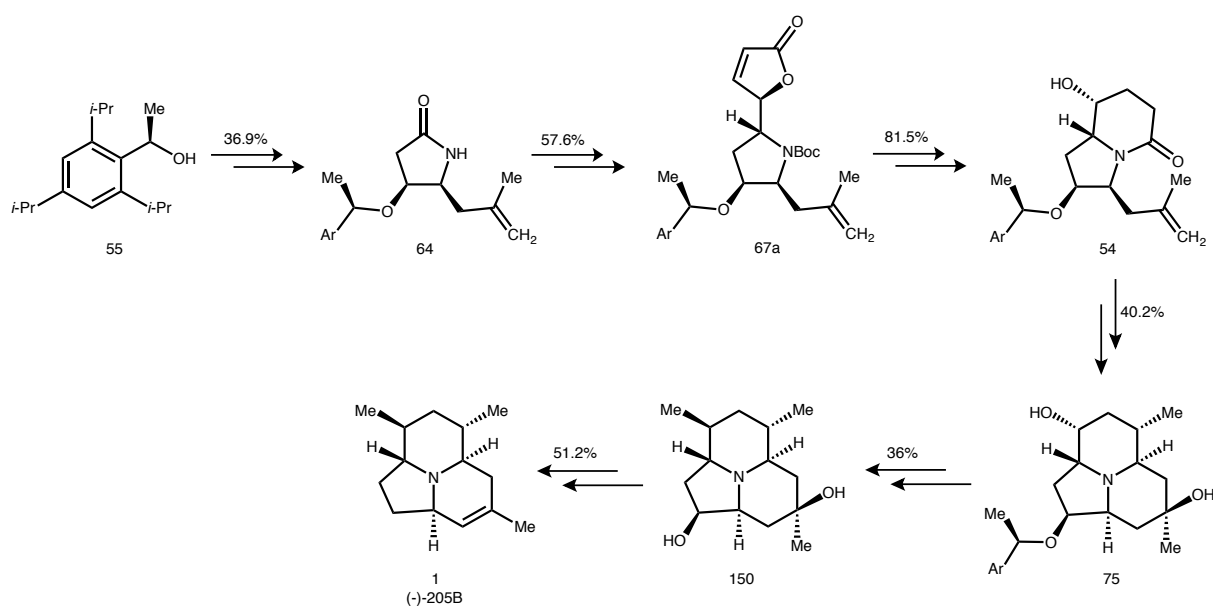
Table 2: Analytical Data Comparison of Alkaloid (-)-205B

## CHAPTER VII: CONCLUSION AND PERSPECTIVES

## Conclusion

In this research project, an efficient and highly stereoselective synthetic strategy was developed for the synthesis of the alkaloid, (-)-205B. This multi-step synthesis features three remarkable reactions for the construction of the 8b-azaacenaphthylene ring and the set-up of the major stereocenters; an asymmetric [2+2] cycloaddition, a stereoselective vinylogous Mannich reaction, and a stereo-directed aza-Prins cyclization. These developed chemical transformations can be of potential use for other natural products syntheses.

In tandem with the total synthesis, a novel synthetic methodology was developed focusing on the stereo-directed alkylation via temporary silyl tether that comes up for a difficulty encountered within the synthesis of the alkaloid 205B. Investigation of this new methodology and expansion is currently under progress in order to define its scope and limitation. Thereafter, the synthesis of the targeted alkaloid **1** was accomplished through efficient transformations for the construction of the tricyclic core and the introduction of the remaining stereocenters. This sequence proceeded efficiently through 23 steps from the chiral auxiliary **55** with an overall yield of 1.3% thus placing this approach among the most effective pathways described so far.



*Scheme 73: Developed Multi-Step Synthesis of (-)-205B*

## Perspectives

The synthetic efforts covered in this thesis were embarked upon not just for their opportunity as challenging targets but also for their relevance to other fields. Neurotoxic activity had inspired our work toward alkaloid (–)-205B.

As discussed in the first chapters, this rare alkaloid **1** belongs to a family of natural products that likely possess potent and diverse neurological functions. Therefore, we look forward to exploring the pharmacological profile of the synthetic (–)-205B. In particular, its selective activity toward the  $\alpha_7$  nAChR will be studied in collaboration with Dr. Christophe Moreau at the Institut de Biologie Structurale in Grenoble. Also, its ability to modulate the toxicity of A $\beta$  peptide will be evaluated in collaboration with Dr. Mireille Albrieux at Grenoble Institute of Neurosciences.

On the other hand, the valuable efficient strategy applied for the synthesis of the advanced intermediate **54** can be applicable for the total synthesis of natural products bearing indolizidine core.

(Figure 20)

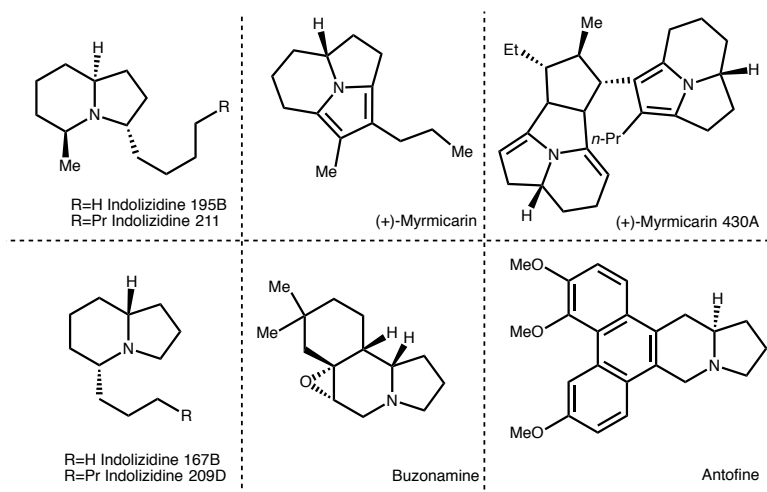
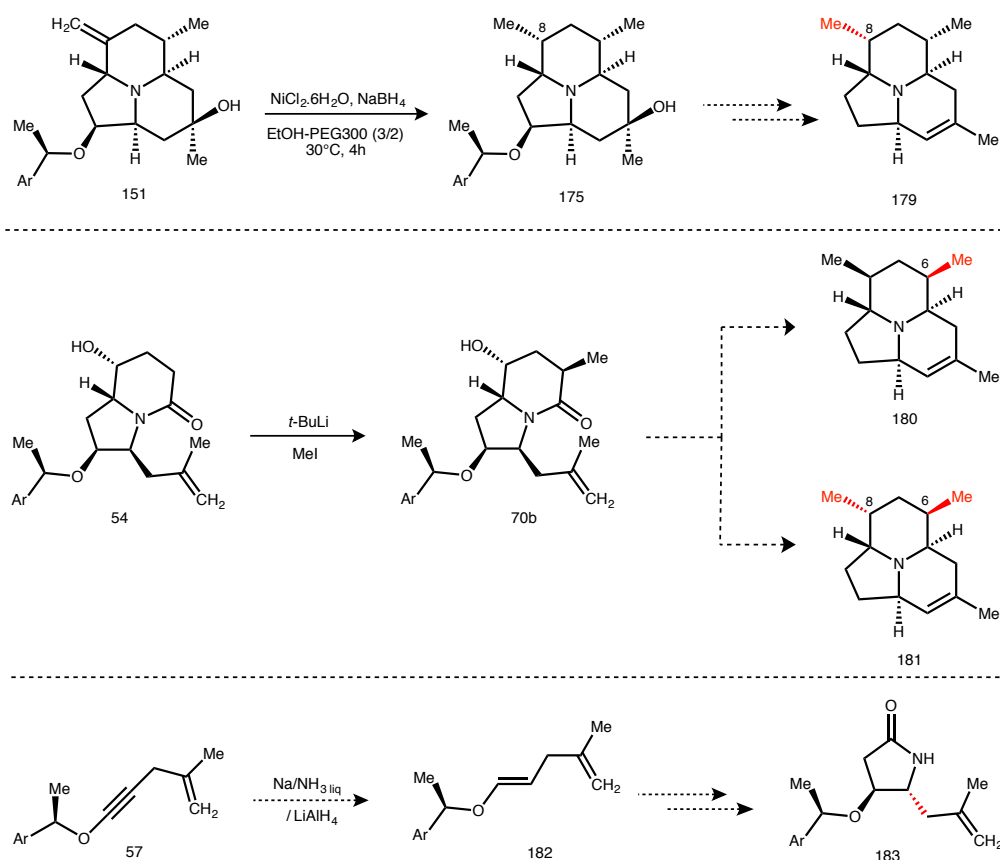


Figure 20: Natural Products bearing Indolizidine core

Furthermore, this new synthetic pathway explores new chemistry that allows the access not only to the target alkaloid but also to a wide scope of isomers. To illustrate, the 8-*epi* **179** can be readily synthesized by applying the standard hydrogenation conditions allowing the installation of the axial C<sub>8</sub>-methyl group. Also, following the previous approach to introduce the C<sub>6</sub>-methyl group axially

(**70b**) can provide the access to both epimers **180** and **181**. Moreover, by looking further on the initial steps of the synthesis, this array of isomers can be extended by applying the conditions of the trans hydrogenation ( $\text{LiAlH}_4$  or  $\text{Na}/\text{NH}_3(\text{liq.})$ ) of the alkyne **57** affecting the stereoselectivity of the [2+2] cycloaddition and the subsequent steps. (*Scheme 74*)

In addition, this strategy also allows the stereoselective synthesis of several analogs of this alkaloid. For instance, introduction of new functional groups can be done via the secondary hydroxyl group of **150**.



*Scheme 74: Isomers of Alkaloid (-)-205B*

## Conclusion

Une stratégie efficace et hautement stéréosélective de l'alcaloïde (-)-205B a été développée dans ce projet. Cette synthèse multi-étapes se caractérise par trois transformations remarquables pour la construction du système tricyclique 8b-azaacenaphtylène et le contrôle des centres stéréogènes correspondants; une cycloaddition [2+2] asymétrique, une réaction de Mannich vinylogue stéréosélective et une cyclisation d'aza-Prins stéréodirigée. Ce travail montre ainsi que ces transformations peuvent être des outils de choix pour la synthèse d'autres produits naturels.

Parallèlement à cette synthèse totale, une nouvelle méthode de transfert de chiralité par réaction d'alkylation intramoléculaire via un lien silylé a été développée, permettant de résoudre efficacement les importantes difficultés rencontrées lors de l'approche précédente. Cette nouvelle méthodologie est actuellement étudiée au laboratoire afin d'étendre son champ d'application et d'évaluer ses limitations. La synthèse de l'alcaloïde cible **1** est ensuite complétée par une construction efficace du système tricyclique et par l'introduction des autres centres stéréogènes. Cette approche est constituée de 23 étapes donne accès à la molécule cible avec un rendement global de 1.3% à partir de l'alcool inducteur. Elle se place parmi les stratégies les plus efficaces rapportées à ce jour

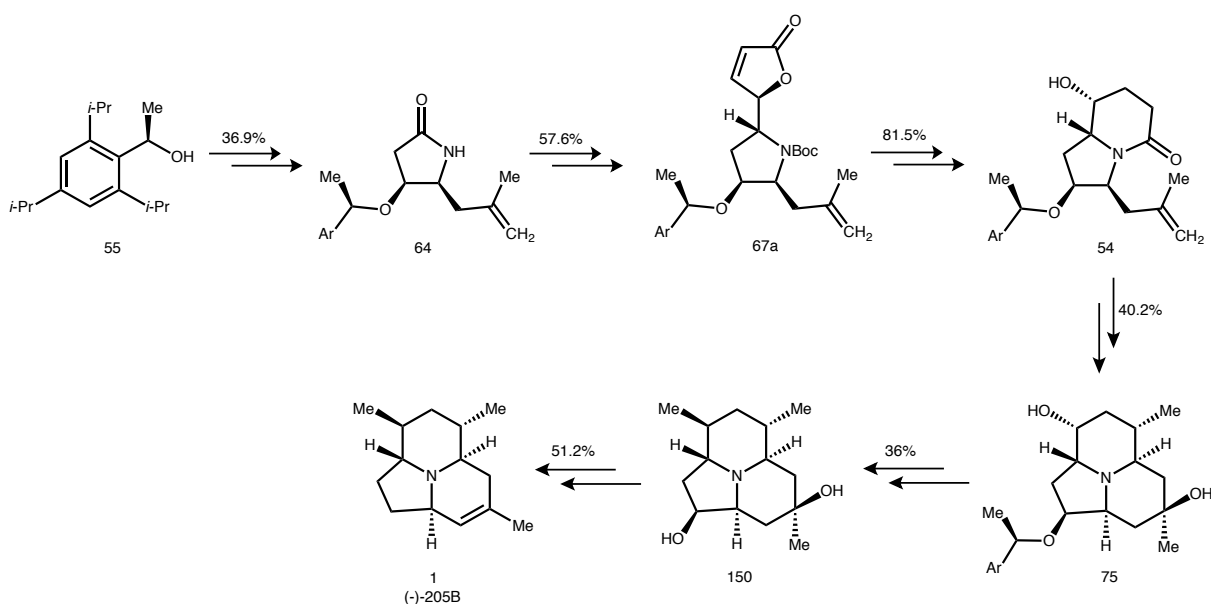


Schéma 69: Développement la synthèse multi-étapes de (-)-205B

## Perspectives

Le travail développé dans cette thèse n'a pas été motivé uniquement par le déficit synthétique représenté par la structure particulière de la molécule cible mais aussi pour l'intérêt de celle-ci dans un autre domaine. En particulier, l'activité neurotoxique de sa source naturelle a également contribué à notre intérêt vis à vis de l'alkaloïde (-)-205B.

Comme mentionné dans les premiers chapitres, cet alcaloïde rare fait partie de la famille des produits naturels pressentis comme possédant des fonctions neurologiques fortes et variées. Ainsi, nous envisageons d'explorer une partie du profil neurologique de notre alcaloïde synthétisé. En particulier, son activité sélective vis à vis des récepteurs nicotiques de type  $\alpha_7$  sera étudié en collaboration avec le Dr. Christophe Moreau de l'Institut de Biologie Structurale de Grenoble, et son effet de modulation de la toxicité du peptide A $\beta$  sera évaluée en collaboration avec le Dr. Mireille Albrieux de l'Institut des Neurosciences de Grenoble.

D'autre part, la stratégie efficace mise en œuvre pour la synthèse de l'intermédiaire avancé **54** peut s'appliquer à la synthèse totale de produits naturels portant le noyau indolizidine (*Figure 20*).

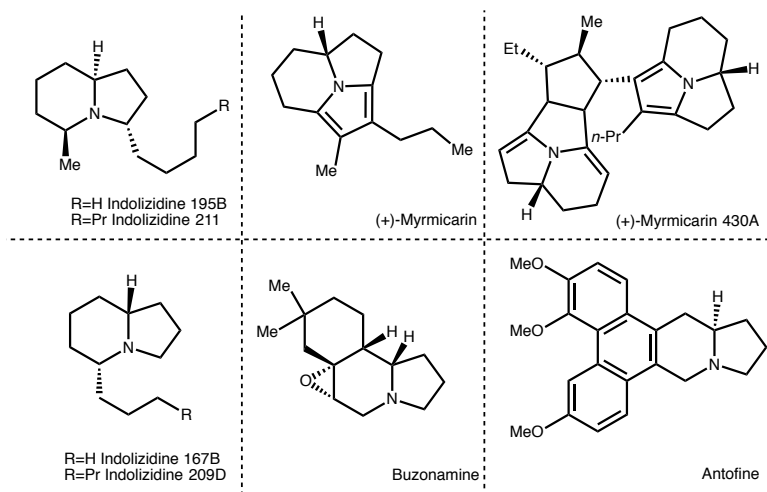


Figure 20: Produits naturels portant le noyau Indolizidine

De plus, cette nouvelle voie de synthèse explore une nouvelle chimie permettant l'accès non seulement à l'alkaloïde cible, mais également à un large éventail d'isomères. Par exemple, l'isomère 8-epi **179** peut être facilement synthétisé en appliquant les conditions standard d'hydrogénation



permettant l'installation en C8 du méthyle en position axiale. En outre, en suivant l'approche précédente conduisant à l'introduction en C6 du méthyle en position axiale (**70b**) l'accès aux épimères **180** et **181** est facilement envisageable. De même, en remontant plus en amont dans la synthèse, cet ensemble d'isomères peut être étendu en appliquant les conditions de l'hydrogénation trans ( $\text{LiAlH}_4$  ou  $\text{Na}/\text{NH}_3\text{liq.}$ ) de l'alcyne **57** affectant la stéréosélectivité de la cycloaddition [2+2] et celle des étapes suivantes. (Schéma 70)

Enfin, cette stratégie permet également la synthèse stéréosélective de plusieurs analogues de cet alcaloïde. Par exemple, l'introduction de nouveaux groupes fonctionnels peut se faire via le groupe hydroxyle secondaire de **150**.

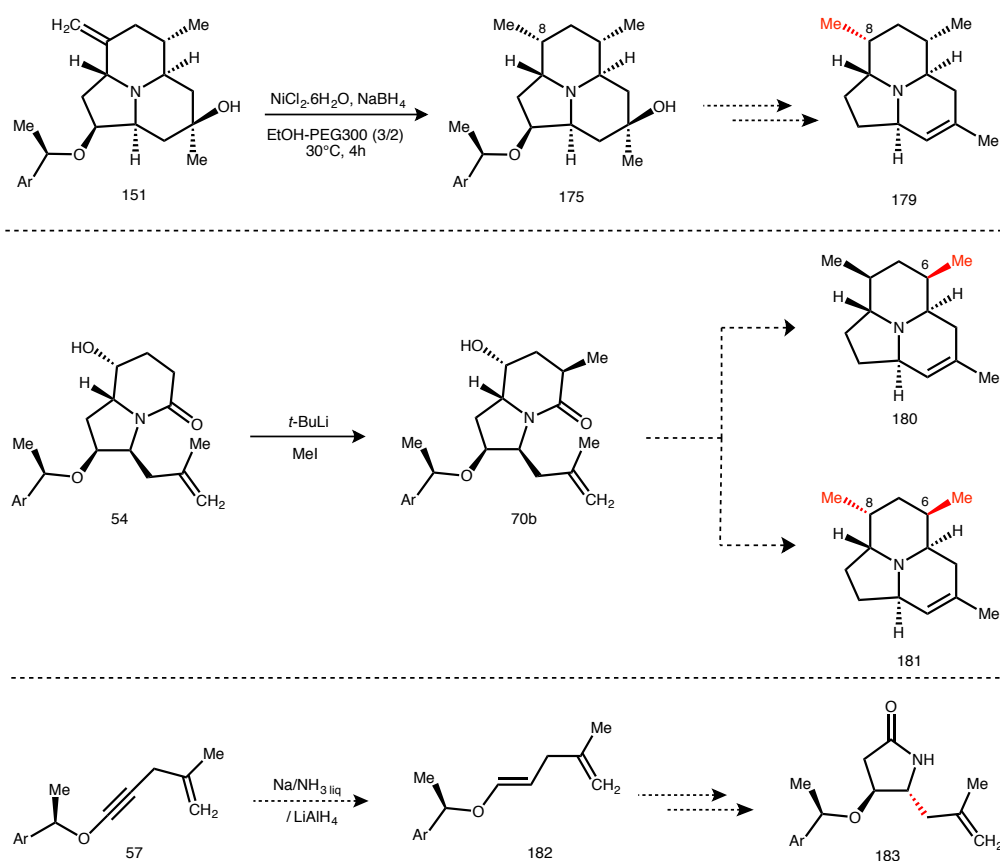


Schéma 70: Isomères de Alcaloïde (-)-205B

## CHAPTER VIII: EXPERIMENTAL PROCEDURE

## Materials and Methods

**Solvents and Reagents.** All experiments were carried out under argon atmosphere with dry solvents under anhydrous conditions unless otherwise stated. Solvents and some reagents were freshly distilled and dried by standard techniques just before use. THF and Et<sub>2</sub>O were distilled over Na-benzophenone. DCM, DMSO, HMDS, diisopropyl amine, HMPA, Et<sub>3</sub>N, acetonitrile, 2,6-lutidine, pyridine, toluene, MeCN and *i*PrOH were distilled over CaH<sub>2</sub>. Camphorsulphonic acid was crystallized from EtOAc and dried under vacuum. Trichloroacetyl chloride and oxalyl chloride were distilled over CaCl<sub>2</sub>. Ethylene diamine was distilled over Na. MeOH was distilled over magnesium turnings (Mg) and iodine. DMF was distilled over CaSO<sub>4</sub>. K(O<sup>*t*</sup>Bu) was purified by sublimation at 0.3 mmHg, 200°C. CsF and MePPh<sub>3</sub>Br were strictly dried at high vacuum for several hours immediately prior to use. Tf<sub>2</sub>O and MsCl were purified by distilling from P<sub>2</sub>O<sub>5</sub>. All other products were directly used as received from commercial sources without any purification.

**Chromatography.** Reactions were monitored by thin layer chromatography (TLC) carried out on 0.20 mm E. Merck silica gel plates (60F–254), using UV light as the visualizing agent and by KMnO<sub>4</sub> and heat as developing agents. Purifications were performed by column chromatography using silica gel 60 M (0.04–0.063 mm).

**Infrared spectra (IR)** were performed using Fourier Transform Infrared Spectrometer (FT/IR–4100) and were recorded as neat samples placed between NaCl pellets.

**Optical rotations ( $\alpha_D^{20}$ )** were recorded on a Perkin Elmer 341 polarimeter.

**Melting points (M<sub>p</sub>)** were measured on Büchi 510 melting point apparatus and are uncorrected.

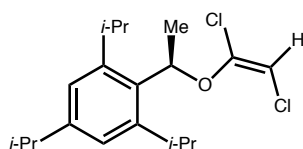
**Mass spectra (MS).** Electrospray ionization (ESI) mass spectra were obtained on an Esquire 3000 Plus Bruker Daltonis instrument with a nanospray inlet. High-resolution mass spectra (HRMS) were carried out on an ESI/QTOF with the Waters Xevo G2–S QToF device. Analyses were performed by the analytical service of Institut de Chimie Moléculaire de Grenoble (ICMG).

**Nuclear magnetic resonance (NMR) spectra** were recorded on Bruker Avance 400 or Varian U<sup>+</sup> 500 spectrometers where chemical shifts are reported as  $\delta$  values in parts per million (ppm) relative to internal chloroform ( $\delta$  7.26 for  $^1\text{H}$  and  $\delta$  77.0 for  $^{13}\text{C}$ ) or benzene ( $\delta$  7.16 for  $^1\text{H}$  and  $\delta$  128.39 for  $^{13}\text{C}$ ). As to avoid the quaternization of tertiary amine with chloroform causing broadening of NMR spectra, a drop of 10% NaOD was added. All coupling constants are given in hertz (Hz) and are calculated using the methods described by Hoyer *et al.*<sup>143</sup>. The following abbreviations were used to explain NMR peak multiplicities: s= singlet, d= doublet, dd= doublet of doublet, t= triplet, q= quartet, sept= septet, m= multiplet, br= broad, app= apparent.

*NB: Analytical data of some compounds are under progress.*

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<sup>143</sup> (a) Hoyer, T. R.; Hanson, P. R.; Vyvyan, J. R. *J. Org. Chem.* **1994**, *59*, 4096-4103. (b) Hoyer, T. R.; Zhao, H. *J. Org. Chem.* **2002**, *67*, 4014-4016.

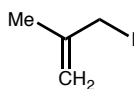


(*R, E*)-2-(1-(1,2-Dichlorovinyl)oxy)ethyl-1,3,5-triisopropylbenzene (**56**). In an argon flushed flask, a 30% suspension of potassium hydride in mineral oil (21.4 g, 160 mmol, 2.3 equiv) was washed three times with pentane. A solution of (*R*)-1-(2,4,6-triisopropylphenyl)ethanol **55** (16.7 g, 67.2 mmol, 1.0 equiv) in 200 ml THF was then added slowly to the KH suspension in 100 ml of dry THF. Also, 2 drops of MeOH was added to catalyze the reaction. The reaction mixture was stirred for 30 min at 0°C then 2h at room temperature. After cooling to -50°C, trichloroethylene (8.2 ml, 91.3 mmol, 1.3 equiv) was added dropwise. The reaction was then allowed to warm to room temperature over 4h and carefully quenched by methanol at 0°C (H<sub>2</sub> evolution). Extraction was then done after diluting the solution with pentane and washing with an aqueous solution of NH<sub>4</sub>Cl. The obtained organic phase was dried over MgSO<sub>4</sub> and concentrated *in vacuo* to leave 24.5 g of crude material. Purification of the crude product over deactivated silica (100% cyclohexane) produced 17.5 g of pure product **56** (76%). Analytical data are in agreement with those reported in the literature.<sup>76</sup>

IR (film):  $\nu$  3087, 1624, 1612, 1081, 1045 cm<sup>-1</sup>.

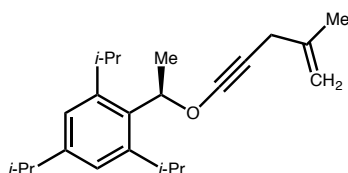
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.05 (s, 2H), 6.00 (q, *J* = 6.8 Hz, 1H), 5.60 (s, 1H), 3.15–3.75 (m, 2H), 2.90 (sept, *J* = 6.9 Hz, 1H), 1.70 (d, *J* = 6.9 Hz, 3H), 1.20–1.35 (m, 18H).

MS (ESI): *m/z* 343 and 341 (M<sup>+</sup>), 248, 231 (100%).



**3-iodo-2-methylprop-1-ene (S1)**. The commercially available methyl allyl chloride (15 ml, 153 mmol, 1.0 equiv) was mixed with sodium iodide (29.0 g, 193.5 mmol, 1.3 equiv) in acetone (30 ml). The mixture was refluxed for 3h followed by the addition of water and extraction with pentane. The organic layer was then washed with Na<sub>2</sub>S<sub>2</sub>O<sub>5</sub> (1M) then with water and dried over MgSO<sub>4</sub>. Pentane was then removed by gentle distillation over copper through a vigreux column to yield quantitatively 31.2 g of crude pale yellow product **S1** which is stored over the copper turnings.

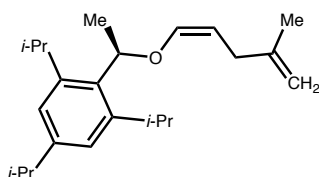
$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  5.19 (m, 1H), 4.89 (m, 1H), 3.91 (d,  $J = 0.8$  Hz, 2H), 1.90 (dd,  $J = 1.4, 0.8$  Hz, 3H).



**(*R*)-1,3,5-Triisopropyl-2-(1-((4-methylpent-4-en-1-ynyl)oxy)ethyl)benzene (57).** A solution of *n*-butyl lithium in hexane (49.7 ml, 2.5 M, 124.25 mmol, 2.5 equiv) was added dropwise to a solution of dichloro enol ether **56** (17.1 g, 49.8 mmol, 1.0 equiv) in 360 ml dry THF at  $-90^\circ\text{C}$ . Once the reaction was warmed to  $-40^\circ\text{C}$ , allyl iodide **S1** (15.4 ml, 143.3 mmol, 2.9 equiv) was added dropwise followed by addition of HMPA (39 ml, 224.16 mmol, 4.5 equiv). The reaction mixture was then allowed to warm to  $0^\circ\text{C}$  over 3h and the mixture was poured to cold  $\text{NH}_4\text{Cl}$  and cold pentane. The aqueous layer was extracted 3 times with cold pentane and the combined organic phase was washed with cold water. The organic layer was dried over  $\text{MgSO}_4$ . The mixture was concentrated *in vacuo* at  $0/+5^\circ\text{C}$  to give of 17.2 g of crude product **57** which was used further without any purification.

IR (film):  $\nu$  2998, 2926, 2807, 2268, 1631, 1460, 1299, 1195  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  7.02 (s, 2H), 5.68 (q,  $J = 6.9$  Hz, 1H), 4.72 (br s, 1H), 4.64 (br s, 1H), 3.25–3.45 (m, 2H), 2.82–2.91 (m, 1H), 2.74–2.75 (m, 2H), 1.72 (d,  $J = 6.9$  Hz, 3H), 1.59–1.60 (m, 3H), 1.23–1.28 (m, 18H).



**(*R, Z*)-1,3,5-Triisopropyl-2-(1-((4-methylpenta-1,4-dienyl)oxy)ethyl)benzene (58).** To a solution of crude ynol ether **57** (17.2 g, 52.7 mmol, 1.0 equiv) in 79 ml dry DMF at  $0^\circ\text{C}$ ,  $\text{Pd/BaSO}_4$  (10%, 6.6 g) and ethylene diamine (1.8 ml, 26.9 mmol, 0.5 equiv) were added. The flask was flushed with vacuum before stirring under hydrogen atmosphere for 10 min at room temperature. Then, 1-hexene (17.3 ml, 139.4 mmol, 2.6 equiv) was added dropwise and the reaction was stirred at room temperature until the complete disappearance of the IR absorbance at  $\sim 2270$   $\text{cm}^{-1}$ . The mixture was then diluted with pentane and filtered over celite. Then the filtrate was washed with water and brine

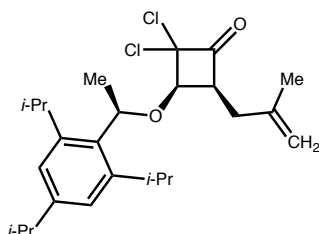
and the organic layer was dried over  $\text{MgSO}_4$  and concentrated *in vacuo* to afford 14.6 g of crude product **58**. No purification was done prior to the next step. Analytical data are in agreement with those reported in the literature.<sup>75</sup>

**IR (film):**  $\nu$  2960, 2929, 2869, 1661, 1608, 1460, 1384, 1255  $\text{cm}^{-1}$ .

**$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):**  $\delta$  7.01 (s, 2H), 6.03 (d,  $J = 6.9$  Hz, 1H), 5.34 (q,  $J = 6.8$  Hz, 1H), 4.72 (br s, 1H), 4.68 (br s, 1H), 4.33 (q,  $J = 6.9$  Hz, 1H), 3.20–3.64 (m, 2H), 2.71–2.96 (m, 3H), 1.74 (s, 3H), 1.61 (d,  $J = 6.8$  Hz, 3H), 1.20–1.27 (m, 18H).

**$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):**  $\delta$  147.7 (C), 145.6 (C), 144.8 (C), 133.2 (CH), 120.6 ( $\text{CH}_3$ ), 109.6 ( $\text{CH}_2$ ), 103.8 (CH), 75.5 (CH), 34.1 (CH), 32.7 ( $\text{CH}_2$ ), 29.2 ( $\text{CH}_3$ ), 24.8 ( $\text{CH}_3$ ), 24.2 ( $\text{CH}_3$ ), 22.7 ( $\text{CH}_3$ ).

**Zn–Cu Couple Preparation.** Zinc powder (20.1 g) was agitated with 100 ml of 10% hydrochloric acid for 15 min. The obtained suspension was filtered, and the zinc was washed 2 times with 100 ml acetone and 2 times with 100 ml  $\text{Et}_2\text{O}$  to produce 13.792 g of activated zinc. A suspension of the activated zinc (13.792 g, 210.95 mmol) in 50 ml of water is degassed with argon for 15 minutes and then treated with hydrated copper sulfate  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  (3.86 g, 15.2 mmol) and lead chloride  $\text{PbCl}_2$  (0.31 g, 1.11 mmol). Degassing is continued for 45 minutes. Filtration was then done under argon and the obtained solid was washed with 200 ml of water and 200 ml of acetone already degassed with argon. The Zn–Cu couple obtained (13.6 g) is dried under vacuum for 5 hours and stored under an inert atmosphere.



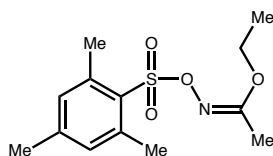
**(3*R*,4*S*)-2,2-Dichloro-4-(2-methylallyl)-3-((*R*)-1-(2,4,6-triisopropylphenoxy)cyclobutan-1-yl)cyclobutan-1-one (**62**).** Freshly distilled trichloroacetyl chloride (5.5 ml, 49.3 mmol, 1.1 equiv) was added dropwise to a solution of crude enol ether **58** (14.6 g, 44.4 mmol, 1.0 equiv) and prepared Zn–Cu (22 g) in 265 ml of dry  $\text{Et}_2\text{O}$  at room temperature. During this addition, sonication was done 3–4 times. The reaction

was followed by TLC until disappearance of the starting material and then diluted with pentane and stirred for 10 min. The mixture was then filtered over celite and concentrated under reduced pressure. Dilution with pentane and concentration were repeated until turbidity is disappeared (all zinc chloride was removed). 20.1 g of crude product **62** was obtained and used for the next step without any further purification. Analytical data are in agreement with those reported in the literature.<sup>75</sup>

IR (film):  $\nu$  2961, 2922, 2870, 1808, 1608, 1460  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  7.09 (d,  $J = 2$  Hz, 1H), 7.02 (d,  $J = 2$  Hz, 1H), 5.47 (q,  $J = 6.8$  Hz, 1H), 4.82 (br s, 1H), 4.79 (br s, 1H), 4.36 (d,  $J = 9.3$  Hz, 1H), 3.86 (sept,  $J = 6.9$  Hz, 1H), 3.64–3.73 (m, 1H), 3.31 (sept,  $J = 6.9$  Hz, 1H), 2.89 (sept,  $J = 6.9$  Hz, 1H), 2.43–2.62 (m, 2H), 1.74 (s, 3H), 1.69 (d,  $J = 6.8$  Hz, 3H), 1.15–1.37 (m, 18H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  195.9 (C), 149.2 (C), 148.4 (C), 147.2 (C), 141.8 (C), 130.8 (C), 123.5 ( $\text{CH}_3$ ), 120.9 ( $\text{CH}_3$ ), 112.8 ( $\text{CH}_2$ ), 77.5 ( $\text{CH}_3$ ), 73.7 ( $\text{CH}_3$ ), 57.5 ( $\text{CH}_3$ ), 34.2 ( $\text{CH}_2$ ), 33.2 ( $\text{CH}_2$ ), 28.6 ( $\text{CH}_3$ ), 28.5 ( $\text{CH}_3$ ), 25.4 ( $\text{CH}_3$ ), 24.1 ( $\text{CH}_3$ ), 23.9 ( $\text{CH}_3$ ), 22.5 ( $\text{CH}_3$ ).

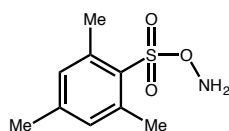


**Ethyl *N*-((mesitylsulfonyl)oxy)acetimidate (**S2**)**. To a solution of ethyl *N*-hydroxy acetimide (8.37 g, 81.1 mmol, 1.0 equiv) in 53 ml of DMF was added dropwise 22.7 ml of triethyl amine (163.17 mmol, 2.0 equiv) under argon. The reaction mixture was cooled to 0°C followed by portionwise addition of *O*-mesitylene sulfonyl chloride (17.75 g, 81.16 mmol, 1.0 equiv). The mixture was stirred vigorously for 1h. It was then diluted with EtOAc (200 ml) and washed with water (3\*150 ml) and brine (150 ml). The aqueous layer was extracted three times with EtOAc followed by drying the combined organic layers over  $\text{MgSO}_4$ . Concentration under reduced pressure afforded 23.1 g of ethyl *N*-((mesitylsulfonyl)oxy)acetimidate **S2** which was used further without purification. Analytical data are in agreement with those reported in the literature.<sup>86c</sup>

IR (film):  $\nu$  2988, 2947, 1682, 1649, 1608  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  6.96 (s, 2H), 3.90 (q,  $J = 7.1$  Hz, 2H), 2.64 (s, 6H), 2.31 (s, 3H), 2.03 (s, 3H), 1.18 (t,  $J = 7.1$  Hz, 3H).

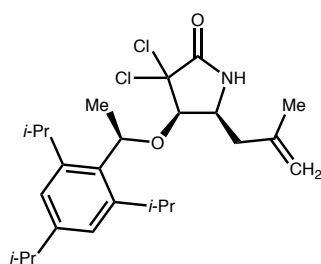




***O*-(mesitylsulfonyl)hydroxylamine (MSH) (**S3**).**<sup>144</sup> 70% perchloric acid (18 mL, 208.7 mmol, 2.6 equiv) was added dropwise to a solution of crude ethyl *N*-(mesitylsulfonyl)oxyacetimidate **S2** (23.1 g, 81.1 mmol, 1.0 equiv) in 34 mL dioxane at 0°C. The resulting mixture was strongly stirred at 0°C for 1h30 min and then 50g of ice, 250 mL of water and 250 mL of Et<sub>2</sub>O were added. The organic layer was washed again with water and then neutralized with K<sub>2</sub>CO<sub>3</sub> for 2 min. After filtration, the filtrate was concentrated under reduced pressure to a total volume of ~70–75 mL. Then ~150 mL of cold pentane was added, and crystallization started immediately. The flask was then kept at –40°C overnight to ensure complete crystallization. Filtration furnished 16.7 g of MSH **S3** as white crystals (95.6 % over 2 steps). Analytical data are in agreement with those reported in the literature.<sup>86c</sup>

**IR (film):**  $\nu$  3339, 2979, 2940, 1610 cm<sup>-1</sup>.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):**  $\delta$  7.00 (s, 2H), 4.86 (br. s, 2H), 2.64 (s, 6H), 2.32 (s, 3H).



**(4*R*,5*S*)-3,3-Dichloro-5-(2-methylallyl)-4-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)pyrrolidin-2-one (**63**).** To a solution of crude cyclobutanone **62** (20.1 g, 45.7 mmol, 1.0 equiv) in 370 mL of dry dichloromethane was added *O*-mesitylenesulfonylhydroxylamine **S3** (34.1 g, 158.4 mmol, 3.5 equiv) portionwise at room temperature, accompanied with a small amount of sodium sulfate. The reaction was followed by IR until the disappearance of the absorption peak at ~1806 cm<sup>-1</sup>. After filtration of the mixture over celite, the filtrate was concentrated under reduced pressure. The remained MSH was removed by dissolving the residue in 180 mL of toluene and passing the solution over basic alumina (590 mL) and eluted with methanol. After concentrating the combined fractions under reduced pressure, the residue was triturated with DCM followed by filtration through celite and evaporation *in*

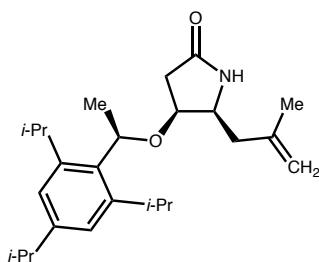
<sup>144</sup> It is reported that MSH decomposes violently once dried thoroughly under vacuum at RT: Mendiola, J.; Rincon, J. A. R.; Mateos, C.; Soriano, J. F.; de Frutos, O. S.; Niemeier, J. K.; Davis, E. M. *Org. Process Res. Dev.* **2009**, *13*, 263-267.

*vacuo* to produce 20.6 g of crude dichlorolactam **63**. Analytical data are in agreement with those reported in the literature.<sup>75</sup>

IR (film):  $\nu$  2961, 2869, 1731, 1606, 1562, 1454  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  7.07 (d,  $J = 1.9$  Hz, 1H), 6.98 (d,  $J = 1.9$  Hz, 1H), 5.67 (q,  $J = 6.9$  Hz, 1H), 4.88 (br s, 1H), 4.71 (br s, 1H), 4.50 (d,  $J = 7.3$  Hz, 1H), 3.89 (sept,  $J = 6.8$  Hz, 1H), 3.72–3.80 (m, 1H), 3.36 (sept,  $J = 6.8$  Hz, 1H), 2.86 (sept,  $J = 6.8$  Hz, 1H), 2.59–2.63 (m, 1H), 2.27–2.31 (m, 1H), 1.71 (d,  $J = 6.9$  Hz, 3H), 1.68 (s, 3H), 1.14–1.31 (m, 18H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  167.5 (C), 148.8 (C), 148.1 (C), 146.5 (C), 130.9 (CH), 123.7 (CH), 120.9 (CH), 114.34 (CH), 82.1 (CH), 53.1 (CH), 53.1 ( $\text{CH}_2$ ), 38.8 ( $\text{CH}_2$ ), 34.4 (CH), 28.4 (CH), 25.4 ( $\text{CH}_3$ ), 24.8 ( $\text{CH}_3$ ), 22.8 ( $\text{CH}_3$ ), 21.8 ( $\text{CH}_3$ ), 21.1 ( $\text{CH}_3$ ), 20.9 ( $\text{CH}_3$ ), 20.8 ( $\text{CH}_3$ ).



(4*S*,5*S*)-5-(2-Methylallyl)-4-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)pyrrolidin-2-one (**64**). A mixture of crude dichlorolactam **63** (20.6 g, 21.21 mmol) and Zn–Cu couple (20.9 g) in 365 ml of MeOH saturated with  $\text{NH}_4\text{Cl}$  was stirred at room temperature for 2h and then refluxed for 5h. After filtration over celite and evaporation under reduced pressure, the obtained residue was dissolved in DCM and washed with water and brine. The organic phase was dried over  $\text{MgSO}_4$  and concentrated *in vacuo* to give 17.4 g of crude material. Purification over silica gel with 0%  $\rightarrow$  5%  $\text{MeOH}_{\text{NH}_3}$ /DCM as eluting system to produce 9.31 g of pure lactam **64** (48.5% over 5 steps/86.5% per step). Analytical data are in agreement with those reported in the literature.<sup>75</sup>

$M_p = 118\text{--}119$   $^\circ\text{C}$ .

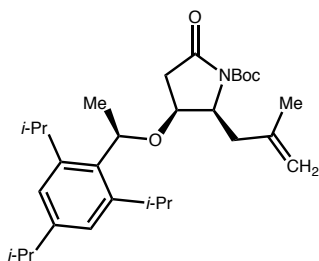
$[\alpha]_{\text{D}}^{20} +76.1$  (c 0.585,  $\text{CHCl}_3$ ).

IR (film):  $\nu$  3225, 2960, 2869, 1698, 1608, 1461  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  7.07 (s, 1H), 6.97 (s, 1H), 5.09 (q,  $J = 6.8$  Hz, 1H), 4.82 (s, 1H), 4.75 (s, 1H), 4.18 (ddd,  $J = 6.8$  Hz, 1H), 3.90 (sept,  $J = 6.5$  Hz, 1H), 3.78 (ddd,  $J = 10.6, 7.0, 2.8$  Hz, 1H), 3.18 (sept,  $J = 6.9$  Hz, 1H), 2.87 (sept,  $J = 6.9$  Hz, 1H), 2.17–2.60 (m, 4H), 1.71 (s, 3H), 1.56 (d,  $J = 6.8$  Hz, 3H), 1.19–1.32 (m, 18H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  174.8 (C), 148.9 (C), 147.9 (C), 146.2 (C), 142.2 (C), 132.2 (C), 123.4 (CH), 120.8 (CH), 113.3 ( $\text{CH}_2$ ), 72.5 (CH), 71.2 (CH), 55.4 (CH), 38.2 ( $\text{CH}_2$ ), 36.7 ( $\text{CH}_2$ ), 34.1 ( $\text{CH}_3$ ), 29.3 ( $\text{CH}_3$ ), 28.1 ( $\text{CH}_3$ ), 25.1 ( $\text{CH}_3$ ), 23.2 ( $\text{CH}_3$ ), 22.4 ( $\text{CH}_3$ ).

MS (ESI):  $m/z$  408 ( $\text{MNa}^+$ , 100%), 386 ( $\text{MH}^+$ ).



***tert*-Butyl (2*S*,3*S*)-2-(2-methylallyl)-5-oxo-3-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)pyrrolidine-1-carboxylate (**65**).** To a solution of lactam **64** (9.2 g, 23.8 mmol, 1.0 equiv) in 60 ml dry dichloromethane at 0°C were added  $\text{Et}_3\text{N}$  (4 ml, 28.7 mmol, 1.2 equiv),  $(\text{Boc})_2\text{O}$  (10.6 g, 48.6 mmol, 2 equiv) in 20 ml of dry dichloromethane and DMAP (3.6 g, 29.5 mmol, 1.3 equiv). The reaction was stirred first 5 min at 0°C then 2h at RT. After checking the disappearance of starting material by TLC, the reaction mixture was diluted with dichloromethane and quenched with saturated  $\text{NH}_4\text{Cl}$ . The organic layer was washed 3 times with HCl (1M) and 1 time with saturated  $\text{NaHCO}_3$ , followed by drying it over  $\text{MgSO}_4$  and evaporating under reducing pressure. The excess of Boc anhydride was removed at 0.2 mbar, 50°C for 1h to yield 10.43 g of pure Boc-lactam **65** (90% yield). Analytical data are in agreement with those reported in the literature.<sup>75</sup>

$M_p = 160\text{--}161$  °C.

$[\alpha]_D^{20} +101.0$  (c 0.49,  $\text{CHCl}_3$ ).

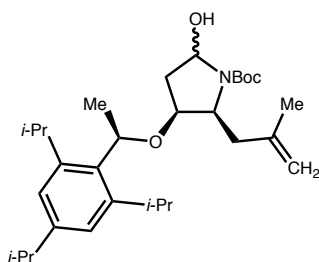
IR (film):  $\nu$  2963, 2927, 2876, 1767, 1645, 1595, 1457, 1176  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  7.06 (s, 1H), 6.95 (s, 1H), 5.05 (q,  $J = 6.8$  Hz, 1H), 4.80 (s, 2H), 4.37 (td,  $J = 7.9, 4.6$  Hz, 1H), 4.05–4.13 (m, 1H), 3.87 (br m, 1H), 3.05–3.20 (br m, 1H), 2.86 (sept,

$J = 6.9$  Hz, 1H), 2.62–2.70 (m, 2H), 2.55 (dd,  $J = 13.8, 4.2$  Hz, 1H), 2.23 (dd,  $J = 13.8, 8.3$  Hz, 1H), 1.79 (s, 3H), 1.46–1.57 (m, 12H), 1.16–1.30 (m, 18H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  170.8 (C), 149.8 (C), 148.8 (C), 145.9 (C), 141.8 (C), 132.1 (C), 123.5 (CH), 120.8 (CH), 114.7 ( $\text{CH}_2$ ), 83.1 (C), 71.7 (CH), 69.8 (CH), 58.5 (CH), 38.1 ( $\text{CH}_2$ ), 37.2 ( $\text{CH}_2$ ), 34.1 ( $\text{CH}_3$ ), 28.0 ( $\text{CH}_3$ ), 27.9 ( $\text{CH}_3$ ), 25.1 ( $\text{CH}_3$ ), 24.0 ( $\text{CH}_3$ ), 23.2 ( $\text{CH}_3$ ), 22.8 ( $\text{CH}_3$ ).

MS (ESI):  $m/z$  508 ( $\text{MNa}^+$ , 100%), 231.



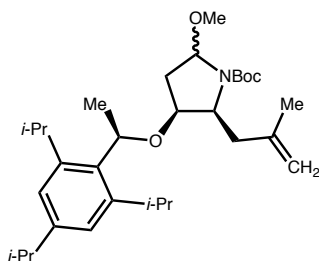
**tert-Butyl (2S,3S)-5-hydroxy-2-(2-methylallyl)-3-((R)-1-(2,4,6-triisopropylphenyl)ethoxy)pyrrolidine-1-carboxylate (S4).** A solution of 1 M  $\text{LiBHEt}_3$  in THF (super-hydride) (30.5 ml, 30.5 mmol, 1.4 equiv) was added to a solution of Boc-lactam **65** (10.4 g, 21.4 mmol, 1.0 equiv) in 70 ml of THF at  $-94^\circ\text{C}$ . The reaction mixture was stirred for 1h15min while maintaining temperature below  $-70^\circ\text{C}$ . A solution of sodium bicarbonate (85 ml) was added slowly followed by 2h stirring till the temperature reached  $0^\circ\text{C}$ . Then,  $\text{H}_2\text{O}_2$  (30% solution, 15 ml) was added at  $0^\circ\text{C}$  and the reaction was stirred at RT for 30 min. After dilution with  $\text{Et}_2\text{O}$ , the aqueous layer was washed 3 times with  $\text{Et}_2\text{O}$ , dried over  $\text{MgSO}_4$  and evaporated under reduced pressure to give 12.6 g of crude hemiaminal product **S4**. Analytical data are in agreement with those reported in the literature.<sup>75</sup>

IR (film):  $\nu$  3448, 2962, 2931, 2869, 1786, 1753, 1681, 1608, 1458, 1392, 1367, 1304,  $1255\text{ cm}^{-1}$

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  7.05 (s, 1H), 6.94 (s, 1H), 5.34 (br s, 1H), 5.05 (q,  $J = 6.8$  Hz, 1H), 4.77 (br s, 1H), 4.72 (br s, 1H), 3.80–3.94 (br m, 3H), 3.10–3.30 (br m, 1H), 2.85 (sept,  $J = 6.5$  Hz, 1H), 2.54–2.63 (m, 2H), 2.20–2.38 (m, 2H), 1.72 (br s, 3H), 1.53 (d,  $J = 6.8$  Hz, 3H), 1.38–1.44 (m, 9H), 1.18–1.31 (m, 18H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  155.0 (C), 148.9 (C), 147.6 (C), 145.5 (C), 142.5 (C), 133.3 (C), 123.4 (CH), 120.6 (CH), 113.6 ( $\text{CH}_2$ ), 80.3 (C), 80.2 (CH), 74.3 (CH), 71.9 (CH), 56.9 (CH), 38.4 ( $\text{CH}_2$ ), 36.4 ( $\text{CH}_2$ ), 34.1 ( $\text{CH}_3$ ), 28.2 ( $\text{CH}_3$ ), 27.9 ( $\text{CH}_3$ ), 24.9 ( $\text{CH}_3$ ), 23.3 ( $\text{CH}_3$ ), 22.8 ( $\text{CH}_3$ ).

MS (DCI, NH<sub>3</sub> + isobutane):  $m/z$  472 (M-16), 372, 358, 231.



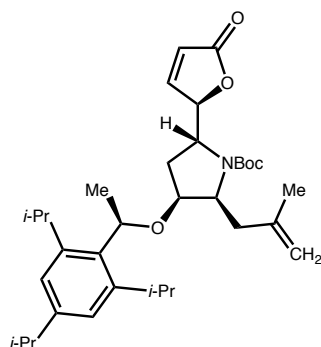
*tert*Butyl (2*S*,3*S*)-5-methoxy-2-(2-methylallyl)-3-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)pyrrolidine-1-carboxylate (**66**). To a solution of crude hemiaminal **S4** (12.6 g, 25.83 mmol, 1.0 equiv) in 70 ml of 2,2-dimethoxypropane at 0°C was added camphorsulfonic acid (2.5 g, 10.8 mmol, 0.4 equiv) and the reaction was stirred at this temperature for 1h30min. The reaction was followed by TLC then diluted with Et<sub>2</sub>O and quenched with NaHCO<sub>3</sub>. The aqueous layer was washed again with Et<sub>2</sub>O and the combined organic layers were dried over MgSO<sub>4</sub> and evaporated under reduced pressure. The excess of dimethoxy propane was removed at 0.2 mbar at RT for 1h30min to yield 12.2 g of crude hemiaminal derivative **66**. Analytical data are in agreement with those reported in the literature.<sup>75</sup>

IR (film):  $\nu$  2962, 2869, 1702, 1607, 1456, 1390, 1367, 1167, 1098 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.04 (s, 1H), 6.95 (s, 1H), 5.05–5.20 (m, 1H), 5.03 (q,  $J$  = 6.8 Hz, 1H), 4.75 (br s, 1H), 4.72 (br s, 1H), 3.79–3.92 (br m, 3H), 3.35–3.39 (m, 3H), 3.10–3.30 (br m, 1H), 2.86 (sept,  $J$  = 6.9 Hz, 1H), 2.56–2.70 (m, 2H), 2.28–2.31 (m, 2H), 1.73 (br s, 3H), 1.48–1.53 (m, 3H), 1.39–1.43 (m, 9H), 1.18–1.32 (m, 18H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  148.9 (C), 147.5 (C), 145.5 (C), 142.9 (C), 133.4 (C), 123.5 (CH), 120.6 (CH), 113.3 (CH<sub>2</sub>), 87.3 (CH), 80.1 (C), 75.2 (CH<sub>2</sub>), 72.2 (CH), 57.6 (CH), 56.7 (CH), 37.6 (CH<sub>2</sub>), 37.3 (CH<sub>2</sub>), 34.1 (CH), 29.3 (CH<sub>3</sub>), 28.5 (CH<sub>3</sub>), 28.2 (CH<sub>3</sub>), 24.9 (CH<sub>3</sub>), 24.0 (CH<sub>3</sub>).

MS (DCI, NH<sub>3</sub> + isobutane):  $m/z$  502 (MH<sup>+</sup>), 472, 431, 372, 231.



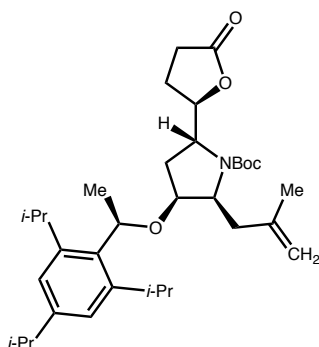
*tert*-Butyl (2*S*,3*S*,5*R*)-2-(2-methylallyl)-5-((*R*)-5-oxo-2,5-dihydrofuran-2-yl)-3-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)pyrrolidine-1-carboxylate (**67a**). To a solution of crude hemiaminal derivative **66** (12.2 g, 24.32 mmol, 1.0 equiv) in 330 ml dichloromethane were added dropwise 2-(trimethylsiloxy) furan (8.5 ml, 50.54 mmol, 2.0 equiv) and BF<sub>3</sub>·Et<sub>2</sub>O (5.4 ml, 43.75 mmol, 1.8 equiv) at −95°C. The reaction mixture was stirred 2h and the temperature was kept below −90°C. The reaction mixture was followed by TLC then diluted with dichloromethane and quenched with saturated NaHCO<sub>3</sub>. The aqueous layer was washed with DCM (3 times) and the combined organic layers were dried over MgSO<sub>4</sub> and evaporated under reduced pressure. The excess of furanone was removed at 0.2 torr at 30 °C for 2–3h to yield 15.1 g of crude butenolide. Elution over silica gel (700 ml) with 10% EtOAc/cyclohexane yielded 7.55 g of pure *threo* butenolide intermediate **67a** over 3 steps (64%). Analytical data are in agreement with those reported in the literature.<sup>75</sup>

IR (film):  $\nu$  2961, 2926, 2868, 2869, 1762, 1692, 1611, 1457, 1387, 1367 cm<sup>−1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.09–7.23 (m, 1H), 7.03 (s, 1H), 6.94 (s, 1H), 5.50–5.90 (m, 2H), 4.98 (q, *J* = 6.8 Hz, 1H), 4.75 (s, 2H), 4.32–4.41 (m, 1H), 3.97 (q, *J* = 6.7 Hz, 1H), 3.74–3.90 (m, 2H), 3.00–3.15 (br m, 1H), 2.85 (sept, *J* = 6.9 Hz, 1H), 2.39–2.56 (m, 1H), 2.07–2.22 (m, 1H), 1.91–1.98 (m, 1H), 1.74–1.85 (m, 4H), 1.49 (d, *J* = 6.7 Hz, 3H), 1.41–1.45 (m, 9H), 1.10–1.31 (m, 18H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  153.3(C), 152.6 (C), 148.7 (C), 145.6 (C), 142.8 (C), 132.5 (C), 125.1 (CH), 123.1(CH), 121.9 (CH), 113.7 (CH<sub>2</sub>), 82.2 (CH<sub>2</sub>), 81.7 (CH<sub>2</sub>), 74.8 (CH), 71.2 (CH), 59.1 (CH), 54.9 (CH), 36.9 (CH), 34.0 (CH), 28.7 (CH<sub>2</sub>), 28.6 (CH<sub>2</sub>), 28.1 (CH), 28.1 (CH<sub>3</sub>), 27.9 (CH<sub>3</sub>), 26.5 (CH<sub>3</sub>), 25.2 (CH<sub>3</sub>), 24.8 (CH<sub>3</sub>), 23.1 (CH<sub>3</sub>).

MS (ESI): *m/z* 576.4 (MNa<sup>+</sup>, 100%).



*tert*-Butyl (2*S*,3*S*,5*R*)-2-(2-methylallyl)-5-((*R*)-5-oxotetrahydrofuran-2-yl)-3-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)pyrrolidine-1-carboxylate (**68**). To a solution of butenolide **67a** (7.31 g, 13.20 mmol, 1.0 equiv) in 175 ml MeOH at 0°C was added 2.5 g of CuCl<sub>2</sub>·2H<sub>2</sub>O (14.66 mmol, 1.1 equiv) and the mixture was stirred at 0°C for 5 min. Then, 6.4 g of sodium borohydride (169.18 mmol, 12.8 equiv) was added portionwise over 2h. The reaction was followed by TLC and quenched with saturated NH<sub>4</sub>Cl. The aqueous layer was extracted 3 times with DCM and the combined organic layers were dried over MgSO<sub>4</sub> and evaporated under reduced pressure. Filtration over 10 ml silica gel provided 7.15 g of pure lactone **68** (97%) eluted with 100% DCM. Analytical data are in agreement with those reported in the literature.<sup>75</sup>

*M<sub>p</sub>* = 148 °C.

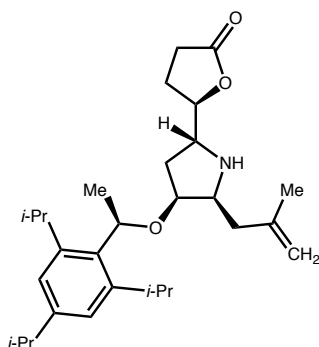
[ $\alpha$ ]<sub>D</sub><sup>20</sup> +81.7 (c 0.77, CHCl<sub>3</sub>).

IR (film):  $\nu$  3063, 2962, 2922, 2868, 1783, 1694, 1607, 1458, 1392, 1369 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.05 (s, 1H), 6.94 (s, 1H), 5.20–5.30 (m, 1H), 5.07 (q, *J* = 6.8 Hz, 1H), 4.76 (s, 2H), 3.80–4.40 (m, 4H), 3.10–3.25 (br m, 1H), 2.85 (sept, *J* = 6.8 Hz, 1H), 1.88–2.60 (m, 8H), 1.77 (br s, 3H), 1.53 (d, *J* = 6.4 Hz, 3H), 1.40–1.45 (m, 9H), 1.15–1.30 (m, 18H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  176.7 (C), 149.1 (C), 147.8 (C), 145.8 (C), 142.8 (C), 131.9 (C), 123.5 (CH), 120.6 (CH), 113.7 (CH<sub>2</sub>), 80.5 (C), 78.6 (CH), 74.4 (CH), 71.2 (CH), 58.8 (CH), 55.3 (CH), 34.1 (CH), 37.0 (CH<sub>2</sub>), 28.6 (CH<sub>2</sub>), 24.2 (CH<sub>2</sub>), 28.5 (CH<sub>3</sub>), 24.2 (CH<sub>3</sub>), 23.9 (CH<sub>3</sub>).

MS (ESI): *m/z* 578.4 (MNa<sup>+</sup>, 100%).



(*R*)-5-((2*R*,4*S*,5*S*)-5-(2-Methylallyl)-4-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)pyrrolidin-2-yl) dihydrofuran-2(3*H*)-one (**69**). To a solution of lactone **68** (7.15 g, 12.86 mmol, 1.0 equiv) in 100 ml DCM at 0°C were added 2,6-lutidine (6.7 ml, 57.53 mmol, 4.4 equiv) and TMSOTf (7.71 ml, 42.6 mmol, 3.3 equiv). The reaction mixture was stirred for 1h at 0°C and it was followed by TLC. Then quenching was done with saturated NH<sub>4</sub>Cl at 0°C and allowed to warm to RT. The reaction was then diluted with DCM and the aqueous layer was washed 3 times with DCM. The combined organic layers were washed further with saturated NaHCO<sub>3</sub> 2 times. Drying over MgSO<sub>4</sub> followed by evaporation under reduced pressure afforded 6.54 g of amine **69** (contaminated with 2,6-lutidine), which is used for the next step without any further purification. Analytical data are in agreement with those reported in the literature.<sup>75</sup>

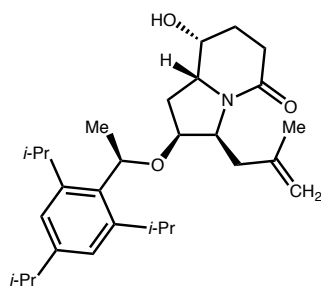
IR (film):  $\nu$  2961, 2930, 2868, 1777, 1608, 1459, 1382, 1176 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.04 (s, 1H), 6.94 (s, 1H), 5.07 (q,  $J$  = 6.8 Hz, 1H), 4.74 (s, 1H), 4.66 (s, 1H), 4.41 (td,  $J$  = 5.6, 7.1 Hz, 1H), 3.70–3.98 (m, 3H), 3.51 (td,  $J$  = 5.6, 7.7 Hz, 1H), 3.15–3.30 (m, 1H), 2.85 (sept,  $J$  = 6.9 Hz, 1H), 2.42–2.70 (m, 2H), 1.76–2.32 (m, 6H), 1.64 (s, 3H), 1.52 (d,  $J$  = 6.8 Hz, 3H), 1.16–1.30 (m, 18H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  176.7 (C), 156.8 (C), 146.5 (C), 144.4 (C), 142.8 (C), 132.8 (C), 122.3 (C), 111.1 (CH<sub>2</sub>), 82.7 (CH), 77.6 (CH), 70.5 (CH), 58.4 (CH), 57.9 (CH), 36.7 (CH<sub>2</sub>), 33.1 (CH<sub>3</sub>), 32.4 (CH<sub>2</sub>), 28.3 (CH<sub>3</sub>), 27.8 (CH<sub>2</sub>), 27.5 (CH<sub>3</sub>), 24.5 (CH<sub>3</sub>), 24.2 (CH<sub>3</sub>), 24.1 (CH<sub>3</sub>), 22.4 (CH<sub>3</sub>), 21.2 (CH<sub>3</sub>).

MS (DCI, NH<sub>3</sub> + isobutane):  $m/z$  456 (MH<sup>+</sup>), 400, 231.





(2*S*,3*S*,8*R*,8*aR*)-8-Hydroxy-3-(2-methylallyl)-2-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)hexahydroindolizine-5(1*H*)-one (**54**). To a solution of amine **69** (6.54 g, 14.35 mmol, 1.0 equiv) in 46 ml dry MeOH was added 40.5 ml of freshly prepared solution of sodium methoxide in MeOH (1 M, 40.5 mmol, 2.8 equiv). The reaction was stirred 1h at RT and then diluted with DCM and quenched with brine. The aqueous layer was washed 3 times with DCM and the combined organic layers were dried over MgSO<sub>4</sub> and evaporated under reduced pressure. Precipitation in Et<sub>2</sub>O gave 4.9 g of pure hydroxyindolizidinone **54** as white solid (84% over 2 steps). Analytical data are in agreement with those reported in the literature.<sup>75</sup>

M<sub>p</sub>= 170–190 °C (decomposition).

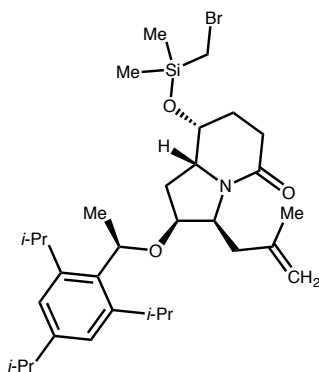
[α]<sub>D</sub><sup>20</sup> +66.5 (c 0.88, CHCl<sub>3</sub>).

IR (film): ν 3348, 3074, 2961, 2922, 2869, 1614, 1461, 1410, 1370, 1326, 1210 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 7.04 (s, 1H), 6.92 (s, 1H), 5.02 (q, *J* = 6.7 Hz, 1H), 4.66 (s, 1H), 4.54–4.61 (m, 2H), 4.06 (ddd, *J* = 2.0 Hz, 1H), 3.95 (q, *J* = 7.0 Hz, 1H), 3.78–3.90 (m, 2H), 3.10–3.22 (m, 1H), 2.84 (sept, *J* = 6.9 Hz, 1H), 2.14–2.44 (m, 5H), 1.84–2.04 (m, 3H), 1.71 (s, 3H), 1.52 (d, *J* = 6.7 Hz, 3H), 1.15–1.29 (m, 18H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ 168.5 (C), 148.5 (C), 147.4 (C), 145.2 (C), 143.8 (C), 133.8 (C), 123.3 (2CH), 120.5, 111.7 (CH<sub>2</sub>), 74.8 (CH), 72.9 (CH), 64.5 (CH), 58.9 (CH), 56.9 (CH), 35.4 (CH<sub>2</sub>), 34.1 (CH), 33.2 (CH<sub>2</sub>), 29.3 (CH), 28.8 (CH), 27.9 (CH<sub>2</sub>), 26.2 (CH<sub>2</sub>), 25.4 (CH<sub>3</sub>), 25.2 (CH<sub>3</sub>), 25.1 (CH<sub>3</sub>), 24.4 (CH<sub>3</sub>), 24.3 (CH<sub>3</sub>), 24.2 (CH<sub>3</sub>), 23.1 (CH<sub>3</sub>), 22.7 (CH<sub>3</sub>).

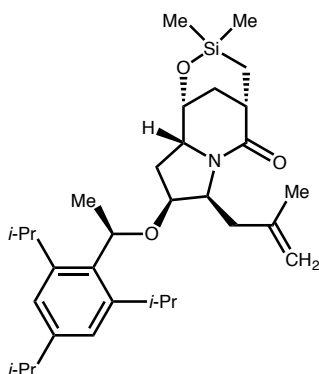
MS (DCI, NH<sub>3</sub> + isobutane): *m/z* 456 (MH<sup>+</sup>), 400, 371, 231.



(2*S*,3*S*,8*R*,8*aR*)-8-(((Bromomethyl)dimethylsilyl)oxy)-3-(2-methylallyl)-2-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)hexahydroindolizin-5(1*H*)-one (**130**). To a solution of alcohol **54** (6.4 mg, 0.014 mmol, 1.0 equiv) in 250  $\mu$ l of dry DCM, Et<sub>3</sub>N (0.030 ml, 0.22 mmol, 15.7 equiv) and (bromomethyl)chlorodimethylsilane (20  $\mu$ l, 27.5 mg, 0.147 mmol, 10.5 equiv) were added. The reaction mixture was stirred at 50°C in a sealed tube for 2.5h. After cooling to room temperature, the reaction mixture was extracted with DCM to give 30.1 mg of crude material which, after silica gel purification (0–20% EtOAc in pentane), gave 8.1 mg (95% yield) of **130** as colorless oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz):  $\delta$  7.02 (s, 1H), 6.92 (s, 1H), 5.01 (q,  $J$  = 6.7 Hz, 1H), 4.60 (s, 1H), 4.58 (ddd,  $J$  = 6.2, 6.2, 8.7 Hz, 1H), 4.45 (s, 1H), 4.14 (ddd,  $J$  = 2.0, 2.0, 4.1 Hz, 1H), 3.95 (ddd,  $J$  = 6.3, 6.3, 7.4 Hz, 1H), 3.80–3.70 (m, 2H), 3.15 (sept,  $J$  = 6.8 Hz, 1H), 2.84 (sept,  $J$  = 6.8 Hz, 1H), 2.43 (s, 2H), 2.41 (ddd,  $J$  = 7.0, 11.9, 18.5 Hz, 1H), 2.29 (ddd,  $J$  = 1.7, 7.2, 18.5 Hz, 1H), 2.27–2.16 (m, 3H), 1.99–1.91 (m, 2H), 1.84 (dddd,  $J$  = 1.9, 7.3, 12.1, 14.1 Hz, 1H), 1.69 (s, 3H), 1.53 (d,  $J$  = 6.6 Hz, 3H), 1.33–1.15 (m, 18H), 0.26 (s, 6H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  168.1 (C), 147.3 (C), 144.8 (C), 143.8 (C), 133.7 (C), 123.2 (CH), 120.4 (CH), 111.5 (CH<sub>2</sub>), 74.6 (CH), 72.9 (CH), 66.1 (CH), 59.1 (CH), 56.7 (CH), 35.4 (CH<sub>2</sub>), 34.0 (CH), 33.4 (CH<sub>2</sub>), 29.2 (CH), 28.7 (CH), 28.2 (CH<sub>2</sub>), 26.2 (CH<sub>2</sub>), 25.1, 24.9, 24.3, 24.0, 23.9, 22.8, 22.4, 15.7 (CH<sub>2</sub>), –2.5 (CH<sub>3</sub>).

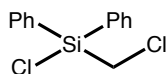


(1*R*,5*S*,8*S*,9*S*,10*aR*)-3,3-Dimethyl-8-(2-methylallyl)-9-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy) hexahydro-1*H*-1,5-methanopyrrolo[1,2-*f*][1,6,2]oxazasilocin-6(3*H*)-one (**131**). To a solution of silyl ether **130** (5.0 mg, 0.008 mmol, 1.0 equiv) in 300  $\mu$ l of dry THF at  $-78^{\circ}\text{C}$  was added 60  $\mu$ l of LiHMDS solution in THF (1.0 M, 0.06 mmol, 7.5 equiv). The reaction temperature was gradually increased to  $-15^{\circ}\text{C}$  over 1 hour. TLC analysis (EtOAc) showed a complete consumption of starting material. The reaction mixture was quenched with water and extracted with DCM. The organic solution was dried on  $\text{MgSO}_4$  and the solvent was removed under reduced pressure to give 5.9 mg of crude material. Purification over silica gel (10  $\rightarrow$  100% EtOAc in pentane) produced 2.8 mg (65%) of **131** as colorless oil and 0.8 mg (22%) of the alcohol **54**. (*vide supra* for data characterization of **54**)

#### Data for compound **131**

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  7.03 (s, 1H), 6.92 (s, 1H), 5.02 (q,  $J = 6.8$  Hz, 1H), 4.64 (s, 1H), 4.57 (s, 1H), 4.56 (ddd,  $J = 5.8, 6.2, 9.4$  Hz, 1H), 4.26 (ddd,  $J = 2.2, 2.2, 4.6$  Hz, 1H), 3.80–3.90 (m, 3H), 3.16 (sept,  $J = 6.8$  Hz, 1H), 2.84 (sept,  $J = 6.8$  Hz, 1H), 2.80 (dddd,  $J = 2.0, 3.1, 5.3, 7.1$  Hz, 1H), 2.41 (ddd,  $J = 7.8, 7.8, 13.6$  Hz, 1H), 2.33 (A of ABX,  $J = 5.8, 14.2$  Hz, 1H), 2.27 (B of ABX,  $J = 9.4, 14.2$  Hz, 1H), 1.98–1.90 (m, 3H), 1.72 (s, 3H), 1.54 (d,  $J = 6.8$  Hz, 3H), 1.31–1.14 (m, 19H), 0.94 (dd,  $J = 7.1, 14.8$  Hz, 1H), 0.14 (s, 3H), 0.17 (s, 3H).

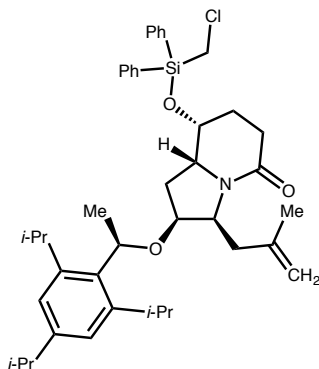
MS (ESI):  $m/z$  532.45 ( $\text{MLi}^+$ , 100%).



Chloro(chloromethyl)diphenylsilane (**133**). To a solution of chloromethyltrichlorosilane (1.0 g, 5.44 mmol, 1.0 equiv) in 8.0 ml of dry  $\text{Et}_2\text{O}$  was added a solution of phenylmagnesium bromide (1.7 M in THF, 6.40 mL, 10.8 mmol, 2.0 equiv) leading to the formation of strong white solid. The reaction

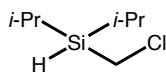
mixture was then heated to reflux for 4 hours. The reaction mixture was filtered over celite and solvent was removed under reduced pressure to give a colorless oil. Addition of dry Et<sub>2</sub>O (4 ml), filtration over celite and evaporation were repeated until no more formation of white precipitate and left 1.56 g (93%) of colorless oil **133**. Analytical data are in agreement with those reported in the literature.<sup>111</sup>

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.80–7.25 (m, 10H), 3.40 (s, 2H).



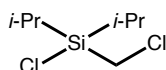
(2*S*,3*S*,8*R*,8*aR*)-8-(((Chloromethyl)diphenylsilyl)oxy)-3-(2-methylallyl)-2-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)hexahydroindolizin-5(1*H*)-one (**132**). To a solution of alcohol **54** (5.4 mg, 0.012 mmol, 1.0 equiv) in 300  $\mu$ l of dry DCM were added Et<sub>3</sub>N (0.050 ml, 0.36 mmol, 30 equiv) and (chloromethyl)chlorodiphenylsilane (30.5 mg, 0.114 mmol, 9.5 equiv). The reaction mixture was stirred at 50°C in a sealed tube for 4.5h. After cooling to room temperature, the reaction mixture was quenched with water and extracted with pentane to give 28.1 mg of crude material. Purification over silica gel (0–20% of EtOAc in pentane) gave 5.7 mg (66%) of **132** as colorless oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz):  $\delta$  7.65–7.58 (m, 4H), 7.52–7.46 (m, 2H), 7.44–7.37 (m, 4H), 7.02 (s, 1H), 6.89 (s, 1H), 4.97 (q,  $J$  = 6.7 Hz, 1H), 4.65 (ddd,  $J$  = 6.6, 6.6, 7.8 Hz, 1H), 4.64 (s, 1H), 4.52 (s, 1H), 4.32 (ddd,  $J$  = 1.9, 1.9, 4.2 Hz, 1H), 4.05 (ddd,  $J$  = 6.2, 6.2, 7.4 Hz, 1H), 3.80 (ddd,  $J$  = 2.8, 7.5, 8.3 Hz, 1H), 3.84–3.72 (m, 1H), 3.30 (d,  $J$  = 2.1 Hz, 2H), 3.15–3.03 (m, 1H), 2.46 (ddd,  $J$  = 7.2, 11.7, 17.8 Hz, 1H), 2.34–2.23 (m, 2H), 2.22–2.15 (m, 2H), 1.90 (ddd,  $J$  = 6.0, 8.3, 12.5 Hz, 1H), 1.85 (dddd,  $J$  = 1.7, 4.2, 7.2, 13.6 Hz, 1H), 1.74 (dddd,  $J$  = 2.0, 7.3, 12.1, 13.9 Hz, 1H), 1.67 (s, 3H), 1.47 (d,  $J$  = 6.7 Hz, 3H), 1.31–1.12 (m, 18H).



**(Chloromethyl)diisopropylsilane (S5).** To a solution of chlorodiisopropylsilane (3.8 ml, 22.3 mmol, 1.0 equiv) and chloriodomethane (2.7 ml, 37 mmol, 1.6 equiv) in 30 ml of dry THF at  $-78^{\circ}\text{C}$ , a solution of MeLi was added dropwise (1.6 M in  $\text{Et}_2\text{O}$ , 22 ml, 35.2 mmol, 1.5 equiv). The reaction mixture was stirred for 3h as temperature increases from  $-78^{\circ}\text{C}$  to  $-20^{\circ}\text{C}$  and then allowed to stir at room temperature for 2h before quenching it with saturated  $\text{NH}_4\text{Cl}$  solution. The aqueous layer was extracted 3 times with pentane. The combined organic layer was dried over anhydrous  $\text{MgSO}_4$  and concentrated under reduced pressure to give 3.6 g of silane **S5**. Analytical data are in agreement with those reported in the literature.<sup>113</sup>

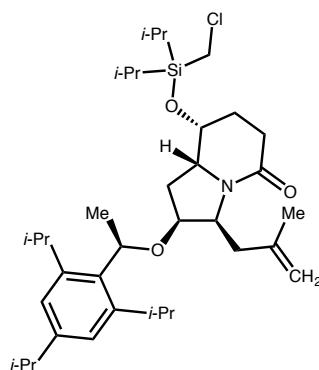
$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  3.63 (quint,  $J = 2.5$  Hz, 1H), 2.95 (d,  $J = 2.5$  Hz, 2H), 1.13–1.21 (m, 2H), 1.07–1.12 (m, 12H).



**Chloro(chloromethyl)diisopropylsilane (134).** A solution of crude (chloromethyl)diisopropylsilane **S5** (3.6 g, 21.9 mmol, 1.0 equiv) in 15 ml of dry DCM was added dropwise to a solution of TCCA (2.8 g, 12.0 mmol, 0.55 equiv) in 25 ml DCM at  $0^{\circ}\text{C}$  under argon. The mixture was stirred for 1h at  $0^{\circ}\text{C}$  then allowed to warm to RT. After dilution with pentane, it was filtered through celite and then concentrated. This was repeated several times till no turbidity is observed (no TCCA remained) to yield 4.2 g of **134** (95% over 2 steps) as a colorless oil. The crude product (>95% purity) was used for the next step without further purification.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  3.03 (s, 2H), 1.38 (sept,  $J = 7.5$  Hz, 2H), 1.14 (d,  $J = 7.5$  Hz, 12H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  26.2 ( $\text{CH}_2$ ), 17.0 ( $2\text{CH}_3$ ), 16.7 ( $2\text{CH}_3$ ), 12.8 ( $2\text{CH}$ ).



(2*S*,3*S*,8*R*,8*aR*)-8-(((Chloromethyl)diisopropylsilyl)oxy)-3-(2-methylallyl)-2-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)hexahydroindolizin-5(1*H*)-one (**135**). To a solution of indolizidinone **54** (925.0 mg, 2.03 mmol, 1.0 equiv) in 5 ml of dry DCM was added 680 mg of a chloro(chloromethyl)diisopropylsilane **134** (3.41 mmol, 1.7 equiv). Also, imidazole (300 mg, 4.40 mmol, 2.1 equiv) and DMAP (45 mg, 0.37 mmol, 0.18 equiv) were added and the solution was stirred at 60°C in a sealed tube for 2h. Additional 1.1 g of the silyl reagent **134** were added in 4-time portions with 2-hour intervals (5.52 mmol, 2.7 equiv). The reaction was followed with TLC until the disappearance of the starting material. Then it was quenched with water and brine, and the aqueous layer was extracted 3 times with pentane. The combined organic phases were dried over MgSO<sub>4</sub> and concentrated under reduced pressure to give 1.7 g of crude material which was purified over silica gel (0–20% EtOAc/cyclohexane) leaving 1.06 g of pure silyl ether **135** (85%), along with 100.0 mg of the siloxane byproduct **137** (7%).

Data for compound **135**:

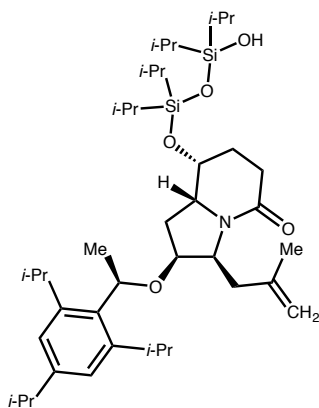
IR (film):  $\nu$ 3582, 3274, 2959, 2868, 1645, 1458, 1070 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.03 (s, 1H), 6.92 (s, 1H), 5.01 (q,  $J$  = 6.6 Hz, 1H), 4.65 (s, 1H), 4.59 (ddd,  $J$  = 6.0, 6.0, 8.5 Hz, 1H), 4.53 (s, 1H), 4.32 (ddd,  $J$  = 1.7, 2.4, 4.2 Hz, 1H), 4.02 (ddd,  $J$  = 5.7, 6.0, 7.3 Hz, 1H), 3.83 (ddd,  $J$  = 2.4, 8.0, 8.0 Hz, 1H), 3.78–3.87 (m, 1H), 2.92 (s, 2H), 3.13 (sept,  $J$  = 6.9 Hz, 1H), 2.84 (sept,  $J$  = 6.9 Hz, 1H), 2.44 (ddd,  $J$  = 6.9, 12.1, 18.0 Hz, 1H), 2.32 (ddd,  $J$  = 1.6, 7.2, 18.0 Hz, 1H), 2.16–2.30 (m, 3H), 2.04 (dddd,  $J$  = 1.6, 4.2, 6.9, 13.9 Hz, 1H), 1.99 (dddd,  $J$  = 5.7, 8.0, 12.6 Hz, 1H), 1.86 (dddd,  $J$  = 1.7, 7.2, 12.1, 13.9 Hz, 1H), 1.67 (s, 3H), 1.50 (d,  $J$  = 6.6 Hz, 3H), 1.14–1.32 (m, 19H), 1.04–1.10 (m, 12H), 0.79 (m, 1H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz):  $\delta$  168.1 (C), 148.3 (C), 147.3 (C), 144.6 (C), 143.8 (C), 134.0 (C), 123.1 (CH), 120.3 (CH), 111.4 (CH<sub>2</sub>), 75.1 (CH), 73.2 (CH), 66.2 (CH), 59.5 (CH), 56.7 (CH), 35.3 (CH<sub>2</sub>), 34.0 (CH), 33.6 (CH<sub>2</sub>), 29.3 (CH), 28.8 (CH), 28.3 (CH<sub>2</sub>), 26.4 (CH<sub>2</sub>), 26.2 (CH<sub>2</sub>), 25.1 (CH<sub>3</sub>), 25.0 (CH<sub>3</sub>), 24.8 (CH<sub>3</sub>), 24.1 (CH<sub>3</sub>), 24.0 (CH<sub>3</sub>), 23.9 (CH<sub>3</sub>), 22.7 (CH<sub>3</sub>), 22.5 (CH<sub>3</sub>), 17.5 (CH<sub>3</sub>), 17.5 (CH<sub>3</sub>), 12.1 (CH<sub>3</sub>), 11.9 (CH<sub>3</sub>).

MS (ESI):  $m/z$  640.42 (MNa<sup>+</sup>, 100%), 618.42 (MH<sup>+</sup>).

HRMS calcd for C<sub>36</sub>H<sub>61</sub>NO<sub>3</sub>SiCl: 618.4109. Found: 618.4123 (MH<sup>+</sup>).



(2*S*,3*S*,8*R*,8*aR*)-8-((3-Hydroxy-1,1,3,3-tetraisopropylidisiloxanyl)oxy)-3-(2-methylallyl)-2-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)hexahydroindolizin-5(1*H*)-one (137).

Data for compound **137**:

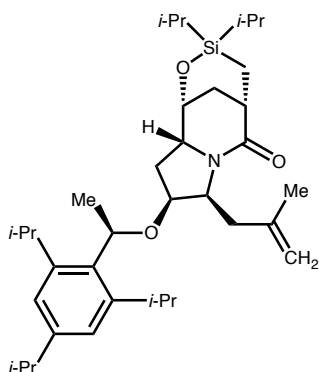
IR (film):  $\nu$  3305, 2958, 2866, 1621, 1464  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  7.03 (s, 1H), 6.92 (s, 1H), 5.00 (q,  $J = 6.7$  Hz, 1H), 4.64 (s, 1H), 4.59 (ddd,  $J = 6.1, 6.1, 8.9$  Hz, 1H), 4.52 (s, 1H), 4.33 (ddd,  $J = 1.9, 2.6, 4.2$  Hz, 1H), 4.04 (ddd,  $J = 5.9, 5.9, 7.3$  Hz, 1H), 3.82 (ddd,  $J = 2.5, 7.6, 7.6$  Hz, 1H), 3.78–3.86 (m, 1H), 3.14 (sept,  $J = 6.9$  Hz, 1H), 2.84 (sept,  $J = 6.9$  Hz, 1H), 2.50 (ddd,  $J = 7.2, 12.0, 18.6$  Hz, 1H), 2.15–2.37 (m, 4H), 2.10 (dddd,  $J = 1.5, 4.3, 7.2, 13.5$  Hz, 1H), 1.97 (ddd,  $J = 5.6, 8.1, 13.1$  Hz, 1H), 1.82 (dddd,  $J = 1.3, 7.1, 11.9, 13.5$  Hz, 1H), 1.66 (s, 3H), 1.50 (d,  $J = 6.7$  Hz, 3H), 1.14–1.31 (m, 18H), 0.90–1.10 (m, 28H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz):  $\delta$  168.7 (C), 148.3 (C), 147.2 (C), 144.5 (C), 143.8 (C), 134.2 (C), 123.1 (CH), 120.3 (CH), 111.4 ( $\text{CH}_2$ ), 75.2 (CH), 73.3 (CH), 65.8 (CH), 59.6 (CH), 56.7 (CH), 35.2 ( $\text{CH}_2$ ), 34.0 (CH), 33.8 ( $\text{CH}_2$ ), 29.3 (CH), 28.9 (CH), 28.2 ( $\text{CH}_2$ ), 26.4 ( $\text{CH}_2$ ), 25.2 ( $\text{CH}_3$ ), 25.0 ( $\text{CH}_3$ ), 24.8 ( $\text{CH}_3$ ), 24.1 ( $\text{CH}_3$ ), 24.0 ( $\text{CH}_3$ ), 23.9 ( $\text{CH}_3$ ), 22.52 ( $\text{CH}_3$ ), 22.49 ( $\text{CH}_3$ ), 17.6 ( $\text{CH}_3$ ), 17.5 ( $\text{CH}_3$ ), 17.42 ( $\text{CH}_3$ ), 17.40 ( $2\text{CH}_3$ ), 17.36 ( $3\text{CH}_3$ ), 13.62 ( $2\text{CH}$ ), 13.59 (CH), 13.5 (CH).

MS (ESI):  $m/z$  716.52 ( $\text{MH}^+$ , 100%).

HRMS calcd for  $\text{C}_{41}\text{H}_{74}\text{NO}_5\text{Si}_2$ : 716.5100. Found: 716.5075 ( $\text{MH}^+$ ).



(1*R*,5*S*,8*S*,9*S*,10*aR*)-3,3-Diisopropyl-8-(2-methylallyl)-9-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)hexahydro-1*H*-1,5-methanopyrrolo[1,2-*A*][1,6,2]oxazasilocin-6(3*H*)-one (**136**). To a solution of silyl ether **135** (1.0 g, 1.62 mmol, 1.0 equiv) in 15 ml THF at  $-78^{\circ}\text{C}$  was added a freshly prepared solution of 0.4M LiHMDS in THF (16 ml, 6.4 mmol, 3.9 equiv). The reaction was allowed to warm to  $-20^{\circ}\text{C}$  over 1h30min, followed by TLC and quenched with brine at  $-25^{\circ}\text{C}$ . The aqueous layer was extracted 3 times with DCM. After drying over  $\text{MgSO}_4$ , the organic phase was concentrated under vacuum to leave 932.2 mg of crude material which was purified over silica gel (0–10% EtOAc/cyclohexane) to give 860.0 mg of pure cyclic silyl ether **136** (91%). **Preparation of LiHMDS solution in THF**; At  $-20^{\circ}\text{C}$ , 4.8 ml of *n*-Buli solution (2.5M, 12 mmol, 1.0 equiv) was added to a solution of HMDS (3 ml, 14.28 mmol, 1.2 equiv) in 22.2 ml THF. The mixture was allowed to stir at  $-20^{\circ}\text{C} < T < -10^{\circ}\text{C}$  for 30 min before being ready to be used.

IR (film):  $\nu$  3357, 2959, 2866, 1644, 1462, 1610  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  6.90 (s, 1H), 6.8 (s, 1H), 4.96 (q,  $J = 6.9$  Hz, 1H), 4.6 (s, 1H), 4.46–4.5 (m, 2H), 4.2 (ddd,  $J = 1.9, 1.9, 4.2$  Hz, 1H), 3.95 (ddd,  $J = 5.0, 7.3, 7.3$  Hz, 1H), 3.89 (sept,  $J = 6.9$  Hz, 1H), 3.8 (ddd,  $J = 2.5, 8.1, 8.1$  Hz, 1H), 3.1 (sept,  $J = 7.05$  Hz, 1H), 2.8 (sept,  $J = 6.9$  Hz, 1H), 2.7 (dddd,  $J = 1.3, 2.3, 5.8, 7.7$  Hz, 1H), 2.3–2.4 (ddd,  $J = 8.0, 8.0, 12.7$  Hz, 1H), 2.16–2.27 (m, 2H), 1.81–1.95 (m, 3H), 1.64 (s, 3H), 1.46 (d,  $J = 6.7$  Hz, 3H), 1.12–1.2 (m, 19H), 0.9–0.95 (m, 8H), 0.73 (d,  $J = 7.2$  Hz, 3H), 0.69 (d,  $J = 7.4$  Hz, 3H), 0.54 (sept,  $J = 7.5$  Hz, 1H).

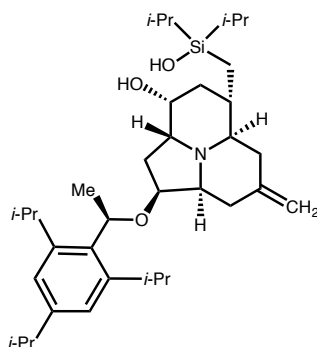
$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz):  $\delta$  170.9 (C), 148.4 (C), 147.2 (C), 145.1 (C), 143.7 (C), 133.3 (C), 123.1 (CH), 120.3 (CH), 111.4 ( $\text{CH}_2$ ), 74.3 (CH), 72.4 (CH), 66.0 (CH), 60.8 (CH), 56.8 (CH), 35.3 ( $\text{CH}_2$ ), 34.0 (CH), 32.9 ( $2\text{CH}_2$ ), 32.7 (CH), 29.1 (CH), 28.4 (CH), 25.1 ( $2\text{CH}_3$ ), 24.9 ( $\text{CH}_3$ ), 24.0



(CH<sub>3</sub>), 24.0 (CH<sub>3</sub>), 23.9 (CH<sub>3</sub>), 22.8 (CH<sub>3</sub>), 22.6 (CH<sub>3</sub>), 17.4 (CH<sub>3</sub>), 17.3 (CH<sub>3</sub>), 16.6 (CH<sub>3</sub>), 16.5 (CH<sub>3</sub>), 13.9 (CH), 13.4 (CH), 13.3 (CH<sub>2</sub>).

MS (ESI):  $m/z$  582.45 (MH<sup>+</sup>, 100%), 604.46 (MNa<sup>+</sup>)

HRMS calcd for C<sub>36</sub>H<sub>60</sub>NO<sub>3</sub>Si: 582.4342. Found: 582.4348 (MH<sup>+</sup>).



(1*S*,2*aR*,3*R*,5*S*,5*aR*,8*aS*)-5-((Hydroxydiisopropylsilyl)methyl)-7-methylene-1-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)decahydro-1*H*-pyrrolo[2,1,5-*de*]quinolizin-3-ol (**146**). Ti(O*i*Pr)<sub>4</sub> (17 μl, 0.06 mmol, 3.3 equiv) was added dropwise to a solution of lactam **136** (9.5 mg, 0.016 mmol, 1.0 equiv) and Ph<sub>2</sub>SiH<sub>2</sub> (31 μl, 0.18 mmol, 10 equiv) in 200 μl hexane at 0°C. The mixture was stirred at RT for 7h, after which the reaction mixture was concentrated *in vacuo*. Formic acid (200 μl) was then added and stirred at RT. After 1 h, the mixture was diluted with Et<sub>2</sub>O and quenched with saturated K<sub>2</sub>CO<sub>3</sub> solution till reaching alkaline pH. The organic phase was then washed with brine, dried (MgSO<sub>4</sub>) and concentrated *in vacuo* to afford 43 mg of crude product. Purification over 3 ml of silica gel gave 7.0 mg of a mixture of olefinated product **146** and formate **139** using 0–10% EtOAc/pentane as eluting system (~71% yield). (*vide infra* for data characterization of **139**)

#### Data for compound **146**

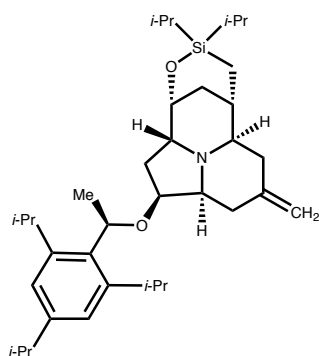
IR (film):  $\nu$  3389, 2958, 2925, 2864, 1645, 1608, 1462, 1381, 1261, 1119 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.03 (s, 1H), 6.94 (s, 1H), 5.01 (q,  $J$  = 6.8 Hz, 1H), 4.67 (s, 2H), 3.99 (ddd,  $J$  = 4.6, 6.6, 9.6 Hz, 1H), 3.92 (sept,  $J$  = 6.8 Hz, 1H), 3.78 (br. s, 1H), 3.39 (app t,  $J$  = 8.2 Hz, 1H), 3.11–3.19 (m, 2H), 2.85 (sept,  $J$  = 6.9 Hz, 1H), 2.73 (dd,  $J$  = 3.1, 12.9 Hz, 1H), 2.50 (t,  $J$  = 12.9 Hz, 1H), 2.07–2.28 (m, 3H), 1.99 (dd,  $J$  = 4.2, 14.3 Hz, 1H), 1.59–1.84 (m, 4H), 1.50 (d,  $J$  = 6.8 Hz, 3H), 1.17–1.33 (m, 18H), 1.09 (dd,  $J$  = 10.7 Hz, 15.3 Hz, 1H), 0.80–1.05 (m, 15H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz):  $\delta$  148.8, 147.4, 147.2, 145.8, 133.4, 123.2, 120.4, 107.9, 74.8, 71.1, 67.3, 64.5, 64.0, 53.9, 34.0, 33.1, 32.5, 32.1, 31.2, 29.6, 29.1, 28.2, 25.1, 24.9, 24.7, 24.5, 24.0, 23.9, 23.2, 20.5, 17.8, 17.5, 17.5, 17.4, 13.4, 13.3.

MS (ESI):  $m/z$  584.6 ( $\text{MH}^+$ , 100%).

HRMS calcd for  $\text{C}_{36}\text{H}_{62}\text{NO}_3\text{Si}$ : 584.44935. Found: 584.44765 ( $\text{MH}^+$ ).



(1*S*,5*R*,5*aR*,7*S*,7*aS*,10*aR*)-3,3-Diisopropyl-9-methylene-7-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy) dodecahydro-1,5-methano[1,6,2]oxazasilocino[7,6,5-*cd*]indolizine (**147**). To a solution of lactam **136** (6.0 mg, 0.010 mmol, 1.0 equiv) and  $\text{Ph}_2\text{SiH}_2$  (22  $\mu\text{l}$ , 0.12 mmol, 12 equiv) in 120  $\mu\text{l}$  hexane was added dropwise  $\text{Ti}(\text{O}i\text{Pr})_4$  (15  $\mu\text{l}$ , 0.05 mmol, 5.0 equiv) at  $0^\circ\text{C}$ . After stirring 5h at RT, the reaction mixture was quenched with water and stirred for 15 min. The aqueous layer was extracted with  $\text{Et}_2\text{O}$  (3 times) then the combined organic layers were dried over  $\text{MgSO}_4$  and concentrated *in vacuo* to afford 35 mg of crude product. Purification over 1 ml of silica gel allowed the isolation of 2.7 mg of the tertiary alcohol **142** (40% yield), and 3.0 mg mixture of the olefinated compound **147** and over-reduced amine **144** in 1:0.15 ratio respectively (47% yield) using 0–10%  $\text{EtOAc}$ /pentane as eluting system. (*vide infra* for data characterization of **142** and **144**)

#### Data for compound **147**

IR (film):  $\nu$  2958, 2926, 28634, 1645, 1608, 1461, 1381, 1262, 1122, 1080  $\text{cm}^{-1}$ .

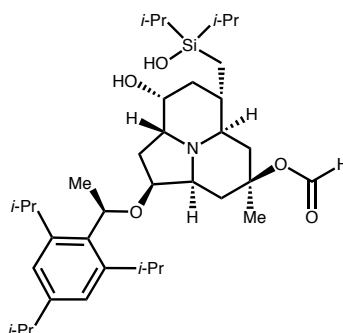
$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  7.04 (d,  $J=1.8$  Hz, 1H), 6.93 (d,  $J=1.8$  Hz, 1H), 5.00 (q,  $J=6.8$  Hz, 1H), 4.67 (s, 2H), 3.97 (app s, 1H), 3.92 (sept,  $J=6.8$  Hz, 1H), 3.90 (ddd,  $J=3.2$  Hz, 6.5 Hz, 9.1 Hz, 1H), 3.24 (app t,  $J=9.1$  Hz, 1H), 3.17 (sept,  $J=6.8$  Hz, 1H), 3.09 (ddd,  $J=4.2$  Hz, 6.7 Hz, 11.9 Hz, 1H), 2.86 (sept,  $J=6.9$  Hz, 1H), 2.79 (app dd,  $J=2.9$  Hz, 12.4 Hz, 1H), 2.41 (t,  $J=12.4$  Hz, 1H),

2.28 (t,  $J$  = 11.9 Hz, 1H), 2.20 (ddd,  $J$  = 9.1, 9.1, 12.6 Hz, 1H), 1.96 (ddd,  $J$  = 1.3, 4.2, 13.9 Hz, 1H), 1.94–1.20 (m, 1H), 1.65–1.79 (m, 4H), 1.49 (d,  $J$  = 6.8 Hz, 3H), 1.12–1.31 (m, 18 H), 0.79–1.05 (m, 15H), 0.53 (ddd,  $J$  = 1.9, 1.9, 14.7 Hz, 1H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz):  $\delta$  148.8, 148.4, 147.1, 145.9, 133.4, 123.1, 120.2, 107.2, 74.5, 70.7, 68.1, 64.3, 62.9, 54.7, 34.0, 32.9, 32.3, 31.6, 31.4, 29.6, 29.2, 28.1, 25.2, 24.8, 24.8, 24.3, 24.0, 23.8, 23.3, 17.9, 17.7, 17.2, 16.8, 15.0, 14.5, 13.1.

MS (ESI):  $m/z$  566.6 ( $\text{MH}^+$ , 100%).

HRMS calcd for  $\text{C}_{36}\text{H}_{60}\text{NO}_2\text{Si}$ : 566.4393. Found: 566.44 ( $\text{MH}^+$ ).



(2*S*,2*aS*,4*R*,5*aR*,6*S*,8*R*,8*aR*)-8-Hydroxy-6-((hydroxydiisopropylsilyl)methyl)-4-methyl-2-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)decahydro-1*H*-pyrrolo[2,1,5-*de*]quinolizin-4-yl formate (139).

$\text{IrCl}(\text{CO})[\text{P}(\text{C}_6\text{H}_5)_3]_2$  (32 mg, 0.041 mmol, 2.4 %mol) was added to a solution of lactam **136** (990.0 mg, 1.7 mmol, 1.0 equiv) in 41 ml toluene at RT. The obtained yellow suspension was stirred at RT for 5 min before the addition of TMSD (750  $\mu\text{l}$ , 4.24 mmol, 2.5 equiv). The reaction mixture was stirred for more 5 min before noticing the total disappearance of starting material by TLC. Formic acid (18 ml) was then added and the solution was stirred for 1h30min at RT. The resultant solution was diluted with  $\text{Et}_2\text{O}$  and then basified with saturated  $\text{K}_2\text{CO}_3$  solution. It was then washed with brine and the aqueous phase was extracted 3 times with  $\text{Et}_2\text{O}$ . The combined organic layers were dried over  $\text{MgSO}_4$  and evaporated under reduced pressure to yield 1 g of crude mixture that is used for the next step without any further purification. Pure unhydrolysed **140** and hydrolysed formate product **139** were obtained after purification over silica gel and eluted with 2% and 10%  $\text{EtOAc}$ /cyclohexane respectively.

Data for compound 139

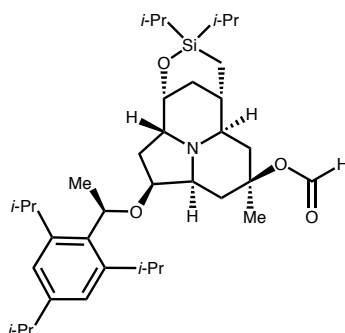
IR (film):  $\nu$  3398, 2959, 2866, 1722, 1607, 1462  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  8.03 (s, 1H), 7.03 (d,  $J=1.6$  Hz, 1H), 6.94 (d,  $J=1.6$  Hz, 1H), 5.00 (q,  $J=6.8$  Hz, 1H), 3.99 (ddd,  $J=4.3$  Hz, 6.7 Hz, 9.3 Hz, 1H), 3.89 (sept,  $J=6.8$  Hz, 1H), 3.78 (app s, 1H), 3.31 (ddd,  $J=1.3$  Hz, 8.4 Hz, 9.3 Hz, 1H), 3.25 (ddd,  $J=3.9$  Hz, 6.7 Hz, 12.8 Hz, 1H), 3.15 (sept,  $J=6.8$  Hz, 1H), 2.79–2.9 (m, 2H), 2.23 (dd,  $J=12.8$  Hz, 12.8 Hz, 1H), 2.14 (ddd,  $J=9.3$  Hz, 9.3 Hz, 13.1 Hz, 1H), 2.08 (ddd,  $J=1.9$  Hz, 3.4 Hz, 14.8 Hz, 1H), 2.0 (dd,  $J=12.8$  Hz, 12.8 Hz, 1H), 1.66–1.80 (m, 4H), 1.62 (ddd,  $J=2.44$  Hz, 6.04 Hz, 14.8 Hz, 1H), 1.57 (s, 3H), 1.49 (d,  $J=6.8$  Hz, 3H), 1.17–1.32 (m, 18 H), 1.1 (dd,  $J=10.4$  Hz, 15.3 Hz, 1H), 0.93–1.05 (m, 12H), 0.8–0.9 (m, 3H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz):  $\delta$  160.3 (CH), 148.8 (C), 147.3 (C), 145.9 (C), 133.1 (C), 123.2 (CH), 120.4 (CH), 84.7 (C), 74.5 (CH), 71.1 (CH), 67.1 (CH), 60.4 (CH), 59.2 (CH), 53.9 (CH), 33.9 (CH), 33.7 ( $\text{CH}_2$ ), 32.6 ( $\text{CH}_2$ ), 31.9 (CH), 31.0 ( $\text{CH}_2$ ), 30.4 ( $\text{CH}_2$ ), 29.1 (CH), 28.0 (CH), 24.9 ( $\text{CH}_3$ ), 24.9 ( $\text{CH}_3$ ), 24.8 ( $\text{CH}_3$ ), 24.6 ( $\text{CH}_3$ ), 24.5 ( $\text{CH}_3$ ), 23.9 ( $2\text{CH}_3$ ), 23.3 ( $\text{CH}_3$ ), 22.9 ( $\text{CH}_3$ ), 20.7 ( $\text{CH}_2$ ), 17.7 ( $\text{CH}_3$ ), 17.5 ( $\text{CH}_3$ ), 17.4 ( $\text{CH}_3$ ), 13.3 (CH), 13.2 (CH).

MS (ESI):  $m/z$  630.6 ( $\text{MH}^+$ , 100%).

HRMS calcd for  $\text{C}_{37}\text{H}_{64}\text{NO}_5\text{Si}$ : 630.4554. Found: 630.4565 ( $\text{MH}^+$ ).



(1*S*,5*R*,5*aR*,7*S*,7*aS*,9*R*,10*aR*)-3,3-Diisopropyl-9-methyl-7-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)dodecahydro-1,5-methano[1,6,2]oxazasilocino[7,6,5-*cd*]indolizin-9-yl formate (140).

Data for compound **140**

IR (film):  $\nu$  2959, 2864, 1722, 1607, 1461  $\text{cm}^{-1}$ .

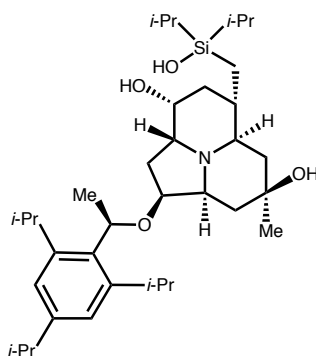
$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  8.05 (s, 1H), 7.04 (d,  $J=1.8$  Hz, 1H), 6.93 (d,  $J=1.8$  Hz, 1H), 4.99 (q,  $J=6.8$  Hz, 1H), 3.97 (app s, 1H), 3.84–3.93 (m, 2H), 3.08–3.23 (m, 3H), 2.78–2.92 (m, 2H),

2.11–2.23 (m, 2H), 2.01 (dd,  $J = 13.1, 13.1$  Hz, 1H), 1.96 (br peak, 1H), 1.58–1.76 (m, 5H), 1.58 (s, 3H), 1.48 (d,  $J = 6.8$  Hz, 3H), 1.14–1.34 (m, 18H), 1.05 (dd,  $J = 7.8, 15.0$  Hz, 1H), 1.0 (d,  $J = 6.4$  Hz, 3H), 0.84–0.98 (m, 5H), 0.83 (d,  $J = 7.3$  Hz, 3H), 0.82 (d,  $J = 7.2$  Hz, 3H), 0.53 (ddd,  $J = 2.0, 2.0, 15.0$  Hz, 1H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz):  $\delta$  160.3 (CH), 148.8 (C), 147.2 (C), 146.0 (C), 133.2 (C), 123.1 (CH), 120.2 (CH), 85.2 (C), 74.3 (CH), 70.7 (CH), 67.9 (CH), 60.1 (CH), 58.3 (CH), 54.7 (CH), 34.0 (CH), 33.4 ( $\text{CH}_2$ ), 32.2 ( $\text{CH}_2$ ), 31.5 ( $\text{CH}_2$ ), 31.2 (CH), 30.2 ( $\text{CH}_2$ ), 29.2 (CH), 28.0 (CH), 25.1 ( $\text{CH}_3$ ), 24.8 ( $\text{CH}_3$ ), 24.7 ( $\text{CH}_3$ ), 24.3 ( $\text{CH}_3$ ), 24.0 ( $\text{CH}_3$ ), 23.8 ( $\text{CH}_3$ ), 23.4 ( $\text{CH}_3$ ), 22.9 ( $\text{CH}_3$ ), 17.9 ( $\text{CH}_3$ ), 17.6 ( $\text{CH}_3$ ), 17.2 ( $\text{CH}_3$ ), 16.8 ( $\text{CH}_3$ ), 15.1 (CH), 14.8 ( $\text{CH}_2$ ), 13.1 (CH).

MS (ESI):  $m/z$  612.6 ( $\text{MH}^+$ , 100%).

HRMS calcd for  $\text{C}_{37}\text{H}_{62}\text{NO}_4\text{Si}$ : 612.4448. Found: 612.4451 ( $\text{MH}^+$ ).



(1*S*,2*aR*,3*R*,5*S*,5*aR*,7*R*,8*aS*)-5-((Hyoxydiisopropylsilyl)methyl)-7-methyl-1-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)decahydro-1*H*-pyrrolo[2,1,5-*de*]quinolizine-3,7-diol (**143**).  $\text{K}_2\text{CO}_3$  (280 mg, 2.03 mmol, 13.5 equiv) was added to a solution of formate **139** (94.0 mg, 0.15 mmol, 1.0 equiv) in 2.7 ml MeOH and stirred for 1h at RT. Then the reaction was diluted with DCM and quenched with brine, and the aqueous layer was extracted 3 times with DCM. The combined organic layers were dried with  $\text{MgSO}_4$  and concentrated under reduced pressure. Purification over silica gel eluted 45.2 mg of unhydrolyzed alcohol **142** (52%) with 10% EtOAc/cyclohexane and 38.0 mg of hydrolyzed alcohol **143** (42%) with 30% EtOAc/cyclohexane.

Data for compound **143**

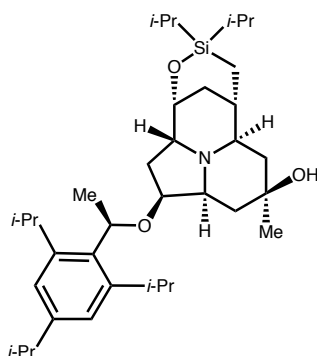
IR (film):  $\nu$  3375, 2959, 2865, 1607, 1462  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  7.03 (d,  $J=1.8$  Hz, 1H), 6.93 (d,  $J=1.8$  Hz, 1H), 5.00 (q,  $J=6.9$  Hz, 1H), 3.99 (ddd,  $J=4.2, 6.6, 9.4$  Hz, 1H), 3.91 (sept,  $J=6.9$  Hz, 1H), 3.76 (app s, 1H), 3.28 (ddd,  $J=1.5, 8.3, 8.3$  Hz, 1H), 3.11–3.22 (m, 2H), 2.85 (sept,  $J=6.9$  Hz, 1H), 2.75 (app dd,  $J=3.0, 13.1$  Hz, 1H), 2.04–2.17 (m, 2H), 1.86 (dd,  $J=13.1, 13.1$  Hz, 1H), 1.59–1.80 (m, 4H), 1.48 (d,  $J=6.9$  Hz, 3H), 1.43 (ddd,  $J=2.1, 3.8, 13.5$  Hz, 1H), 1.16–1.31 (m, 22H), 1.1 (dd,  $J=10.5, 15.3$  Hz, 1H), 0.93–1.05 (m, 13 H), 0.81–0.91 (m, 2H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz):  $\delta$  148.8 (C), 147.2 (C), 145.9 (C), 133.3 (C), 123.2 (CH), 120.3 (CH), 74.5 (CH), 71.3 (C), 71.0 (CH), 67.2 (CH), 61.2 (CH), 60.1 (CH), 53.7 (CH), 37.2 ( $\text{CH}_2$ ), 33.6 (CH), 32.8 ( $\text{CH}_2$ ), 32.0 ( $\text{CH}_2$ ), 31.0 (CH), 29.1 ( $\text{CH}_2$ ), 28.0 (CH), 25.8 ( $\text{CH}_3$ ), 25.0 ( $\text{CH}_3$ ), 24.9 ( $\text{CH}_3$ ), 24.6 ( $\text{CH}_3$ ), 24.5 ( $\text{CH}_3$ ), 23.9 ( $2\text{CH}_3$ ), 23.2 ( $\text{CH}_3$ ), 20.8 ( $\text{CH}_2$ ), 17.7 ( $\text{CH}_3$ ), 17.5 ( $2\text{CH}_3$ ), 17.4 ( $\text{CH}_3$ ), 13.4 (CH), 13.2 (CH).

MS (ESI):  $m/z$  602.46 ( $\text{MH}^+$ , 100%).

HRMS calcd for  $\text{C}_{36}\text{H}_{64}\text{NO}_4\text{Si}$ : 602.4605. Found: 602.4611 ( $\text{MH}^+$ ).



(1*S*,5*R*,5*aR*,7*S*,7*aS*,9*R*,10*aR*)-3,3-Diisopropyl-9-methyl-7-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy) dodecahydro-1,5-methano[1,6,2]oxazasilocino[7,6,5-*cd*]indolizin-9-ol (142).

#### Data for compound 142

IR (film):  $\nu$  3365, 2959, 2864, 1608, 1461  $\text{cm}^{-1}$ .

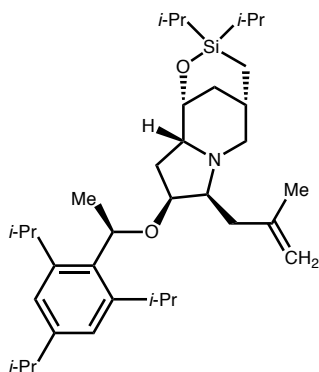
$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  7.04 (d,  $J=2.0$  Hz, 1H), 6.92 (d,  $J=2.0$  Hz, 1H), 4.98 (q,  $J=6.9$  Hz, 1H), 3.96 (app s, 1H), 3.87–3.93 (m, 2H), 3.08–3.19 (m, 3H), 2.86 (sept,  $J=6.9$  Hz, 1H), 2.77 (ddd,  $J=0.8, 3.0, 12.8$  Hz, 1H), 2.16 (ddd,  $J=9.2, 9.2, 12.6$  Hz, 1H), 1.95 (br s, 1H), 1.82 (dd,  $J=12.8$ ,

12.8 Hz, 1H), 1.58–1.75 (m, 4H), 1.47 (d,  $J = 6.9$  Hz, 3H), 1.40 (ddd,  $J = 2.0, 3.7, 13.4$  Hz, 1H), 1.15–1.28 (m, 22H), 0.82–1.07 (m, 15H), 0.53 (ddd,  $J = 1.9, 1.9, 15.0$ , 1H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz):  $\delta$  148.8 (C), 147.1 (C), 146.0 (C), 133.4 (C), 123.1 (CH), 120.2 (CH), 74.3 (CH), 71.6 (C), 70.6 (CH), 68.0 (CH), 60.9 (CH), 59.2 (CH), 54.5 (CH), 36.8 ( $\text{CH}_2$ ), 34.0 (CH), 33.4 ( $\text{CH}_2$ ), 32.3 ( $\text{CH}_2$ ), 31.6 ( $\text{CH}_2$ ), 31.4 (CH), 29.2 (CH), 28.0 (CH), 25.7 ( $\text{CH}_3$ ), 25.2 ( $\text{CH}_3$ ), 24.8 ( $\text{CH}_3$ ), 24.7 ( $\text{CH}_3$ ), 24.3 ( $\text{CH}_3$ ), 24.0 ( $\text{CH}_3$ ), 23.8 ( $\text{CH}_3$ ), 23.3 ( $\text{CH}_3$ ), 17.9 ( $\text{CH}_3$ ), 17.7 ( $\text{CH}_3$ ), 17.2 ( $\text{CH}_3$ ), 16.8 ( $\text{CH}_3$ ), 15.0 (CH), 14.8 ( $\text{CH}_2$ ), 13.1 (CH).

MS (ESI):  $m/z$  584.6 ( $\text{MH}^+$ , 100%), 606.6 ( $\text{MNa}^+$ ).

HRMS calcd for  $\text{C}_{36}\text{H}_{62}\text{NO}_3\text{Si}$ : 584.4499. Found: 584.4500 ( $\text{MH}^+$ ).



(1*R*,5*S*,8*S*,9*S*,10*aR*)-3,3-Diisopropyl-8-(2-methylallyl)-9-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)octahydro-1*H*-1,5-methanopyrrolo[1,2-*f*][1,6,2]oxazasilocine (**144**). A solution of 1M LAH in  $\text{Et}_2\text{O}$  (135  $\mu\text{l}$ , 0.135 mmol, 6.0 equiv) was added dropwise to a solution of lactam **136** (13.0 mg, 0.022 mmol, 1.0 equiv) in 300  $\mu\text{l}$  of dry  $\text{Et}_2\text{O}$  and stirred for 5h30min at RT. The reaction was followed by TLC then quenched with water, and the aqueous layer was extracted 3 times with  $\text{Et}_2\text{O}$ . The organic layers were dried over  $\text{MgSO}_4$  and evaporated under reduced pressure. Purification over silica gel gave 8.2 mg of pure unhydrolyzed amine **144** as colorless oil (65%) which was eluted with 100% cyclohexane.

IR (film):  $\nu$  2959, 2864, 1608, 1461, 1268  $\text{cm}^{-1}$ .

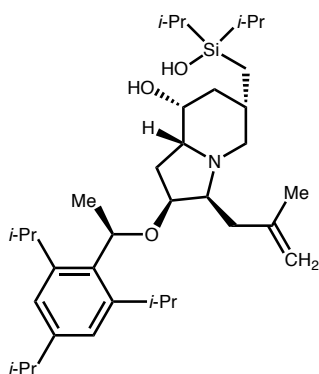
$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  7.02 (d,  $J = 1.7$  Hz, 1H), 6.92 (d,  $J = 1.7$  Hz, 1H), 5.07 (q,  $J = 6.8$  Hz, 1H), 4.77 (br s, 1H), 4.75 (br s, 1H), 3.96 (sept,  $J = 6.8$  Hz, 1H), 3.89 (app s, 1H), 3.87 (ddd,  $J = 6.4, 6.4, 9.2$  Hz, 1H), 3.35 (ddd,  $J = 4.0, 6.4, 6.4$  Hz, 1H), 3.19 (sept,  $J = 6.8$  Hz, 1H), 2.84 (sept,  $J = 6.9$

Hz, 1H), 2.81 (dd,  $J = 2.9, 11.0$  Hz, 1H), 2.70 (app t,  $J = 8.6$  Hz, 1H), 2.65 (ddd,  $J = 1.9, 1.9, 10.9$  Hz, 1H), 2.33 (dd,  $J = 4.0, 14.7$  Hz, 1H), 2.09–2.19 (m, 3H), 1.77 (s, 3H), 1.76 (dddd,  $J = 2.2, 2.2, 3.6, 13.6$  Hz, 1H), 1.64 (ddd,  $J = 6.4, 8.6, 12.3$  Hz, 1H), 1.50 (d,  $J = 6.8$  Hz, 3H), 1.43 (dddd,  $J = 2.2, 2.2, 4.4, 13.6$  Hz, 1H), 1.13–1.32 (m, 18H), 0.74–0.99 (m, 3H), 0.97 (d,  $J = 7.2$  Hz, 3H), 0.90 (d,  $J = 7.1$  Hz, 3H), 0.75 (d,  $J = 7.4$  Hz, 3H), 0.54 (d,  $J = 7.3$  Hz, 3H), 0.42 (ddd,  $J = 1.9, 1.9, 14.8$  Hz, 1H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz):  $\delta$  148.7 (C), 147.1 (C), 146.0 (C), 145.8 (C), 133.1 (C), 122.9 (CH), 120.6 (CH), 110.9 ( $\text{CH}_2$ ), 74.3 (CH), 70.6 (CH), 68.7 (CH), 63.5 (CH), 62.3 (CH), 55.4 ( $\text{CH}_2$ ), 35.3 ( $\text{CH}_2$ ), 34.1 (CH), 31.6 ( $\text{CH}_2$ ), 29.6 ( $\text{CH}_2$ ), 29.0 (CH), 27.6 (CH), 27.6 (CH), 25.2 ( $2\text{CH}_3$ ), 25.1 ( $\text{CH}_3$ ), 24.1 ( $\text{CH}_3$ ), 24.0 ( $\text{CH}_3$ ), 24.0 ( $\text{CH}_3$ ), 23.4 ( $\text{CH}_3$ ), 23.0 ( $\text{CH}_3$ ), 18.1 ( $\text{CH}_3$ ), 17.9 ( $\text{CH}_3$ ), 16.9 ( $\text{CH}_3$ ), 16.2 ( $\text{CH}_3$ ), 15.2 (CH), 13.1 (CH), 12.7 ( $\text{CH}_2$ ).

MS (ESI):  $m/z$  568.46 ( $\text{MH}^+$ , 100%).

HRMS calcd for  $\text{C}_{36}\text{H}_{62}\text{NO}_2\text{Si}$ : 568.4550. Found: 568.4542 ( $\text{MH}^+$ ).



(2*S*,3*S*,6*S*,8*R*,8*aR*)-6-((Hydroxydiisopropylsilyl)methyl)-3-(2-methylallyl)-2-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)octahydroindolizin-8-ol (**141**). Formic acid (200  $\mu\text{l}$ ) was added to 150  $\mu\text{l}$  ethereal solution of 7.5 mg amine **144** (0.013 mmol). The reaction mixture was stirred for 2h30min at RT, then diluted with  $\text{Et}_2\text{O}$  and quenched with saturated  $\text{K}_2\text{CO}_3$  solution until the pH become alkaline. Then it was washed with brine and the aqueous phase was extracted 3 times with  $\text{Et}_2\text{O}$ . The combined organic layers were dried over  $\text{MgSO}_4$  and evaporated under reduced pressure. Elution with 20%  $\text{EtOAc}$ /cyclohexane over silica gel gave 5.0 mg of the hydrolyzed amine **141** as white solid (65%).

IR (film):  $\nu$  3366, 2958, 2865, 1608, 1462, 1382, 1261, 881  $\text{cm}^{-1}$ .

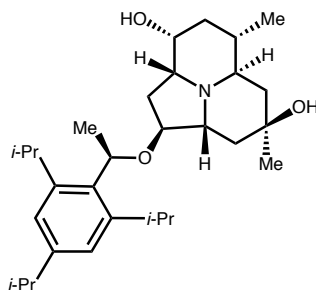


$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  7.04 (d,  $J$  = 1.8 Hz, 1H), 6.95 (d,  $J$  = 1.8 Hz, 1H), 5.04 (q,  $J$  = 6.8 Hz, 1H), 4.74 (br s, 2H), 4.00 (ddd,  $J$  = 6.3, 6.3, 8.7 Hz, 1H), 3.91 (sept,  $J$  = 6.8 Hz, 1H), 3.77 (app s, 1H), 3.38 (ddd,  $J$  = 3.3, 6.3, 9.3 Hz, 1H), 3.19 (sept,  $J$  = 6.8 Hz, 1H), 2.96 (ddd,  $J$  = 2.3, 6.8, 9.2 Hz, 1H), 2.86 (sept,  $J$  = 6.9 Hz, 1H), 2.78 (dd,  $J$  = 3.5, 11.3 Hz, 1H), 2.48 (app d,  $J$  = 11.3 Hz, 1H), 2.31 (app d,  $J$  = 15.4 Hz, 1H), 2.12–2.22 (m, 2H), 1.90–1.97 (m, 2H), 1.75 (ddd,  $J$  = 6.3, 9.2, 12.9 Hz, 1H), 1.72 (s, 3H), 1.54 (ddd,  $J$  = 2.5, 6.2, 14.5 Hz, 1H), 1.50 (d,  $J$  = 6.8 Hz, 3H), 1.16–1.32 (m, 18H), 0.80–1.03 (m, 15H), 0.69 (dd,  $J$  = 6.7, 15.0 Hz, 1H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz):  $\delta$  148.8 (C), 147.2 (C), 145.7 (C), 145.3 (C), 133.5 (C), 123.1 (CH), 120.4 (CH), 111.3 ( $\text{CH}_2$ ), 75.8 (CH), 71.2 (CH), 68.2 (CH), 63.8 (CH), 61.6 (CH), 56.7 ( $\text{CH}_2$ ), 36.3 ( $\text{CH}_2$ ), 33.9 (CH), 31.2 ( $\text{CH}_2$ ), 31.1 ( $\text{CH}_2$ ), 29.1 (CH), 28.4 (CH), 28.2 (CH), 25.3 ( $\text{CH}_3$ ), 24.9 ( $\text{CH}_3$ ), 24.8 ( $\text{CH}_3$ ), 24.5 ( $\text{CH}_3$ ), 23.9 ( $\text{CH}_3$ ), 23.9 ( $\text{CH}_3$ ), 23.2 ( $\text{CH}_3$ ), 22.9 ( $\text{CH}_3$ ), 17.9 ( $\text{CH}_2$ ), 17.6 ( $\text{CH}_3$ ), 17.5 ( $2\text{CH}_3$ ), 17.3 ( $\text{CH}_3$ ), 13.4 (CH), 13.3 (CH).

MS (ESI):  $m/z$  586.47 ( $\text{MH}^+$ , 100%), 608.46 ( $\text{MNa}^+$ ).

HRMS calcd for  $\text{C}_{36}\text{H}_{64}\text{NO}_3\text{Si}$ : 586.4655. Found: 586.4652 ( $\text{MH}^+$ ).



(1*S*,2*aR*,3*R*,5*S*,5*aR*,7*R*,8*aR*)-5,7-Dimethyl-1-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)decahydro-1*H*-pyrrolo[2,1,5-*de*]quinolizine-3,7-diol (**75**). To a solution of the crude tricyclic silylated compounds **139** and **140** (116.0 mg) in 4.7 ml DMSO were added KO<sup>t</sup>Bu (340 mg, 3.03 mmol, ~15 equiv), CsF (250 mg, 1.65 mmol, ~8 equiv) and 140  $\mu\text{l}$  of  $\text{H}_2\text{O}$  (3%) at RT. After stirring 9h at 120°C, the reaction was diluted with  $\text{Et}_2\text{O}$ , quenched with water and the aqueous layer was extracted 3 times with  $\text{Et}_2\text{O}$ . After drying the combined organic layers over  $\text{MgSO}_4$ , evaporation was done under reduced pressure. Purification over 15 ml silica gel yielded 41.0 mg of the corresponding protodesilylated alcohol **75** (52% yield over 2 steps) eluted with 3%  $\text{MeOH}_{\text{NH}_3}/\text{DCM}$ .

$[\alpha]^{20}_{\text{D}} +14.6$  (c 0.48,  $\text{CHCl}_3$ ).

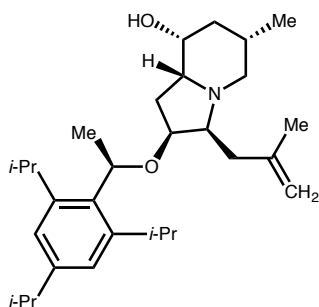
IR (film):  $\nu$  3408, 2960, 2928, 2869, 1607, 1459, 1372, 1263, 1112, 1082  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR ( $\text{C}_6\text{D}_6$ , 500 MHz):  $\delta$  7.26 (d,  $J = 1.8$  Hz, 1H), 7.10 (d,  $J = 1.8$  Hz, 1H), 5.06 (q,  $J = 6.8$  Hz, 1H), 4.19 (sept,  $J = 6.9$  Hz, 1H), 3.91 (ddd,  $J = 4.9, 6.4, 9.2$  Hz, 1H), 3.56 (app s, 1H), 3.19 (sept,  $J = 6.9$  Hz, 1H), 2.95 (t,  $J = 7.9$  Hz, 1H), 2.89 (ddd,  $J = 3.9, 6.4, 12.2$  Hz, 1H), 2.80 (sept,  $J = 6.9$  Hz, 1H), 2.48 (ddd,  $J = 1.7, 3.0, 13.1$  Hz, 1H), 2.27 (ddd,  $J = 7.9, 9.2, 12.8$  Hz, 1H), 2.00 (br s, 1H), 1.51–1.65 (m, 4H), 1.61 (d,  $J = 6.8$  Hz, 3H), 1.31–1.48 (m, 12H), 1.22–1.24 (m, 6H), 1.20 (d,  $J = 6.9$  Hz, 3H), 1.14 (d,  $J = 7.4$  Hz, 3H), 1.05 (s, 3H), 0.97 (app d,  $J = 12.8$  Hz, 1H).

$^{13}\text{C}$  NMR ( $\text{C}_6\text{D}_6$ , 125 MHz):  $\delta$  149.4, 148.0, 146.5, 134.2, 123.7, 120.8, 75.6, 71.4, 70.6, 67.2, 61.4, 58.2, 54.0, 38.5, 35.1, 34.6, 31.8, 31.2, 29.5, 28.6, 26.0, 25.4, 25.3, 24.8, 24.8, 24.3, 24.3, 24.1, 23.5.

MS (ESI):  $m/z$  472.4 ( $\text{MH}^+$ , 100%).

HRMS calcd for  $\text{C}_{30}\text{H}_{50}\text{NO}_3$ : 472.3791. Found: 472.3789 ( $\text{MH}^+$ ).



(2*S*,3*S*,6*S*,8*R*,8*aR*)-6-Methyl-3-(2-methylallyl)-2-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)octahydroindolizin-8-ol (**145**). KO<sup>t</sup>Bu (1.2 g, 10.7 mmol, ~12 equiv) and TBAF (1M in THF, 6.3 ml, 6.3 mmol, ~7 equiv) were added to a solution of 560.0 mg crude silylated compounds (**139**, **140** and **144**) in 21 ml DMSO. The reaction mixture was stirred for 9h at 120°C. The mixture was then diluted with Et<sub>2</sub>O and quenched with water. The aqueous layer was extracted with Et<sub>2</sub>O 3 times. The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated. The crude product was purified over 26 ml silica gel to afford 130.0 mg of the alcohol **75** (38% over 2 steps) and 7.1 mg of the bicyclic amino alcohol **145** (2% over 2 steps). (*vide supra* for data characterization of **75**)

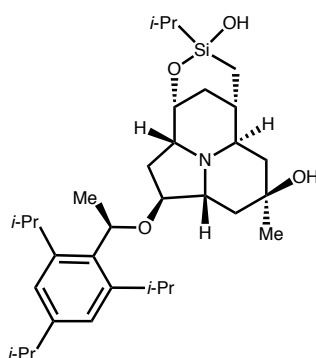
#### Data for compound **145**

IR (film):  $\nu$  3433, 2960, 2928, 2870, 1645, 1608, 1459, 1381, 1261, 1123, 1080, 1045  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  7.04 (d,  $J = 1.7$  Hz, 1H), 6.94 (d,  $J = 1.7$  Hz, 1H), 5.04 (q,  $J = 6.8$  Hz, 1H), 4.74 (s, 2H), 4.00 (ddd,  $J = 6.1, 6.1, 8.6$  Hz, 1H), 3.91 (sept,  $J = 6.8$  Hz, 1H), 3.79 (ddd,  $J = 3.4, 3.4, 6.1$  Hz, 1H), 3.31 (ddd,  $J = 3.3, 6.4, 9.3$  Hz, 1H), 3.20 (sept,  $J = 6.8$  Hz, 1H), 3.07 (ddd,  $J = 2.9, 7.6, 8.9$  Hz, 1H), 2.86 (sept,  $J = 6.9$  Hz, 1H), 2.70 (dd,  $J = 4.0, 11.1$  Hz, 1H), 2.34 (dd,  $J = 4.7, 11.1$  Hz, 1H), 2.28–2.34 (m, 1H), 2.12–2.22 (m, 2H), 1.70–1.80 (m, 2H), 1.73 (s, 3H), 1.60 (ddd,  $J = 3.7, 5.4, 13.7$  Hz, 1H), 1.47–1.55 (m, 1H), 1.50 (d,  $J = 6.8$  Hz, 3H), 1.15–1.32 (m, 18H), 1.01 (d,  $J = 7.2$  Hz, 3H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz):  $\delta$  148.8, 147.1, 145.8, 145.5, 133.4, 123.1, 120.4, 111.0, 75.9, 71.1, 68.2, 64.5, 61.2, 55.1, 36.8, 33.9, 31.9, 30.8, 29.1, 28.1, 27.8, 25.3, 24.9, 24.8, 24.4, 23.9, 23.9, 23.2, 22.9, 21.3.

HRMS calcd for  $\text{C}_{30}\text{H}_{50}\text{NO}_2$ : 456.38361. Found: 456.38254 ( $\text{MH}^+$ ).



(1*S*,5*R*,5*aR*,7*S*,7*aR*,9*R*,10*aR*)-3-Isopropyl-9-methyl-7-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)dodecahydro-1,5-methano[1,6,2]oxazasilocino[7,6,5-*cd*]indolizine-3,9-diol (**149**). To a solution of silylated formate **139** (95.0 mg, 0.151 mmol, 1 equiv) in 2.3 ml DMSO were added 450 mg of  $\text{KO}^t\text{Bu}$  (4.01 mmol, 26.5 equiv) and 1.2 ml of 1M TBAF solution in THF (1.2 mmol, 7.9 equiv). The reaction mixture was stirred 4h at  $120^\circ\text{C}$  then it was diluted with  $\text{Et}_2\text{O}$  and quenched with water. The aqueous layer was extracted 3 times with  $\text{Et}_2\text{O}$ , and the combined organic layers were dried over  $\text{MgSO}_4$  and evaporated under reduced pressure. Purification over 9 ml silica gel yielded 37.0 mg of the intermediate **149** (44% yield) using 30%  $\rightarrow$  70% of  $\text{EtOAc}$ /cyclohexane as eluant system.

IR (film):  $\nu$  3365, 2959, 2866, 1608, 1462, 1362, 1114  $\text{cm}^{-1}$ .

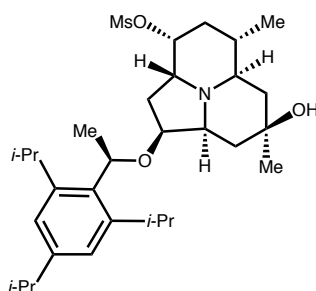
$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  7.04 (d,  $J = 1.9$  Hz, 1H), 6.93 (d,  $J = 1.9$  Hz, 1H), 4.99 (q,  $J = 6.8$  Hz, 1H), 4.04 (app s, 1H), 3.85–3.94 (m, 2H), 3.16 (app dd,  $J = 8.5, 8.5$  Hz, 1H), 3.07–3.15 (m, 2H),

2.86 (sept,  $J = 6.9$  Hz, 1H), 2.73 (app dd,  $J = 2.9, 13.0$  Hz, 1H), 2.13 (ddd,  $J = 8.5, 8.5, 12.7$  Hz, 1H), 1.97 (br s, 1H), 1.83 (dd,  $J = 13.0, 13.0$  Hz, 1H), 1.78–1.84 (m, 1H), 1.61–1.71 (m, 3H), 1.48 (d,  $J = 6.8$  Hz, 3H), 1.43 (ddd,  $J = 2.1, 3.8, 13.7$  Hz, 1H), 1.15–1.28 (m, 22H), 0.74–0.94 (m, 9H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz):  $\delta$  148.8 (C), 147.2 (C), 145.9 (C), 133.2 (C), 123.1 (CH), 120.2 (CH), 74.2 (CH), 71.5 (C), 70.7 (CH), 69.6 (CH), 60.9 (CH), 58.9 (CH), 54.1 (CH), 36.5 ( $\text{CH}_2$ ), 34.0 (CH), 33.6 ( $\text{CH}_2$ ), 32.1 (CH), 32.0 ( $\text{CH}_2$ ), 31.6 ( $\text{CH}_2$ ), 29.2 (CH), 28.0 (CH), 25.9 ( $\text{CH}_3$ ), 25.1 ( $\text{CH}_3$ ), 24.8 ( $\text{CH}_3$ ), 24.7 ( $\text{CH}_3$ ), 24.3 ( $\text{CH}_3$ ), 24.0 ( $\text{CH}_3$ ), 23.8 ( $\text{CH}_3$ ), 23.3 ( $\text{CH}_3$ ), 19.6 ( $\text{CH}_2$ ), 17.0 ( $\text{CH}_3$ ), 15.8 ( $\text{CH}_3$ ), 14.6 (CH).

MS (ESI):  $m/z$  558.51 ( $\text{MH}^+$ , 100%).

HRMS calcd for  $\text{C}_{33}\text{H}_{56}\text{NO}_4\text{Si}$ : 558.3979. Found: 558.3987 ( $\text{MH}^+$ ).



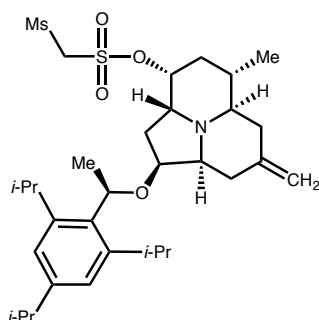
(1*S*,2*aR*,3*R*,5*S*,5*aR*,7*R*,8*aS*)-7-Hydroxy-5,7-dimethyl-1-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)decahydro-1*H*-pyrrolo[2,1,5-*de*]quinolizin-3-yl methanesulfonate (**155**). To a solution of alcohol **75** (5.0 mg, 0.011 mmol, 1.0 equiv) in 200  $\mu\text{l}$  DCM were added 15  $\mu\text{l}$  of pyridine (0.185 mmol, 17 equiv), 12  $\mu\text{l}$  of  $\text{MsCl}$  (0.155 mmol, 14.6 equiv) and ~3 mg of DMAP (0.024 mmol, 2.3 equiv) at RT. The reaction mixture was stirred for 6h at RT before being quenched with saturated  $\text{NaHCO}_3$  solution and diluted with DCM. The aqueous layer was separated, and the organic layer was washed with saturated  $\text{NaHCO}_3$  (2 times) and brine. The organic layer was dried over  $\text{MgSO}_4$  and concentrated *in vacuo*. Purification over silica gel using  $\text{MeOH}_{\text{NH}_3}/\text{DCM}$  (0.5%  $\rightarrow$  2%) as eluent afforded 1.0 mg of the mesylated product **155** (17.2%) and 1.0 mg of the starting alcohol **75** (20%). (*vide supra* for data characterization **75**)

Data for compound **155**

IR (film):  $\nu$  3407, 2959, 2925, 2854, 1608, 1461, 1377, 1261, 1173, 1122, 1099  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  7.01 (s, 1H), 6.92 (s, 1H), 5.08 (q,  $J = 6.8$  Hz, 1H), 4.89 (br. s, 1H), 4.01 (ddd,  $J = 3.9, 6.2, 8.5$  Hz, 1H), 3.89 (sept,  $J = 6.7$  Hz, 1H), 3.41 (ddd,  $J = 1.9, 8.1, 8.1$  Hz, 1H), 3.08–3.20 (m, 2H), 2.98 (s, 3H), 2.84 (sept,  $J = 6.8$  Hz, 1H), 2.71 (ddd,  $J = 3.3, 3.3, 12.6$  Hz, 1H), 2.02–2.14 (m, 1H), 1.96 (ddd,  $J = 4.4, 5.9, 15.4$  Hz, 1H), 1.87 (ddd,  $J = 4.3, 4.3, 14.8$  Hz, 1H), 1.81–1.90 (m, 1H), 1.55–1.75 (m, 3H), 1.50 (d,  $J = 6.8$  Hz, 3H), 1.45 (ddd,  $J = 2.0, 3.9, 16.2$  Hz, 1H), 1.12–1.35 (m, 22H), 1.05 (d,  $J = 7.1$  Hz, 3H).

HRMS calcd for  $\text{C}_{31}\text{H}_{52}\text{NO}_5\text{S}$ : 550.35607 Found: 550.35461 ( $\text{MH}^+$ ).



(1*S*,2*aR*,3*R*,5*S*,5*aR*,8*aS*)-5-Methyl-7-methylene-1-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy) decahydro-1*H*-pyrrolo[2,1,5-*de*]quinolizin-3-yl (methylsulfonyl)methanesulfonate (**156**). To a stirred solution of **75** (5.5 mg, 0.012 mmol, 1 equiv) in 180  $\mu\text{l}$  DCM were added  $\text{Et}_3\text{N}$  (30  $\mu\text{l}$ , 0.21 mmol, 17.5 equiv) and  $\text{MsCl}$  (10  $\mu\text{l}$ , 0.14 mmol, 11.7 equiv) at ambient temperature. The mixture was stirred for 4h at room temperature and followed by TLC till the consumption of all the starting materials. After which it was diluted with DCM and extracted with saturated  $\text{NaHCO}_3$  (2 times) and brine. The organic extract was then dried over  $\text{MgSO}_4$  and the solvent was evaporated to afford 1:0.2 mixture of **156** and **155** respectively. Chromatography of the residue over silica gel using 0.25%  $\text{MeOH}_{\text{NH}_3}/\text{DCM}$  as eluent furnished **156** (3.1 mg, 48%). (*vide supra* for data characterization **155**)

#### Data for compound **156**

IR (film):  $\nu$  2957, 2925, 2854, 1641, 1608, 1459, 1363, 1345, 1290, 1260, 1176, 1112  $\text{cm}^{-1}$ .

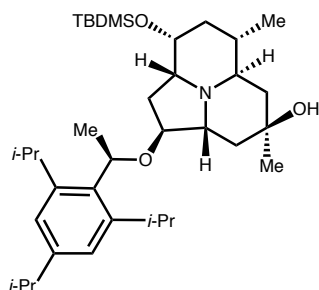
$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  7.03 (d,  $J = 1.6$  Hz, 1H), 6.95 (d,  $J = 1.6$  Hz, 1H), 5.06 (q,  $J = 6.7$  Hz, 1H), 4.81 (ddd,  $J = 2.5, 2.5, 4.1$  Hz, 1H), 4.79 (s, 1H), 4.71 (s, 1H), 4.02 (dd,  $J = 8.8, 13.2$  Hz, 1H), 4.01 (q,  $J = 7.5$  Hz, 1H), 3.89 (sept,  $J = 6.9$  Hz, 1H), 3.79 (dd,  $J = 8.4, 13.2$  Hz, 1H), 3.45–3.52 (m, 1H), 3.48 (t,  $J = 8.1$  Hz, 1H), 3.40 (ddd,  $J = 3.3, 7.3, 10.1$  Hz, 1H), 3.18 (sept,  $J = 6.8$  Hz, 1H), 2.84

(sept,  $J = 6.9$  Hz, 1H), 2.74 (dd,  $J = 2.6, 15.8$  Hz, 1H), 2.58 (s, 3H), 2.39 (dd,  $J = 4.0, 15.8$  Hz, 1H), 2.34–2.39 (m, 1H), 2.15 (ddd,  $J = 3.0, 7.2, 12.8$  Hz, 1H), 2.05 (ddd,  $J = 8.3, 8.3, 12.8$  Hz, 1H), 1.88 (dd,  $J = 9.5, 14.5$  Hz, 1H), 1.64–1.70 (m, 2H), 1.51 (d,  $J = 6.7$  Hz, 3H), 1.15–1.34 (m, 22H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz):  $\delta$  148.8, 147.6, 145.8, 143.3, 132.7, 123.1, 120.7, 112.7, 74.7, 74.1, 71.3, 65.9, 63.9, 53.8, 49.8, 38.5, 38.2, 34.0, 33.6, 32.6, 29.7, 29.1, 28.0, 25.2, 25.1, 24.1, 24.0, 24.0, 23.3, 22.7, 22.7, 22.5.

MS (ESI):  $m/z$  610.37 ( $\text{MH}^+$ , 100%).

HRMS calcd for  $\text{C}_{32}\text{H}_{52}\text{NO}_6\text{S}_2$ : 610.32306. Found: 610.32244 ( $\text{MH}^+$ ).

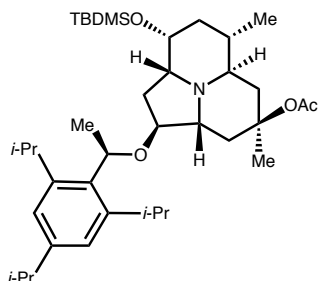


(2*S*,2*aR*,4*R*,5*aR*,6*S*,8*R*,8*aR*)-8-((*tert*-Butyldimethylsilyl)oxy)-4,6-dimethyl-2-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)decahydro-1*H*-pyrrolo[2,1,5-*de*]quinolin-4-ol (**171**). To a solution of alcohol **75** (8.0 mg, 0.017 mmol, 1.0 equiv) in dry DCM (300  $\mu\text{l}$ ) were added  $\text{Et}_3\text{N}$  (30  $\mu\text{l}$ , 0.215 mmol, 12.6 equiv) and DMAP (4 mg, 0.032 mmol, 1.8 equiv) at room temperature. Tertbutyldimethylsilyl chloride (40 mg, 0.266 mmol, 15.6 equiv) was also added in 2 portions with 3h30min interval. The reaction mixture was stirred for 7h at 60°C, quenched with water and diluted with pentane. The aqueous layer was washed with pentane (3 times) and the combined organic layers were dried over  $\text{MgSO}_4$ . Evaporation of the solvent provided the crude product, which was purified by 1 ml silica gel chromatography and eluted with 20% EtOAc in cyclohexane to provide protected-alcohol **171** (6.6 mg, 67 %).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  7.02 (d,  $J = 2.0$  Hz, 1H), 6.91 (d,  $J = 2.0$  Hz, 1H), 5.08 (q,  $J = 6.9$  Hz, 1H), 3.83–4.0 (m, 3H), 3.28 (ddd,  $J = 2.2, 8.0, 8.0$  Hz, 1H), 3.20 (sept.,  $J = 6.9$  Hz, 1H), 2.95 (ddd,  $J = 3.2, 5.5, 12.1$  Hz, 1H), 2.84 (sept.,  $J = 6.9$  Hz, 1H), 2.65 (ddd,  $J = 3.1, 6.3, 11.8$  Hz, 1H), 2.01 (ddd,  $J = 7.2, 8.5, 12.9$  Hz, 1H), 1.77–1.89 (m, 2H), 1.57–1.72 (m, 3H), 1.52 (d,  $J = 6.9$  Hz, 3H),

1.38–1.52 (m, 2H), 1.18–1.28 (m, 22H), 1.04 (d,  $J = 7.0$  Hz, 3H), 0.86 (s, 9H), 0.05 (s, 3H), 0.01 (s, 3H).

**MS (ESI):**  $m/z$  586.52 ( $MH^+$ , 100%).

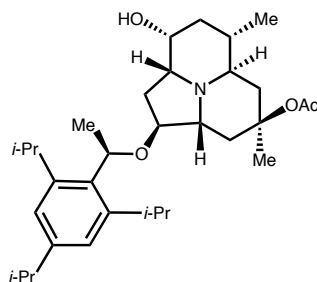


(2*S*,2*aR*,4*R*,5*aR*,6*S*,8*R*,8*aR*)-8-((*tert*-Butyldimethylsilyl)oxy)-4,6-dimethyl-2-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)decahydro-1*H*-pyrrolo[2,1,5-*de*]quinolizin-4-yl acetate (**172**). To a solution of the tertiary alcohol **171** (9.5 mg, 0.016 mmol) in 500  $\mu$ l of DCM at RT were added  $Et_3N$  (190  $\mu$ l, 1.36 mmol),  $Ac_2O$  (125  $\mu$ l, 1.32 mmol) and 8 mg of DMAP (0.06 mmol) sequentially over the whole course of the reaction. The reaction mixture was stirred for 15h at 60°C, after which it was quenched with water and diluted in pentane. The resultant aqueous phase was washed with pentane (3 times) and the combined organic layers dried over  $MgSO_4$ . The solvent was evaporated *in vacuo* to obtain the crude product. Upon purification over silica gel (5–10% EtOAc in cyclohexane), furnished 6.0 mg of the acylated compound **172** (60% yield).

**IR (film):**  $\nu$  2956, 2926, 2852, 1733, 1462, 1249, 1108, 1078  $cm^{-1}$ .

**$^1H$  NMR ( $CDCl_3$ , 400 MHz):**  $\delta$  7.02 (d,  $J = 1.8$  Hz, 1H), 6.91 (d,  $J = 1.8$  Hz, 1H), 5.06 (q,  $J = 6.9$  Hz, 1H), 3.94 (sept,  $J = 6.8$  Hz, 1H), 3.89 (ddd,  $J = 2.3, 5.5, 7.6$  Hz, 1H), 3.85 (quint,  $J = 2.3$ , 1H), 3.31 (ddd,  $J = 2.2, 8.1, 8.1$  Hz, 1H), 3.19 (sept,  $J = 6.9$  Hz, 1H), 3.0 (ddd,  $J = 3.5, 5.6, 11.9$  Hz, 1H), 2.84 (sept,  $J = 6.9$  Hz, 1H), 2.70 (ddd,  $J = 2.9, 5.7, 12.1$  Hz, 1H), 1.97 (s, 3H), 1.73–2.06 (m, 7H), 1.52 (d,  $J = 6.9$  Hz, 3H), 1.39–1.46 (m, 1H), 1.17–1.32 (m, 22H), 1.06 (d,  $J = 7.0$  Hz, 3H), 0.86 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H).

**MS (ESI):**  $m/z$  628.58 ( $MH^+$ , 100%).

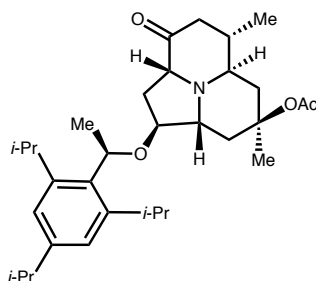


(2*S*,2*aR*,4*R*,5*aR*,6*S*,8*R*,8*aR*)-8-Hydroxy-4,6-dimethyl-2-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)decahydro-1*H*-pyrrolo[2,1,5-*de*]quinolizin-4-yl acetate (**173**). To a THF solution (500  $\mu$ l) of the silylated alcohol **172** (5.8 mg,  $9.2 \times 10^{-3}$  mmol, 1.0 equiv) was added 40 mg of TBAF. $\text{H}_2\text{O}$  (0.14 mmol, 15 equiv) at RT. The reaction mixture was stirred for 24h before diluting with Et<sub>2</sub>O and quenching with water. The aqueous layer was extracted with Et<sub>2</sub>O (3 times) and the combined organic layers were dried over MgSO<sub>4</sub>, then concentrated under vacuum to afford 23.7 mg of the crude product. Purification over silica gel allows the isolation of 4.5 mg (eluted with 1–2% MeOH<sub>NH3</sub>/DCM) of the deprotected compound **173** (95% yield).

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.03 (d,  $J$  = 1.9 Hz, 1H), 6.93 (d,  $J$  = 1.9 Hz, 1H), 5.00 (q,  $J$  = 6.8 Hz, 1H), 3.94 (ddd,  $J$  = 4.7, 6.5, 9.2 Hz, 1H), 3.90 (sept,  $J$  = 6.9 Hz, 1H), 3.70 (q,  $J$  = 3.0 Hz, 1H), 3.33 (ddd,  $J$  = 1.7, 8.1, 8.1 Hz, 1H), 3.12–3.21 (m, 2H), 2.84 (sept,  $J$  = 6.9 Hz, 1H), 2.73 (ddd,  $J$  = 1.5, 3.1, 12.9 Hz, 1H), 2.19 (ddd,  $J$  = 7.9, 9.2, 12.9 Hz, 1H), 2.13 (t,  $J$  = 12.9 Hz, 1H), 2.00 (s, 3H), 1.91 (ddd,  $J$  = 0.7, 12.5, 13.2 Hz, 1H), 1.66–1.79 (m, 5H), 1.50 (d,  $J$  = 6.8 Hz, 3H), 1.14–1.30 (m, 25H).

MS (ESI):  $m/z$  514.38 (MH<sup>+</sup>, 100%).

HRMS calcd for C<sub>32</sub>H<sub>52</sub>NO<sub>4</sub>: 514.3891. Found: 514.3877 (MH<sup>+</sup>).



(2*S*,2*aR*,4*R*,5*aR*,6*S*,8*aR*)-4,6-Dimethyl-8-oxo-2-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)decahydro-1*H*-pyrrolo[2,1,5-*de*]quinolizin-4-yl acetate (**174**). A solution of oxalyl chloride (5  $\mu$ l, 0.06 mmol, 6.0 equiv) in dry DCM (150  $\mu$ l) was cooled at  $-78^\circ\text{C}$  and treated dropwise with DMSO (20  $\mu$ l, 0.28



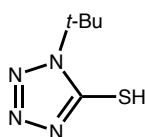
mmol, 29.0 equiv). After stirring for 40 min at  $-80^{\circ}\text{C} < T < -65^{\circ}\text{C}$ , the mixture was re-cooled to  $-78^{\circ}\text{C}$  and acylated alcohol **173** (5.0 mg,  $9.7 \times 10^{-3}$  mmol, 1.0 equiv) was added slowly as a solution in dry DCM (200  $\mu\text{l}$ ). Once the reaction mixture was stirred for 1 h at  $-80^{\circ}\text{C} < T < -65^{\circ}\text{C}$ ,  $\text{Et}_3\text{N}$  (40  $\mu\text{l}$ , 0.28 mmol, 29.0 equiv) was injected slowly and then the mixture was allowed to stir for 1 h so the temperature reached  $0^{\circ}\text{C}$ . The reaction mixture was diluted in DCM and quenched with  $\text{H}_2\text{O}$ . The aqueous layer was washed with DCM (3 times) then the combined organic layers were dried over  $\text{MgSO}_4$  and concentrated under reduced pressure to give 18.0 mg of the crude ketone **174** contaminated with DMSO and  $\text{Et}_3\text{N}$  (with ratio 1:17:6 respectively). Due to the instability of ketone **174** over silica gel, no further purification was done and an estimated yield from the NMR was provided (3.7 mg, 74%).

IR (film):  $\nu$  2958, 2925, 2854, 1732, 1658, 1246  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  7.00 (d,  $J = 1.8$  Hz, 1H), 6.89 (d,  $J = 1.8$  Hz, 1H), 5.00 (q,  $J = 6.8$  Hz, 1H), 3.90 (ddd,  $J = 4.2, 6.0, 7.9$  Hz, 1H), 3.89 (sept,  $J = 6.8$  Hz, 1H), 3.74 (dd,  $J = 7.2, 9.2$  Hz, 1H), 3.13 (sept,  $J = 6.8$  Hz, 1H), 3.05 (ddd,  $J = 3.8, 6.0, 11.7$  Hz, 1H), 2.81 (sept,  $J = 6.9$  Hz, 1H), 2.46–2.52 (m, 1H), 2.19–2.36 (m, 2H), 2.14 (ddd,  $J = 1.8, 3.1, 12.5$  Hz, 1H), 1.97 (s, 3H), 1.75–1.97 (m, 3H), 1.52–1.66 (m, 3H), 1.48 (d,  $J = 6.8$  Hz, 3H), 1.13–1.28 (m, 21H), 0.99 (d,  $J = 6.7$  Hz, 3H).

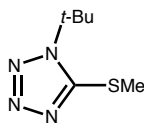
MS (ESI):  $m/z$  512.45 ( $\text{MH}^+$ , 100%).

HRMS calcd for  $\text{C}_{32}\text{H}_{50}\text{NO}_4$ : 512.3734. Found: 512.3720 ( $\text{MH}^+$ ).



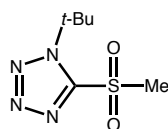
**1-(tert-butyl)-1H-tetrazole-5-thiol (S6)**. To a refluxing solution of sodium azide (2.80 g, 43.1 mmol, 1.0 equiv) in 15.0 ml of water was added a solution of *t*-butylisothiocyanate (5.0 g, 43.4 mmol, 1.0 equiv) dropwise in 10 ml of *i*-PrOH. The mixture is refluxed for 16h, cooled to  $0^{\circ}\text{C}$  and 7 ml of 37% HCl solution was added. The solvents were removed under reduced pressure and the crude oil was triturated at  $0^{\circ}\text{C}$  with 30 ml of water and filtrated. The resulting solid was washed with water, dry over  $\text{P}_2\text{O}_5$  under reduced pressure for 48h to furnish 5.24 g (76%) of **S6** as light yellow solid. Analytical data are in agreement with those reported in the literature.<sup>127</sup>

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  1.86 (s, 9H).



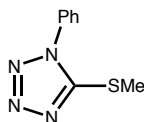
**1-(*tert*-Butyl)-5-(methylthio)-1H-tetrazole (S7).** To a suspension of sodium hydride (1.42 g, 60% in mineral oil, 33.3 mmol, 1.0 equiv) in 20.0 ml of dry THF at 0°C was added drop wise a solution of 5.17 g of the thiol **S6** (32.7 mmol, 1.0 equiv) in 60 ml of dry THF. After stirring for 20 min at 0°C, methyl iodide was added (2.6 ml, 6.67g, 47.0 mmol, 1.4 equiv) and the reaction mixture was stirred over night at room temperature then quenched with saturated  $\text{NH}_4\text{Cl}$  solution (30 ml) and extracted with DCM to give 5.70 g (100%) of **S7** as light yellow solid. Analytical data are in agreement with those reported in the literature.<sup>127</sup>

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  2.81 (s, 3H), 1.72 (s, 9H).



**1-(*tert*-Butyl)-5-(methylsulfonyl)-1H-tetrazole (S8).** To a solution of the thioether **S7** (5.90 g, 34.2 mmol, 1.0 equiv) in 150.0 ml of EtOH at 0°C was added dropwise a solution of ammonium molybdate tetrahydrate (3.41 g, 2.76 mmol, 0.08 equiv) in 34 mL of 30%  $\text{H}_2\text{O}_2$ . After stirring for 5h at room temperature, EtOH was removed under reduced pressure. The residue was dissolved in DCM, washed with water and brine, dried and evaporated to give 6.78 g (97%) of **S8** as yellow solid. Analytical data are in agreement with those reported in the literature.<sup>127</sup>

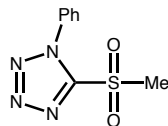
$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  3.66 (s, 3H), 1.85 (s, 9H).



**5-(Methylthio)-1-phenyl-1H-tetrazole (S9).** To a solution of 60% NaH (1.3 g, 32.5 mmol, 1.16 equiv) in 30 ml THF, 1-phenyl-1H-tetrazole-5-thiol (5.0 g, 28.1 mmol, 1.0 equiv) was added as a solution in 78 ml dropwise over 20 min. After stirring 30 min at 0°C, MeI (2.2 ml, 35.3 mmol, 1.26 equiv) was added dropwise at 0 °C and the reaction mixture was stirred for 14h at room temperature. Then the

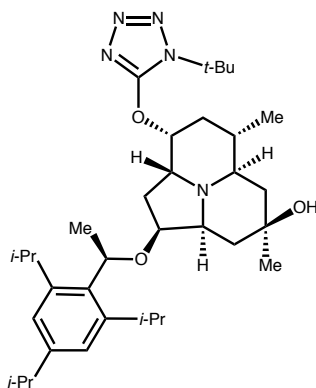
mixture was quenched with saturated  $\text{NH}_4\text{Cl}$  and diluted with EtOAc. Both layers were separated, and the organic layer was washed with brine and then dried over  $\text{MgSO}_4$ . After filtration, the solvent was removed *in vacuo* to afford **S9** as pale yellow solid (6.0 g) that was used in the next step without any further purification. Analytical data are in agreement with those reported in the literature.<sup>133</sup>

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.54–7.60 (m, 5H), 2.84 (s, 3H).



**5-(Methylsulfonyl)-1-phenyl-1H-tetrazole (S10)**. To a solution of sulfide **S9** (6.0 g, 31.2 mmol, 1.0 equiv) in 195 ml EtOH were added ammonium molybdate tetrahydrate (15.7 g, 12.70 mmol, 0.4 equiv) and 30%  $\text{H}_2\text{O}_2$  (16 ml, 156.66 mmol, 5.0 equiv) at 0 °C. Then, the mixture was stirred for 24 h at room temperature. The reaction mixture was concentrated under high vacuum and then diluted with DCM. The organic layer was washed with water followed with brine, dried over  $\text{MgSO}_4$  and then concentrated *in vacuo*. Crystallization from cyclohexane afforded the sulfone product **S10** (5.88 g, 93% yield) as a white solid. Analytical data are in agreement with those reported in the literature.<sup>133</sup>

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.58–7.73 (m, 5H), 3.64 (s, 3H).



**(2S,2aS,4R,5aR,6S,8R,8aR)-8-((1-(tertButyl)-1H-tetrazol-5-yl)oxy)-4,6-dimethyl-2-((R)-1-(2,4,6-triisopropylphenyl)ethoxy)decahydro-1H-pyrrolo[2,1,5-de]quinolizin-4-ol (164)**. Oxalyl chloride (12  $\mu\text{l}$ , 0.142 mmol, 6.6 equiv) in dry THF (150  $\mu\text{l}$ ) was treated dropwise with DMSO (70  $\mu\text{l}$ , 0.98 mmol, 46.0 equiv) at  $-78^\circ\text{C}$ . After stirring for 40 min at  $-80^\circ\text{C} < T < -65^\circ\text{C}$ , the mixture was re-cooled to  $-78^\circ\text{C}$  and alcohol **75** (10.0 mg, 0.021 mmol, 1.0 equiv) was added slowly as a solution in 200  $\mu\text{l}$  of THF. Once the reaction mixture was stirred for 1h at  $-80^\circ\text{C} < T < -65^\circ\text{C}$ ,  $\text{Et}_3\text{N}$  (70  $\mu\text{l}$ , 0.50 mmol, 23.6

equiv) was injected slowly and the reaction was allowed to warm slowly to  $-20^{\circ}\text{C}$  over 1h. Meanwhile, a mixture of 170 mg of  $\text{TBTSO}_2\text{CH}_3$  **S8** (0.83 mmol) and 830  $\mu\text{l}$  of freshly prepared LiHMDS solution (0.95 M in THF, 0.79 mmol) in 450  $\mu\text{l}$  THF was stirred for 30 min at  $-80^{\circ}\text{C} < T < -60^{\circ}\text{C}$ . The reaction bath was cooled back to  $-80^{\circ}\text{C}$  and the reaction was treated with a freshly prepared solution of  $\text{TBTSO}_2\text{CH}_2\text{Li}$  (800  $\mu\text{l}$  in THF, 0.61 M, 0.49 mmol, 23 equiv). The reaction mixture was stirred for 2h30min allowing the temperature to reach  $0^{\circ}\text{C}$ , then stirred 1h at RT. After dilution with  $\text{Et}_2\text{O}$  followed by quenching with  $\text{H}_2\text{O}$ , the aqueous layer was extracted with  $\text{Et}_2\text{O}$  (3 times) and the combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. Purification over silica gel afforded 4.0 mg of the alkene **151** (40%) and 1.5 mg of the byproduct **164** (12%) using 0.5–1%  $\text{MeOH}_{\text{NH}_3}/\text{DCM}$  as eluant system. (*vide infra* for data characterization of **151**)

#### Data for compound **164**

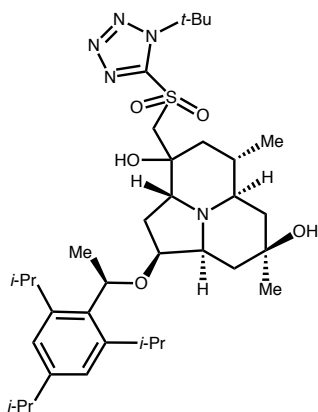
IR (film):  $\nu$  3399, 2959, 2927, 2856, 1607, 1551, 1461, 1438, 1374, 1261, 1155, 1120  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  7.03 (d,  $J = 1.7$  Hz, 1H), 6.90 (d,  $J = 1.8$  Hz, 1H), 5.23 (ddd,  $J = 2.5, 2.5, 5.0$  Hz, 1H), 5.00 (q,  $J = 6.8$  Hz, 1H), 3.88–3.96 (m, 2H), 3.53 (ddd,  $J = 2.5, 8.2, 8.2$  Hz, 1H), 3.14 (ddd,  $J = 3.6, 6.3, 12.4$  Hz, 1H), 3.08 (sept.,  $J = 6.8$  Hz, 1H), 2.84 (sept.,  $J = 6.8$  Hz, 1H), 2.70 (ddd,  $J = 2.9, 2.9, 12.6$  Hz, 1H), 1.95–2.07 (m, 2H), 1.87–1.91 (m, 2H), 1.62–1.75 (m, 3H), 1.59 (s, 9H), 1.48 (d,  $J = 6.8$  Hz, 3H), 1.46–1.52 (m, 1H), 1.35 (ddd,  $J = 2.9, 2.9, 10.9$  Hz, 1H), 1.15–1.30 (m, 21H), 1.07 (d,  $J = 7.1$  Hz, 3H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz):  $\delta$  21.3, 23.2, 23.9, 23.9, 24.4, 24.6, 25.0, 25.1, 25.8, 27.9, 28.5, 29.1, 29.7, 31.2, 31.6, 31.7, 34.0, 34.9, 39.0, 57.5, 59.5, 61.4, 70.7, 71.3, 74.6, 80.4, 120.2, 123.2, 133.0, 145.9, 147.3, 149.0, 161.0.

MS (ESI):  $m/z$  596.29 ( $\text{MH}^+$ , 100%).

HRMS calcd for  $\text{C}_{35}\text{H}_{58}\text{N}_5\text{O}_3$ : 596.4534. Found: 596.4526 ( $\text{MH}^+$ ).



(1*S*,2*aR*,5*S*,5*aR*,7*R*,8*aS*)-3-(((1-(*tert*-Butyl)-1*H*-tetrazol-5-yl)sulfonyl)methyl)-5,7-dimethyl-1-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)decahydro-1*H*-pyrrolo[2,1,5-*de*]quinolizine-3,7-diol (165-H).

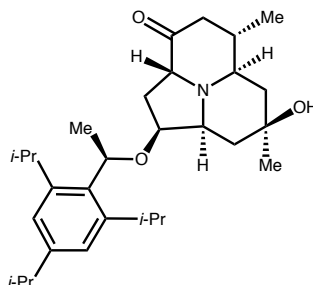
Oxalyl chloride (10  $\mu$ l, 0.12 mmol, 3.7 equiv) in dry DCM (200  $\mu$ l) was treated dropwise with DMSO (25  $\mu$ l, 0.35 mmol, 11.0 equiv) at  $-78^{\circ}\text{C}$ . The mixture was stirred for 40 min at  $-80^{\circ}\text{C} < T < -65^{\circ}\text{C}$  and the alcohol **75** (15.0 mg, 0.032 mmol, 1.0 equiv) was added in 450  $\mu$ l DCM at  $-78^{\circ}\text{C}$ . The reaction mixture was then stirred for 1h at  $-80^{\circ}\text{C} < T < -65^{\circ}\text{C}$  and  $\text{Et}_3\text{N}$  (80  $\mu$ l, 0.57 mmol, 18 equiv) was then injected slowly followed by increasing the temperature slowly to  $-40^{\circ}\text{C}$  over 45 min. When the TLC showed a complete consumption of starting material, the Swern solution was concentrated *in vacuo* at  $-5^{\circ}\text{C}$  and 500  $\mu$ l of dry THF was added. The bath was cooled back to  $-80^{\circ}\text{C}$  and treated with a solution of freshly prepared  $\text{TBTSO}_2\text{CH}_2\text{Li}$  in THF (1 ml, 0.67 M, 0.67 mmol, 21 equiv). The reaction mixture was stirred for 3h where temperature was maintained below  $-40^{\circ}\text{C}$ . At this temperature, the reaction was quenched with brine and diluted with  $\text{Et}_2\text{O}$ . The aqueous layer was washed with  $\text{Et}_2\text{O}$  (3 times) and the combined organic layers dried over  $\text{MgSO}_4$  and concentrated under reduced pressure. Purification over silica gel afforded 10.2 mg of the hydroxy sulfone intermediate (48%, hydrolyzed form of **165**) using 0.5%  $\text{MeOH}_{\text{NH}_3}/\text{DCM}$  as eluant.

IR (film):  $\nu$  3461, 2961, 2928, 2870, 1607, 1573, 1462, 1407, 1345, 1307, 1163, 1116  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  7.02 (d,  $J = 1.8$  Hz, 1H), 6.93 (d,  $J = 1.8$  Hz, 1H), 5.00 (q,  $J = 6.8$  Hz, 1H), 4.15 (d, AB system,  $J = 14.7$  Hz, 1H), 3.94 (ddd,  $J = 4.9, 6.4, 9.2$  Hz, 1H), 3.88 (sept,  $J = 6.8$  Hz, 1H), 3.77 (d, AB system,  $J = 14.7$  Hz, 1H), 3.29 (t,  $J = 7.8$  Hz, 1H), 3.11–3.21 (m, 2H), 2.84 (sept,  $J = 6.9$  Hz, 1H), 2.68 (ddd,  $J = 2.6, 2.6, 12.9$  Hz, 1H), 2.19 (ddd,  $J = 7.8, 9.2, 13.0$  Hz, 1H), 2.13 (dd,  $J = 3.2, 14.2$  Hz, 1H), 1.85 (s, 9H), 1.48–1.94 (m, 6H), 1.48 (d,  $J = 6.8$  Hz, 3H), 1.15–1.32 (m, 22H), 1.12 (d,  $J = 7.4$  Hz, 3H).

MS (ESI):  $m/z$  674.50 ( $MH^+$ , 100%).

HRMS calcd for  $C_{36}H_{60}N_5O_5S$ : 674.43097. Found: 674.42996 ( $MH^+$ ).



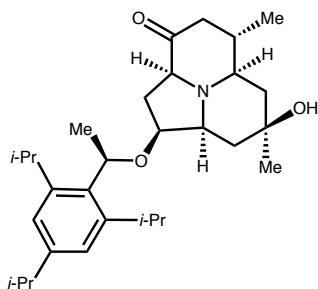
(1*S*,2*aR*,5*S*,5*aR*,7*R*,8*aS*)-7-Hydroxy-5,7-dimethyl-1-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy) decahydro-3*H*-pyrrolo[2,1,5-*de*]quinolizin-3-one (**153**). To a solution of alcohol **75** (110.0 mg, 0.233 mmol, 1.0 equiv) in 2.4 ml MeCN were added DMAP (22.7 mg, 0.186 mmol, 0.8 equiv), 2,2'-bipyridyl (22.7 mg, 0.145 mmol, 0.6 equiv) and 2-azaadamantane *N*-oxyl (12.9 mg, 0.085 mmol, 0.4 equiv) and CuCl (37.7 mg, 0.381 mmol, 1.6 equiv) at room temperature. The mixture was stirred at the room temperature under open air atmosphere for 30 min. The reaction was monitored by TLC, noting the color change of the mixture from brown to green indicating the completion of the reaction. The reaction was quenched with saturated  $NaHCO_3$  and  $Na_2S_2O_3$  and the mixture was stirred vigorously at room temperature for 5 min. The mixture was then diluted with pentane and the aqueous layer extracted with pentane (3 times). The combined organic layers were dried over  $MgSO_4$  and evaporated yielding 203.0 mg of product **153** in mixture with 2,2'-bipyridyl. It was used for the next step without any further purification.

IR (film):  $\nu$  3408, 2959, 2926, 2867, 1727, 1649, 1561, 1457, 1380, 1228, 1103  $cm^{-1}$ .

$^1H$  NMR ( $CDCl_3$ , 400 MHz):  $\delta$  7.01 (s, 1H), 6.92 (s, 1H), 5.03 (q,  $J = 6.9$  Hz, 1H), 3.94 (ddd,  $J = 4.3, 6.0, 7.9$  Hz, 1H), 3.89 (sept,  $J = 6.7$  Hz, 1H), 3.74 (dd,  $J = 7.0, 9.1$  Hz, 1H), 3.16 (sept,  $J = 6.9$  Hz, 1H), 3.06 (ddd,  $J = 4.2, 6.0, 11.3$  Hz, 1H), 2.83 (sept,  $J = 6.9$  Hz, 1H), 2.56 (ddd,  $J = 3.5, 7.4, 11.1$  Hz, 1H), 2.22–2.36 (m, 3H), 1.87–2.06 (m, 2H), 1.51–1.70 (m, 4H), 1.13–1.31 (m, 21H), 1.02 (d,  $J = 6.7$  Hz, 3H).

MS (ESI):  $m/z$  470.43 ( $MH^+$ , 100%).

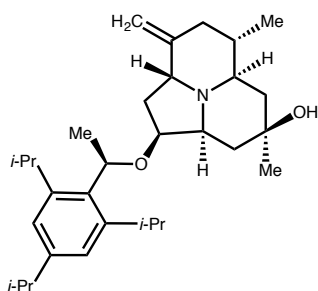
HRMS calcd for  $C_{30}H_{48}NO_3$ : 470.3629. Found: 470.3616 ( $MH^+$ ).



(1*S*,2*aS*,5*S*,5*aR*,7*R*,8*aS*)-7-Hydroxy-5,7-dimethyl-1-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy) decahydro-3*H*-pyrrolo[2,1,5-*de*]quinolizin-3-one (**159**). A solution of *n*-BuLi in hexane (2.5 M, 75  $\mu$ l, 0.1875 mmol, 8.8 equiv) was added to a solution of methyltriphenylphosphonium bromide (77 mg, 0.215 mmol, 10.1 equiv) in 0.3 ml THF at 0°C. The resulting yellow suspension was stirred for 30 min at 0°C then the mixture was cooled down to -35°C. The ketone **153** (10.0 mg, 0.021 mmol, 1.0 equiv) was added to this suspension as a solution in 0.3 ml THF and stirred for 30 min at -35°C <  $T < -20^\circ\text{C}$  then it was warmed up to 0°C and stirred for 40 min at 0°C with subsequent 40 min at ambient temperature. The reaction was quenched with H<sub>2</sub>O and the aqueous layer was extracted with Et<sub>2</sub>O (3 times). The combined organic layers were dried over MgSO<sub>4</sub> and the solvent was evaporated under reduced pressure. Purification over silica gel afforded 5.3 mg of the epimerized ketone **159** (50% over 2 steps) using 20% EtOAc/pentane as the eluant.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.00 (s, 1H), 6.91 (s, 1H), 5.04 (q,  $J = 6.8$  Hz, 1H), 3.99 (ddd,  $J = 6.5, 6.5, 8.8$  Hz, 1H), 3.89 (sept,  $J = 6.7$  Hz, 1H), 3.78 (dd,  $J = 5.8, 9.3$  Hz, 1H), 3.12–3.20 (m, 2H), 2.83 (sept,  $J = 6.9$  Hz, 1H), 2.71 (ddd,  $J = 5.8, 8.8, 13.9$  Hz, 1H), 2.64 (ddd,  $J = 3.6, 6.0, 11.8$  Hz, 1H), 2.28 (dd,  $J = 4.5, 14.3$  Hz, 1H), 1.79–1.90 (m, 2H), 1.70 (dd,  $J = 9.7, 14.3$  Hz, 1H), 1.40–1.62 (m, 4H), 1.50 (d,  $J = 6.8$  Hz, 3H), 1.16–1.35 (m, 21H), 1.03 (d,  $J = 6.8$  Hz, 3H).

MS (ESI):  $m/z$  452.36 (MH<sup>+</sup>–H<sub>2</sub>O, 100%).



(2*S*,2*aS*,4*R*,5*aR*,6*S*,8*aR*)-4,6-Dimethyl-8-methylene-2-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy) decahydro-1*H*-pyrrolo[2,1,5-*de*]quinolizin-4-ol (**151**). A solution of 0.6 M NaHMDS in toluene (3.8 ml,

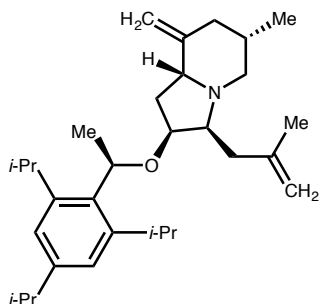
2.28 mmol, ~9.8 equiv) was added to a solution of methyltriphenylphosphonium bromide (913 mg, 2.55 mmol, ~10.9 equiv) in 6.4 ml THF at  $-78^{\circ}\text{C}$ . The yellow suspension was stirred for 45 min as the temperature was allowed to warm to  $0^{\circ}\text{C}$  then stirred 15 min at this temperature. The mixture was cooled back to  $-90^{\circ}\text{C}$  and crude ketone **153** (203.0 mg, ~0.233 mmol, 1.0 equiv) was added as a solution in 9 ml THF. The reaction mixture was stirred for 1 h at  $-90^{\circ}\text{C} < T < -80^{\circ}\text{C}$  and temperature was increased to  $0^{\circ}\text{C}$  over 2 h followed by stirring at RT for 1 h. Quenching was done with water and the aqueous layer was extracted with pentane (3 times). The combined organic layers were dried with  $\text{MgSO}_4$  and the solvent was evaporated *under vacuo*. Partial purification over 11 ml of silica gel allowed the isolation of 600.0 mg of alkene **151** in mixture with excess of Wittig reagent in a ratio of ~1.0:17.7 respectively (45% estimated yield over 2 steps) using 10% EtOAc/cyclohexane as eluant system. No further purification was done for the alkene as it was noticed its instability over silica gel was noticed and used for the next step in its impure form.

IR (film):  $\nu$  3387, 2958, 2925, 2854, 1658, 1607, 1462, 1379, 1260, 1104  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  7.01 (d,  $J = 2.0$  Hz, 1H), 6.91 (d,  $J = 2.0$  Hz, 1H), 5.06 (q,  $J = 6.8$  Hz, 1H), 4.71 (q,  $J = 1.6$  Hz, 1H), 4.69 (q,  $J = 1.6$  Hz, 1H), 4.02 (ddd,  $J = 2.8, 6.9, 8.6$  Hz, 1H), 3.92 (sept.,  $J = 6.8$  Hz, 1H), 3.65 (t,  $J = 8.0$  Hz, 1H), 3.19 (sept.,  $J = 6.8$  Hz, 1H), 3.16 (ddd,  $J = 3.6, 6.9, 12.3$  Hz, 1H), 2.83 (sept.,  $J = 6.9$  Hz, 1H), 2.67 (ddd,  $J = 3.0, 3.0, 12.7$  Hz, 1H), 2.39 (dd,  $J = 5.6, 14.4$  Hz, 1H), 1.69–2.01 (m, 6H), 1.50 (d,  $J = 6.8$  Hz, 3H), 1.41 (ddd,  $J = 2.3, 3.6, 13.4$  Hz, 1H), 1.16–1.3 (m, 22H), 0.98 (d,  $J = 7.0$  Hz, 3H).

MS (ESI):  $m/z$  468.22 ( $\text{MH}^+$ , 100%).

HRMS calcd for  $\text{C}_{31}\text{H}_{50}\text{NO}_2$ : 468.3836. Found: 468.3827 ( $\text{MH}^+$ ).



(2*S*,3*S*,6*S*,8*aR*)-6-Methyl-3-(2-methylallyl)-8-methylene-2-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)octahydroindolizine (**166**). To a solution of oxalyl chloride (30  $\mu\text{l}$ , 0.35 mmol, ~5.5 equiv) in 450



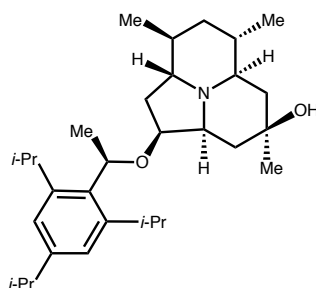
$\mu\text{l}$  DCM was added dropwise DMSO (90  $\mu\text{l}$ , 1.27 mmol,  $\sim 19.9$  equiv) at  $-78^\circ\text{C}$ . The mixture was stirred for 40 min at  $-80^\circ\text{C} < T < -65^\circ\text{C}$  and 30.0 mg of a mixture of alcohol **75** and tertiary amine **145** of ratio 1:0.09 respectively was added in 900  $\mu\text{l}$  THF at  $-78^\circ\text{C}$ . The reaction mixture was then stirred for 1h at  $-80^\circ\text{C} < T < -65^\circ\text{C}$  and  $\text{Et}_3\text{N}$  (300  $\mu\text{l}$ , 2.15 mmol,  $\sim 33$  equiv) was then injected slowly and temperature allowed to warm slowly to  $-35^\circ\text{C}$  over 1h. When the TLC showed a complete consumption of the starting alcohols, the Swern solution was concentrated *in vacuo* at  $-5^\circ\text{C}$  and 1.1 ml of dry THF was added. The bath was cooled back to  $-80^\circ\text{C}$  and treated with a solution of freshly prepared  $\text{TBTSO}_2\text{CH}_2\text{Li}$  in THF (1.7 ml, 0.65 M, 1.11 mmol,  $\sim 17$  equiv). The reaction mixture was stirred for 2h allowing the temperature to reach  $-20^\circ\text{C}$  then stirred 1h at RT. After dilution with  $\text{Et}_2\text{O}$  followed by quenching with brine, the aqueous layer was extracted with  $\text{Et}_2\text{O}$  (3 times) and the combined organic layers dried over magnesium sulfate and concentrated under reduced pressure. Purification over silica gel afforded 8.8 mg of a mixture of the tricyclic alkene **151** and the bicyclic alkene **166** in a ratio of 1:0.66 respectively using 1%  $\text{MeOH}_{\text{NH}_3}/\text{DCM}$  as eluant (30% yield). Further purification gave analytical pure material of alkene **166**. (*vide supra* for data characterization of **151**)

#### Data for compound **166**

IR (film):  $\nu$  2959, 2925, 2854, 1650, 1607, 1462, 1378, 1260, 1123, 1081, 1025  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  7.04 (d,  $J = 1.9$  Hz, 1H), 6.93 (d,  $J = 1.9$  Hz, 1H), 5.04 (q,  $J = 6.8$  Hz, 1H), 4.75 (s, 1H), 4.83 (s, 1H), 4.72 (s, 1H), 4.70 (s, 1H), 4.10 (ddd,  $J = 3.0, 7.3, 7.3$  Hz, 1H), 3.93 (sept.,  $J = 6.8$  Hz, 1H), 3.72 (dd,  $J = 7.2, 9.6$  Hz, 1H), 3.13–3.23 (m, 2H), 2.85 (sept,  $J = 6.9$  Hz, 1H), 2.66 (app d,  $J = 10.3$  Hz, 1H), 2.34 (dd,  $J = 3.8, 15.0$  Hz, 1H), 2.02–2.24 (m, 3H), 1.76–1.89 (m, 3H), 1.71 (s, 3H), 1.51 (d,  $J = 6.8$  Hz, 3H), 1.17–1.43 (m, 19H), 0.83 (d,  $J = 6.4$  Hz, 3H).

HRMS calcd for  $\text{C}_{31}\text{H}_{50}\text{NO}$ : 452.38869. Found: 452.38764 ( $\text{MH}^+$ ).

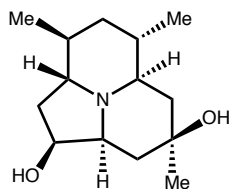


(2*S*,2*aS*,4*R*,5*aR*,6*S*,8*S*,8*aR*)-4,6,8-Trimethyl-2-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)decahydro-1*H*-pyrrolo[2,1-*de*]quinolizin-4-ol (**152**). To a solution of alkene **151** (4.7 mg, 0.010 mmol, 1.0 equiv) in 250  $\mu$ l *i*PrOH were added phenyl silane (60  $\mu$ l, 0.486 mmol, 48.0 equiv), *tert*-butyl hydroperoxide solution (5.0–6.0M in decane, 12  $\mu$ l, 0.06–0.072 mmol, 6.0–7.0 equiv) and Mn(dpm)<sub>3</sub> (2 mg,  $3.3 \times 10^{-3}$  mmol, 33% by mole) at RT. The reaction mixture was stirred for 4h then the solvent was evaporated. The crude mixture was directly loaded on silica gel eluted with 1% MeOH<sub>NH3</sub>/DCM to afford 4.0 mg of the alkane **152** (85% yield).

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz):  $\delta$  7.00 (d, *J* = 1.9 Hz, 1H), 6.90 (d, *J* = 1.9 Hz, 1H), 5.00 (q, *J* = 6.8 Hz, 1H), 4.01 (ddd, *J* = 2.7, 7.1, 9.6 Hz, 1H), 3.92 (sept, *J* = 6.9 Hz, 1H), 3.16 (sept, *J* = 6.8 Hz, 1H), 3.14 (ddd, *J* = 3.8, 7.1, 12.4 Hz, 1H), 2.83 (sept, *J* = 6.9 Hz, 1H), 2.72 (ddd, *J* = 7.0, 9.4, 9.4 Hz, 1H), 2.68 (ddd, *J* = 1.4, 3.1, 13.0 Hz, 1H), 1.81–1.91 (m, 2H), 1.54–1.76 (m, 3H), 1.48 (d, *J* = 6.8 Hz, 3H), 1.39–1.47 (m, 1H), 1.36 (ddd, *J* = 2.3, 3.8, 13.4 Hz, 1H), 1.15–1.34 (m, 23H), 1.13 (ddd, *J* = 2.3, 3.0, 12.5 Hz, 1H), 1.09 (d, *J* = 7.1 Hz, 3H), 0.83 (d, *J* = 6.4 Hz, 3H).

MS (ESI): *m/z* 470.39 (MH<sup>+</sup>, 100%).

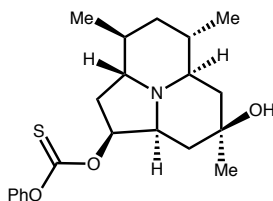
HRMS calcd for C<sub>31</sub>H<sub>52</sub>NO<sub>2</sub>: 470.39926. Found: 470.39795 (MH<sup>+</sup>).



(1*S*,2*aR*,3*S*,5*S*,5*aR*,7*R*,8*aS*)-3,5,7-Trimethyldecahydro-1*H*-pyrrolo[2,1-*de*]quinolizine-1,7-diol (**150**). To a solution of the tertiary alcohol **152** (5.3 mg, 0.011 mmol) in 250  $\mu$ l of DCM at 0 °C was added dropwise 25  $\mu$ l TFA with vigorous stirring. The reaction mixture was stirred for another 1 h at 0°C, after which it was quenched with 10% NaOH solution and diluted with DCM. The aqueous phase was washed with DCM (3 times) then the resultant organic phases were dried over MgSO<sub>4</sub>. The solvent was evaporated *in vacuo* to obtain the crude product which furnished 2.0 mg of pure diol **150** (75% yield) upon purification over silica gel with 6.0% MeOH<sub>NH3</sub>/DCM as eluant system.<sup>145</sup>

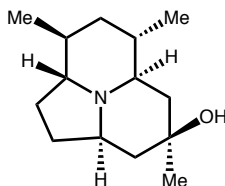
<sup>145</sup> Starting from 110 mg of alcohol **75** afforded 600 mg of alkene **151** contaminated with Wittig reagent (as described in the previous pages); then subjecting this crude alkene **151** to Shenvi hydrogenation followed by acidic treatment for chiral auxiliary cleavage allowed the isolation of 20 mg of pure alcohol **150** (36% over 4 steps).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  4.33 (ddd,  $J = 1.9, 5.1, 7.1$  Hz, 1H), 2.96 (ddd,  $J = 3.3, 5.1, 12.1$  Hz, 1H), 2.84 (ddd,  $J = 6.9, 9.1, 10.4$  Hz, 1H), 2.50 (ddd,  $J = 2.8, 5.5, 12.0$  Hz, 1H), 1.85 (ddd,  $J = 2.0, 6.9, 13.4$  Hz, 1H), 1.72 (ddd,  $J = 7.3, 9.0, 13.4$  Hz, 1H), 1.32–1.71 (m, 8H), 1.26 (s, 3H), 1.02 (d,  $J = 7.0$  Hz, 3H), 0.79 (d,  $J = 6.5$  Hz, 3H).



*O*-((1*S*,2*aR*,3*S*,5*S*,5*aR*,7*R*,8*aS*)-7-Hydroxy-3,5,7-trimethyldecahydro-1*H*-pyrrolo[2,1,5-*de*]quinolizin-1-yl) *O*-phenyl carbonothioate (**176**). To a solution of the diol **150** (5.0 mg, 0.021 mmol, 1.0 equiv) in 250  $\mu\text{l}$  DCM were added DMAP (10.0 mg, 0.082 mmol, 3.9 equiv) and *O*-phenyl chlorothionoformate (7.0  $\mu\text{l}$ , 0.051 mmol, 2.4 equiv). The reaction mixture was stirred for 5 h at RT and then quenched with 10% NaOH and diluted with DCM. The aqueous layer was then extracted with DCM (3 times) and the combined organic phases were dried over  $\text{MgSO}_4$  and concentrated under reduced pressure. The residue was purified over silica gel to afford 6.5 mg of **176** (83% yield) eluted with 0–0.5%  $\text{MeOH}_{\text{NH}_3}/\text{DCM}$ .

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  7.39–7.45 (m, 2H), 7.27–7.31 (m, 1H), 7.07–7.12 (m, 2H), 5.70 (ddd,  $J = 2.6, 6.6, 9.2$  Hz, 1H), 3.58 (ddd,  $J = 3.6, 6.6, 12.4$  Hz, 1H), 2.78 (ddd,  $J = 6.8, 9.5, 9.5$  Hz, 1H), 2.72 (ddd,  $J = 2.2, 2.9, 12.7$  Hz, 1H), 1.94–2.11 (m, 3H), 1.83 (t,  $J = 12.6$  Hz, 1H), 1.46–1.74 (m, 4H), 1.21–1.39 (m, 2H), 1.28 (s, 3H), 1.13 (d,  $J = 7.2$  Hz, 3H), 0.84 (d,  $J = 6.6$  Hz, 3H).



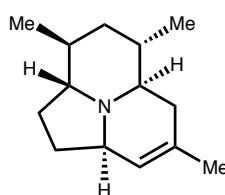
(2*aR*,4*S*,5*aR*,6*S*,8*S*,8*aR*)-4,6,8-Trimethyldecahydro-1*H*-pyrrolo[2,1,5-*de*]quinolizin-4-ol (**177**). To a refluxing solution of the *O*-phenyl carbonothioate **176** (17.5 mg, 0.047 mmol, 1.0 equiv) in 2.8 ml of benzene was added dropwise a mixture of AIBN (3.6 mg, 0.022 mmol, 0.5 equiv) and  $\text{TMS}_3\text{SiH}$  (34.5  $\mu\text{l}$ , 0.11 mmol, 2.3 equiv) in 510  $\mu\text{l}$  benzene over 45 min. The mixture was refluxed for

additional 4h30min, then cooled and evaporated. The residue was loaded directly on silica gel for purification to give 10.2 mg of tertiary alcohol **177** (98%) eluted with 3% MeOH<sub>NH3</sub>/DCM.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz): δ 3.11 (dddd, *J* = 2.2, 4.0, 7.5, 11.8 Hz, 1H), 2.78 (ddd, *J* = 2.2, 3.0, 12.8 Hz, 1H), 2.43 (ddd, *J* = 6.5, 9.6, 9.6 Hz, 1H), 1.88–2.09 (m, 2H), 1.64–1.77 (m, 3H), 1.26–1.54 (m, 7H), 1.26 (s, 3H), 1.14 (d, *J* = 7.2 Hz, 3H), 0.82 (d, *J* = 6.5 Hz, 3H).

MS (ESI): *m/z* 224.15 (MH<sup>+</sup>, 100%).

HRMS calcd for C<sub>14</sub>H<sub>26</sub>NO: 224.2009. Found: 224.2008 (MH<sup>+</sup>).



(2a*R*,3*S*,5*S*,5a*R*,8a*R*)-3,5,7-Trimethyl-2,2a,3,4,5,5a,6,8a-octahydro-1*H*-pyrrolo[2,1,5-*de*]

quinolizine (**1**). To a solution of the tertiary alcohol **174** (10.4 mg, 0.05 mmol, 1.0 equiv) in 6 ml of benzene was added *p*-TsOH.H<sub>2</sub>O (70 mg, 0.37 mmol, 7.4 equiv) followed by refluxing the reaction mixture for 8 h. The reaction was then cooled down and diluted with DCM and quenched with 10% NaOH. The aqueous layer was extracted 4 times with DCM and the combined organic layers were dried over magnesium sulphate and evaporated *in vacuo* to obtain the crude product containing both isomers **1** and **175** in a ratio of 6:1 respectively. Purification over silica gel using pentane/EtOAc (10% → 50%) as eluant afforded **1** (6.0 mg, 63% yield) as a colorless oil.

R<sub>f</sub> 0.20 (100% EtOAc).

IR (film): ν 2955, 2925, 2852, 1658, 1459, 1376 cm<sup>-1</sup>.

<sup>1</sup>H NMR (C<sub>6</sub>D<sub>6</sub>, 500 MHz): δ 5.17 (br s, 1H), 3.89 (br s, 1H), 2.97 (ddd, *J* = 1.2, 4.7, 11.6 Hz, 1H), 2.15 (ddd, *J* = 5.2, 9.9, 9.9 Hz, 1H), 1.96–2.09 (m, 2H), 1.80 (dddd, *J* = 1.6, 5.1, 8.7, 10.7 Hz, 1H), 1.59 (s, 3H), 1.53–1.60 (m, 1H), 1.20–1.40 (m, 6H), 1.30 (d, *J* = 7.1 Hz, 3H), 0.81 (d, *J* = 6.5 Hz, 3H).

<sup>13</sup>C NMR (C<sub>6</sub>D<sub>6</sub>, 125 MHz): δ 129.91, 126.79, 60.97, 58.95, 57.02, 36.35, 33.34, 33.11, 30.13, 29.17, 28.72, 24.15, 20.76, 19.41.

HRMS calcd for C<sub>14</sub>H<sub>23</sub>N: 206.19033 Found: 206.19045 (MH)<sup>+</sup>.

# EXPERIMENTAL PROCEDURE

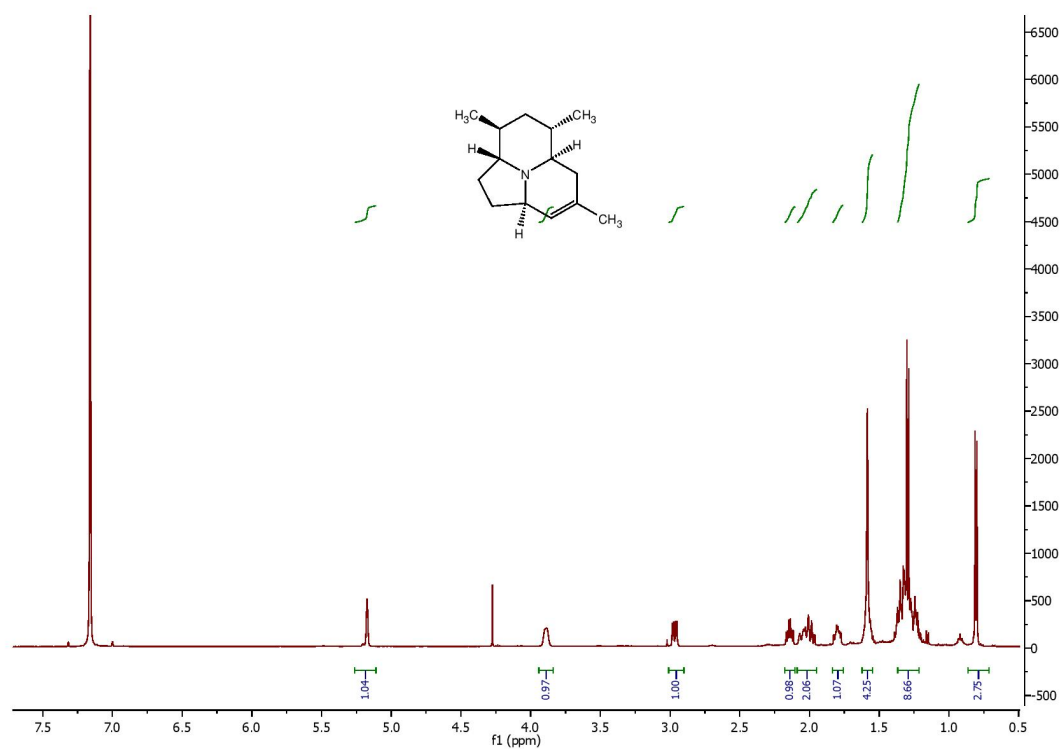


Figure 21:  $^1\text{H}$  NMR of alkaloid (-)-205B

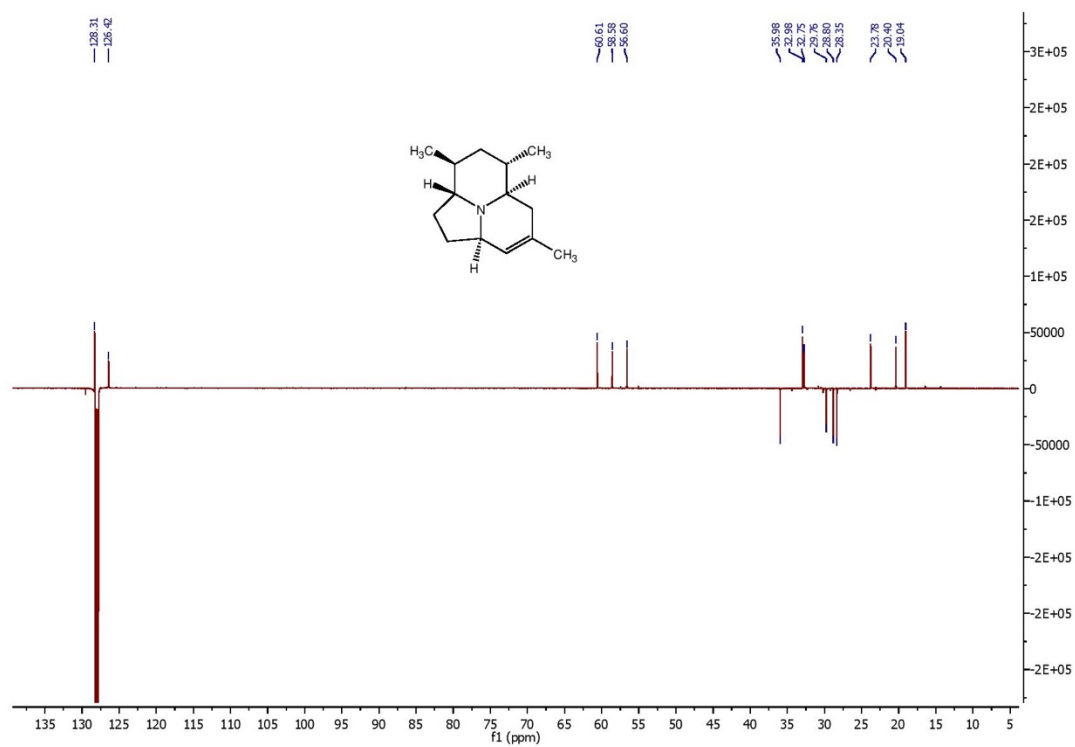


Figure 22:  $^{13}\text{C}$  NMR of alkaloid (-)-205B