Contribution à la synthèse totale de l'alcaloïde (-)-205B

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Abbreviations

Ac	Acetate
AIBN	Azobisisobutyronitrile
aq.	Aqueous
atm.	Atmosphere
Bn	Benzyl
Boc	*tert*-butoxycarbonyl
cat.	Catalyst
CSA	Camphor sulphonic acid
DCM	Dichloromethane
DIBAL-H	Diisopropylbutylaluminium hydride
DMAP	*N*,*N*-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	*N*,*N*-dimethylsulfoxyde
EDA	Ethylene diamine
eq.	Equivalents
HMPA	Hexamethylphosphoramide
HOMO	Highest Occupied Molecular Orbital
IR	Infrared
LAH	Lithium Aluminium Hydride
LDA	Lithium diisopropylamide
LUMO	Lowest Unoccupied Molecular Orbital
***m*-CPBA**	*meta*- chloroperbenzoic acid
min	Minute
MOM	Methyloxymethyl
nAChR	Nicotinic Acetyl Choline Receptors
NaHMDS	Sodium bis(trimethylsilyl)amide
NMP	N-Methyl pyrolidinone
NMR	Nuclear Magnetic Resonance

PMB	*para*-methoxybenzyl
pTSA	*para*-toluenesulphonic acid
Py	Pyridine
RT	Room Temperature
RCM	Ring Closing Metathesis
SEMCl	2-(Chloromethoxyethyl)trimethylsilane
TBS	tert-Butyldimethylsilyl
TBDPS	tert-Butyldiphenylsilyl
TESOTf	Triethylsilyltrifluoromethanesulphonate
TBSOTf	*tert*-butyldimethylesilyl trifluoromethansulphonate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
Ts	Tosyl
UV	Ultraviolet

General Introduction

General Introduction

Throughout ages, Nature has been a vast and renewable source of useful compounds that have served mankind. The innate human curiosity for a better understanding of the naturally occuring components of the environment around him and his need to find sources of food, fabric and medicines for survival has prompted him to constantly exploit this realm.

Historically, owing to their toxicity, one of the major applications of compounds extracted from Nature had been as poisons for hunting and defence purposes. However, all over the world traditional medicine has also been largely dominated by use of plants. For instance, the so called 'Ebers Papyrus',[1] an Egyption record dating back to 1500 B. C., is one of the oldest texts ever known which mentions the use of over 700 medicinal compounds mainly obtained from vegetal sources. In the Chinese traditional medicine, the 'Bencao Gangmu', a compendium of Materia Medica containing thousands of medicinally important plant recipies[2] was written between 1518 and 1593 B.C. Also, the famous Indian Ayurvedic medicine, with its origin dating back to 1000 B.C., also enlists various physiologically beneficial herbal preparations.[3]

The Mediterranean countries have also actively contributed to this invaluable collection. During the first century of our era, the Greek physician, Dioscorides[4] had written a five volume treatise on the medicinal uses of several hundreds of plant based compounds. In the 10th century, the Persian scholar Avicenna wrote 'The Canon of Medicine', a vast medicinal encyclopaedia containing a special volume on pharmacology of plants, animal and mineral products. Translated into Latin, this compendium has been in use in Europe for several centuries.[5]

In the modern world, the evolution of organic synthesis and advent of pharmacology has facilitated even more productive applications of this vast resorvoir of natural resources. It is due to this reason that organic synthesis, of which the total synthesis of natural products was a flagship, has remained an indispenisble component of synthetic organic chemistry.

[1] Aboelsoud, N. H. *J. Med. Plant. Res*. **2010**, *4*, 82-86
[2] Zhou, J.; Yan, X Traditional Chinese Medicines : Molecular Structures, Natural Sources and Applications, II Edtn.
[3] Balachandran, P., Govindarajan , R. *Expert. Opin. Drug. Discov*. **2007**, *2*, 1631-1652
[4] De Vos, P. *J. Ethnopharmacol*. **2010**, *132*, 28-47
[5] a. Tekol, Y. *Phytoter. Res*. **2007**, *21*, 701-702 b.M. Mossadegh; F. Naghibi Chapter 1, Traditional Medicine and Materia Medica c. M. Mossadegh; F. Naghibi Eds. 2002. URL : http:/www.itmrc.org/publication/Ch_1.htm

The term 'natural product'[6] has been applied to primary or secondary metabolites derived from plants, microorganisms, vertebrates and invertebrates which are required for their survival and sustenance. Most compounds extracted from nature are secondary metabolites – products from conditional pathways that are turned on in a particular context or situation. As secondary metabolites, they are not directly responsible for the growth and development of an organism and were initially regarded as waste products. However, research has revealed that organisms which have evolved over ages produce these complex and often toxic chemicals for different purposes like self-defence, communication etc. For example: Colored phenolics or fragmented terpenoids are used to attract pollinating and seed-dispersing animals.

An enormous number of natural products possessing intriguing molecular structures and diversity have been listed over the past few decades. These compounds are often classified on the basis of their chemical structures, which in turn reflect the strategies for their assembly by biosynthetic pathways using enzymes in the organisms that produce them. Figure 1 outlines the biogenesis of various natural products that have been classified to date[6.]

Broadly speaking, each class of compounds is known to play specific roles in the producer organisms. However, extraction of these compounds has enabled extensive studies of their chemical structures and properties leading to their application in the food and fabric industry for example as flavors, perfumes etc.

A fascinating aspect of natural products, however, is that even today they are regarded as the foremost inspiration for seeking new structures of therapeutics of numerous diseases that mankind is inflicted with. Their importance in the drug industry has been clearly demonstrated by an analysis of the sources of the clinically approved drugs that exist in the market. In a recent review, Newmann *et al*[7] shows that in the last 25 years (up to October 2008), only 37% of approved drugs are of purely synthetic origin while the rest are unmodified natural products, modified natural products or a synthetic compound with natural product pharmacophore in their structures.

[6] Bhat, S. V. In *Chemistry of Natural Products*, Springer, **2005**
[7] Newmann , D. J; Cragg G. M. *Chem. Rev.* **2009,** *109,* 3012–3043

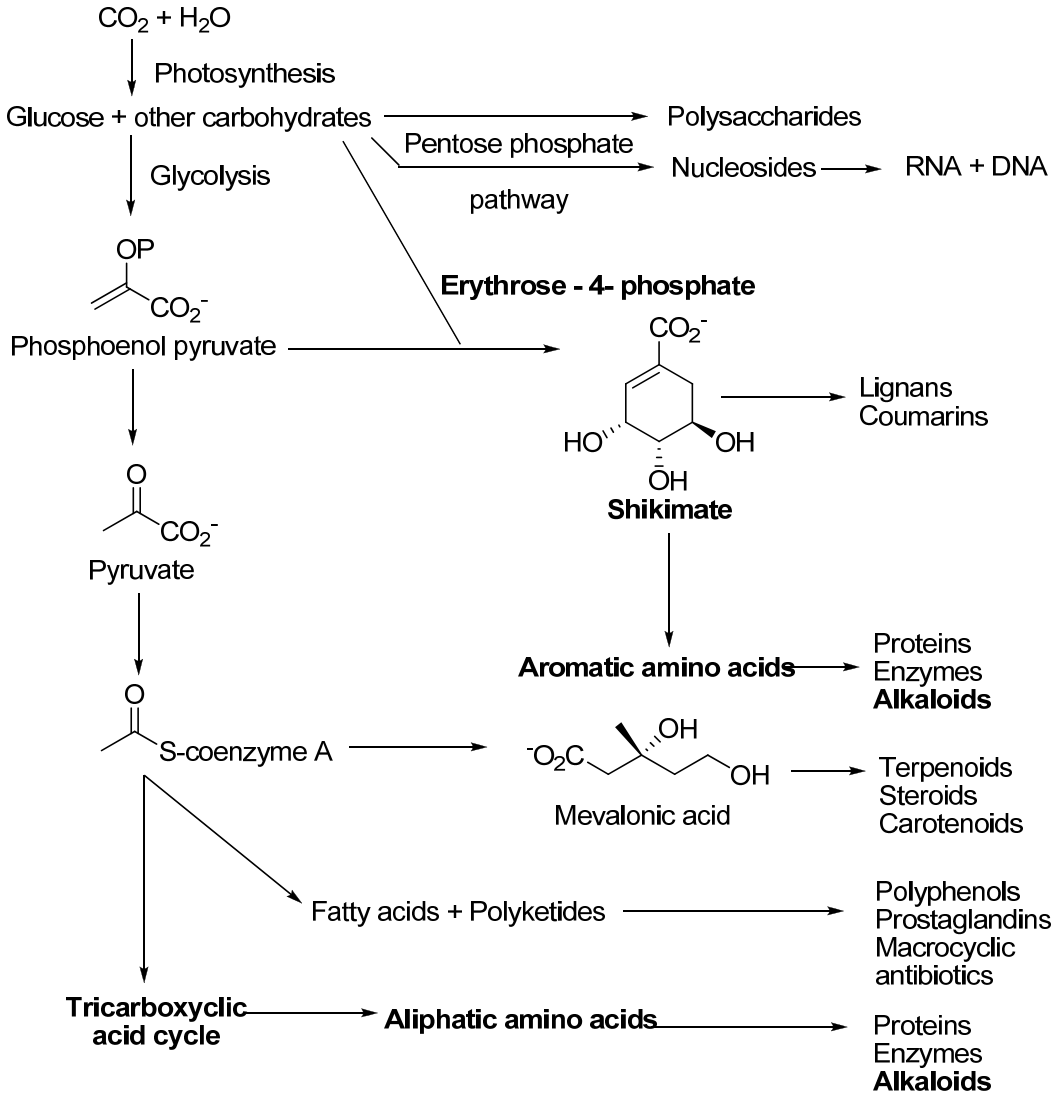


Figure 1 : Outline of biogenesis of natural products

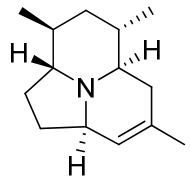
Some classical examples of natural products that have been extracted from different sources have been listed in Figure 2. These complex molecules possessing diverse chemical structures and exhibiting a wide range of biological activities, have been successfully synthesised in laboratories.[8]

Thus, it is worthy to note that through total or hemi-synthesis, synthetic organic chemistry facilitates the production of not only these scarce natural products but also some of their more effective analogues, in quantities that can meet their commercial requirement as medicines.

[8] Nicolau, K.C. *Molecules that changed the world*, WILEY, Edition I.

Owing to the importance of the synthesis of natural products in both chemistry and biology, our laboratory has been involved in the synthesis of numerous biologically active molecules, especially alkaloids which is perhaps one of the most widespread and important classes of biological active natural products.

Thus, this thesis is devoted to the studies directed towards the total synthesis of Alkaloid (-)-**205B**.



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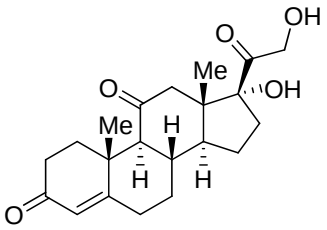
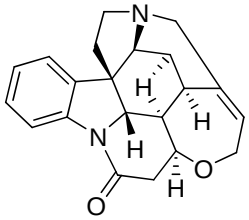


Cortisone

Class : Steroid harmone

Source : One of the end-products of steroidogenesis

Property : Reduction of inflammation and pain

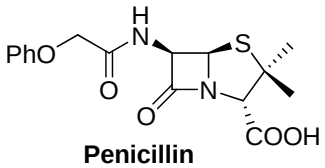


Strychnine

Class : Alkaloid

Source : Beans of *Strychnos ignatii*

Property : Antagonist for glycine-receptor

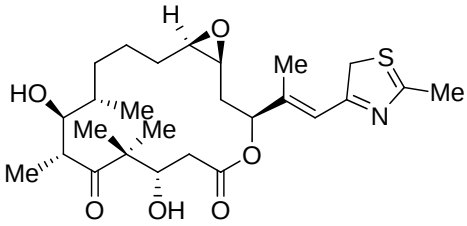


Penicillin

Class : β-lactam antibiotic

Source : *Penicillium fungi*

Property : Treatment of bacterial infections

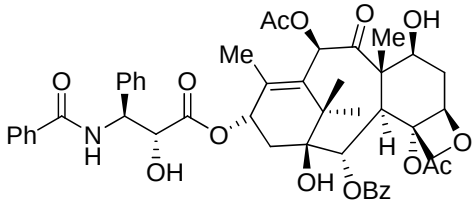


Epithilone A

Class : Polyketide macrolactone

Source : Myxobacterium *Sorangium cellulosum,* soil- dwelling bacteria

Property : Anti-cancer agent



Taxol

Class : Diterpene

Source : Bark of *Taxus brevifolia*

Property : Anti-cancer agent

Figure 2 : Well-known natural products with different sources of origin,structures and biological activity

Chapter 1: Alkaloids

1.1 ***Introduction: Alkaloids***

Secondary metabolites known as alkaloids are one of the most commonly encountered classes of nitrogenous compounds found extensively in the plant kingdom and have been extracted from organisms ranging from fungi to mammals.

The term 'alkaloid' essentially means a chemical substance with an alkali-like character.[9] This term was coined in 1819 by Meisner who defined alkaloids as

'Plant-derived substances which act as alkalis and are known to possess considerable amount of pharmacological activity.'

This definition was published around the time when very few alkaloids extracted from plants such as coniine (extracted from the yellow pitcher plant) and morphine (discovered in 1804 in the unripe seedpods of opium) were known. These compounds were also known to possess significant physiological activities.

With an increase in the number and variety of structurally diverse *N*-containing compounds isolated from sources other than plants, this definition underwent several modifications over the period of time. Besides the source of origin, structural complexity, presence of nitrogen in a heterocyclic ring and the physiological activity of the molecules, a few other factors were taken into consideration in refining this definition.

The most recent and first 'modern' definition of alkaloids was given by Pelletier[9] in 1983, according to which:

'*an alkaloid is a cyclic organic compound containing nitrogen in a negative oxidation state which is of limited distribution among living organisms'.*

Pelletier's definition imposing the restriction that alkaloids have limited distribution among living organisms established that they should essentially be secondary metabolites, thereby eliminating ubiquitous compounds like amino acids, nucleic acids, aminosugars, peptides and vitamins from this class of compounds. In addition, the requirement that nitrogen should be in a negative oxidation state led to the exclusion of compounds having nitro and nitroso groups from

[9] Hesse, M. *Alkaloids - Nature's Curse or Blessing ?* Wiley-VCH: Zürich, **2002**.

this category.[10] The presence of nitrogen in a cyclic structure and exhibiting biological activity continued to be debated.

However, one common property of this class of compounds is their basicity. Taking into account the various structural entities that have been classified as alkaloids, a more general definition of alkaloids was proposed by Hesse[9] in 2002, which is as follows:

'Alkaloids are nitrogen-containing organic substances of natural origin with a greater or less degree of basic character.'

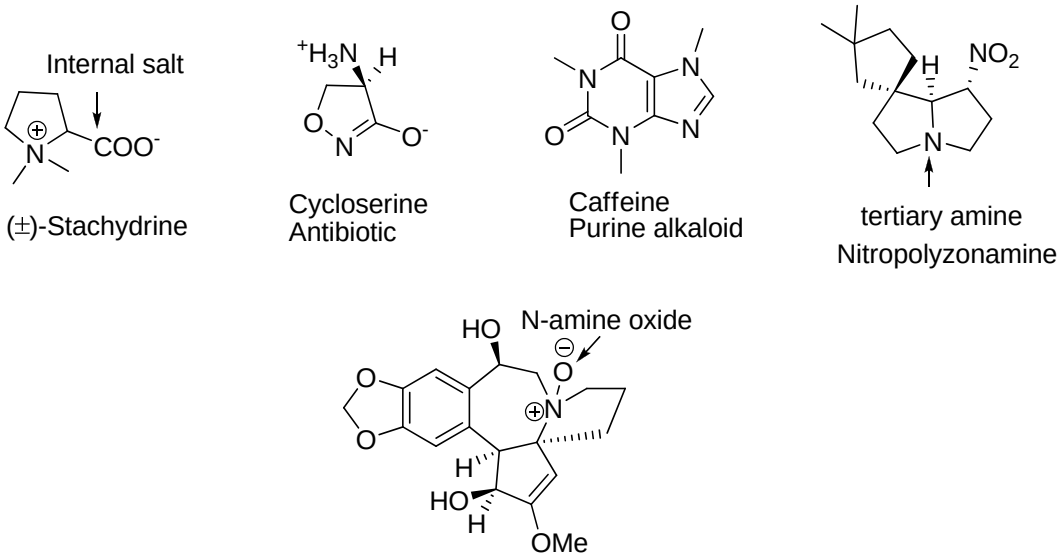


Figure 3 : Examples encompassed by 'modern definition' of alkaloids

Thus, as this class of compounds was present widely across the plant kingdom, extensive studies were performed to understand its biosynthetic origin as well as ecological role in the biosystem.

[10] Mann, J. In *Natural Products*; Longman Group UK, Ltd.: Harlow, 1994, Chapter 7.

1.2 ***Biosynthesis***

As depicted in Figure 1 in the previous section, the biogenesis of alkaloids involves aliphatic amino acids precursors', ornithine and lysine or aromatic amino acids such as phenylalanine, tyrosine or tryptophan. Most compounds (See Figure 4 for selected examples) covered by Pelletier's definition have a part of their structure derived from amino-acids and their derivatives. Alkaloids are also known to be synthesized from polyketides or terpenoids with incorporation of nitrogen atom from ammonia.[10] The main structural types of the compounds derived from aliphatic amino acids include pyrolidine, piperidine, pyrrolizidine, quinolizidine and pyridine alkaloids. The alkaloids from aromatic amino acids have been classified as tetrahydroisoquinoline alkaloids or complex indole derivatives.

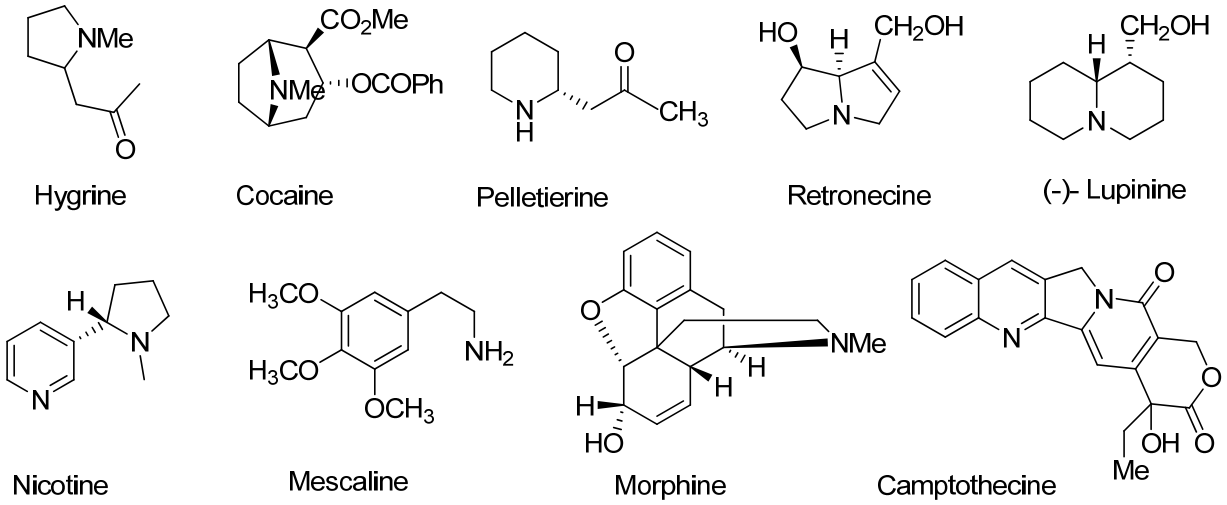


Figure 4 : Alkaloids belonging to different structural classes based on their biogenesis

An interesting point that was noted in the biosynthetic studies of alkaloids was that an alkaloid never occurs alone in Nature. They are usually present as mixtures in a particular biosynthetic unit (leaves, roots) in varying proportions and differ mainly in their functional groups.[11] It was also observed that as nitrogen is a limiting factor for plant growth and these alkaloids are expensive to be synthesized, plants have an efficient transportation and storage mechanism for these molecules. This was an important indication that alkaloids may not be waste products as considered previously but may in fact have important ecological roles to play.

[11] van Wyk, B.-E. and Wink, M. *Medicinal Plants of the World* **2004**, TimberPress, Briza, Pretoria

1.3 *Ecological role of Alkaloids:*

As mentioned above, secondary metabolites, in general, are produced by living organisms to serve various functions for their efficient survival. Of these, alkaloids constitute a major class and are known to be produced by more than 20% of all the species in the plant kingdom.[12] Very often, alkaloids are known to be operating with a synergistic effect along with other secondary metabolites for the optimal functioning of the organism that produces them. It has also been observed that the structural type of the alkaloids isolated from different species of any given plant is often found to be similar. This can be attributed to the fact that due to similarities in geographical locations, competing organisms or predators etc., these species have conditioned themselves in an identical fashion. For example: Most plants living at high altitudes in UV-rich environments possess high levels of quinoline and indole alkaloids. They presumably store them due to the UV-absorbing properties of these molecules.

The most elementary function of alkaloids in the plant kingdom and also in the animal kingdom is storage of toxic nitrogenous compounds for chemical defense. Alkaloids can assume their role as deterrents for predators if they are present at the right place, concentration and time. It has been proven that it is for this purpose that most alkaloids are stored in the aerial parts of the plants like leaves, seeds etc. The role of alkaloids in chemical defense of plants has been demonstrated by the simple yet elegant experiment by growing sweet (< 0.02% of alkaloid content) and bitter (2-6% alkaloid content) lupins (quinolizidine alkaloids) in the same field. While the rabbits (predators) prefer the sweet ones, the latter remain untouched, thereby leaving them unharmed. A similar phenomenon is exhibited by plants against other competing organisms.

In recent years, alkaloids have been extracted from a variety of organisms other than plants such as microorganisms (bacteria, fungi), marine animals (sponges), amphibians (toads, frogs) and a few mammals (Canadian Beaver). Selected examples are shown in Figure 5:

[12] Fattorusso, E. and Taglialatela-Scafeti, O., In *Modern Alkaloids,* WILEY-VCH, Chapter 1

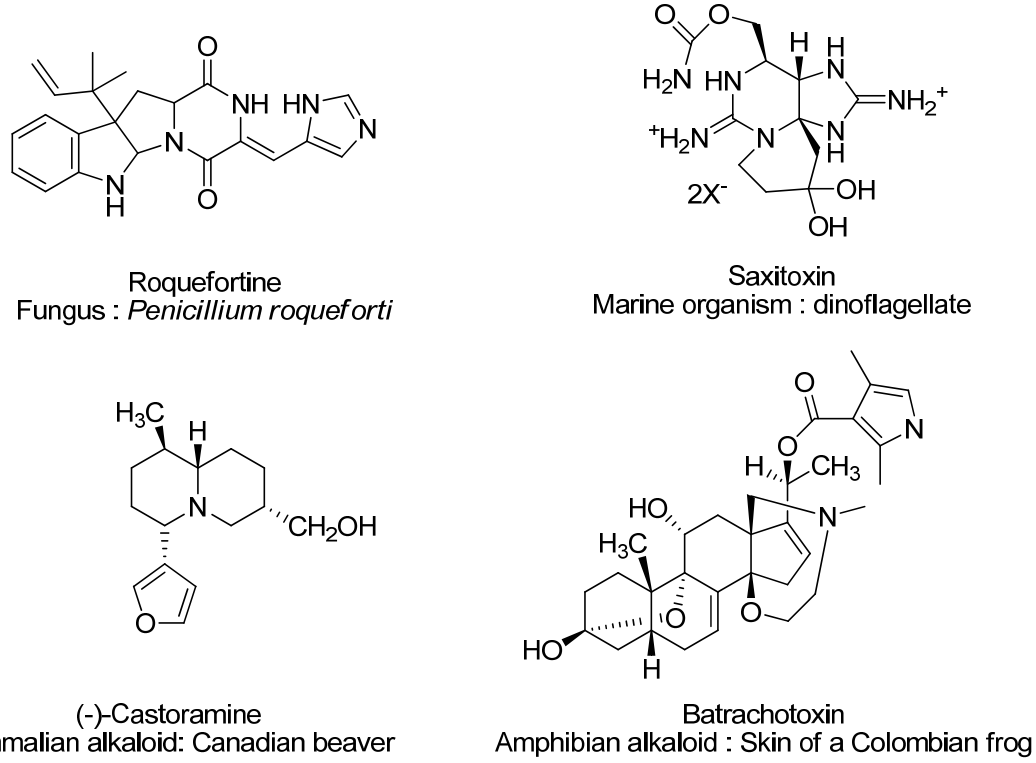


Figure 5 : Some examples of non-plant alkaloids

The physical property common to all alkaloids, is their bitterness, which helps in keeping predators away. However, in the chemical sense, it has been studied that not only do these molecules possess antibacterial, antifungal properties[11] etc, in order to protect the organism that synthesizes them, they also show appreciable amount of toxicity towards the predators. Interestingly, investigations directed towards understanding the mode of action of these toxic chemicals on their predators have affirmed that when administered in right quantities, these lethal molecules are extremely efficacious in bringing about useful pharmacological effects on human beings and other animals. An excellent example is provided by one of the first amphibian alkaloids to be extracted namely Batrachotoxin[13] (Figure 5) extracted from the skin of Columbian frogs of *Phyllobates* species. This toxin was used as a poison by the native Indians of western Columbia for poisoning the darts for hunting animals. However, in the past few decades, its ability to act as a powerful neurotoxin and cardiovascular properties have been elucidated. [14]

[13] Daly, J. W.; Garraffo, H. M.; Spande, T. F. In Alkaloids: Chemical and Biological Perspectives; Pelletier, S. W.; Ed.; Permagamon: New York, 1999; Vol. 13, 1-61
[14] Albuquerque, E. X.; Daly, J. W, Witkop, B., *Science* **1971**, *172*, 995-1002

From this brief overview, it is clear that alkaloids in general are widely distributed in the living world and display a wide diversity in their roles. We shall now focus, in more detail, on the Amphibian Alkaloids.

Chapter 2:

Alkaloids from the Amphibian Skin

2.1 *Introduction: Amphibian Alkaloids*

As discussed previously, alkaloids isolated from plants have been known since a long time. However, not much attention was paid towards the possibility of exploiting the animal kingdom for these natural resources.

It was only as recent as in the 1960-70s that a wide range of peptides and biogenic amines from the amphibian skin[15] were studied in detail by the initiative of Vittorio Erspamer in Italy. His work demonstrated that many classes of peptides found in frogs' skin may actually play the role of hormones or neuromodulatory agents in mammals. In the 1970-80s, Michael Zasloff focused his studies on anti-microbial peptides. His research established that nearly all amines and peptides found in amphibian skin have their counterpart in mammalian tissues where they usually occur in much less variety and concentration.[16] Following this, the presence of steroidal bufadienolides in the glands of bufanoid toads of genus *Bufo,* was first mentioned by Wieland and later by Mayer.[17] Another class of amphibian toxins was enlisted by Mosher from a newt of the genus *Taricha,* namely the tetrodotoxins like zetekitoxin[18] (See Figure 6).

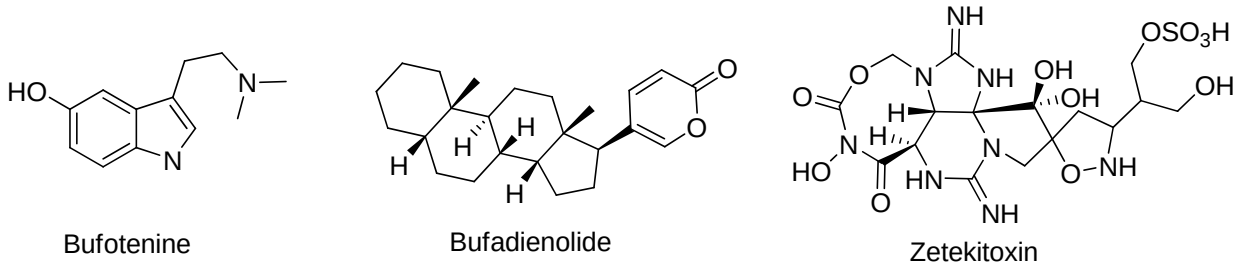


Figure 6 : Earliest natural products extracted from amphibian skin

[15] Erspamer, Y. *Annu. Rev. Pharmacol*., **1971** *11*, 327-50
[16] Bevins, C.L.; Zasloff , M. *Annu. Rev. Biochem*., **1990** *59*, 395-414
[17] Flier, J.; Edwards, M. W.; Daly, J. W.; Myers, C. W. *Science* **1980,** *208*, 503-506
[18] Mosher, H. S.; Furhman, F. A.; Buchwald, H. D.; Fischer, H.G. *Science* **1964**, *144,* 1100-1110

Examples of 'animal alkaloids' such as steroidal samandarines from the European fire and alpine salamanders *Salamandra salamandra* had already been published by Schopf.[19] (See Figure 7)

However, an outstanding contribution to the field of alkaloids derived from amphibian skin has been made John Daly and his co-workers at the National Institutes of Health, Maryland since they ventured into this field from the early 1960s. Spanning over four decades, their voluminous body of research on isolation, structure elucidation and biological activities of lipophilic alkaloids from skin glands of frogs native to South America is seen as one of the revolutionary developments in this area to date.[20]

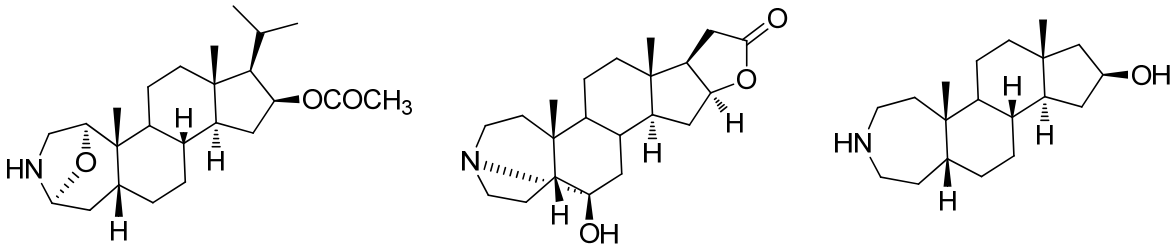


Figure 7 : Alkaloids from European salamanders (Salamandridae, *Salamandra*)

Their earliest involvement in this field dates back to 1963 with the isolation of batrachotoxins (see Figure 5) from the poison-dart frog *Phyllobates aurotaenia*. After the successful structure elucidation of Batrachotoxin, Albuquerque identified its target as a site on the voltage-dependent sodium channel of nerve and muscles Soon after, batrachotoxin and its radioactive analogue became an important tool in understanding the allosteric control of sodium channel functions by local anesthetic, anticonvulsant and antiarrythmitic drugs.[21]

The success of batrachotoxins gained the attention of both chemists and pharmacologists alike and led to collaborations that resulted in identification and providing structures to some of the most important molecules of this family known to date. Pumiliotoxin from the Equadorian frog *Epipedobates tricolor* and Pumiliotoxin A and B from skin extracts of *Dendrobates pumilio* in Panama became the initial members of this growing family of 'Dendrobatid alkaloids' in the late 1960s. It was studies that the pumiliotoxins, although toxic, at lower doses exhibit marked

[19] Schopf, C. I. *Experientia* **1963**, *19*, 329-338
[20] Reviews: a. Daly, J. W. *J. Nat. Prod.* **1998***, 61*, 162-172 b. Daly, J. W., *J. Med. Chem*. **2003**, *46*, 4, 445
[21] Brown, G. B.; Tieszan, S. C., Daly, J. W.; Warnick, J. E.; Albuquerque, E. X. *Cell. Mol. Neurobiol.* **1981**, *1*, 19-40

cardiotonic activity apparently due to prolonging open-time of voltage-dependent sodium channels.[22]

Around the same time, another major class of alkaloids was extracted from *Dendrobatus histrionicus,* which were categorised as histrionicotoxins. The discovery of this sub-class became a major breakthrough when Albuquerque defined them to be potent 'high-affinity' non-competitive blockers of the neuromuscular and central neuronal nicotinic channels.[23]

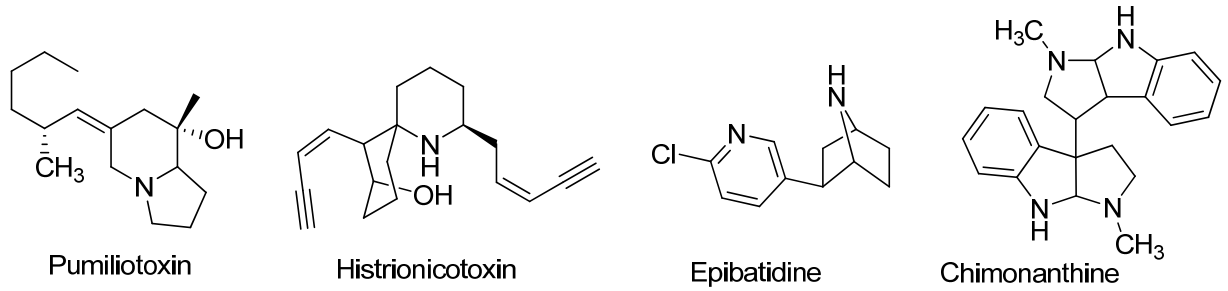


Figure 8 : Representative alklaoids of the frog poison alkaloid family

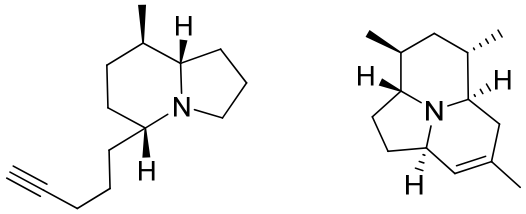
Two other alkaloids, epibatidine[24] from the skin extracts of *Epipedobates tricolor* and pseudophryaminol from genus *Pseudophryne* of Australian frogs belonging to the Myobatrachidae family, also proved to be remarkable as they were also established to be potent blockers of nicotinic channels and had biological functions similar to histrionicotoxins. Epibatidine was later found to be an impressive analgesic showing potency 200 times more than morphine when tested on mice.[20b]

By the late 1970s, more than 200 alkaloids had already been discovered from four families of frog namely Dendribatidae, Mantillidae, Bufonidae and Myobatrachidae. Owing to the rate at which these alkaloids were isolated, it became necessary to develop a coding system for these alkaloids in order to tabulate them systematically.

[22] Daly, J. W.; McNeal, E.; Gusovsky, F.; Ito, F.; Overman, L. E. *J. Med. Chem*. **1988**, *31*, 477-480
[23] a. Lapa, A. J.; Albuquerque, E. X.; Sarvey, J. M.; Daly, J. W.; Witkop, B. *Exp. Neurol*. **1975**, *47*, 558-580 b. Daly, J. W.; Nishizawa, Y.; Edwards, J. A.; Waters, J. A.; Aronstam R. S. *Neurochem Res*. **1991**, 16, 489-500
[24] Daly, J. W.; Myers, C.W. *Science* **1967**, *156*, 970-973

2.2 *Coding system of Dendrobatid alkaloids*

This numbering system was introduced for the first time in 1978[25] and consisted of a boldface number corresponding to the nominal mass followed by a boldface letter, which indicated the isomer. For example if the nominal mass of 205 is considered, seven alkaloids corresponding to this molecular weight have been discovered so far. While the structures of **205** (**A** and **B**) are known, tentative structures for (**E, F, G**) have been proposed whereas the structure of (**C** and **D**) are completely unknown (See Figure 9).

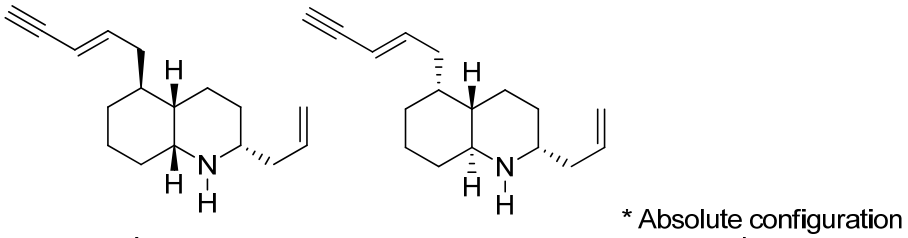


205A
5,8 substituted indolizidines

205B
Tricyclic

Figure 9 : An illustration of the Coding System for dendrobatid alkaloids

In addition, identification of different stereoisomers in the subsequent years, led to incorporation of prefixes such as *cis, trans, epi, iso etc.* (Figure 10).



(+)-*cis*-**243A**

(-)-*trans*-**243A**

Figure 10 : Modifications incorporated in the original Coding System

[25] Daly , J. W.; Brown, G. B.; Mensah-Dwumah, M.; Myers, C.W. *Toxicon* **1978**, *16*, 163-188

2.3 *Structural sub-classes of Dendrobatid alkaloids*

Over 30 years, through the tedious process of understanding the ecological role, origin and biosynthesis of these alkaloids, John Daly's pioneering research in this field had contributed more than over 400 of these alkaloids by 1998.[20] In a more recent evaluation in 2005, the total number of these alkaloids has increased to over 800.[26] Therefore, for the sake of convenience, Daly *et al* divided these alkaloids in 20 different classes based on their structure (Figure 11). This included the steroidal alkaloids extracted from European salamanders (Figure 7) and batrachotoxins, one class of 'Coccineline-like' tricyclics and another class comprising of newly discovered spiropyrrolizidines. However, structural studies of a large number of alkaloids placed under the category of 'tentative structures' are underway.

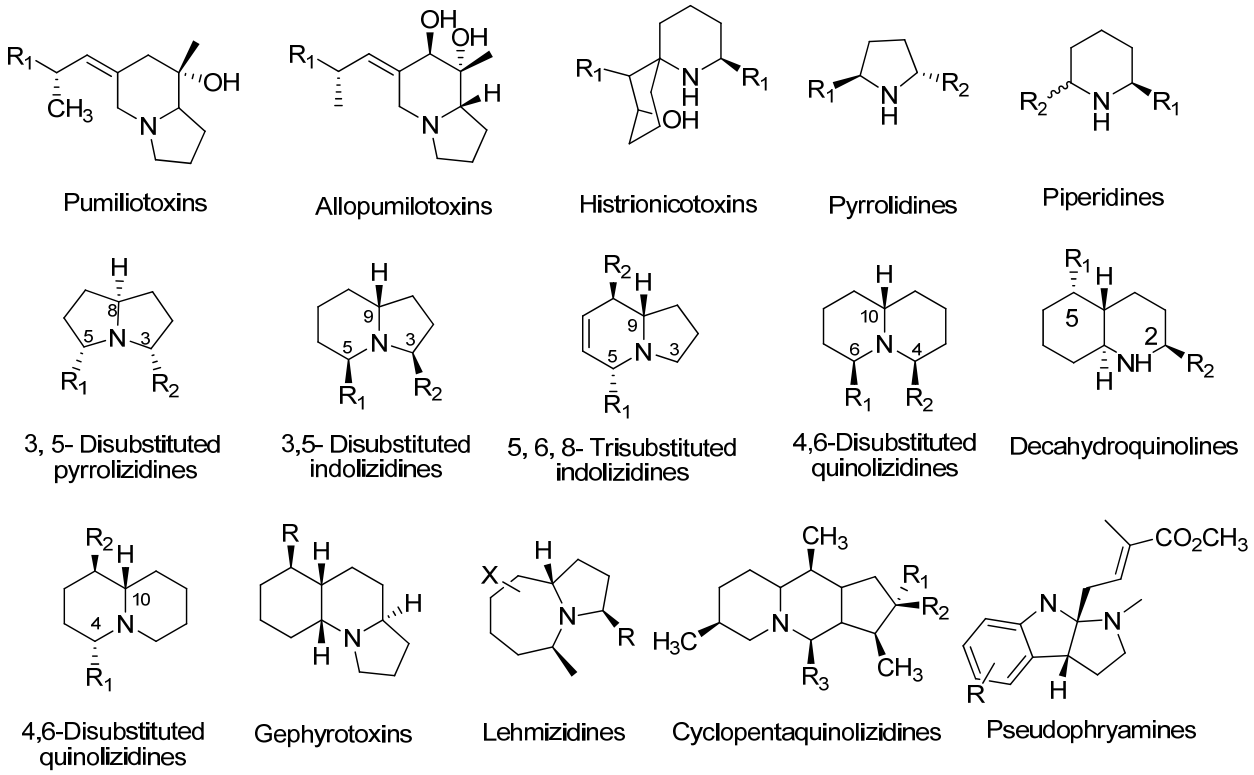


Figure 11 : General structures of various classes of amphibian alkaloids

[26] Daly, J. W.; Spande, T. F.; Garraffo, H. M. *J. Nat. Prod.* **2005**, *68*, 1556-1575

With the discovery of a vast number of these alkaloids, it became increasingly important to investigate their biogenesis and ecological role. We shall now discuss the studies that were conducted towards achieving this goal.

2.4 *Biogenesis and ecological role*

In spite of the fact that these alkaloids had invited considerable attention, their biosynthesis and a thorough understanding of their ecological role remained unaddressed.

As tribal populations all over the world were known to use animal alkaloids as dart and arrow poisons for hunting purposes, the toxicity of these alkaloids was well-established. It was therefore inferred that similar to the plant-kingdom, animal-alkaloids might also act as chemical defense agents against predators. Studies initiated towards the origin of these alkaloids in animals, led to the discovery of samandarines, one of the first examples of 'animal-alkaloids' from the skin of alpine salamanders. Soon after, it was established that samandarines are in fact biosynthesized by these animals from cholesterol.[27] This was done by raising three generations of salamanders in captivity and since no change in the content of the alkaloids was observed in the glands of these animals, it was inferred that these chemicals are not acquired from external sources.

Considering that dendrobatid alkaloids had no precedent in any other known source from Nature, at the outset, it was suspected that they are also synthesized *de novo* by the frogs from biosynthetic precursors.[20] The first example of an alternate natural source of dendrobatid alkaloids, was found in 1990, after three decades of research in this field, when Daly's group in collaboration with Dumbacher, an ornithologist, detected that homohistrionicotoxin, previously categorized as a dendrobatid alkaloid only, was also a major alkaloid in the feathers and skin of passerine birds of the genus *Pitohui*.[28] This unprecedented discovery of homobatrachotoxin from passerine birds was compelling enough to give birth to the idea that the amphibians might not be actually biosynthesizing these alkaloids but acquiring them from external sources, in other words, *sequestering* them from their surroundings. If this was the case, the source and mode of uptake through symbiosis or dietary sources, had to be recognized.

[27] Mebs, D.; Pogoda, W. *Toxicon* **2005**, *45*, 603-606
[28] Dumbacher, J. P.; Beehler, B. M.; Spande, T. F.; Garaffo, H. M.; Daly, J.W. *Science* **1992**, *258*, 799-810

In 1980 Duffey *et al*[29] had elaborately reviewed the concept of 'sequestration' in the animal kingdom. The term 'sequestration' was defined as deposition of secondary phytochemicals into specialized tissues or glands of insects in order to facilitate chemically mediated defense or communication. It was also mentioned that efficient sequestration requires that the properties of a chemical be complementary with the normal physiology of the sequestrator.

In order to substantiate this proposition, when the dendrobatid frogs were raised in captivity, it was observed that they completely lacked these alkaloids[30] but when they were fed with fruit flies sprayed with alkaloid-containing powder or myrmicine ants containing alkaloids, they ready accumulated them in their skin[31]. Through these series of experiments, it was unambiguously concluded that these alkaloids accumulated in the frogs through their dietary sources.

However, at this stage two important points needed consideration. Firstly, a better understanding of the mechanism of alkaloid-uptake of the frogs would be valuable. Secondly, if the above conclusions regarding the dietary sources were indeed true, a deeper investigation of the probable dietary sources of these frogs would be informative, in particular because it could provide a new and alternative source of these scarce pharmacologically promising molecules.

Subsequent biological studies on the frogs revealed that none of the species possessed any enzymes associated with alkaloid synthesis or metabolism.[20] This was consistent with the fact that the sequestered alkaloids were stored without undergoing any change, chemically (degradation/ functionalization) or quantitatively.

However, it is interesting to note that the only exception in this aspect was reported in 2003 which provided evidence for the presence of an enantioselective pumiliotoxin 7-hydroxylase which converts a toxic Pumiliotoxin (+)-**251D** to a more toxic allopumiliotoxin (+)-**267A**[32]. This example has been exemplified to be an evolutionary development in one lineage of dendrobatid frogs in order to enhance the anti-predator potency of stored pumiliotoxins (PTXs).

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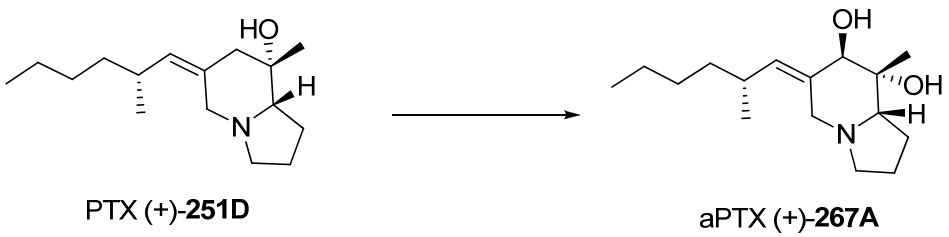
[29] Duffey, S. S. *Annu. Rev. Entomol* **1980**, *25*, 447-477

[30] a. Daly, J. W.; Myers, C. W.; Warnick, J. E.; Albuquerque, E. X. *Scienc*e **1980**, *208*, 1383-1385 b. Daly, J. W.; Secunda, S. I.; Garraffo, H., M.; Spande, T. F.; Wisneiski, A.; Nishishara, C.; Cover, J. F.; Jr., *Toxicon* **1992**, *30*, 887-898

[31] a. Daly, J. W.; Secunda, S. I.; Garraffo, H., M.; Spande, T. F.; Wisneiski, A.; Cover, J. F.; Jr. *Toxicon* **1994**, *32*, 657-663 b. Daly, J. W.; Garraffo, H. M.; Spande, T. F.; Jaramillo, C.; Rand, S. *J. Chem. Ecol*. **1994**, *20*,943-955

[32] Daly, J. W.; Garraffo, H., M.; Spande, T. F.; Clark, V. C.; Ma, J.; Ziffer, H.; Cover, J. F. Jr. *Proc. Natl. Acad. Sci. U. S. A*. **2003**, *100*, 11092-11097



PTX (+)-**251D** aPTX (+)-**267A**

Figure 12 : Enantioselective enzymatic conversion of (+)-PTX 251D to aPTX (+)-267A

Considerable research is currently being conducted towards the understanding of the over-expressed systems present in these amphibians to accumulate these alkaloids. It has been found out that the frogs from genus *Phyllobatus* have evolved modified sodium channels which do not respond to batrachotoxins, thereby allowing them to eat the unknown anthropod source containing this toxin[33] without danger.

On the other hand, extensive research is currently under progress to identify the dietary sources of these anurans. Although dietary arthropods that contain batrachotoxins, histrionoicotoxins and epibatidine have still not been identified, some classes of dendrobatid alkaloids are undoubtedly believed to come from ants (PTXs), beetles (coccinellene-like tricyclics) and small millipedes (spiropyrrolizidines).[34]

In 2007, Daly *et al*[35] isolated as many as 80 alkaloids from oribatid mites previously found in the neotropical poison frogs which has unraveled the first major link to the source of these alkaloids in the dietary source of the frogs. Although, many alkaloids whose structures are still under investigation, have been categorized as 'tentative tricyclics'[26], structures of five tricyclic alkaloids have been confirmed to date (see Figure 13) and our target molecule, Alkaloid (-)-**205B** is one of these compounds, which we shall now discuss in detail.

[33] Daly, J. W., Myers, C. W, Warnick, J.E., Albuquerque, E. X. *Science* **1980,** 208, 13830-1385
[34]a. Daly, J. W. *Proc. Natl. Acad. Sci. U. S. A.* **1995**, *92*, 9-13 b. Daly, J. W., Garraffo, H., M., Myers, C. W. *Pharm. News* **1997**, *4*, 9-14
[35] Saporito, R. A., Donnelly, M. A., Norton, R. A., Garraffo, H. M., Spande, T. F., Daly, J. W. *Proc. Natl. Acad. Sci. U. S. A.* **2007**, *104*, 8885-8890

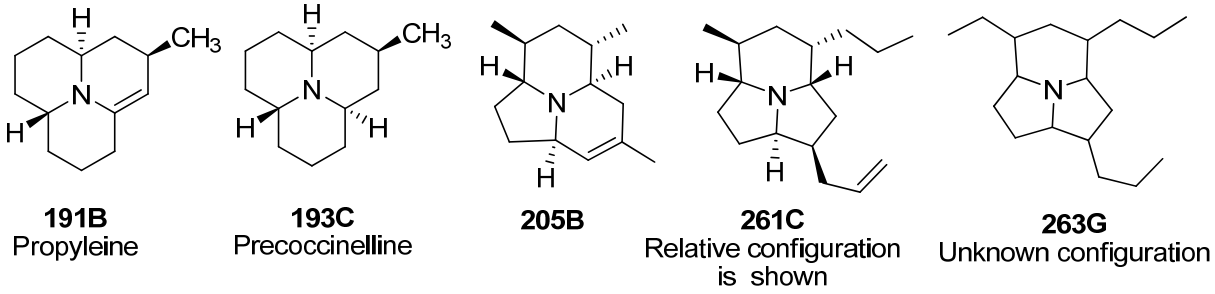


Figure 13 : Coccinelline-like tricyclics

2.5 *Alkaloid* (-)-205B*: Isolation and Structure determination*

The alkaloid (-)-**205B** is one of the five tricyclic alkaloids belonging to the family of dendrobatid alkaloids.[26] It was first isolated in 1987 as a trace alkaloid from the skin of the South American neotropical frog *Dendrobates pumilio* native to Panama.[36]

Soon after its discovery, based on the spectral analysis of the natural product, a provisional structure, **2** was assigned which comprised of an azatricyclododecene skeleton with the relative stereochemistry as depicted in Figure 14. Subsequently, the presence of a weak Bohlmann's band at 2796 cm^{-1} in the IR spectrum led to the re-evaluation of spectral data and after extensive NMR, FTIR and HRMS studies, the revised structure, **1** was published in 1998.[37] Thus, this rare tricyclic alkaloid possesses an unprecedented 8b-azaacenaphthylene ring system with five stereocentres.

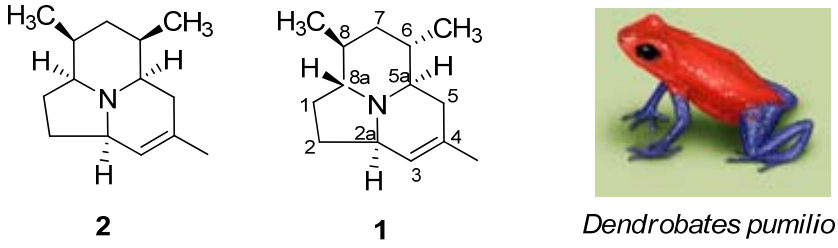


Figure 14 : Originally proposed structure 2 and corrected structure 1

[36] Tokuyama, T.; Nishimori, N.; Shimada, A.; Edwards, M.W.; Daly, J. W. *Tetrahedron* **1987,** *43*, 643-652
[37] Tokuyama, T.; Garraffo, H. M.; Spande, T. F.; Daly, J. W. *Anal. Asoc. Quim. Argentina* **1998,** *86,* 291-298

In 2003, when the first total synthesis of this alkaloid was attempted by Toyooka *et al* [38], they succeeded in obtaining its unnatural isomer, thus establishing the absolute stereochemistry of the natural product as 2a*R*, 5a*R*, 8*S*, 6*S*, 8a*R*.

Due to lack of material, its biological activity has never been tested unlike its unnatural isomer (*ca* Chapter 3). Apart from providing synthetic material for biological testing, this compound has been of considerable interest to synthetic research groups due to its challenging structure, for which two syntheses of this molecule have been reported to date. We shall discuss these approaches in detail (Chapter 4) after a brief overview of the physiological activities of this family.

[38] Toyooka, N.; Fukutome, A.; Shinoda, H.; Nemeto, H. *Angew. Chem. Int. Ed.* **2003**, *42*, 3808-3810

Chapter 3:

Amphibian Alkaloids: Biological perspectives

3.1 ***General principles:***

With the basic knowledge that secondary metabolites serve as chemical defense in Nature by acting as toxins against predators, a detailed understanding of the mode of action of these molecules would serve as a helpful starting point for investigation of their biomedical properties and also for the design and synthesis of new pharmacologically active entities.

Several secondary metabolites which act as defense systems are known to have multiple targets in their predators. Alkaloids, however, are one sub-class which exclusively targets certain components in the animal cell. The various sites in the animal cell which are targeted by secondary metabolites have been identified and are schematically represented in Figure 15.[12] Out of the possible target-sites, those specifically targeted by alkaloids have been italicized.

The successful identification of these sites was automatically followed by the need to understand more closely the chemical interactions of alkaloids with these molecular targets. Most alkaloids during evolution were designed in a manner that made them capable of mimicking endogenous substances such as neurotransmitters. It is for this reason that they have been occasionally addressed as 'neurotransmitter analogs'.[39] It is the amino acid origin of both alkaloids and neurotransmitters like acetylcholine in animals that has been invoked as an explanation for this similarity.

In addition, studies of many alkaloids have revealed that they can act as powerful neurotoxins,[40] selectively chosen by plants for defense specifically against animals and not other plants. This is seen as an evolutionary modulation which could be attributed to the fact that nerve cells are present only in animals.

[39] Patrick, G. L., *An Introduction to Medicinal Chemsitry,* II Edition, Oxford Press
[40] Wink, M., *Studies in Natural Products Chemistry* **2000**, *21*, 2, 3-122

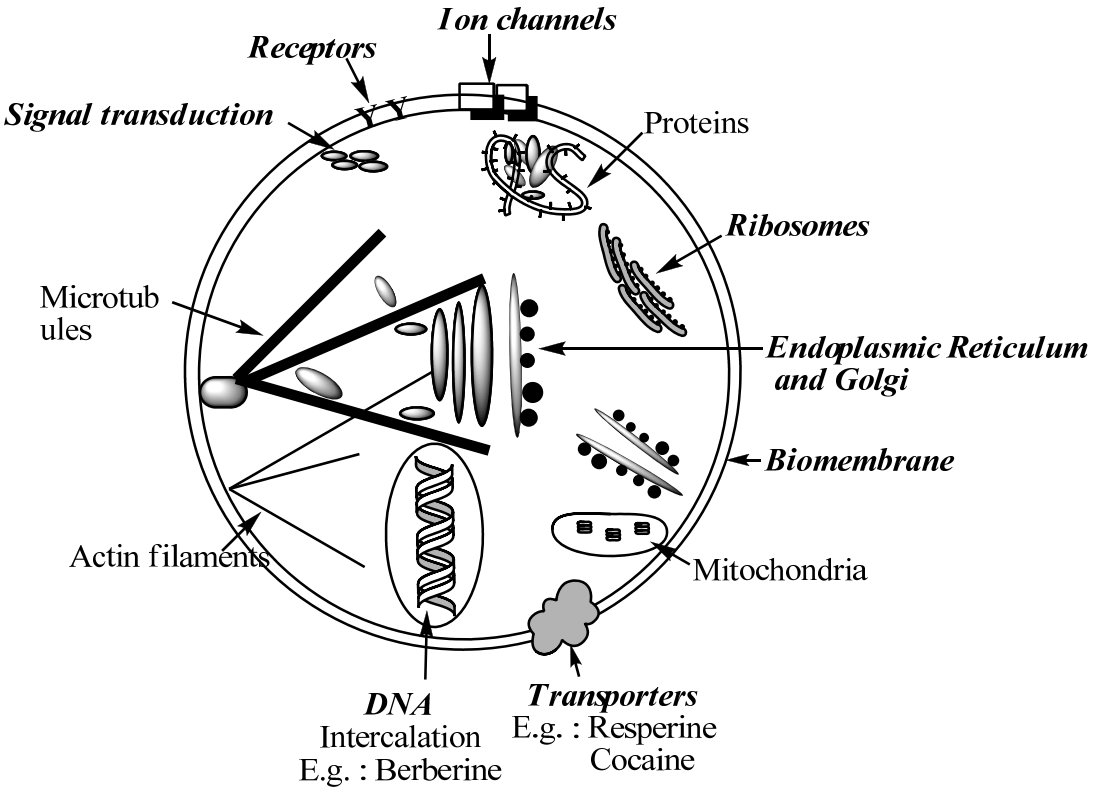


Figure 15: Molecular targets for secondary metabolites in animal cell

Neurotransmitters are chemicals released by the nerve-cells that act as chemical messengers. They function by binding to active sites on neuroreceptors which allows efficient transmission of information between nerve cells. Due to their structural similarities with neurotransmitters, alkaloids can also bind to these receptors and activate or deactivate them and alter the functioning of Na^+, K^+ and Ca^{2+} ion channels. Recent pharmacological studies on frog alkaloids have shown that these alkaloids have a strong influence on neuronal receptors, a brief description of which has been outlined in the following section.

3.2 *Nicotinic Acetyl Choline Receptors: Structure and functions*

Broadly speaking, neuronal disorders mainly arise due to an increase or decrease in the concentration of neurotransmitters toward the specific receptor binding sites on the target cells. Cholinergic nicotinic neuronal transmission has been identified as one of major pathways that regulate physiological processes like memory and recognition. Nicotinic acetylcholine receptors (nAChRs), in this cholinergic nervous system, are ligand-gated ion channels comprising of five subunits (Figure 16). The nAChRs derive their name from the fact that these channel pores open when nicotine binds to them.

These Ligand Gated Ion Channels (LGICs) are a group of pore forming trans-membrane proteins which open and close in response to the binding of a neurotransmitter. They differ from Voltage Gated Ion Channels which are transmembrane ion channels which are activated by the potential difference near the channel. For example: Voltage-gated Ca^{2+} channels play a role in the neurotransmitter release in pre-synaptic nerve endings. To date, 12 nAChR subunits (α2-α10 and β2-β4) have been identified[41]. The most important subtypes present in mammalian central nervous system contain α7, β2 and β4. Various combinations of these subunits give rise to different subtype receptors. Out of these, neuronal nAChRs consist of combinations of α (α2-α6) and β (β2-β4) subunits or α-subunits homomers (α7 or α9) or α-subunit heteromers (α9 and α10).

These nAChRs have been linked to several neuronal disorders. For example, significant damage of the α4β2 subunits has been observed in the cortical autopsies of patients suffering from Alzheimer's disease.[42] Thus, treatment of central nervous system disorders such as schizophrenia, Alzheimer's disease, epilepsy and bipolar disorder, therefore requires agonists to activate the receptors (that can act as chemical messengers in the lack of neurotransmitters) or antagonists (that block the binding sites making them unavailable for the excess of chemical messengers), for the improved functioning for the damaged nerve cells.

[41] Hogg, R. C.; Raggenbass, M.; Bertrand, D. *Rev. Physiol. Biochem. Pharmacol.* **2003**, *147*, 1-46
[42] Weiland, S.; Bertrand, D.; Leonard, S. *Behav. Brain. Res* **2000**, *113*, 43-56

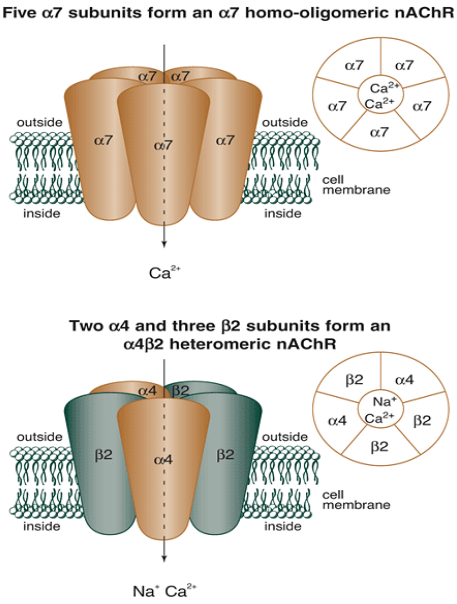


Figure 16: Diagrammatic representation of the nAChR ion-channel pentamers

Interestingly, Freedman *et al*[43] had published a survey in 1993 reporting that patients suffering from schizophrenia resort to excessive smoking. Subsequently, Bertrand and co-workers[44] demonstrated that chronic exposure to nicotine, a tobacco compound (alkaloid) in a healthy adult human being leads to an increase in the number of binding sites on cell surfaces (termed upregulation of α2β4 receptors), which leads to changes in the normal composition of their nerve cells. It was therefore considered whether the possible cause of excessive smoking in schizophrenics could be related to their need to self-administer nicotine from an external source, (through smoking), due to their neuropsychotic disorder[45] which is also known to alter neuroreceptors. Around the same time, the link between α7 subunits and ailments such as schizophrenia and bipolar disorder was also discovered as colossal damage of the α7 subunit was observed in patients suffering from these diseases.

Thus, these on-going developments in biology have provided very important leads to chemists in proposing potential nAChR agonists and antagonists for developing therapeutics for these neuronal disorders. As a result, research in this area has gained appreciable attention from

[43] Adler, L. E.; Hoofer, L. D.; Wiser, A.; Freedman, R. *Am. J. Psychiatry* **1993**, *150*, 1856-1861
[44] Buisson, B.; Bertrand, D. *Journal of Neuroscience* **2001**, *21*, 1819-1829
[45] Martin, L. F.; Kem, W. R., Freedman, R. *Psychopharmacology* **2004**, *174*, 54-64

academia and industry. In the past decade, heavy investments have been made by leading pharmaceutical companies in development of alkaloid-based nAChRs agonists and antagonists.[29]

A few existing examples of synthetic drug-candidates undergoing clinical trials as nAChR agonists and potential nAChR antagonists have been listed in Figure 17.[46]

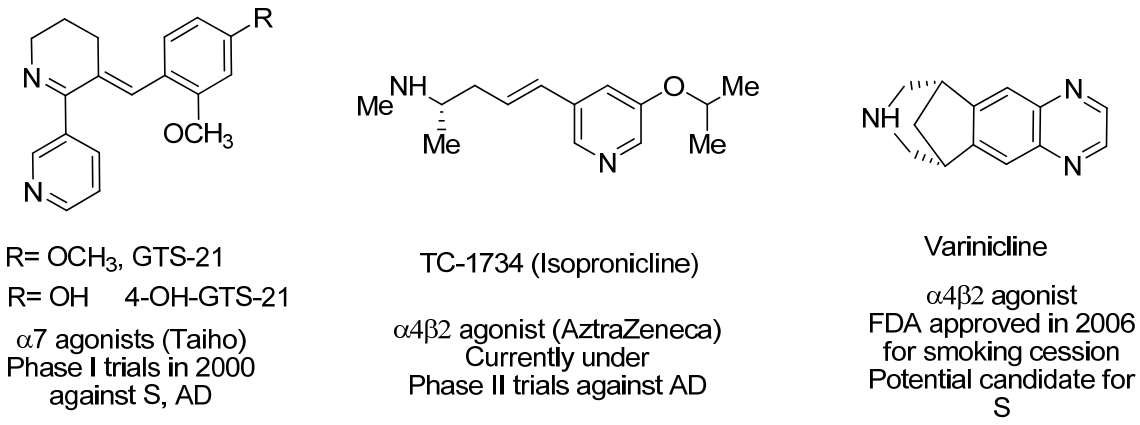


Figure 17 : nAChR agonists and antagonists

[46] Arneric, S. P., Holladay, M.; Williams M. *Biochemical Pharmacology* **2007**, 1092-1101

3.3 *Alkaloids from frog skin: Pharmacological activities known*

Over the past two decades, alkaloids from the skin of frogs have been seen as being potential candidates for the synthesis of potential agonists and antagonists drugs related to nervous system dysfunctions. Amongst them, epibatidine, one of the first compounds to be recognized for its pharmacological prowess as an analgesic.[20] The first total synthesis of both enantiomers of epibatidine reported from Corey's laboratory in 1993, made it possible to have access to sufficient amount of synthetic product to study the mode of action of this molecule more deeply. In 1994, these investigations revealed that it is in fact an agonist of the α4β2 nicotinic receptors[47].

Following this breakthrough, several less toxic analogues of epibatidine were synthesized. One of these, ABT-594, developed by Abbott Labs, underwent phase I and phase II trials as an analgesic[48](Figure 18). While many other analogues are still under investigation, this clue has opened doors to ground-breaking disclosures in the field of pharmacology related to neuronal disorders with respect to this class of compounds.

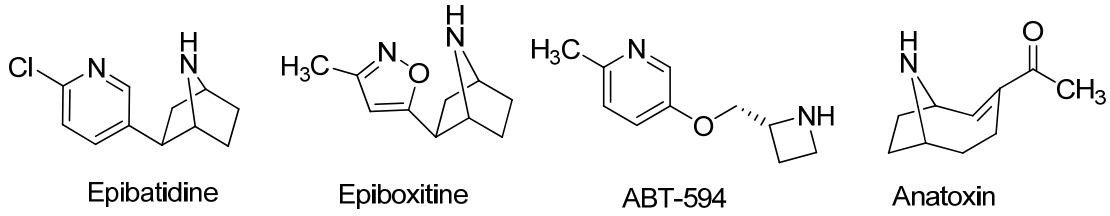


Figure 18 : Epibatine and its analgoues

Thanks to the synthetic efforts of the Overman's group, several analogues of pumiliotoxins (PTXs) were also synthesized and tested for biological activity. It was found that the most potent analogue, 2,5-di-*n*-propyl-*cis*-decahydroquinoline (PTX-C_{II}), reversibly block the nictonic receptors and was a potential antagonists.[49] Soon after, histrionicotoxins and some indolizidines belonging to this family were also discovered to be nicotinic antagonists.[50]

[47] Badio, B.; Garraffo, H.M.; Spande, T. F.; Daly, J. W. *Med. Chem. Res.* **1994**, *4*, 440-448
[48] Daly, J. W.; Garraffo, H. M.; Spande, T. F.; Decker, M. W.; Sullivan, J. P.; Williams, M. *Nat. Prod. Rep.* **2000**, *17*, 131-135
[49] Warnick, J. E.; Jessup, P. J.; Overman, L. E.; Edelfrawi, M. E.; Nimit, Y.; Daly, J. W.; Albuquerque, E. X *Mol. Pharmacol.* **1982**, *22*, 565-573
[50] Daly, J. W.; Nishizawa, Y.; Padgett, W. L *Neurochem. Res*. **1991,** *12*, 1213-1218

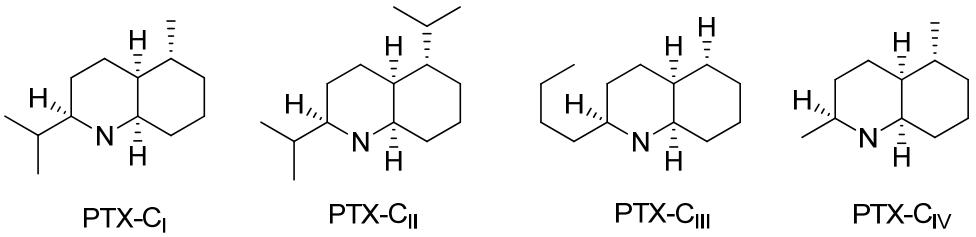


Figure 19 : Pumiliotoxin C analogues : nAChRs antagonists

* Structures of natural products were tentative at the time of biological studies

Thus, with significant advancements in the isolation, structure elucidation and synthesis in the past decade, dendrobatid alkaloids are today seen as an impressive reservoir of likely candidates for the nAChR related therapeutics.

Having accomplished the total syntheses of various alkaloids of this family, Toyooka *et al*[51] forayed into this arena with their report on the pharmacology of many dendrobatid alkaloids and their analogues identifying indolizidine **235B'**, quinolizidine, 1-epi-**207I** and the tricyclic **205B** as selective non-competitive inhibitors of nAChRs in 2004. In particular, (-)-**235B'** is found to be an open channel blocker of the α4β2 nAChR, which could prove useful in the treatment of epilepsy. Alkaloid (-)-**223A** exhibited blocking effects on both α4β2 and α7receptors and (-)-1-epi-**207I** and (+)-**205B** (the unnatural isomer of (-)-**205B)**, were found to be selective blockers of α7 receptors. (+)-**205B** has also been listed in the database of medicinal compounds as potential drug candidates for the treatment of schizophrenia.[44]

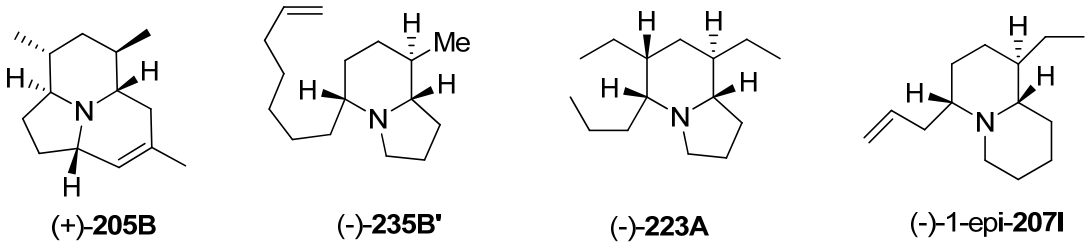


Figure 20 : Representative molecules (and analogues) from the dendrobatid family tested for potential nAChRs agonists and antagonists

[51] Toyooka, N.; Tsuneki, H.; Kobayashi, S.; Dejun, Z.; Kawasaki, M.; Kimura, I.; Sasaoka, T.; Nemoto, H *Current Chemical Biology* **2007**, *1*, 97-114

Although, major accomplishments have been made in this direction, scarcity of material available from nature has largely been a limiting factor for studying the pharmacological potency of these molecules.

Therefore, with a requisite knowledge of the occurrence and biological significance of this vast resource of alkaloids, we shall now concentrate our efforts on the syntheses of Alkaloid (-)-**205B.**

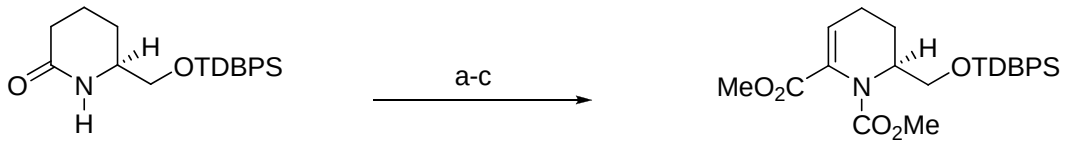
Chapter 4:

Reported syntheses of (-)-205B

4.1 *Total Synthesis of the Antipode of Alkaloid 205B*'

In 2003, Toyooka *et al* reported the first total synthesis[38,52] of the alkaloid **205B** as the antipode of the natural product. The key transformations of this synthesis were a series of Michael-type additions to enaminoesters for introduction of the methyl substituents.

This synthesis began with a known lactam **3** which was obtained in 5 steps from commercially available *p*-methoxylbenzyl hex-5-enoate.[53] Lactam **3** was converted into enaminoester **4** via the formation of an enol triflate of the carbamate intermediate, followed by a Pd-catalysed CO insertion.

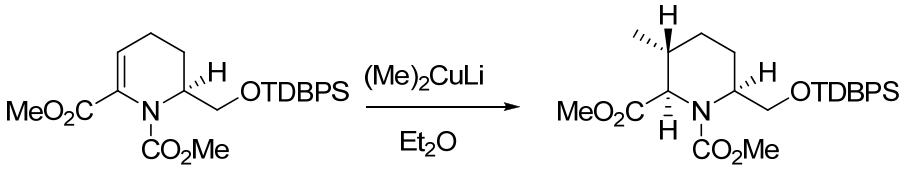


3 **4**

a) n-BuLi, $ClCO_2Me$ (98%), b) LiHMDS, Comin's Reagent (96%), c) CO, $Pd(PPh_3)_4$, MeOH (88%)

Scheme 1: Synthesis of enaminoester 4

The treatment of enaminoester **4** with $(CH_3)_2CuLi$ furnished the methylated product **5** as a single stereoisomer in 98% yield[54].



4 **5**

Scheme 2 : Michael-type addition to the enaminoester

The stereochemistry can be explained by the preferential conformation of the substrate which places the alkoxy methyl substituent in the axial position to avoid $A^{1,3}$ allylic strain with the methoxy carbonyl group on the nitrogen atom. The steric and stereoelectronic effects therefore

[52] Toyooka, N.; Fukutome, A.; Shinoda, H.; Nemoto, H. *Tetrahedron* **2004**, *60*, 6197-6216
[53] Hodgekinson, T. J.; Shipman, M. *Synthesis* **1998**, 1141-1144
[54] Momose, T.; Toyooka, N. *J. Org. Chem*. **1994**, *59*, 943-945

favoured axial attack of the methyl cuprate on this conformer giving rise to the corresponding enolate which upon protonation leads to the observed stereochemistry, once again, to avoid the $A^{1,3}$ allylic strain of the methoxycarbonyl substituent with the carbamate functionality.

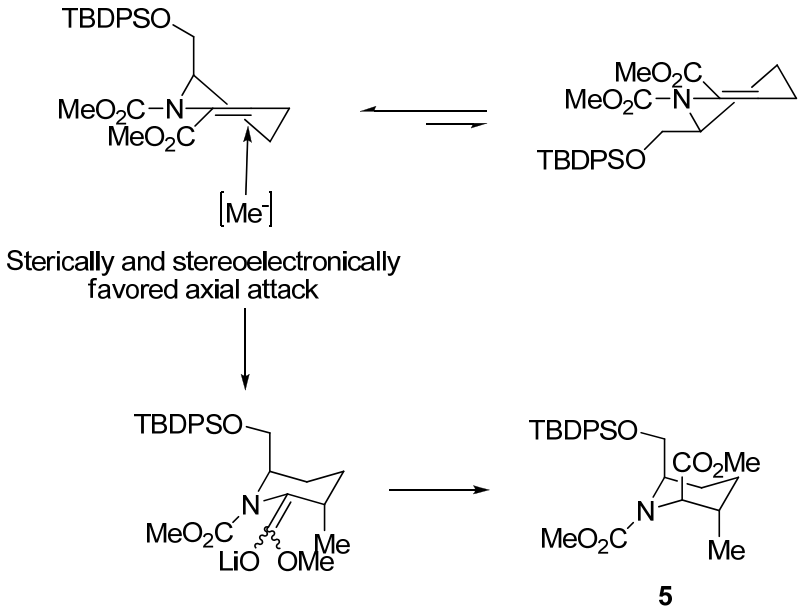
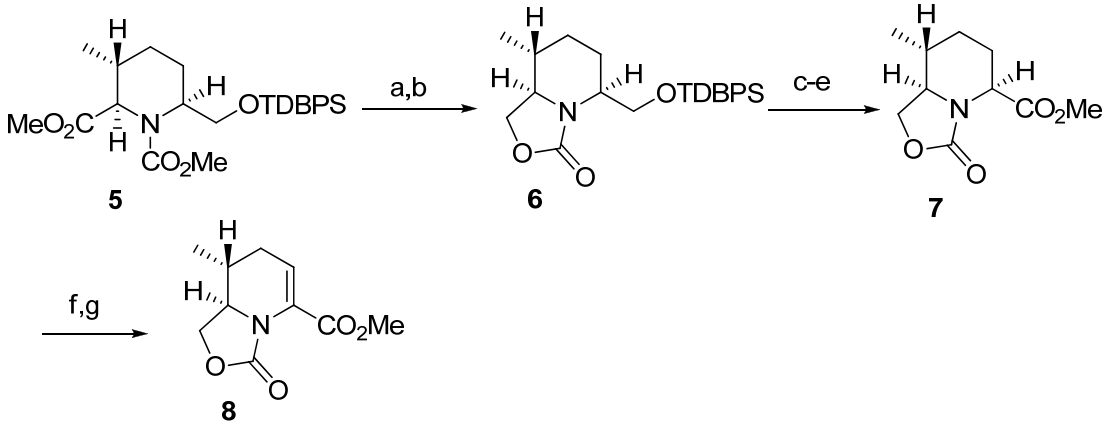


Figure 21: Stereoselectivity in the Michael-type addition

The oxazolidinone **6** was then constructed smoothly when the alcohol obtained by the reduction of the ester in **5** was treated with NaH. Removal of the silyl protection on the alcohol, followed by an oxidation-esterfication sequence furnished compound **7,** which was then subjected to Matsumara protocol involving an oxidative elimination of a thiopheyl intermediate to get the enaminoester **8.**

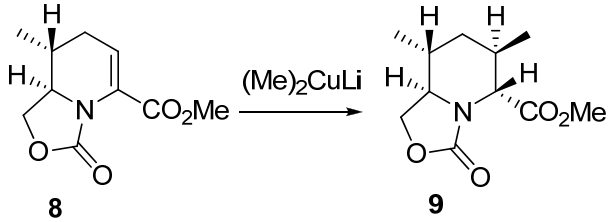


5 **6** **7** **8**

a) $LiBEt_3H$,THF (99%), b) NaH,THF (99%), c) TBAF,THF (99%), d) Swern Oxidation, e) Pinnick Oxidation, CH_2N_2,EtOAc (86% for 3 steps), f) LiHMDS, PhSSPh,THF (99%), g) mCPBA,2,6-Lutidine

Scheme 3: Synthesis of enaminoester 8

At this stage, a second Michael-type conjugate addition was performed, which resulted in the formation of only one isomer, thus giving rise to the tetrasubstituted piperidine ring in **9**.



8 **9**

Scheme 4: The key Michael-type addition

In this case, the stereochemistry was explained by the fact that the bicyclic nature of the carbamate protection leads to the conformation in which the α-nitrogen alkoxy methyl substituent occupies a pseudo-equatiorial position. Again, a stereoelectronically driven methyl cuprate addition followed by a stereoselective protonation gave the product with the observed stereochemistry.

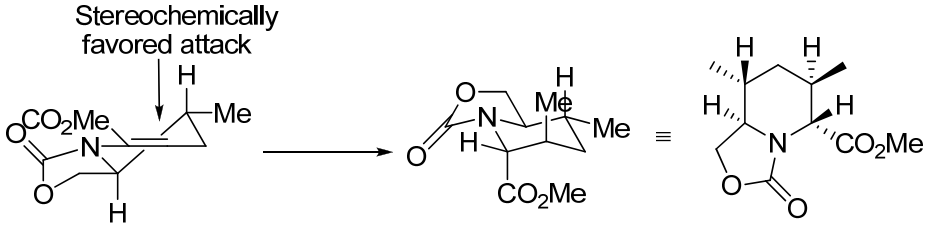
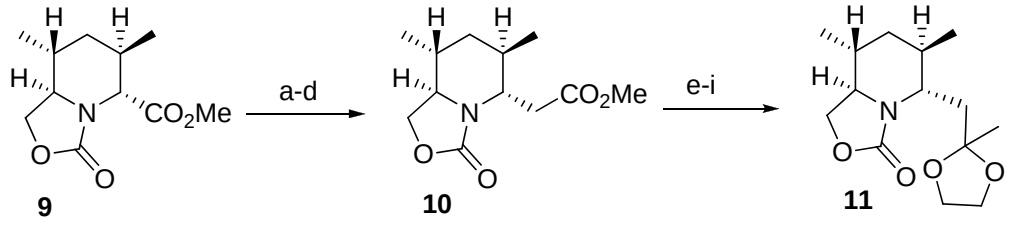


Figure 22 : Stereochemical course of the second Micheal-type addition

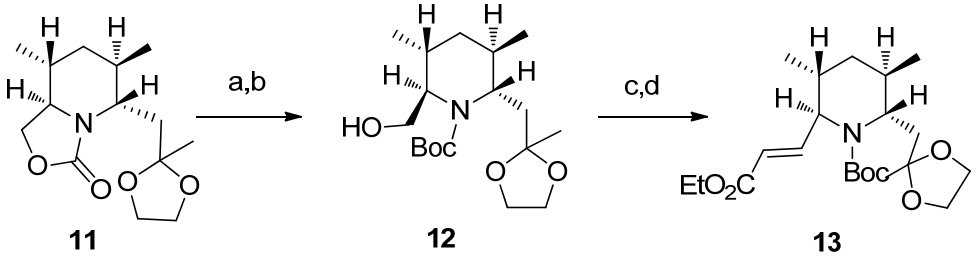
An Arndt-Eistert sequence was then employed to extend the carbon chain and obtain homologated ester **10,** which was transformed into a ketone via the Weinreb amide and finally protected as an ethylene acetal **11.**



a) LiOH,MeOH/H_2O,Reflux b) $ClCO_2Et$,Et_3N,THF c) CH_2N_2,Et_2O d) $PhCO_2Ag$, Et_3N, MeOH,RT (71% over 4 steps) e) LiOH,MeOH/H_2O,Reflux f) 1,1'-Carbonyldiimidazole g) Et_3N,(MeO)MeNH.HCl, THF (98% over 2 steps h) MeMgBr,THF (73%) i) Ethylene Glycol, pTsOH, Benzene, reflux (86%)

Scheme 5 : Synthesis of the acetal 11

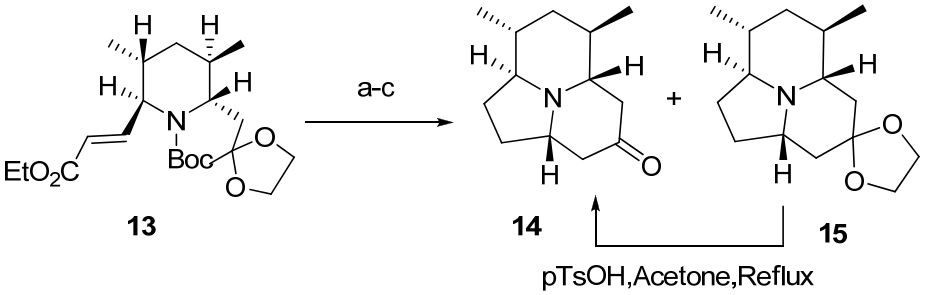
An oxazolidinone ring opening, followed by protection of the free amine with the Boc protecting group gave the tetra-substituted piperidine **12**. The primary alcohol, thus obtained, was oxidized and engaged in a Wittig-Horner reaction which afforded the β-unsaturated ester **13**.



a) 2 M KOH in iPrOH b) Boc_2O, NaOH, Dioxane/H_2O (74% over 2 steps) c) Swern Oxdn d) $(EtO)_2P(O)CH_2CO_2Et$, NaH,THF (74% over 2 steps)

Scheme 6 : Synthesis of enoate **13**

The double bond of enoate **13** was hydrogenated followed by partial reduction of the ester to the corresponding saturated aldehyde. The stage was now set to attempt the bis-cyclisation reaction. A simple treatment of this intermediate with *p*-TsOH at reflux in benzene/acetone mixture triggered the cleavage of the Boc and the acetal protecting groups, thereby leading to the formation of the tricyclic system via an intramolecular Mannich condensation to furnish the ketone **14** with a little amount of acetal **15** which could be easily converted to the ketone.



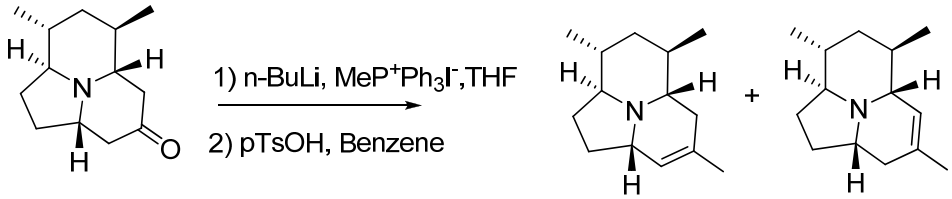
13 14 15

a) 10% Pd-C,H_2,EtOAc b) DIBAL,CH_2Cl_2 c) pTsOH, Acetone, reflux
(**14**: 62% over 3 steps)

Scheme 7: Construction of the tricyclic system

With this advanced intermediate in hand, their final task was to introduce the trisubtituted alkene unit. Efforts were made to trap the triflate obtained from the regioselective enolate using a chiral lithium base, followed by a cross coupling reaction with $(CH_3)_3Al$ in presence of $(PPh_3)_4Pd$[55] to achieve this transformation but unfortunately this elegant approach was unsuccessful.

Finally, the carbonyl was transformed into an exo-alkene using Wittig reaction and an acid-catalyzed isomerisation furnished the product with an isomeric ratio of 6.5:1 in favor of the desired isomer **16** which was obtained with yield 63%. This result was supported by theoretical studies which confirmed that the desired isomer is lower in energy by 2.01 kcal/mol.



14 16 17

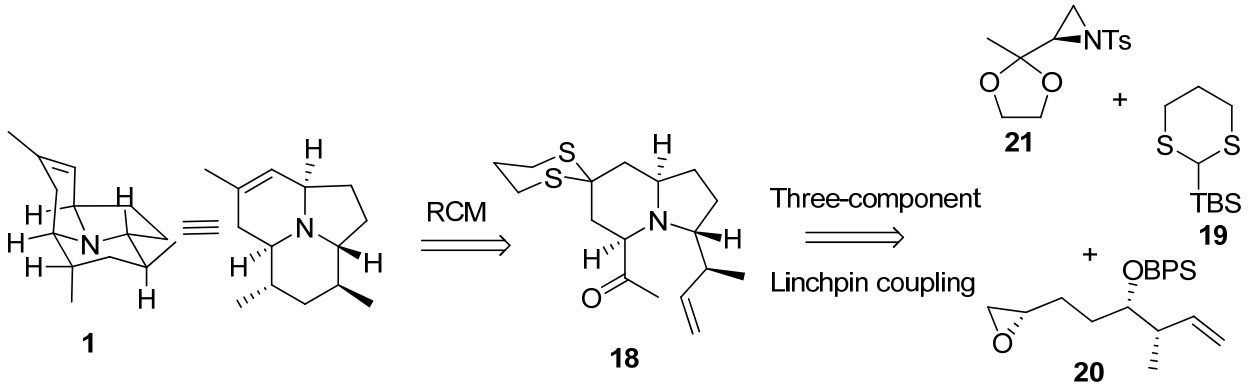
Scheme 8 : Completion of the synthesis

Thus, the highlight of this synthesis is the efficient stereocontrol over the chiral centres and the remarkable one-pot formation of the tricyclic system. Also, being the first total synthesis, it was instrumental in establishing the absolute stereochemistry of the nature product. The length of the synthesis which required more than 30 steps for the longest linear sequence is however, the main drawback of the synthesis.

[55] Takai, K.; Sato, M.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 108-115

4.3 *A convergent Multi-Component Linchpin Coupling strategy for synthesis of Alkaloid* (-)-205B

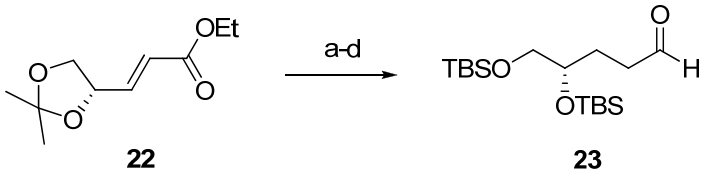
Soon after, the Smith group, in 2005, [56, 57] reported the completion of the first total synthesis of the natural isomer (-)-**205B**. Their strategy entailed a dithiane three-component 'linchpin' coupling reaction comprising of a one-pot sequential reactions of a suitably functionalised epoxide **20** and an aziridine **21**. (Scheme 9)



Scheme 9 : Retrosynthetic Strategy of Smith's Syntheis of (-)-205B

Synthesis of epoxide 20

The first component of this multi-component reaction, epoxide **20,** was synthesized from the known aldehyde **23,** which in turn was obtained in 4 steps from commercially available ester **22** with an overall yield of 95%.

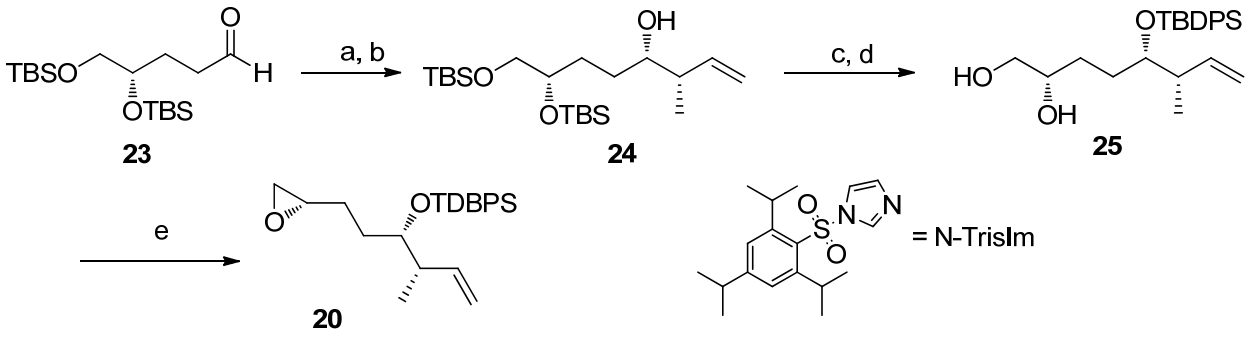


a) 2M HCl, EtOH b) H_2, Pd/C, EtOH c) TBSCl, imidazole, DMAP, CH_2Cl_2 d) DIBAL, CH_2Cl_2 (95% over 4 steps)

Scheme 10: Synthesis of aldehyde 23- precursor of epoxide 20

[56] Smith. A., B. III; Kim, Dae-Shik *Org. Lett.* **2005,** *15*, 3247-3250
[57] Smith. A., B. III; Kim, Dae-Shik, *J. Org. Chem*. **2006**, *71*, 2547-2557

Brown's asymmetric crotylation[58] of aldehyde **23** afforded the corresponding homo allyl-alcohol **24** with an excellent diastereoselectivity. Protection of this newly formed secondary alcohol with TBDPSCl followed by selective cleavage of TBS group generated diol **25.** The epoxide formation was completed via a one-flask Fraser-Reid protocol[59] with an overall yield of 65% for the four step sequence.



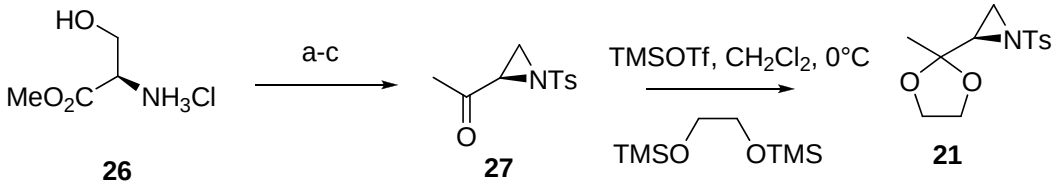
23 **24** **25** **20**

a) (+) Ipc_2B $BF_3.Et_2O$,THF b) NaOH, H_2O_2 81%, 11: 1 (dia) c) BPSCl, Imidazole, DMAP, CH_2Cl_2
d) CSA, MeOH/CH_2Cl_2 (88% for 2 steps) e) NaH,TrisIm,THF (99%)

Scheme 11: Synthesis of epoxide 20

Synthesis of aziridine 21

Aziridine **21** was obtained in 4 simple steps from the commercially available serine methyl ester **26**. These steps involved the tosylation of the nitrogen of the ester, followed by a Mitsunobu ring closure to furnish the aziridine moiety. Subsequent treatment with MeLi gave the corresponding ketone **27** which was then protected as an ethylene acetal under Noyori's conditions.



26 **27** **21**

a) TsCl, Et_3N, CH_2Cl_2, b) Ph_3P, DEAD, THF c) MeLi, THF (92% yield over 3 steps)

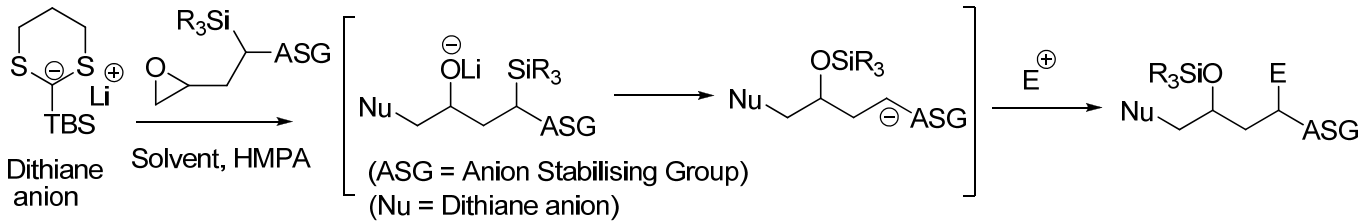
Scheme 12 : Synthesis of aziridine 21

[58] Brown, H. C.; Bhat, K. S.; *J. Am. Chem. Soc*. **1986**, *108*, 5919
[59] Hicks, D. R.; Fraser-Reid, B. *Synthesis* **1974**, 203

At this stage, the two components, epoxide **20** and aziridine **21** were both ready to be linked by executing the key 'linchpin' coupling reaction developed in Smith's group.[60]

The Multi-Component dithiane linchpin coupling strategy is based on the concept of anion-relay chemistry. This efficient strategy has been successfully used to generate upto 5 C-C bonds in a one-pot reaction by successive addition of suitably functionalised electrophiles to a silyl dithiane-derived carbanion, which acts as the linchpin (meaning = pivot).[61]

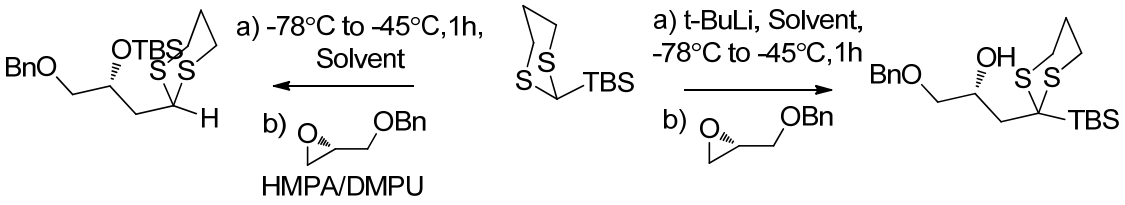
The treatment of silyl-dithiane with *t*-BuLi generates the carbanion, which when treated with an electrophile, such as an epoxide, leads to the formation of the alkoxide. This alkoxide undergoes a Brook Rearrangement, which in turn, generates another anion in the structure, ready to be trapped with a second electrophile. Therefore, the negative charge is 'relayed through space' from the dithiane to the carbanion via the alkoxide. (Scheme 13).



Scheme 13 : Three component-Linchpin coupling Strategy

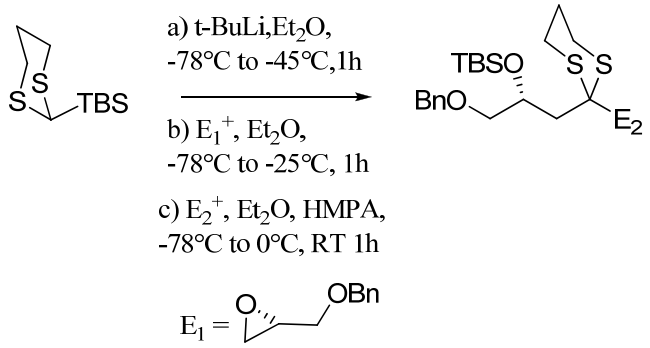
Initially, this reaction was performed in either Et_2O or THF with HMPA as an additive and was mostly employed for the synthesis of symmetrical adducts where two equivalents of the same epoxide acted as the electrophiles. It was subsequently observed that the Brook Rearrangement did not occur if HMPA is not present in the reaction medium. Thus, if a solution containing the epoxide (first electrophile) pre-mixed with HMPA is added to a solution of the dithiane carbanion which is generated separately, it efficiently triggered the Brook Rearrangement giving rise to the expected unsymmetrical product upon addition of the second electrophile. However, if HMPA is not added, the rearrangement product was not observed. This behavior was termed as 'solvent-controlled Brook rearrangement'.

[60] a. A. Smith, A. B. III ; Ming, X *J. Am. Chem. Soc*. **2006**, *128*, 66 b. A. Smith, A. B. III; Xian, M; Kim, W.-S., Kim, D.-S. *J. Am. Chem. Soc*. **2006**, *128*, 12368 c. A. Smith, A. B. III ; Wuest, W. M. *Chem .Comm*. **2008**, 5883
[61] a. Smith, A.B. III; Tomoika, T. *Org. Lett*. **2008**, *10*, 4359 b. Smith, A.B. III; Doughty, M. *Angew.Chem. Int. Ed*. **2001**, *40*, 196



Scheme 14: Solvent-controlled Brook Rearrangement

An important consequence of this solvent-controlled Brook Rearrangement was the development of linchpin coupling reactions where two different electrophiles could be linked in one pot.[62] This was achieved by first generating the dithiane carbanion, followed by addition of the first electrophile and by the addition of the second electrophile as a solution in Et_2O and HMPA, which triggered the Brook Rearrangement leading to the clean formation of the unsymmetrical adducts as the major product (Scheme 15).

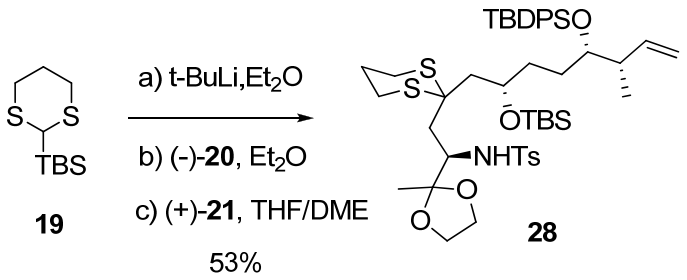


Scheme 15: Synthesis of unsymmetrical adducts using solvent-controlled Brook Rearrangement

The synthetic strategy applied for alkaloid (-)-**205B** is in fact a direct application of this methodology, where the epoxide **20** and aziridine **21** act as the two electrophiles respectively.

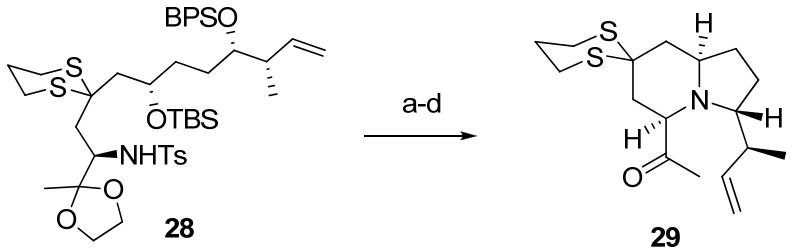
Therefore, the lithiation of the dithiane **19** was achieved by treating it with *t*-BuLi and followed by addition of epoxide **20**. Aziridine **21**, was then added as a solution in THF in presence of DME (a polar solvent which provided best results) to trigger the solvent-controlled Brook Rearrangement, which smoothly led to the formation of the linkage product **28** in an acceptable yield for this three-bond formation process.

[62] a. Smith, A. B. III; Boldi, A. M. *J. Am. Chem. Soc*. **1997**, *119*, 6925 b. Smith, A. B. III; Pitram, S. M.; Boldi, A. M.; Gaunt, M. J.; Sfouggatakis, C.; Moser, W. H. *J. Am. Chem. Soc*. **2003***, 125*, 14435



Scheme 16: Three-Component Linchpin Coupling to form the carbon skeleton of (-)-205B

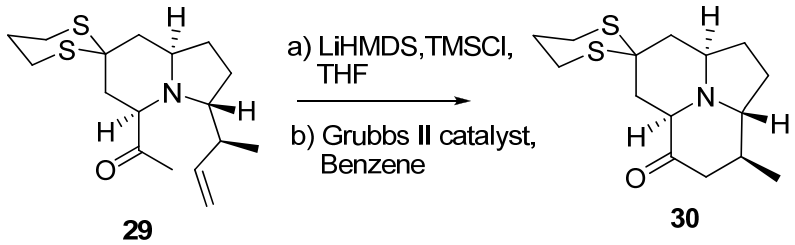
Following this operation, both the silyl protecting groups were removed and the diol thus obtained, was activated by bis-mesylation. In an elegant reaction, treatment of the bismesylate with Na-amalgam first led to the deprotection of nitrogen, followed by *in situ* double cyclisation to furnish the indolizidine skeleton in 70% yield, which upon acidic treatment in acetone cleaved the acetal group to give ketone **29**. At this stage, the stereochemistry of four centres of the target molecule had been fixed.



a) TBAF,THF, b) MsCl, Et_3N, CH_2Cl_2 c) K_2CO_3, MeOH, 5% Na-Hg,Na_2HPO_4 (70% for 2 steps d) 2M HCl, Acetone, Reflux (83%)

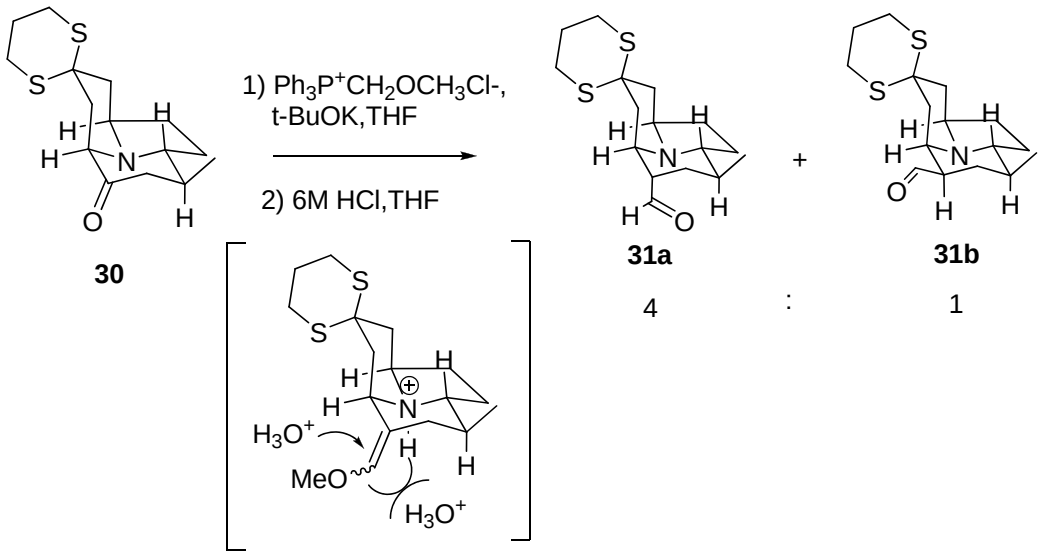
Scheme 17: A one-pot double cyclisation to generate the indolizidine system

The final cyclisation that gave access to the desired 8b-azaacenaphthylene ring system was realised by a ring closing metathesis (RCM) of the kinetic silyl enol ether of ketone **29** to furnish the tricyclic ketone **30** in 81% yield over 2 steps.



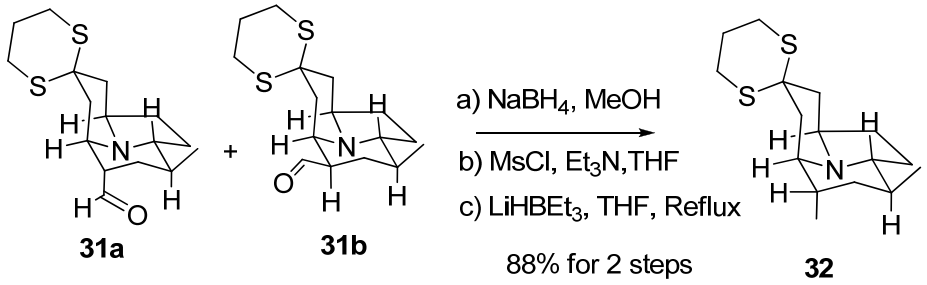
Scheme 18: Construction of the tricyclic core

Once the tricyclic backbone had been assembled, attention was diverted towards the introduction of the axial methyl group. Various trials to install this group mostly led to the undesired equatorial isomer. An elegant solution was eventually found, which involved a Wittig olefination of ketone **30** with $Ph_3P^+CH_2OCH_3Cl^-$ using t-BuOK yielded a *E/Z* mixture of methyl enol ethers, which upon careful acidic hydrolysis gave the axial aldehyde as the major product **31a**. This selectivity has been explained on the basis of the fact that the equatorial delivery of the proton for the hydrolysis of the enol ether is favored over the axial delivery due to electrostatic repulsion between the hydronium ion and the protonated nitrogen in spite of the fact that the β-face of the enol ether is relatively more sterically hindered.



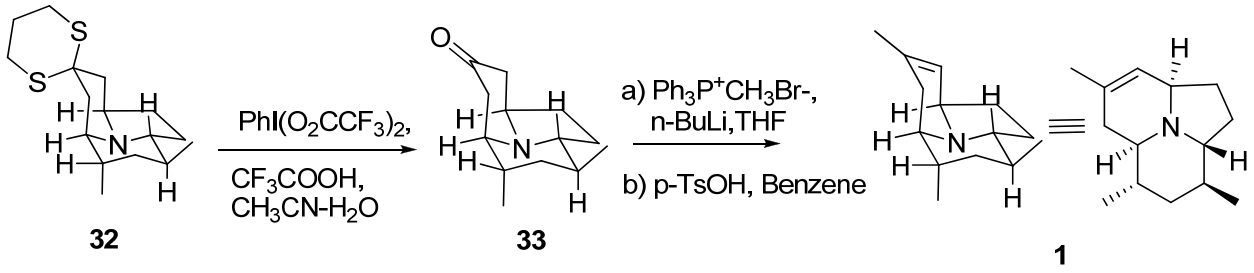
Scheme 19: Introduction of the C6 axial methyl group

The mixture of aldehydes was then reduced using $NaBH_4$ provided the axial hydroxyl methyl group as the major product. Mesylation, followed by reduction of the corresponding mesylate afforded dithiane **32** bearing the axial Me-group.



Scheme 20: Introduction of the axial methyl group

The completion of the synthesis was realized by the removal of the dithiane using the Stork Protocol leading to ketone **33** to which Toyooka's endgame was employed to obtain the natural alkaloid (-)-**205B** as the major product in 50% yield over three steps.



32 **33** **1**

Scheme 21: Completion of the synthesis of (-)-205B

This novel strategy was very elegant and specifically was a significant improvement over the previous synthesis in that the number of steps in the longest linear sequence were much less. However, even this synthesis required more than 25 steps to obtain the final product, starting from commercially available starting materials. In addition, the introduction of the axial methyl group proved to be a challenging task as a four step-sequence was required for a single transformation.

With this overview of the two previous syntheses, both belonging to the chiral pool, we now wish to disclose our studies directed towards the non-chiral pool synthesis of (-)-**205B.**

Chapter 5:

Results and Discussions

As mentioned in the previous chapter, the objective of this project is to develop a non-chiral pool approach to this molecule. We aspire to achieve this objective by employing a diastereoselective [2+2] thermal cycloaddition reaction for asymmetric induction, followed by a regioselective Beckmann rearrangement. The efficiency of this methodology is manifested in the number of successful enantioselective syntheses of various natural products that have already been reported from our laboratory.[63] In this section, we shall concentrate on the mechanistic aspects of the two key transformations of our strategy mentioned above.

During this discussion, we shall also trace the development of Stericol, a chiral auxiliary developed in our laboratory and its contribution in the development of the diastereoselective version [2+2] thermal cycloaddition reaction.

5.1 The [2 +2] Cycloaddition

Four-membered carbocycles are often encountered as substructures of complex natural products.[64] Also, from a synthetic viewpoint, cyclobutenes and cyclobutanones are seen as versatile intermediates[65] in organic synthesis as they undergo a variety of reactions including ring expansion. The [2+2] cycloaddition reaction has been extensively applied for the construction of cyclobutanones.[66]

Although, this reaction is observed to proceed with remarkably high degree of regio- and stereoselectivity, the intriguing mechanism of this reaction has been of considerable theoretical interest over the past few decades.[67] Woodward and Hoffmann had proposed that these ketene-alkene cycloadditions are a case of concerted [$_{\pi}2_{s}$ + $_{\pi}2_{a}$] reaction in which the olefinic portion of

[63]a. Roche, C.; Greene, A., E., Delair P. *Org. Lett*. **2003**, *10*, 1741-1744 b. Rasmussen, M.; Delair, P.; Greene, A. E *J. Org. Chem.* **2001**, *66*, 5438-5443 c. Darses, B.; Greene, A. E.; Coote, S. C; Poisson, J-F *Org. Lett*. **2008**, *10*, 821-804 d. Reddy, P. V.; Veyron, A.; Koos, P.; Bayle, A.; Greene, A. E.; Delair, P. *Org. Biomol. Chem*. **2008**, *6*, 1170-1172

[64] Wong, H. N. C.; Lau, K. L.; Tam, K. F. *Top. Curr. Chem*. **1986***, 133*, 83-157

[65] 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

[66] Brady, W. T. *Tetrahedron* **1981**, *37*, 2949

[67] Wang, X., Houk, K. N. *J. Am. Chem. Soc*. **1990**, *112*, 1754-1756

the ketene acts as the antarafacial component. As this explanation accounted well for the stereoselectivity of the reaction, it was initially widely accepted.[68]

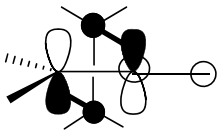


Figure 23(a): Mechanistic pictures of the ketene-olefin cycloaddition

In 1985, on the basis of *ab-initio* calculations, Burke[69] suggested that the lowest energy reaction pathway for this reaction could be concerted as proposed by Woodward and Hoffman but non-synchronous. This implied that in the transition state, the single bond between the carbonyl carbon of the ketene and one carbon of the alkene is almost formed, while the bond between the methylene of the ketene and the second carbon of the alkene hasn't been formed to the same extent.

In 1990, Moyano *et al*[70] stated that Burke's suggestion for [2+2] cycloaddition reaction between a dichloroketene and substituted alkene, could be best described as a concerted but non-synchronous process which followed a $[_{\pi}2_s + (_{\pi}2_s + {}_{\pi}2_s)]$ mechanism as depicted diagrammatically in Figure 23b.

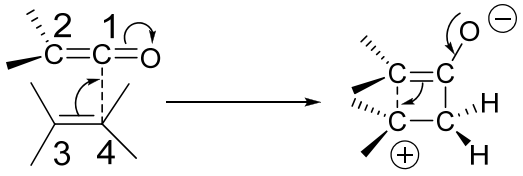


Figure 23(b): π-electron movement associated with the $[_{\pi}2_s + (_{\pi}2_s + {}_{\pi}2_s)]$ mechanism.

The three notable aspects of this reaction are its regioselectivity, stereoselectivity and in our case, diastereoselectivity, which can be explained as follows.

[68] Woodward, A. B.; Hoffmann, R. "The Conservation of Orbital Symmetry", Verlag-Chemie, Academic Press, Weinheim, **1970.**
[69] Burke, L. A. *J. Org. Chem*. **1985**, *50*, 3149-3155
[70] Valenti, E.; Pericas, M. A.; Moyano, A. *J. Org. Chem*. **1990**, *55*, 3582-3593

Stereoselectivity and Regioselectivity:

As shown in Figure **23(b)**, the reaction involves the movement of 4 e^- pairs, in two separate processes, which occur simultaneously but at different rates. The first one is a nucleophilic attack by the π (3, 4) bond to the carbon C1 of the ketene. The π-bond becomes delocalized over C3-C4-C1 at the transition state and ends up as the σ-bond in the product. The second process, which involves the nucleophilic attack of the π (1, 2) olefinic bond of the ketene on the alkene, occurs mostly after the transition state has been reached. This non-synchronous but concerted approach efficiently explains the stereoselectivity of the reaction in that the stereochemistry of the olefin is totally retained in the cyclobutanone product.

In addition, the regioselectivity can be explained by taking into account the electronic and steric factors based on the substitution on the alkene and the ketene. So, out of all the possible approaches between dichloroketene and a substituted alkene, the one with the least steric crowding amongst the substituents would be favored. However, the non-synchronous character of the mechanism also needs to be taken into account. Therefore, as mentioned above, if the C1-C4 bond formation occurs slightly in advance, the electron deficiency created on C3, can be compensated by a suitable substituent on the carbon. For example, if we consider an enol-ether, the electron donating property of the alkloxy group (R_2-O-), would participate in the stabilization of the lack of electron density on C3. As a consequence, of the two possible approaches depicted in Figure 24, transition state II would be lower in energy, leading to the cyclobutanone where the carbons bearing the chlorines and the alkoxy substituents are adjacent to each other.

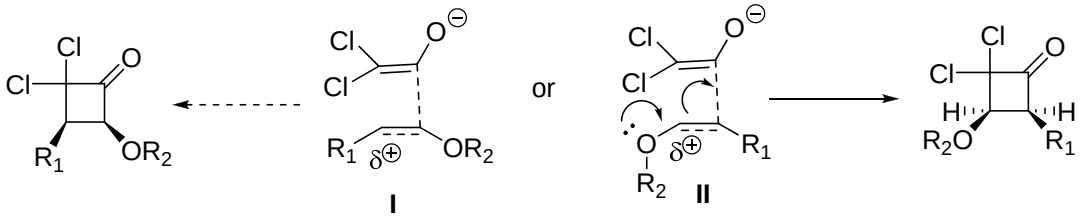
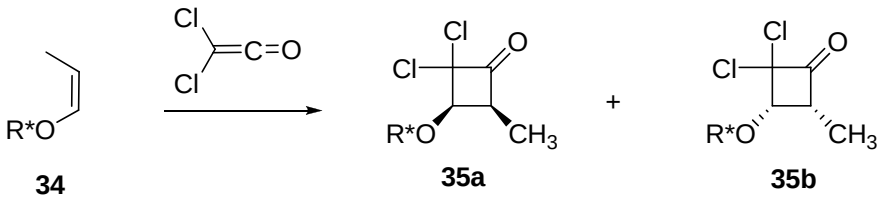


Figure 24 : Regioselectivity of the [2+2] cycloaddition

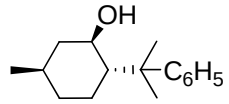
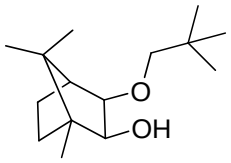
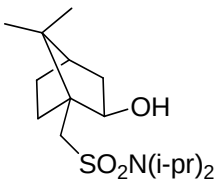
Diastereoselectivity of the [2+2] thermal cycloaddition: Development and application of Stericol®:

As discussed above, the stereoselectivity and regioselectivity of the [2+2] cycloaddition are well-known; however, the possibility of a diastereoselective version of this reaction was relatively unexplored.

In 1985, Greene *et al*[71] discovered that when *Z*-enol-ethers obtained from known chiral auxiliaries (Scheme 22) are engaged in a [2+2] cycloaddition reaction with dichloroketene, significant asymmetric induction could be achieved.



34 **35a** **35b**

Starting Enol Ether	Diastereoselectivity
R*OH	**35 a : 35 b**
	75 : 25
	10 : 90
	90 : 10

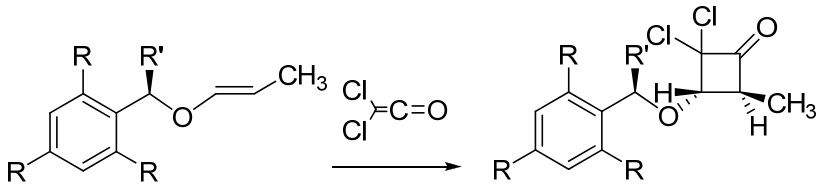
Scheme 22: Asymmetric Induction with chiral enol ethers

Although these chiral alcohols led to high stereoselectivities in the [2+2] cycloaddition, their removal was not particularly easy. To resolve this problem, it was thought that a benzylic type chiral alcohol would be a more appropriate choice.

[71] a. Greene, A. E.; Charbonnier, F. *Tetrahedron Lett*. **1985**, *26,* 5525-5528 b. Greene. A. E.; Charbonnier, F.; Luche, M.-J.; Moyano, A. *J. Am. Chem. Soc*. **1987**, *109*, 4752-4753

To this end, Greene and de Azevado[72] studied the stereoselectivity of this [2+2] cycloaddition on a chiral secondary benzyl alcohol. This work was initiated by using 2-methyl-1-phenylpropanol which had previously given high stereoselectivity in the [4+2] cycloaddition.[73]Although, the results were not particularly encouraging in the beginning, by increasing the bulk between the alklyl and the aromatic parts of this secondary alcohol, the authors could reach an impressive facial selectivity giving rise to 95:5 ratio of diastereoisomers, with triisopropylphenyl ethanol as the chiral inductor.

Later, Greene *et al*[74] developed an efficient and easily scalable access to the optically pure forms of this chiral auxiliary which has now been commercialized under the name of Stericol®. Besides imparting an impressive diastereoselectivity, an attractive feature of this chiral auxiliary is that it could be cleaved readily under acidic conditions (TFA/ DCM).



36 (a-d)	**37(a-d)**
R = H ; R' = iPr	55 : 45
R = H ; R' = CH_3	75 : 25
R = Me ; R' = CH_3	85 : 15
R = iPr ; R' = CH_3	**95 : 5**

Scheme 23: Asymmetric induction using a new chiral auxilliary

The explanation that was offered to justify these results is that due to steric reasons these enol ethers, possibly take up specific conformations which lead to facial preferences in the cycloaddition reaction. This was suggestive of the fact that the diastereoselective outcome of the reaction could perhaps be strongly influenced by the bulk of the chiral auxiliary appended to the enol ether.

[72] De Azevado, M. B. M.; Greene, A. E. *J. Org. Chem*. **1995**, *60*, 4940-4942
[73]a. Wettlaufer, D. G.; Posner, G. H *Tetrahedron Lett*. **1986**, *27*, 667 b. Wettlaufer, D. G.; Posner, G. H. *J. Am. Chem. Soc.* **1986**, *108*, 7373.
[74] Delair, P.; Kanazawa, A. M.; Azevado, M.; Greene, A. E. *Tetrahedron : Asymmetry* **1996**, *7*, 2707-2710

Theoretical calculations performed on a precursor of the cycloaddition have shown that the diastereoselectivity could be the result of the fact that in the lowest energy conformation of the enol-ether one of the *iso*-propyl groups of the chiral auxiliary, efficiently blocks the C_α-si of the C=C of the enol ether, thus directing the approach of the ketene exclusively on the C_α-re as is clearly illustrated in Figure **25.**

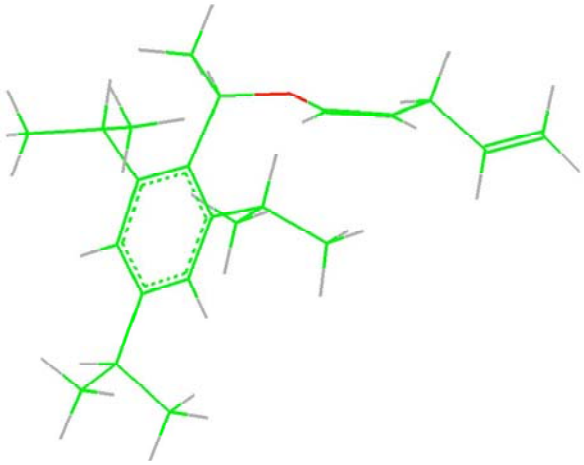


Figure 25: Lowest energy conformation of a precursor of the cycloaddition

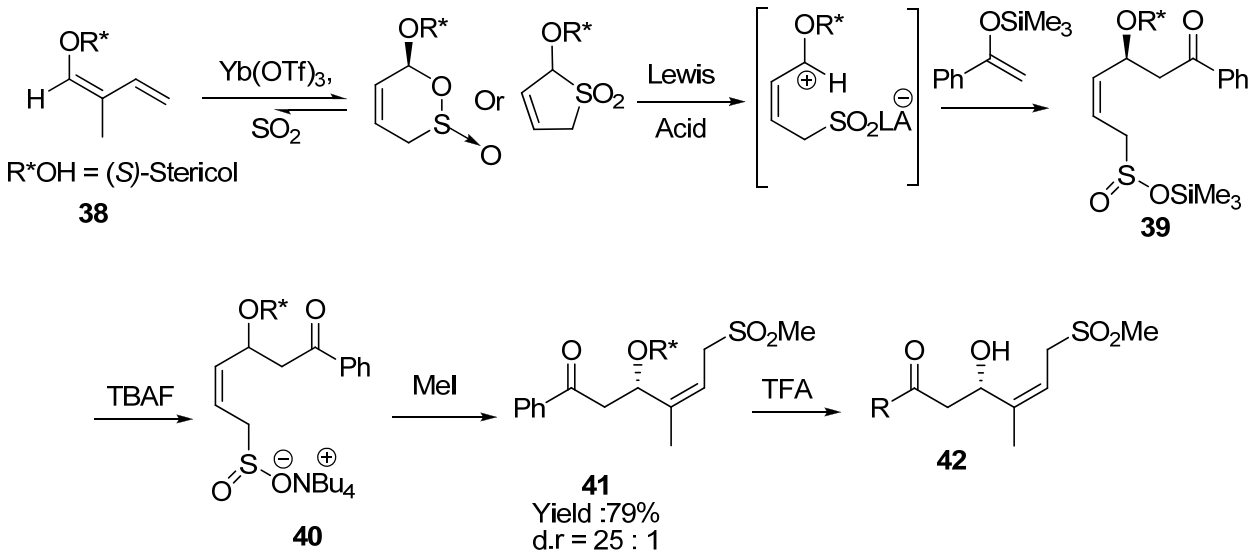
Also, based on the previously obtained results in our laboratory,[63] an empirical rule has been derived in that the *R*-enantiomer of Stericol leads to the *R*-configuration of the carbon bearing the chiral inductor in the dichlorocyclobutanone.

Since this pioneering work done in our laboratory, Stericol has attracted the attention of several research groups which have employed it in different applications during the development of new methodology.

For instance, in 2000, Vogel *et al*[75] used this chiral alcohol for development of an asymmetric version of the novel C-C bond forming transformation previously developed by their group. This operation involved a Lewis-acid promoted addition of SO_2 to 1-alkoxy or 1-silyloxy-1,3-dienes, which, in turn reacts with enoxysilanes to give an unstable trimethylsilyoxysulfinates intermediate (**39**, Scheme 24). A subsequent desilylation-methylation sequence of this intermediate furnished the corresponding methyl sulphones (**41**, Scheme 24). Many chiral

[75] Narkevitch, V.; Schenk, K.; Vogel, P. *Angew. Chem. Int. Ed*. **2000**, *39*, 1806-1808

auxiliaries were investigated for development of a chiral version of this reaction, for example: (*R*)-1-phenylethanol (*R*)-1-phenylpropan-1-ol, (S)-1-(naphthalen-1-yl) ethanol. In this study, (*S*)-Stericol was found to give clearly the highest diastereoisomeric ratio (25 : 1).(Scheme **24**).

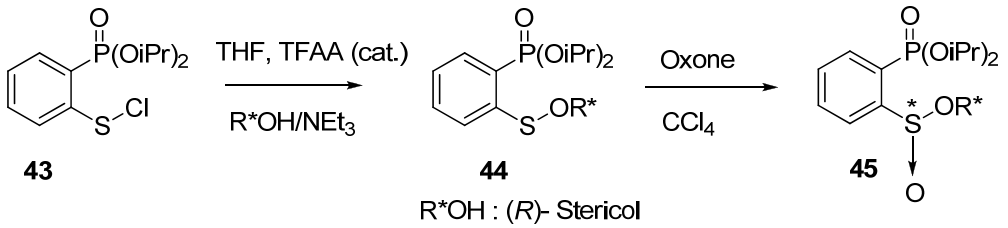


Scheme 24 : Application of Stericol for asymmetric synthesis of methyl sulphones

Later in 2005, Drabowicz *et al*[76] reported the asymmetric synthesis of chiral benzenesulfinates with a phosponate group at the *ortho*-position via a diastereoselective oxidation of the corresponding chiral sulphenates. These sulphenates could be converted to *o*-phosphorylated sulfoxides by treatment with MeMgBr, are found to be very effective when appended to phosphorous ligands in Pd-catalysts employed in Tsuji-Trost allylation reactions.[77] In order to achieve this goal, amongst the host of chiral alcohols such as (-)-Borneol, (-)-8-phenyl-menthol, diacetone-D-glucose, that were used, (*R*)-Stericol gave a very high distereoisomeric ratio of 93/7 (Scheme 25).

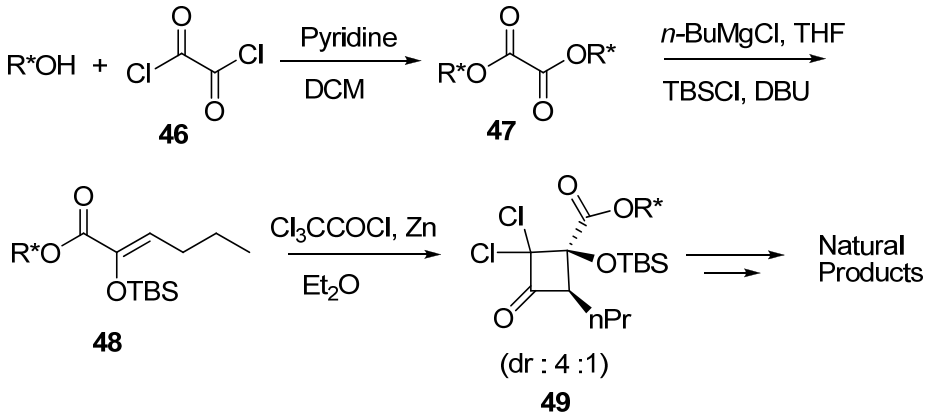
[76] Hamel, M.; Grach, G.; Abrunhosa, I.; Gulea, M.; Masso, S.; Vazeux, M.; Drabowicz, J.; Mikolajczyk, M. *Tetrahedron : Asymmetry* **2005**, *16*, 3406-3415

[77] Hiroi, K.; Suzuki, Y.; Abe, I.; Kawagishi, R. *Tetrahedron* **2000**, *56*, 4701-4710.



Scheme 25: Stiochiometric oxdation of chiral benzenesulphenates to corresponding epimeric sulfinites

In view of the synthesis of a fungal metabolite possessing antibiotic activity, MaGee *et al*[78] recently reported during their studies directed towards a new stereoselective [2+2] cycloaddition and development of an asymmetric version of this reaction of dicholoroketen with chiral enoxy-esters. They observed first that the acyclic enoxy-esters **48** effectively participated in the cycloaddition with dichloroketene leading to the cyclobutanones adducts (Scheme 26). Among the bulky chiral auxiliaries tested such as Menthol, Fenchol or (*R*)-2,2-diphenylcyclopentanol, the enoxy-ester derived from (*S*)-Stericol, generated optical cycloadducts with one of the best diastereoisomeric ratios.



Scheme 26 : Application of Stericol for studies in stereocselective [2+2] cycloadditions with DCK

Thus, Stericol has visibly found several applications in various reactions and it is believed that further applications will be reported in the near future.

[78] MaGee, D. I.; Mallais, T. C.; Mayo, P. D. M.; Strunz, G. M. *Tetrahedron* **2006**, *62*, 4153-4161

Dichlorocyclobutanones: A versatile intermediate in organic synthesis

In our strategy, the Stericol-tethered enol ether undergoes the [2+2] thermal cycloaddition with dichloroketene generated *in situ* by treatment of Cl_3CCOCl with an excess of Zn-Cu couple to form the cyclobutanone. The use of dichloroketene (DCK) in particular is due to its easy accessibility and higher reactivity than the parent ketene (CH_2=C=O). In addition, the strong influence of the chloro-substituents on the regioselectivity of the subsequent ring expansion reaction is another benefit of the use of this ketene. However, a limitation associated with its usage is its susceptibility towards polymerization in solution.[79]

One remarkable reactivity of these cyclobutanones intermediates is their ability to undergo ring opening reactions to relieve the ring strain.[80] Over the years, the ring-expansion reactions of cyclobutanones with diazomethane, *m*-CPBA and Tamura's Reagent (*o*-mesitylenesulphonylhydroxylamine, MSH) generating cyclopentanones, γ-lactones and γ-lactams respectively, have been extensively applied in the successful synthesis of natural products in our laboratory.[63]

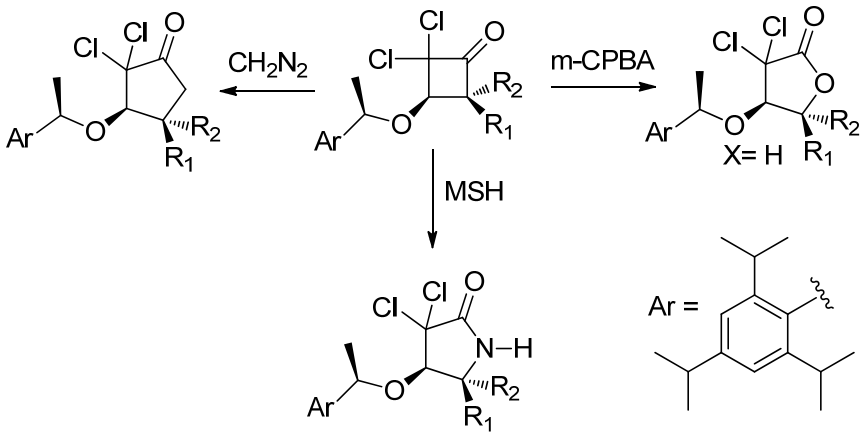
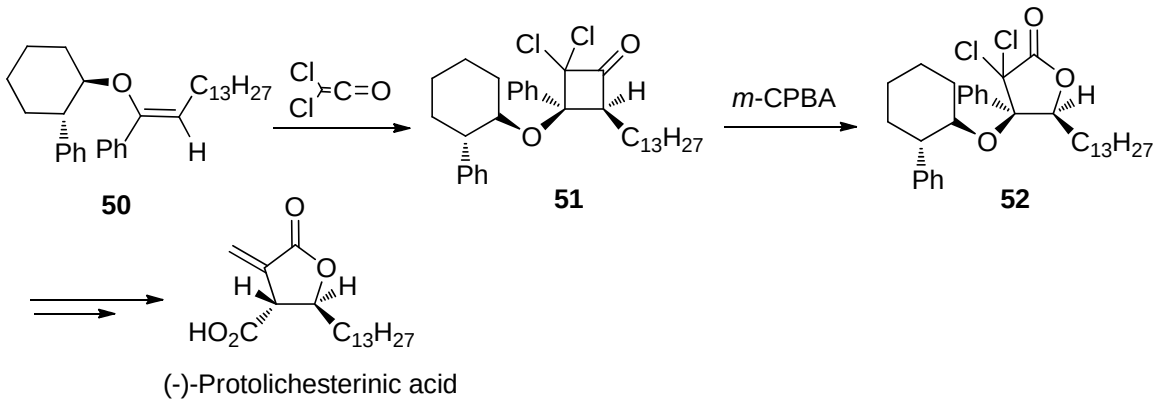


Figure 26: Ring expansion of a cyclobutanone intermediate

For instance, during the first total synthesis of (-)-Protolichesterinic acid, an antitumoral agent and a popular member of the fatty acid lactones extracted from *Parmelia* species of lichens

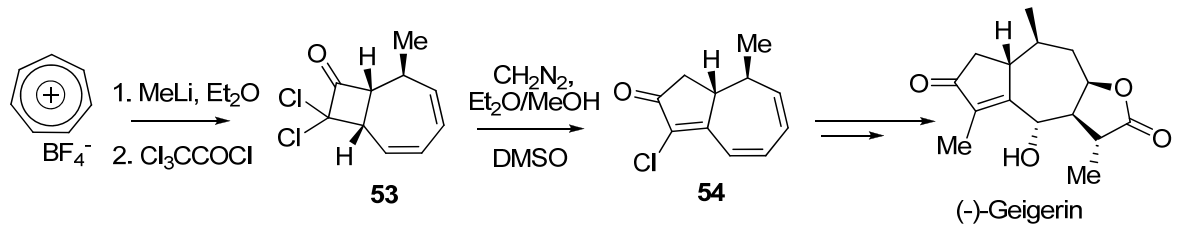
[79] a. Bak, D. A, *J. Org. Chem* **1979**, *44*, 107, b. Brady, W. T. *Tetrahedron* **1981**, *37*, 2949-2966
[80] Conia, J. M., Robson, M. J. *Angew. Chem. Int. Ed.* **1975**, *14*, 473-485

indigeneous to India, reported from our laboratory by Greene *et al*[81], a successful ring expansion was performed under Baeyer-Villiger conditions to create the lactone moiety.



Scheme 27 : Ring expansion of dichlorocyclobutanone for the formation of a lactone

Recently, Depres *et al*,[82] had synthesized hydroazulenone, **54**, a key intermediate, in their synthesis of (±)-Geigerin, a biologically active sesquiterpene lactone belonging to the family of guaianolides, by treatment of the dichlorocyclobutanone precursor with diazomethane. This versatile methodology could provide access to both the guaian-6, 12- and -8, 12-olides classes of naturally occurring guaianolides.

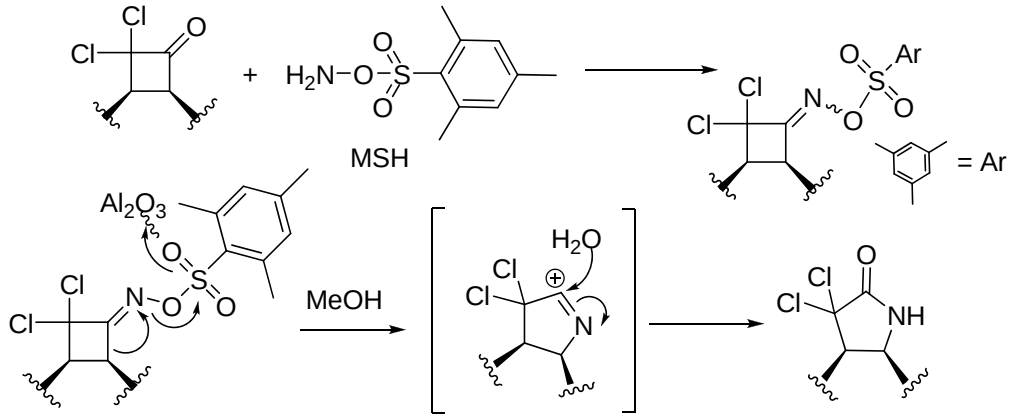


Scheme 28: Synthesis of a key intermediate in the synthesis of Geigerin, via a ring expansion with CH_2N_2

Ring expansion reaction of dichlorocyclobutanone through Beckmann rearrangement with Tamura's Reagent[83] (MSH, Scheme **29**) has been a successful method to introduce N-atom into molecular structures and has been effectively employed used for the synthesis of some alkaloids in our laboratory. The oxime obtained in the condensation reaction between the

[81] Murta, M.; M., De Azevado, M.; Greene, A. E. *J. Org. Chem* **1993**, *58*, 7537
[82] Carret, S.; Depres, J. P. *Angew. Chem. Intl. Ed* **2007**, *46*, 6870-6873
[83] Tamura, Y.; Minamikawa, J.; Ikeda, M. *Synthesis* **1977**, 1-17

dichlorocyclobutanone and Tamura's reagent is treated with Al_2O_3. This Lewis-acid triggers the Beckman-type ring expansion which gives the dichloropyrrolidinone as a single regioisomer. The remarkable regioselectivity is attributed to the presence of the two chlorine atoms on the α-position to the carbonyl, which tremendously reduce the migratory aptitude of the adjacent C-C bond due to their electron withdrawing nature.[84] As a consequence, the ring expansion takes place exclusively with the migration of the bond relatively rich in electrons. (Scheme 29)



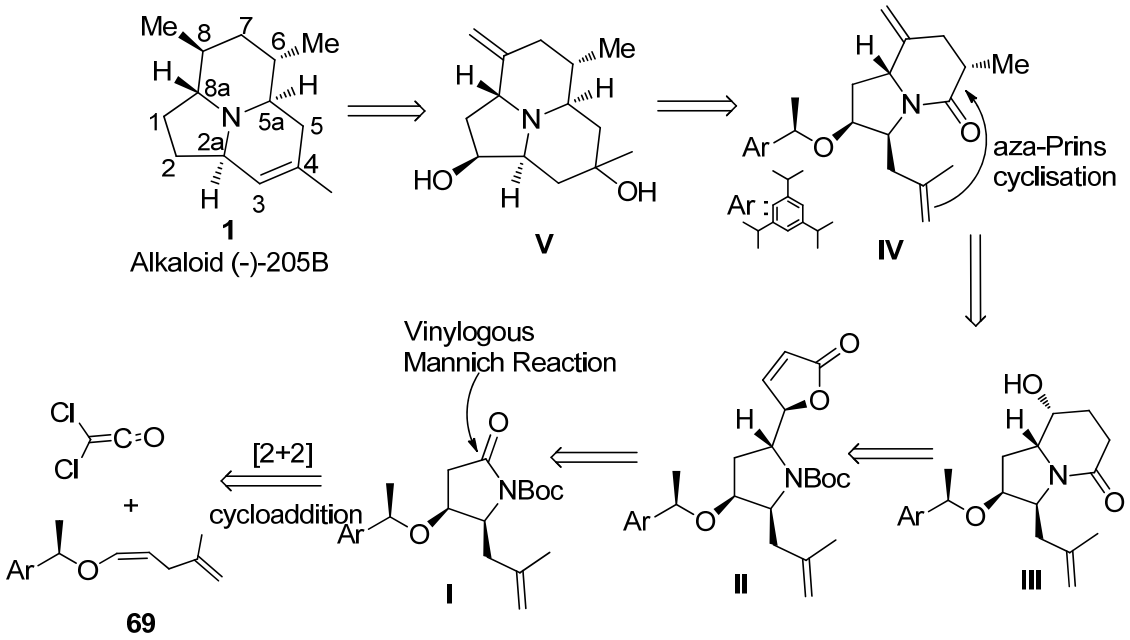
Scheme 29: Mechanism of the regioselective Beckmann ring expansion

The reductive removal of the chlorines then furnishes a γ-lactam, an important intermediate in our strategies for alkaloid synthesis.

Based on this methodology, a retrosynthetic strategy for alkaloid (-)-**205B** has been proposed**.**

[84] Luh, T-Y; Chow, H-F; Leung, W. Y.; Tam, S. W. *Tetrahedron* **1985,** *41*, 519-525

5.2 *Retrosynthetic Strategy*

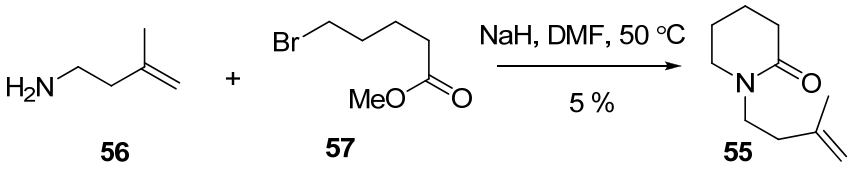


Scheme 30 : Retrosynthetic Strategy

As proposed in the retrosynthetic strategy (Scheme **30**), our target molecule is envisaged to come from and advanced tricyclic intermediate **V** by sequential functional group transformation (hydrogenation, deoxygenation and dehydration). This tricyclic intermediate could be constructed through an acid-mediated aza-Prins cyclisation reaction of indolizidinone **IV** and followed by removal of chiral inductor**.** Lactam **IV** could be accessible by the methylenation of the ketone obtained by oxidation of the secondary alcohol in hydroxyindolizidinone **III,** which in turn could be synthesized from pyrolidinone **I** *via* a vinylogous Mannich reaction followed by lacatamisation. Finally, the first key intermediate, pyrolidinone **I** could be obtained by applying the previously discussed methodology to the enol-ether **69**.

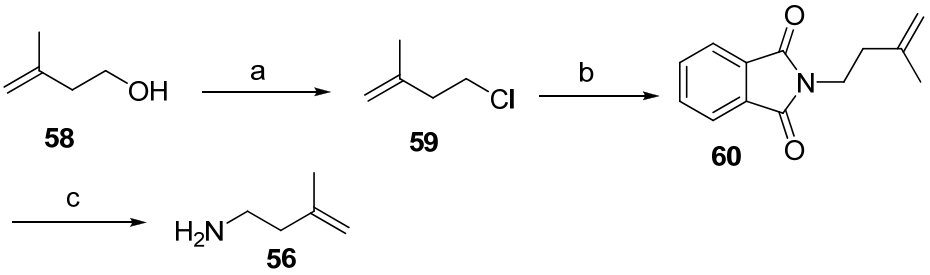
Thus, our access to the tricyclic core of Alkaloid (-)-**205B** was pivoted on the success of the aza-Prins cyclisation. Literature precedents on this relatively less exploited reaction indicated that it could prove to be a challenging task.[85] Therefore, before embarking on the synthesis of (-)-**205B,** model studies were performed in order to have a deeper insight into this important transformation.

For this purpose, model lactam **55** was synthesized by lactamisation of a δ-bromo ester **57** with amine **56** as shown in Scheme 31.



Scheme 31: Synthesis of model lactam 55

The primary amine **56** was obtained from commercially available alcohol in three steps which involved its conversion to the corresponding chloroalkene, followed by treatment with potassium phthalimide under refluxing conditions in DMF to furnish the N-alkyl phthalimide. Finally, the free amine was liberated by refluxing the phthalimide in EtOH in presence of hydrazine monohydrate followed by the distillation of the resulting organic phase.

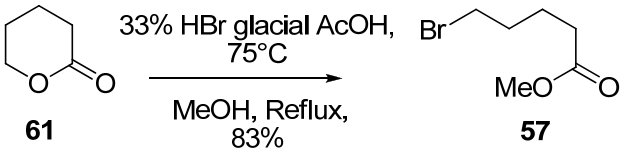


Key : a. $SOCl_2$, Bu_3N, Et_2O b. Potassium phthalimide , DMF,c. $N_2H_4.H_2O$, EtOH
Overall yield : 24% over 3 steps

Scheme 31a: Synthesis of amine 56

[85] a. Liu, J. L.; Hsung, R. P.; Peters, S. D. *Org. Lett* **2004**, 6, 3989-3992 b. Jakubec, P.; Cockfield, D. M.; Dixon, D. J. *J. Am. Chem. Soc.* **2009,** *131*, 16632-16633 c. Gless, R. D.; Rapoport, H. *J. Org. Chem*. **1979***, 44*, 1324 d. Baylis, A.M.; Davies, M. P. H.; Thomas, E. J. *Org. Biomol. Chem*. **2007***, 5*, 3139 e. Belanger, G.; Larouche-Gauthier, R.; Menard, F.; Nantel, M.; Barabe, F. *Org. Lett*. **2005**, *7*, 4431-4434

The δ-bromo ester **57** was obtained by refluxing the commercially available δ-valerolactone in presence of 33% HBr in glacial acetic acid over 5h, followed by refluxing the resultant bromo-acid in dry MeOH.

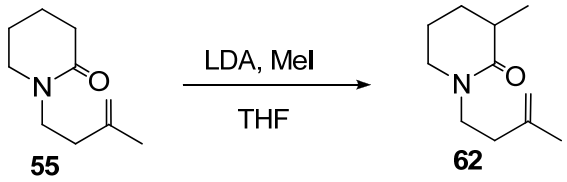


Scheme 31b : Synthesis of δ-valerolactam 57

Thus, lactam **55** was obtained in only 5% yield over 5 steps from the commercially available starting material. It would be worthy to note that the synthesis of this model lactam was also attempted by direct alkylation of the commercially available δ-valerolactam. To this end, the 2-methyl allyl iodide was synthesized by refluxing compound **59** with NaI in acetone followed by treatment with δ-valerolactam in toluene in presence of KOH. In spite of this very direct access, the desired alkylated lactam was obtained in an even lower yield than the above mentioned sequence.

5.3.1 *Model studies for the alkylation and aza- Prins cyclisation*

Methylation of lactam **55** proceeded smoothly with LDA[86] in presence of an excess of MeI, which furnished the purified methylated product **62** in 70% yield based on recovered starting material.

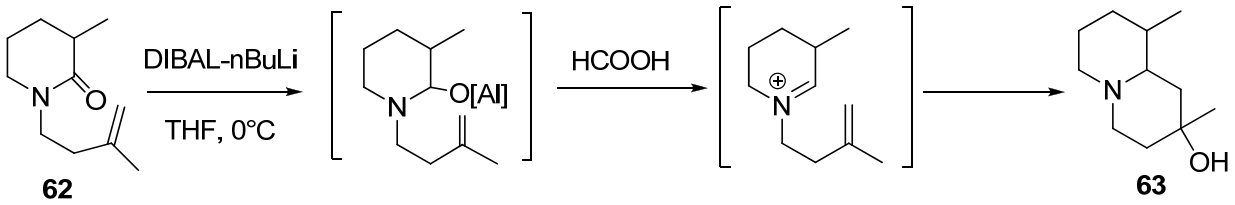


Scheme 32 : Model studies for the methylation reaction

Consistently reproducible results for the alkylation encouraged us to proceed to our studies on the aza-Prins cyclisation. For this crucial reaction, it was envisaged that the hemiaminal resulting

[86] Brewster, A. G., Broady, S., Davies, C. E., Heightman, T. D., Hermitage, S. A., Hughes, M., Moloney, M. G., Woods, G. *Org. Biomol. Chem*. **2004**, *2*, 1031-1043

from the partial reduction of lactam **62,** upon addition of a proton source like HCOOH, would generate the iminium ion *in situ*, which would subsequently be attacked by the nucleophilic double bond present on the side chain affording the quinolizidine structure.



62 **63**

Scheme 33 : Schematic representation of the aza - Prins cylisation on the model lactam

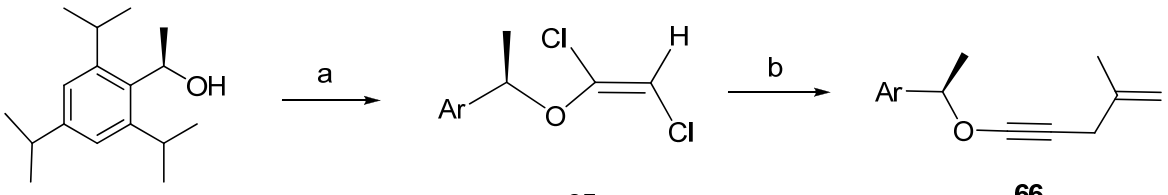
After some experimentation with a range of reducing agents, we found that the partial reduction of the lactam **62** could be achieved by treating it with the ate-complex formed by an equimolar mixture of DIBAL and *n*-BuLi in THF at 0 °C. Addition of HCOOH at -78°C and warming up the reaction to room temperature provided quindolizidine **63** in a very satisfactory 85% yield after purification.

Armed with the basic knowledge of this key reaction, we embarked on the total synthesis of Alkaloid (-)-**205B**.

5.3.2 *Formation of pyrrolidinone (I)*

The key intermediate, pyrolidinone **I** was envisioned to be obtained by subsequent transformations of the dichlorocyclobutanone synthesized using the strategy previously discussed. To this end, we began with the synthesis of the enol-ether, the coupling partner for the thermal [2+2] cycloaddition. Based on the empirical rule for asymmetric induction, (*R*)-enantiomer of Stericol was found to be the appropriate isomer to begin the synthesis. Although, the correct stereochemistry has been shown in all the schemes along this manuscript, we have performed our synthesis with (±)-Stericol.

The synthesis commenced with the treatment of (±)-Stericol, the chiral inductor **64**, with KH, followed by addition of trichloroethylene at low temperature to yield the crude dichloroenol ether **65**. Upon purification over silica gel deactivated with Et_3N (2.5% v/v) the pure enol ether was obtained as a colorless oil in 77 %. This dichloroenol ether[71] was alkylated using 2-methyl allyl iodide to obtain the acetylenic enol ether **66**.[87] This alkylating agent was synthesized in 65% yield from the commercially available chloro precursor by refluxing in acetone with excess NaI[88] followed by distillation under vacuum.



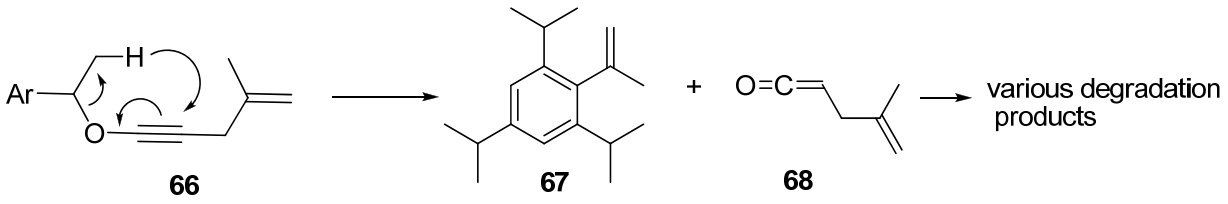
64 **65** **66**

Key : a) KH, THF, RT; $Cl_2C{=}CHCl$,-50°C to RT (77%). b) n-BuLi, THF, -80°C;  , -40°C, HMPA.

Scheme 34 : Synthesis of acetylenic enol ether 66

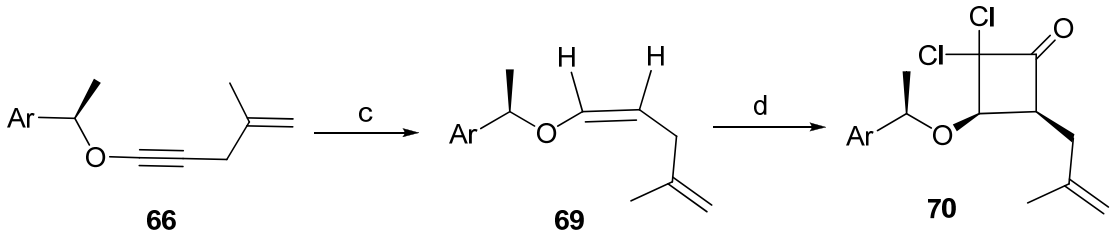
It has previously been observed that ynol ether **66** is thermally unstable[89] and also undergoes degradation on silica gel to generate a styrene derivative. A possible mechanism for this could be as follows:

[87] Darses, B; Milet, A; Philouze, C.; Greene, A. E.; Poisson, J-F *Org. Lett*. **2008**, *10*, 4445-4447
[88] Letsinger, R., L.; Traynham, J. G. *J. Am. Chem. Soc*. **1948,** *70*, 2818
[89] Ramasheshan, M. L.L.; MaGee, D. I. *Tetrahedron* **1993**, 49, 2159-2168



Scheme 35 : Possible mechanism for the degaradation of the acetylenic enol ether 66

Therefore, without much delay, the acetylenic enol ether **66** was partially reduced to enol ether **69** by hydrogenation using 10% Pd-Ba_2SO_4 as the catalyst in presence of EDA and 1-hexene. This transformation is visibly difficult due to the presence of the terminal olefin which is also susceptible to hydrogenation. Thus, the additives present in the reaction mixture during hydrogenation play an important role in limiting the over-reduction. The use of EDA was inspired from a publication by Campos et al[90] who demonstrated that this bidentate amine poisons the Pd-catalyst and is therefore, effective in controlling the over-reduction of the terminal olefin. The role of 1-hexene is that of a sacrificial (additive) alkene. Once the triple bond is consumed, the rate of hydrogenation of the terminal olefin is no longer negligible. Therefore, 1-Hexene is added in excess to the reaction mixture as it will be more readily available for hydrogenation than the terminal olefin of the substrate itself, thereby reducing the possibility of over-reduction of the substrate.



c) 10% Pd-Ba_2SO_4, H_2 , DMF, 0°C, EDA ,1-hexene , 72 % from (2) d) Zn-Cu, Cl_3CCOCl, Et_2O, RT.

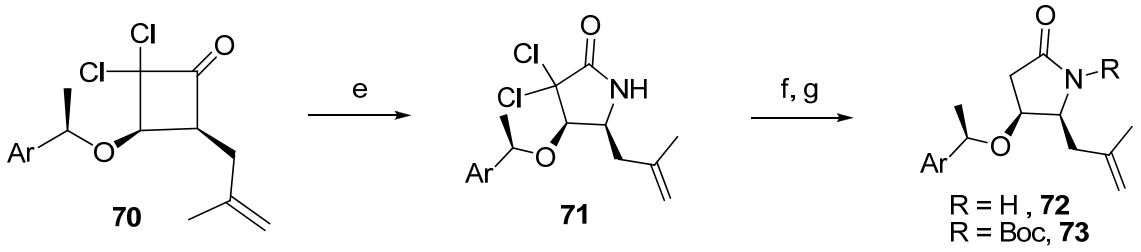
Scheme 36 : Synthesis ofdichlorocyclobutanone 70

In spite of these precautions, the possibility of over-reduction could not be completely eliminated. In order to verify if the saturated compound was present in the product, an authentic sample was prepared by alkylating the dichloroenol ether **66,** with 2-methyl propyl triflate and

[90] Campos. K. R.; Journet, M.; Cai, D.; Kowal, J., J., Lee, S., Larson, R., D., Reider, P. J. *J. Org. Chem*. **2003,** *68*, 2338-2342

synthesizing the corresponding enol ether. Upon comparison, only 5-7 % of saturated product (estimated by ^{1}H NMR) was observed under the reaction conditions mentioned above. This sequence could be successfully performed on a relatively large scale (15 g).

With ample amount of enol-ether in hand, we attempted the cycloaddition reaction with involved the treatment of enol ether **5** with Zn-Cu couple and trichloroacetyl chloride in dry ether.[91] Performing this reaction under different conditions repeatedly failed to produce the desired cycloadduct. Although we had avoided the purification of the enol ether initially because it is known to degrade on silica gel, this purification finally proved to be the solution to our problem. When the cycloaddition was carried out with purified enol ether **69** (purification performed over deactivated silica gel; 72% yield over 2 steps from **65**), it proceeded smoothly to give the dichlorocyclobutanone **70**, as a single regioisomer, with excellent diastereoselectivity (92:8 as evaluated by ^{1}H NMR). Following this, the Beckmann ring expansion[83] with Tamura's reagent as described before, furnished the crude dichlorolactam **71**. No purification was performed as both these intermediates are known to undergo degradation on silica gel.



Key : e) MSH, Na_2SO_4, CH_2Cl_2 (dry), RT, 48 hours; Al_2O_3 Basic, MeOH f) Zn-Cu, MeOH-NH_4Cl, RT; Reflux, 2h g) Boc_2O, DMAP, Et_3N, DCM, RT (81%).

Scheme 37 : Synthesis of pyrrolidinone (I)

Zn-mediated dechlorination[92] of the dichlorolactam was achieved sequentially by first stirring it with activated Zn at room temperature in MeOH saturated with NH_4Cl (mono-chlorinated product was observed on TLC) and subsequently refluxing the reaction mixture. Upon purification over silica gel, pure lactam **72** was obtained in 42% yield over 3 steps. Subjecting this lactam to the standard conditions[93] for Boc-protection uneventfully furnished the crude N-Boc lactam **73**. Purification of this substrate was performed rapidly on a short pad of silica gel

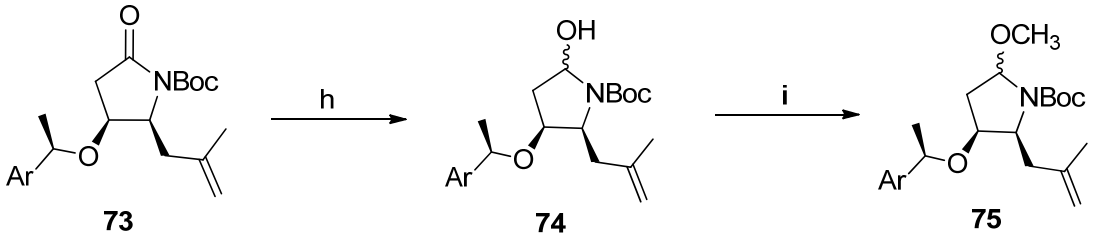
[91] Hassner, A., Krepski, L. R. *J. Org. Chem*. **1978**, *43*, 3173-3179
[92] Johnstan, B. D., Slessor, K. N., Oehlschlager, A.,C. *J. Org. Chem*. **1985**, *50*, 114-117
[93] Greene, T. W. Protecting groups in organic Synthesis 3rd Edition, WILEY.

deactivated with Et_3N to obtain the desired product in 80% yield as a white solid. Significantly lower yields were obtained when the column was performed with normal silica gel (63- 200 μ).

5.3.3 ***Formation of the indolizidine system III***

Having successfully synthesized our first key synthetic intermediate in sufficient quantity, our next target was the synthesis of butenolide **II** (Scheme 30) - the precursor of the indolizidine ring system.

This sequence began with the partial reduction[94] of the N-Boc lactam **73** to the corresponding hemiaminal **74**, which was methylated readily on treatment with a large excess of 2,2-dimethoxypropane in presence of catalytic amount of CSA to give aminal **75**.[95] Classical conditions like MeOH in presence of cat. *p*TSA[96] also gave the desired methylated product but in lower yield. Compound **75** was also unstable on silica gel as well as led to degradation products on long storage even at low temperature. It was, therefore, immediately engaged in the vinylogous Mannich reaction.



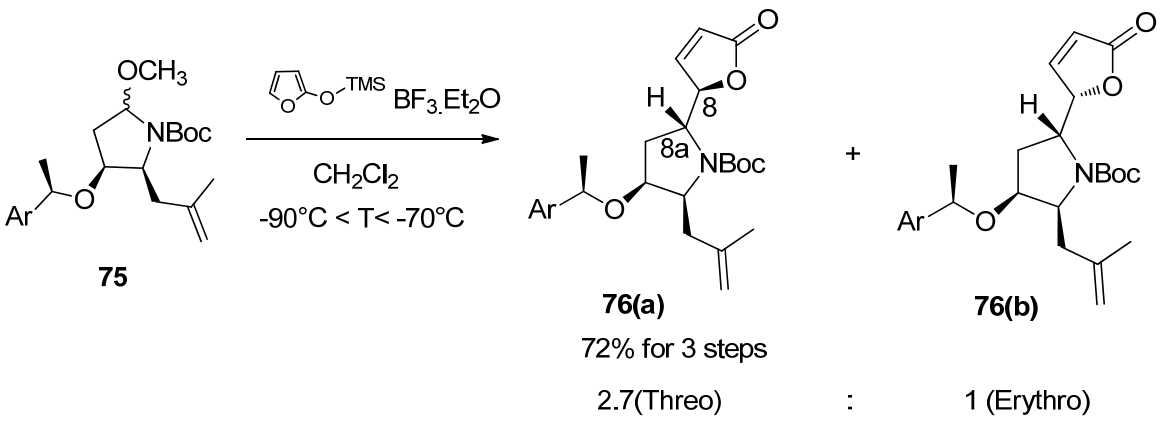
73 **74** **75**

Key : h) Superhydride, THF,-78°C to 0°C; H_2O_2, 0°C. i) 2,2-Dimethoxy propane, CSA, 0°C

Scheme 38 : Partial reduction- methylation of N-Boc lactam 73

To this end, the addition of $BF_3.Et_2O$ to a solution of 2-silyloxyfuran and hemiaminal **75** in dry DCM, furnished the corresponding butenolide as a mixture of two diastereoisomers of **76a** and **76b.** The major diastereoisomer **76a** (expected *threo* adduct) was isolated in an excellent yield 72% over 3 steps and the minor isomer **76b** (expected *erythro* adduct) was isolated in 8% yield over 3 steps.

[94] Collado, I.; Ezquerra, J.; Pedregal, C. *J. Org. Chem* **1995,** *60,* 5011
[95] Arndt, H-D.; Welz, R;, Muller, S.; Zeimer, B.; Koert, U. *Chem. Eur. J.* **2004**, *10*, 3945-3962
[96] Agami, C.; Dechoux, L.; Hamon, L.; Melaimi, M. *J. Org. Chem* **2000**, *65*, 6666-6669



Scheme 39 : Formation of the diastereoisomers of the butenolide intermediate

The formation of the butenolide intermediate introduces two new stereocentres in the molecule at positions 8 and 8a[97] (Scheme 39). In order to assign their relative stereochemistry and designate the two diastereoisomers as *erythro* and *threo,* we made use of the literature published on the stereochemical outcome of this type of reaction by Martin et al.[98, 99]

Mechanistically, this reaction is known to proceed via the generation of an iminium ion that readily undergoes a vinylogous Mannich reaction with the nucleophilic silyoxy-furan. Using ab-initio calculations, Martin had demonstrated that the lowest energy transition state is obtained by a 'Diels-Alder' like-approach in which the oxygen of the furan is away from the carbonyl of the acyl iminium ion (Figure **27a**). This approach led to the formation of *threo*-adduct which explained the stereochemical outcome of the *threo*-selective vinylogous Mannich reactions.

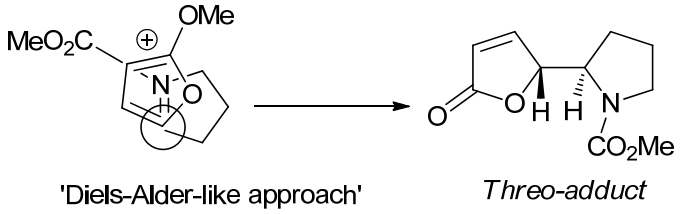


Figure 27a : Theoretical studies on the stereochemical outcome of the vinylogous Mannich reaction

[97] The numbering system used throughout this manuscript refers to the numbering of the final product. (Figure 14)
[98] Bur, S. K.; Martin, S. *Org. Lett*. **2000**, *2*, 3445-3447
[99] a. Casiraghi, G.; Colomo, L.; Rassu, G.; Spanu, P. *J. Org. Chem*. **1990**, *55*, 2565 b. Zanardi, F.; Battistini, L.; Rassu, G.; Auzzas, L.; Pinna, L.; Marzocchi, L.; Acquotti, D.; Casiraghi, G. *J. Org. Chem*. **2000**, *65*, 2048 c. Martin, S. F.; Barr, K. J.; Smith, J. W.; Bur, S. K. *J. Am. Chem. Soc*. **1999**, *121*, 6990 d. de-Oliviera, M.; Santos, L.; S. Pilli, R.A. *Tetrahedron Lett*. **2001**, *42*, 6995

In addition, an empirical rule for the structure assignment of the two diastereoisomers was deduced on the basis of their ^{1}H and ^{13}C spectra in $CDCl_3$. This rule[100] states that the chemical shift of C8 (Scheme **39**) is further downfield in the *threo* isomer than in the corresponding *erythro* isomer and the chemical shift of C8a is further upfield in the *threo*-isomer.

In our case, in the ^{13}C NMR recorded on 400 MHz for the major isomer, the chemical shift of C8 and C8a are at 123 ppm and 55 ppm respectively. On the other hand, in the minor isomer the chemical shifts for the same carbons were present at 82 and 58 ppm respectively. Therefore, by applying Martin's empirical rule, we could establish that the major isomer obtained in our reaction was indeed the *threo* adduct. This assignment is also in agreement with the above mentioned theoretical calculation results.

In addition, out of the four diastereoisomers possible, only two major diastereoisomers were isolated under the reaction conditions in our case, which shows that this reaction had apparently proceeded with total iminium face selectivity. This could be attributed to the fact that the two substituents already present on the iminium ion (Figure **27b**) are both on the same side due to which the nucleophile approaches the iminium ion exclusively from the sterically less hindered face, thereby imparting the stereochemistry at position 8a.(Scheme 39).

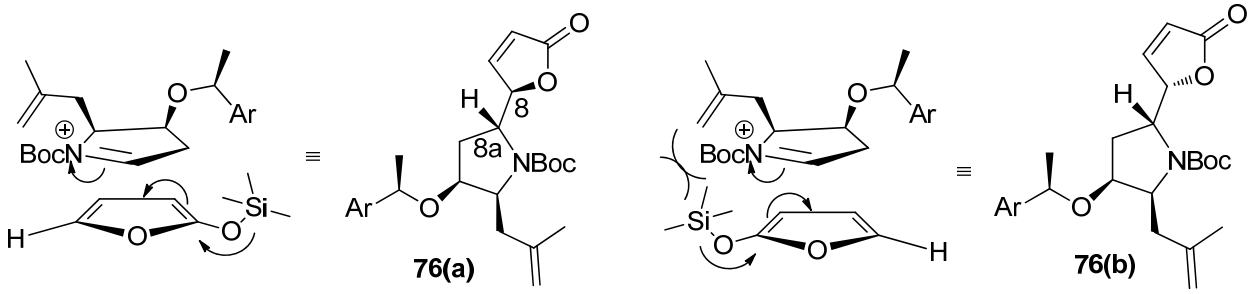


Figure 27b : Formation of the two diastereoisomers of butenolide 76

Encouraged by these results, we enthusiastically continued the synthesis with the major isomer **76a**.

In this direction, a next major challenge that we confronted was the chemoselective 1, 4-reduction of double bond in the butenolide ring in presence of the olefinic side chain. For our

[100] Martin, S. F.; Corbett, J. W. *Synthesis* **1992**, 55-57

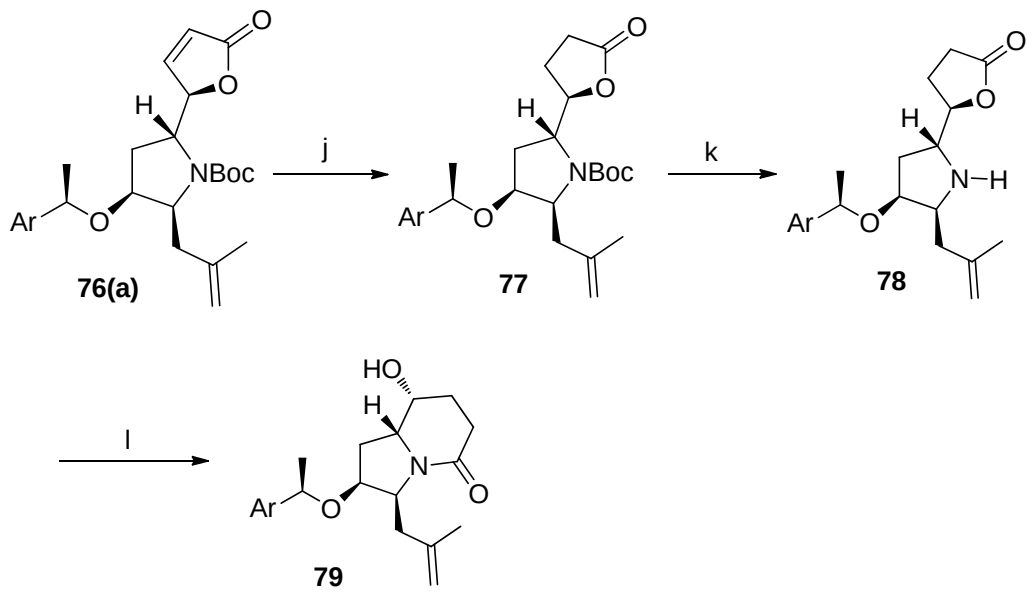
molecule, the classical hydrogenation reaction[101] was certainly not applicable and relatively mild reducing conditions, such as metal-mediated reductions had to be employed.

In our search for appropriate reaction conditions to perform this transformation, we found that during the synthesis of Okadoic acid, Dankwerdt *et al*[102] had reported that the double bond in the butenolide could be chemoselectively reduced using $NaBH_4$ in MeOH in presence of $CuCl_2.H_2O$. In this case, the reaction condition was more selective towards the conjugated double bond than the conventional nickel boride obtained by treatment of $NaBH_4$ with $NiCl_2$[103,104].

Pleasingly, subjecting butenolide **76(a)** to the conditions mentioned above, with constant monitoring of the reaction mixture by TLC, furnished lactone **77,** which was filtered through silica gel to remove the copper salt. The pure product was isolated in 90% yield as a white solid.

The next step towards the formation of the indolizidinone intermediate was a selective N-Boc deprotection reaction in the presence of the acid-sensitive chiral inductor. This goal was achieved smoothly by using TMSOTf in the presence of 2,6-lutidine which afforded aminolactone **78** and left the chiral inductor unaffected. Finally, the lactone ring opening reaction was triggered by addition of catalytic amount of sodium methoxide in the solution of aminolactone **78** in dry MeOH[105]. The methyl ester thus formed *in situ*, facilitated the intramolecular lactamisation to generate the desired indolizidine skeleton. The hydroxyindolizidinone **79** (structure **III**, Scheme 30) was obtained as a white powder in 72 % yield over 3 steps after recrystallisation from diethyl ether.

[101] Rassu, G.; Carta, P.; Pinna, L.; Battistini, L.; Zanardi, F.; Acquotti, D.; Casiraghi, G. *Eur. J. Org. Chem*. **1999**, 1395-1400
[102] 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
[103] Khurana, J. M.; Gogia, A. *Chem. Rev.* **1986**, *86*, 763-780
[104] Rassu, G.; Auzzas, L.; Pinna, L.; Zambrano, V.; Zanardi, F.; Battistini, L.; Gaetani, E.; Curti, C.; Casaraghi, G. *J. Org. Chem* **2003**, *68*, 5881
[105] Hanessian, S.; McNaughton-Smith, G. *Bioorg.& Med. Chem. Lett*. **1996**, *6*, 1567-1572

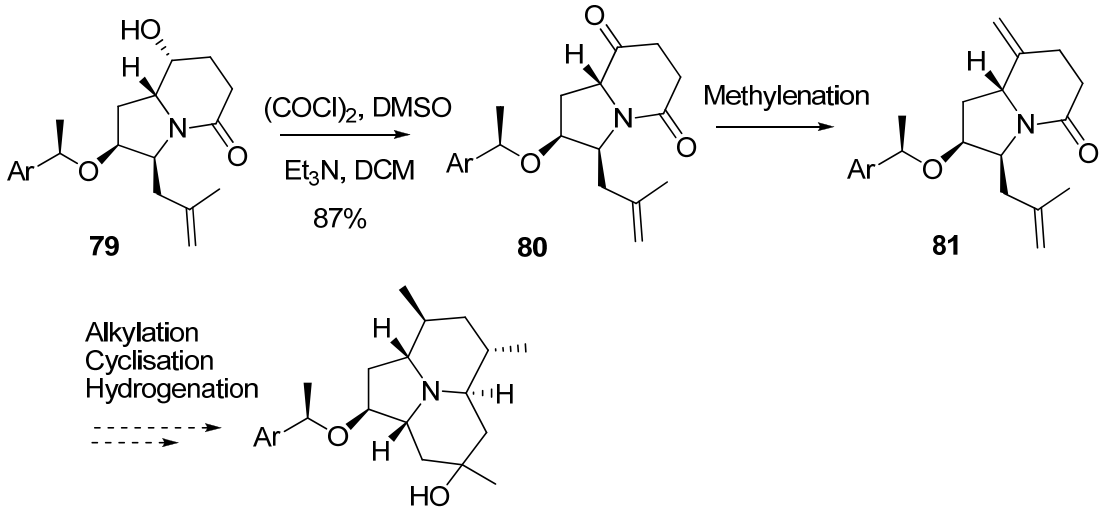


Key : j) $CuCl_2H_2O$, $NaBH_4$, MeOH, 0°C k) 2,6-Lutidine,TMSOTf, DCM, RT l) CH_3ONa, dry MeOH, RT (72% over 3 steps)

Scheme 40 : Formation of the indolizidinone III

5.3.4 *Installation of the equatorial Methyl group on C8*

With the requisite indolizidinone in hand, we now aimed at introducing the equatorial methyl group on C8. As indicated in Scheme **41**, it was expected that oxidation of the secondary alcohol to ketone, followed by the classical Wittig reaction would furnish the exocyclic methylene, which upon hydrogenation at a later stage in the synthesis would generate the methyl group with the desired stereochemistry.



Scheme 41 : Synthetic plan for introduction of the C-8 equatorial Me-group

Convinced with the plausibility of this plan, we embarked on this sequence by oxidizing the secondary alcohol under Swern oxidation conditions[106] which proceeded smoothly to give ketone **80** in 87% yield.

Our initial attempts to transform the resultant ketone into a methylene used the classical Wittig reaction. Several trials with n-BuLi and PPh_3CH_3I in THF by varying reaction conditions such as number of equivalents of the reactants, temperature of addition of the ketone and reaction time, gave the desired product in yields between 30-35 % with the recovery of starting material, in the best cases.[107] With a hope to increase the basicity of the base, the reaction solvent was changed to toluene. Again, numerous attempts were made to perform the reaction with a range of

[106] Sudau, A.; Munch, W.; Bars, J-W.; Nubbemeyer, U. *Eur. J. Org. Chem*. **2002**, 3304-3314
[107] Mal, S. J.; Kar, G. K.; Ray, J. K. *Tetrahedron* **2004**, *60*, 2805

different bases such as potassium *t*-amylate[108] and *t*-BuOK[109] in toluene or NaH in DMSO[110] but no improvement was observed in the behavior of the substrate. Use of PPh_3CH_3Br, which was more soluble on toluene than the corresponding iodide was also not of much avail.

All these observations suggested that the ketone would in fact be readily enolisable, thereby preventing the attack of the phospohorous ylide, which led to the recovery of starting material. To test this hypothesis, the reaction was performed in *t*-butanol in order to render the enolisation process reversible but again, only starting material was recovered.

Without achieving much success with the Wittig reaction conditions, we turned our attention towards commercially available reagents used for carbonyl methylenation[111], such as Petasis reagent. Again, the desired product was isolated in only 30% yield with recovery of starting material. Owing to the fact that the Tebbe reagent is known to be more effective for sterically encumbered carbonyls and is less basic than the Wittig reagent, it was naturally the next option that we explored. The results, however, were again disappointing as only starting material was recovered.

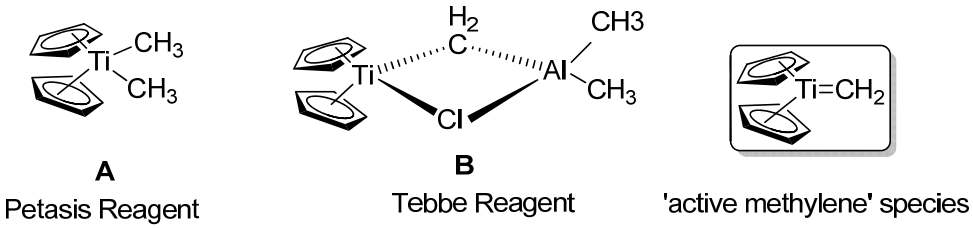


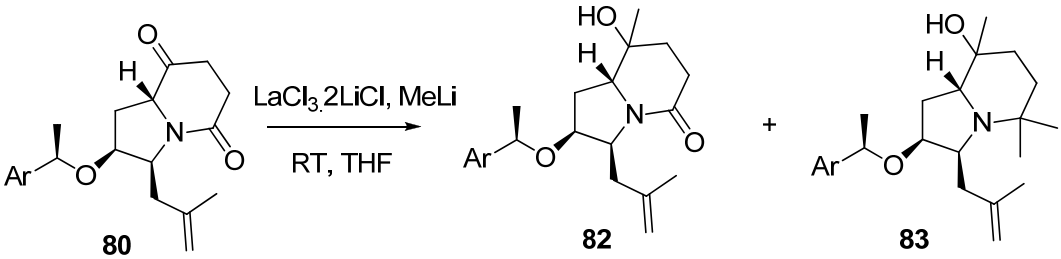
Figure 28: Commercially available methylenating reagents

Subsequently, in order to test the reactivity of this carbonyl, we decided to test more common nucleophilic reagents. Unfortunately, repeated recovery of clean starting material was observed with MeMgBr and $(CH_3)_3SiCH_2Li$[112] (Peterson's olefination) in THF under mild (RT) conditions or decomposition under refluxing conditions. These results further strengthened our assumption regarding the possibility of enolization of the ketone. Assuming that the enolisation could be our

[108] a. Conia, J.-M.; Limasset, J.-C. *Bull.Soc.Chim.Fr.* **1967**, *6*, 1936 b. Dauben, W. G.; Walker, D. M. *J. Org. Chem.* **1981**, *46*, 1103-1108, c. Pati, L. K.; Roy, A.; Mukherjee, D. *Tetrahedron* **2002**, *58*, 1773-1778
[109] Chandrashekhar, S.; Yaragorla, S. R.; Sreelakshmi, L.; Reddy, C. R. *Tetrahedron* **2008**, *64*, 5174-5183
[110] Bannerjee, M.; Mukhopadhyay, M.; Achari, B.; Bannerjee, A. K. *J. Org. Chem*. **2005**, *71*, 2787-2796
[111] Review: Hartley, R. C.; Li, J.; Main, C. A.; McKeirnan, G. J. *Tetrahedron* **2007**, *63*, 4825-4864
[112] Johnson, C. R.; Bradley, D. T. *J. Org. Chem* **1987**, *52*, 281-283

major impediment, we concentrated our efforts towards conditions conducive for methylenation for enolisable ketones.

In 2009, Knochel *et al*[113] reported a lewis-acid promoted activation of carbonyls, using $LaCl_3.2LiCl$, a commercially available solution in THF. This complex facilitated the addition of organometallic reagents to ketones and it was demonstrated to be especially effective in case of readily enolisable ketones. The solution of the lanthanum salt was added to the substrate at 0°C and stirred at RT for an hour before addition of the organometallic reagent at 0°C. The results reported in Knochel's publication could be satisfactorily reproduced when this reaction was tested on cyclohexanone as model compound. Motivated by this new possibility, we attempted to execute this transformation on ketone **80.** Upon using MeMgBr as the organometallic agent, only clean starting material was recovered. However, with MeLi, after 24 h of reaction, the ^{1}H NMR on the crude material revealed a 1:1 mixture of a new product and the starting material.



80 **82** **83**

Scheme 42: Lewis-acid promoted activation of enolisable ketones towards nucleophilic addition reactions

The separation of the two products on silica gel led to a significant loss of material presumably due to degradation of starting material. However, a small amount of this new material could be isolated. On examining more closely, the spectral data of this material indicated that it was actually a mixture of two compounds. Based on the ^{1}H NMR and mass spectroscopy data, these two compounds could possibly be assigned as indolizidinone **82** and indolizidine **83** (Scheme 42). Although these are very preliminary results, but there visibly wasn't any major improvement in the behavior of the ketone.

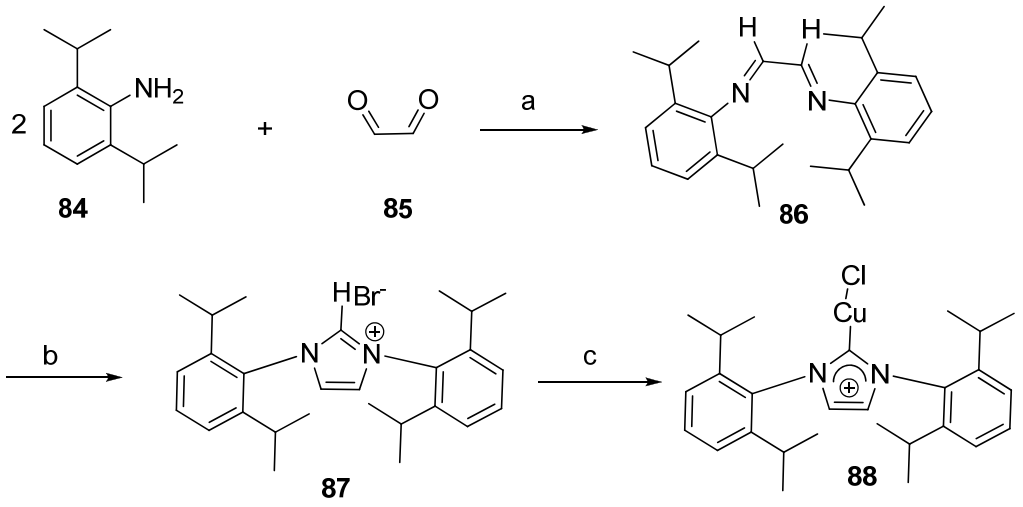
Without being discouraged by these series of results, we relentlessly searched for various less basic methylenating reagents during which the Zn-mediated methylenation seemed to be a

[113] a. Krasovskiy, A.; Kopp, F.; Knochel, P. *Angew. Chem. Intl.* **2006**, *45*, 497-500 b. Metzger, A.; Gavryushin, A.; Knochel, P. *SynLett*. **2009**, *9*, 1433-1436

reasonable option. The well known Takai protocol with Zn and diiodomethane in presence of $TiCl_4$[114] proved to be ineffective in our case as only the starting material was recovered even when the reaction was carried out with catalytic amounts of $PbCl_2$.[115]

In 2004, a new method of alkylidenation was reported by Yan *et al*[116] which involved an efficient 'CH_2' transfer from CH_2Cl_2 to a carbonyl compound in presence of Mg and $TiCl_4$. However, when this method was applied to our substrate, it only led to degradation products even at 0°C.

Another relatively recent method for carbonyl olefination was published by Lebel *et al*[117]. This olefination which was catalyzed by a copper-carbene complex was reported to be particularly effective in case of enolisable ketones. As we had not yet achieved any significant success by employing conventional methylenating procedures, we decided to test this novel method on our substrate. In order to test this, the imidazolium salt- precursor for the carbene was first synthesized in 3 steps as indicated in the scheme 43.



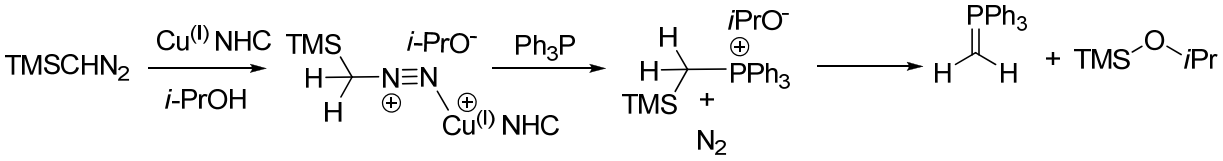
Key : a. *n*-propanol, 60-70°C, 80%, b. MOMBr, THF, 40°C, 30%, c. Cu(I)Cl, *t*-BuONa, THF, quant.

Scheme 43 : Preparation of the imidazolium salt - Precursor of the NHC-carbene

[114] a. Takai *et al Organic Synthesis* **1998**, *9*, 404 b. Comprehensive Functional Group Transformations, Vol. 1, 751
[115] Takai, K., Kakiuchi, T., Kataoka, Y., Utimoto, K. *J. Org. Chem* **1994**, *59*, 2668-2670
[116] a.Yan, T.-H, Chien, C.-T., Tsai, C.-C., Lin, K.-W., Wu, Y.-H. *Org. Lett*. **2004**, *6*, 4961-4963 b.Yan, T.-H, Chien, C.-T., Tsai, C.-C., Lin, K.-W., Wu, Y.-H. *Org. Lett*. **2004**, *6*, 4965-4967
[117] a. Lebel, H., Davi, M., Diez-Gonzalez, S., Nolan, S. P. *J. Org. Chem*. **2007**, *72*, 144-149 b. Lebel, H., Paquet, V., *J. Am. Chem. Soc.* **2004,** *126*, 320-328 and references therein.

The procedure for this reaction involved the addition of a large excess of propan-2-ol to a mixture of Ph_3P and the copper catalyst followed by sequential addition, at room temperature, of the carbonyl compound and $TMSCHN_2$. The reaction mixture was refluxed and followed by TLC to check for consumption of starting material.

In this catalytic process, the Cu-carbene complex is believed to activate the diazo-compound towards protonation by *iso*-propanol. The new nitrogen-Cu species thus formed undergoes a decomposition initiated by the PPh_3 that releases the metal catalyst, molecular nitrogen and a silyl phospohonium salt which collapses to generate the active ylide.



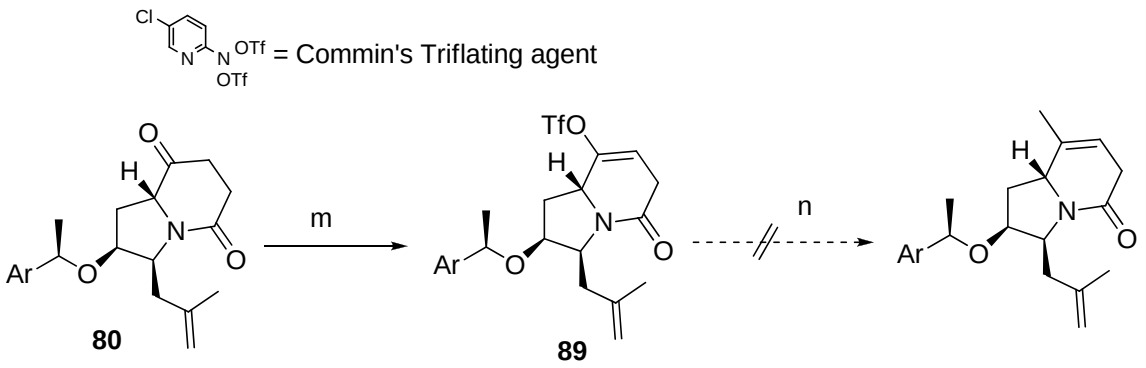
Scheme 44 : Proposed catalytic cycle for the Cu-NHC catalysed olefination reaction

After a thorough characterization of the synthesized NHC-precursor by spectral analysis to ensure its quality, the olefination reaction was first tested on 4-*t*-butylcyclohexanone and acetophenone as model compounds. In both the cases, the crude methylene derivatives were obtained in satisfactory crude yields but unfortunately, ketone **80** did not give any trace of the desired product and only degradation of starting material was observed.

Disappointingly, with most of the extensively applied methodologies used to generate the methylene functionality from our ketone failing to give us the desired outcome, presumably due to enolisation that was difficult to prevent, we finally decided to explore if we could benefit from this reactivity.

In this event, we shifted our focus on the scope of the Pd-cross-coupling reaction to directly introduce the methyl group at the desired position. After some experimentation, the enol triflate **89,** of ketone **80** was isolated in 74% yield by using the Commin's triflimide.[118] This triflate was engaged in a Pd-cross coupling reaction with MeMgBr[119] but only degradation products were obtained.

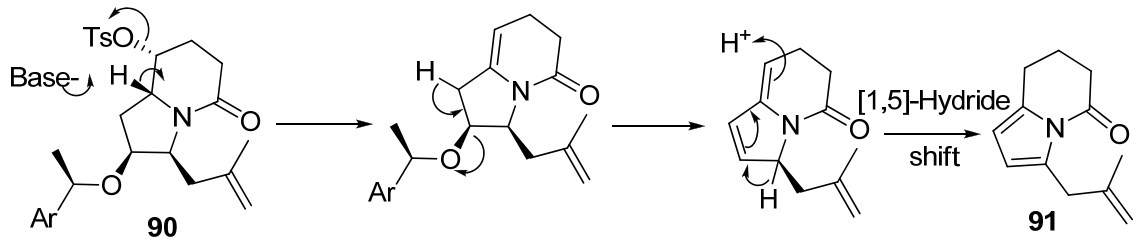
[118] Maulide N.; Vanherck, J-C.; Marko, I. E *Eur. J. Org. Chem.* **2004**, 3962-3967
[119] Ishihara, K.; Nakano, K. *J. Am. Chem. Soc*. **2007**, *129*, 8930-8931



Key : m) NaHMDS, Commins Triflating reagent, THF, -90°C to 0°C n) Pd($PPh_3)_4$, CH_3MgBr, Et_2O, RT

Scheme 45 : Attempts to introduce the Me- using coupling reaction

After several unsuccessful attempts on the ketone, we decided to consider the option of transforming the secondary alcohol in compound **79** itself to a good leaving group (e.g. tosylate), followed by its nucleophilic displacement with a cyano group. Although the desired tosylate, **90** could be obtained in quantitative yield using the classical procedure involving the treatment of the alcohol with tosyl chloride in presence of Et_3N and DMAP,[120] it was observed that the displacement reaction of this tosylate with the cyanide in NMP[121] or HMPA[122] led to the formation of an extremely polar, dark green product, which clearly indicated the loss of the chiral inductor from its structure. Based on the ^1H NMR, a possible structure and mechanism of formation of this product has been proposed. (Scheme 46):

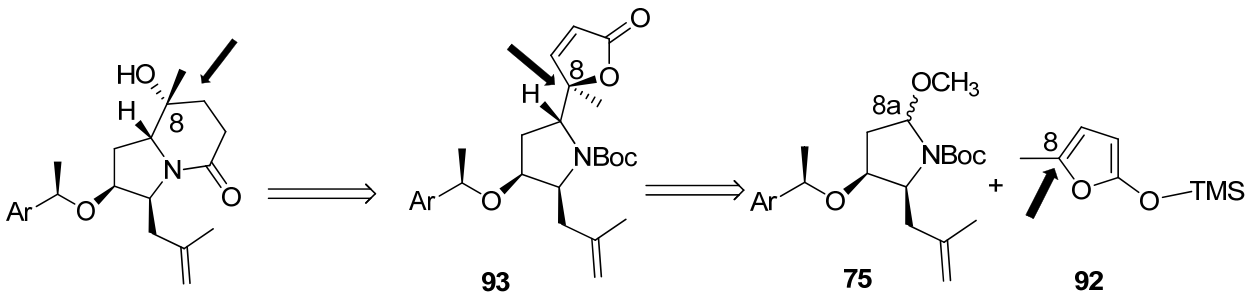


Scheme 46 : Proposed mechanism for the formation of a possible elimination product 90

At this juncture, it has become increasingly evident that either due to enolisation or due steric reasons, introduction of the methyl group after the formation of the indolizidinone skeleton was an unexpectedly daunting task.

[120] Adolfsson, H.; Nordstrom, K.; Warnmark, K.; Moberg, K. *Tetrahedron : Asymmetry* **1972**, *7*, 1967-1971
[121] Fringuelli, F.; Minuti, L.; Taticchi *Synthetic Commun.***1990**, *20*, 1497-1510
[122] Boyer, F.-D.; Ducrot, P.-H. *Synthesis* **2000**, *13*, 1868-1877

In order to circumvent this problem, an alternative strategy was designed with a possibility of incorporating the Me-group at an earlier stage in the synthesis via the vinylogous Mannich reaction, Scheme 47.

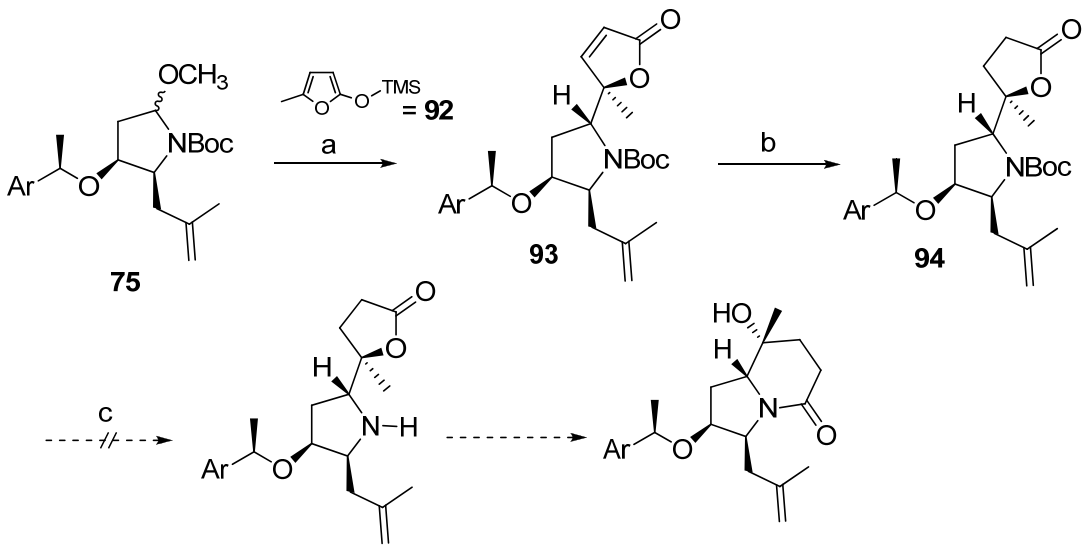


Scheme 47 : Introduction of the C8 methyl group during the vinylogous Mannich reaction

For executing this strategy, it was envisaged that if reagent **92**, 5-methyl-2-silyoxyfuran was used in the vinylogous Mannich reaction, it would be reasonable to expect that the reaction would yield butenolide **93** with the Me-group on C8. Thus, the 4-step sequence was repeated by using 5-substituted furan for the butenolide formation during the vinylogous Mannich reaction. This substituted furan **92** is not commercially available and was therefore synthesized from the commercially available 5-methyl-2-furanone by treatment with TMSCl in presence of Et_3N, followed by bulb-to-bulb distillation under vaccum.[123]

When aminal **75** was subjected to the vinylogous Mannich reaction with compound **92,** the butenolide **93** was obtained in 46% yield over 3 steps. Chemoselective reduction of the double bond in the butenolide ring gave lactone **94.** Removal of the Boc-group repeatedly gave back the starting material under standard conditions and long reaction time led to degradation products.

[123] Browm, S. P.; Goodwin, N. C.; MacMillan, D. W. C. *J. Am. Chem . Soc*. **2003**, *125*, 1192



Key : a) $BF_3.Et_2O$, **92**, Dry DCM, -90°C to -70°C (46 % for 3 steps from **73**) b) $CuCl_2.H_2O$, $NaBH_4$, MeOH, 0°C c) 2,6-Lutidine,TMSOTf, DCM, RT T

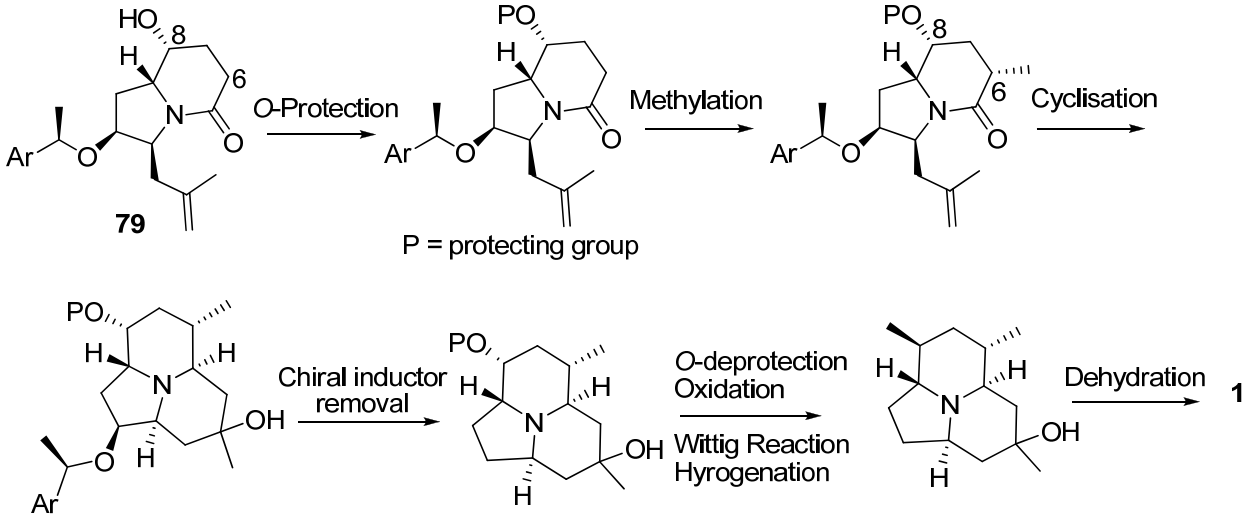
Scheme 48 : Alternate strategy for the introduction of the C8 methyl group

Based on these observations and the disappointingly low efficiency for the formation of the butenolide intermediate **93**, in comparison to the original sequence without the Me-group, it was inferred that the presence of the methyl group perhaps hampers the efficiency of this sequence. Therefore, even this strategy failed to provide the solution for our problem.

In conclusion, it was believed that easy enolisation and presence of the bulky chiral inductor could be the two major factors that could influence the reactivity of ketone **80**. The chiral inductor could interfere by taking up a conformation that hindered the efficient approach of the attacking species at C8 rendering this position unreactive. However, we do not have any theoretical evidence to lend credence to this proposition. Nevertheless, recalling from the previous chapter that in Smith's synthesis of Alkaloid (-)-**205B**, a Wittig reaction was successfully performed on the tricyclic intermediate, the introduction of this methyl substituent was postponed to a later stage in the synthesis on an intermediate structurally resembling the one in Smith's synthesis and we decided to concentrate our efforts on the introduction of the C6 methyl group.

5.3.5 *Introduction of C6 axial Methyl group*

Considering that the introduction of the C8 methyl group shall now be attempted on an advanced tricyclic intermediate, a new synthetic pathway as depicted in Scheme **49** was considered. In this route, it was envisaged that once the C8 hydroxyl group is protected by a suitable protecting group, the C6 axial methyl group would be introduced, followed by the aza-Prins cyclisation.

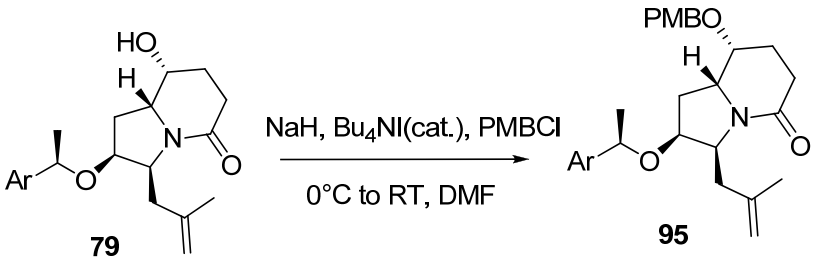


Scheme 49 : Alternative Pathway to the tricyclic intermediate

Besides facile protection and deprotection procedures, an important point to be considered in making the choice of a protecting group was its ability to survive under the acidic conditions employed for the removal of the chiral inductor. In the procedure that has been standardized in our laboratory to perform this operation, the substrate is treated with a solution of 10% TFA in dichloromethane at room temperature. Evidently, if the C8 hydroxyl protecting group is not robust enough to survive under these conditions, it would lead to the formation of a diol (C8 and C2) in which the two secondary alcohol groups would be difficult to discriminate.

Although the silyl protecting groups appeared to fairly qualify these criteria, it was surprising that none of the conventional methods for introduction of the silyl moiety such as TESCl with imidazole, TESOTf with pyridine or TBDMSCl/ TBDMSOTf with different solvents and bases, generated the expected product. Prolonged reaction times or warming the reaction mixture also did not bring any improvement.

Nevertheless, subjecting alcohol **79** to the standard procedure for the formation of the PMB-ether[124] provided the expected product as a white powder in 95% yield after purification over silica gel.



Scheme 50 : Protection of the C8 hydroxyl

The recrystallisation of compound **95** in diethyl ether gave sufficiently pure crystals for analysis by X-Ray crystallography. This analysis unambiguously confirmed the stereochemistry of all the stereogenic centres, in particular the axial orientation of the alcohol on C8. (Scheme **28**)

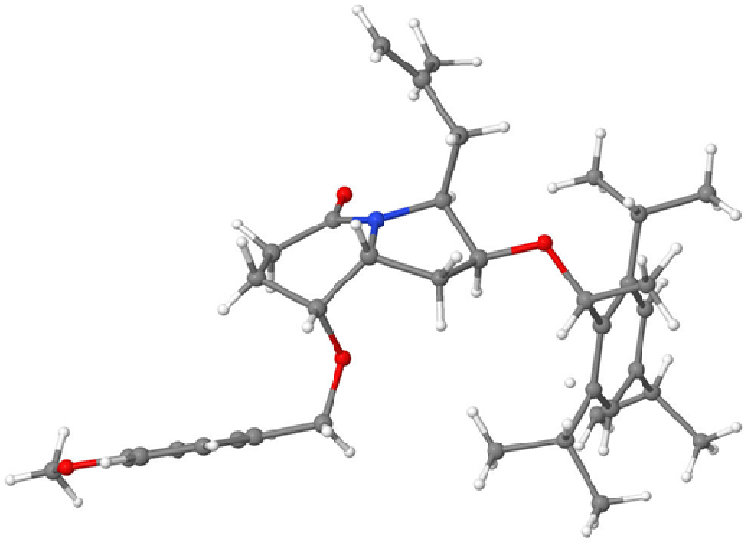


Figure 29: X-Ray Crystallographic data of PMB-ether 95

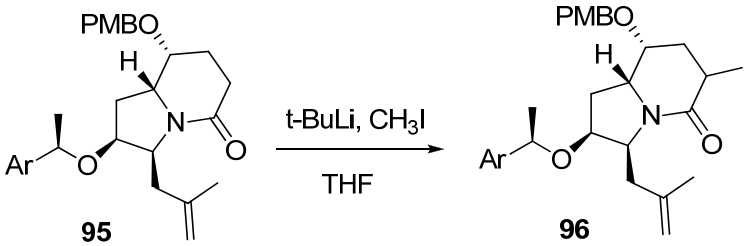
Motivated by these much-awaited positive results, we now confronted the task of introducing the axial C6 Methyl group.

[124] Jung, M. E.; Berliner, J. A.; Koronaik, L.; Gugiu, B. G.; Watson, A. D. *Org. Lett*. **2008**, *10*, 4207

Based on our model studies, we initiated our methylation attempts by treatment of PMB-ether **95** with LDA at -78°C followed by addition of excess of MeI and warming upto 0°C. These conditions however gave back largely the starting material and a small amount of a new compound was isolated in 20% yield. Analysis of the spectral data indicated that this compound was the expected methylated product **96**. Disappointingly, the reaction suffered from lack of reproducibility and no improvement in this behavior was observed by changing the reaction conditions such as number of equivalents of the base, the reaction temperature for enolate generation and subsequently alkylation and duration of the time given for enolate generation.

Assuming that the enolisation might be difficult due to steric hindrance of the base and/or the substrate, LDA was replaced by *s*-BuLi.[125] It was observed that when the reaction was carried out in either Et_2O or THF under the previously mentioned reaction conditions, a complex mixture of products was obtained. At lower temperature for enolate generation as well as alkylation (-78°C to -60°C after each addition), the methylated product was again obtained in small quantity with recovery of mainly starting material. Longer reaction time for enolate generation led to degradation products. Addition of HMPA (10% of the volume) to facilitate the alkylation of the lithium enolate also did not prove to be very helpful.

To our delight, treatment of lactam **95** with an excess of *t*-BuLi in THF,[126] at -78°C followed by addition of MeI, completely consumed the starting material and cleanly afforded only one isomer of the methylated product **96** in 76% yield after a rapid filtration over a short pad of silica gel. Pleased with this initial success in achieving the methylation, we investigated the stereochemistry of the product obtained.



95 **96**

Scheme 51 : Methylation of substrate 95

[125] Liu, L.-X.; Ruan, Y.-P.; Guo, Z.-Q.; Huang, P-Q. *J. Org. Chem*, **2004**, *69*, 6002-6009
[126] Hanesain, S.; Papeo, G.; Fettis, K.; Therrien, E.; Viet, M. T. P. *J. Org. Chem* **2004**, *69*, 4891-4899

Regarding the stereochemical outcome of the reaction**,** it was assumed that if the benzyl-oxy group adopts an axial orientation in the generated enolate by analogy with the X-Ray data of **95**, the stereoelectronic effects would favor the axial entry of methyl iodide. This approach, would however be hindered by 1,3-diaxial interactions with the benzyloxy group that would disfavor this approach. However, considering the fact that methyl iodide is a relatively small electrophile, the axial approach could therefore be expected to be favored leading to the alkylated product with axial stereochemistry. In the case that the equatorial epimer would be obtained, a deprotonation-protonation sequence should generate the desired epimer.

In order to determine the stereochemistry at position C6 some NMR studies on the lactam **96** were performed. Assuming that the conformation of the methylated product in the solution is the same as that of the conformation of the ether in the solid state (by analogy with X-ray data), the H_{8a} and H_8 hydrogens are in axial and equatorial positions respectively. A nOe experiment of the substrate revealed a strong correlation between H_{8a} and one of the two H_7 protons, which was assigned as H_{7axial}. In the ^1H NMR spectrum, the signal of this proton fortunately, did not overlap with any other signal, which allowed us to determine the values of the different coupling constants. In order to simplify the shape of the signal, the coupling constant between the two H_7 was eliminated by irradiation of H_{7eq}. Thus, by simplifying the signal, the two remaining coupling constants were determined to be 1.5 Hz and 12.0 Hz. The smaller value is consistent with the coupling between H_{7axial} and the equatorial H_8 proton. However, the larger value can be explained only if H_6 is axial. Therefore, contrary to our aforementioned assumption, the Me-group was in fact present at the equatorial position and compound **96** was therefore turned out to be the *undesired diastereoisomer* (Figure 30).

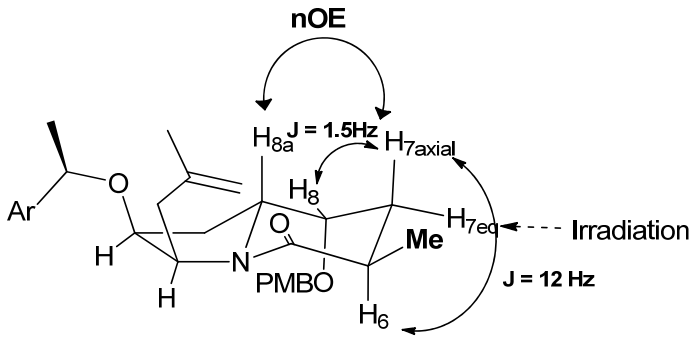
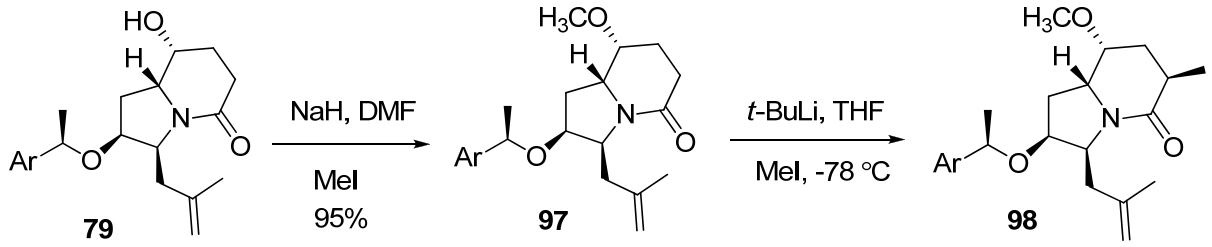


Figure 30: NMR studies for determining the stereochemistry of methylation at C6

Evidently, the steric effects dominated over the stereoelectronic factors in this reaction. So, in order to attain the desired diastereoisomer, compound **96** had to be epimerized. Therefore, before trying to epimerize compound **96**, we decided to test the influence of the protecting group at C8 hydroxyl, on the stereochemical outcome of this reaction. The relatively less bulky methyl ether **97** was thus synthesized uneventfully under the previous *O*-protection conditions.

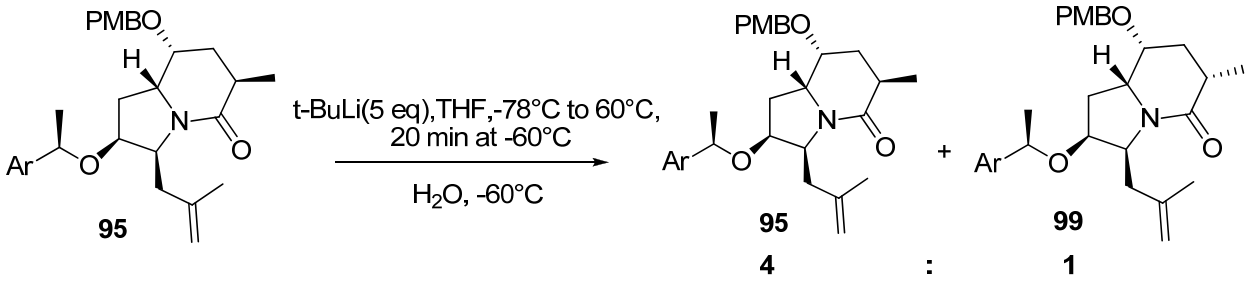


Scheme 52 : Study of the effect of protecting group on C8 hydroxyl on the stereochemical outcome of methylation on C6

The methylation of compound **97** also proceeded smoothly furnishing only one stereoisomer **98** as the product. Performing the same spectral analyses as previously described, on this product, indicated that the Me-group was again present in the equatorial position**.** Thus, it was conclusive that the entry of the MeI was either independent of the C8 hydroxyl protecting group or had negligible impact on the stereochemical outcome of the alkylation. These results also indicated that the reversal of stereoselectivity to obtain the desired isomer could not be avoided.

To this end, it was expected that reaction conditions similar to methylation of lactam **95,** could also generate the enolate of lactam **96.** However, slightly harsher conditions vis-a-vis temperature or reaction time might be required due to the Me- group already present on the carbon involved in the enolisation.

When an excess of *t*-BuLi was added to the substrate in THF at -78°C and the reaction mixture was stirred at -60°C for 20 min, followed by quenching with H_2O, along with the starting material, a new spot (indicative of new compound) was seen on the TLC. On purification over silica gel, starting material was separated and all NMR data obtained for the new compound supported the possibility that lactam **99** (Scheme **53**) could indeed be the expected C6 epimer. The ratio of the two was estimated to be 4: 1 in favor of the undesired epimer **95** based on the ^{1}H NMR of the crude mixture.



Scheme 53 : Preliminary investigation of the epimerisation of lactam 95

With these preliminary results which seemed encouraging, we decided to optimize this epimerisation protocol later and investigated the behavior of substrate **95** towards the more important aza-Prins cyclisation without delay.

Again, based on our model studies**,** initial attempts for partial reduction of the lactam were made using DIBAL-*n*-BuLi ate-complex. It was expected that if the reaction proceeded smoothly, the tricyclic amine thus obtained, would possess the desired stereochemistry at position 5a as the olefinic moiety is suitably oriented to attack the iminium in the desired fashion as indicated:

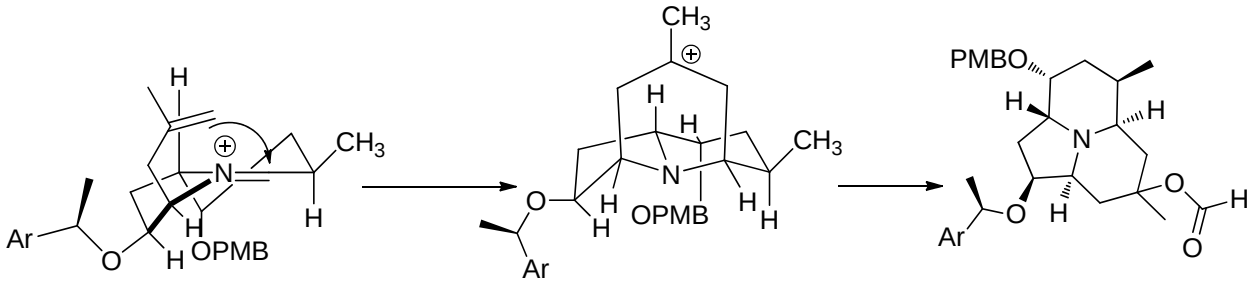
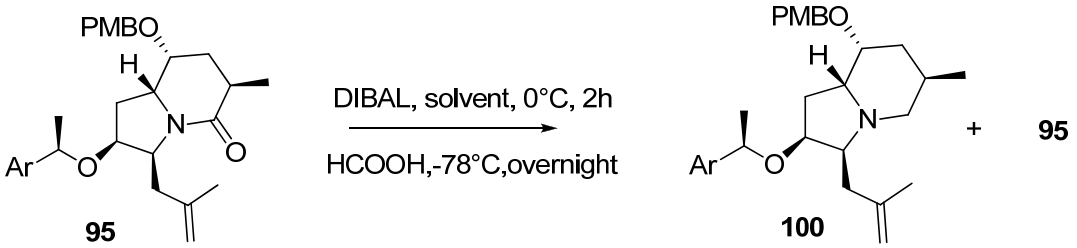


Figure 31: Mechanistic representation of the aza-Prins cyclisation

The treatment of substrate **95** with excess of DIBAL-*n*-BuLi complex in THF, unfortunately gave back the starting material even under refluxing conditions. The bulky nature of the reducing agent was suspected to be responsible for this lack of reactivity.

Substituting the DIBAL-*n*-BuLi complex, with a solution of DIBAL in THF, indicated the presence of a more polar product on TLC along with the starting material. Upon treatment with HCOOH, followed by conventional workup and separation of the crude mixture over silica gel, the new product was identified as the tertiary amine **100,** formed as a result of a complete

reduction of the starting material. Using a 1M solution of DIBAL in DCM[127] at lower temperature, also led to the recovery of starting material and small amount of **100.**



Scheme 54 : Formation of the tertiary amine, a product of complete reduction of lactam 95

As the formation of this over-reduced product was observed with DIBAL even at 0°C, we decided to replace it with Superhydride. However, no reaction was observed at all with this reagent in THF even with long reaction times at room temperature.

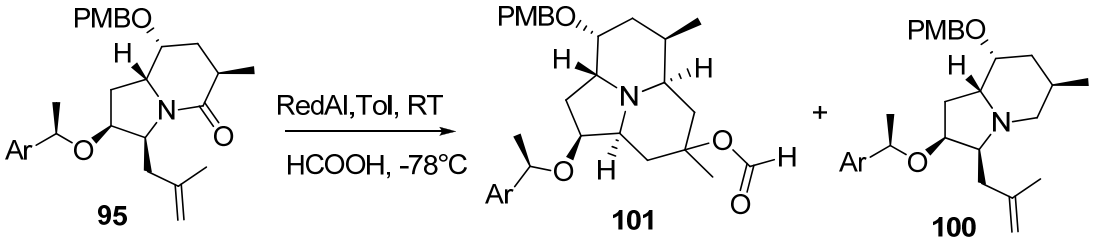
Subsequently, we decided to try the partial reduction of lactam using the commercially available Alane-complex[128] ($AlH_3.EtNMe_2$ in THF). Based on literature precedents, this reagent was known to be effective for partial reductions of lactam at low temperature and apparently required short reaction time. It, therefore, seemed to be an attractive choice which could avoid the problem of over-reduction. Disappointingly, treatment of substrate **95** with this reagent also resulted in the recovery of starting material after several hours of reaction at low temperatures and formation of a small amount of **100** at room temperature.

The next trial was attempted with RedAl[129] in THF, which also led to recovery of starting material. However, upon changing the solvent from THF to toluene, a considerable increase in the reactivity of RedAl was observed as expected and the starting material was completely consumed in less than 30 min. Acid treatment at low temperature and allowing the reaction mixture to warm up to room temperature, indicated the presence of the a new compound on TLC along with the presence of the spot corresponding to the previously identified amine **100.**

The ^{1}H NMR-spectrum revealed that this crude mixture was in fact a mixture 1:1 (approx.) of two compounds. Upon separation over silica gel the new compound was separated from the more

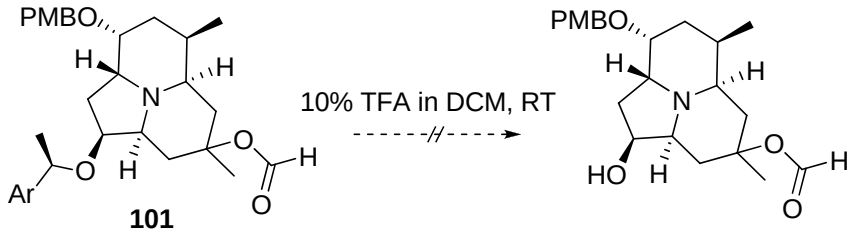
[127] Bull, S. D.; Davies, G. D.; Nicholson, R. L.; Sanganee H. J.; Smith, A. D. *Org. Biomol. Chem.* **2003**, *1*, 2886-2899
[128] a. Kawasaki, T.; Shinada, M.; Ohzono, M.; Ogawa, A.; Terashima, R.; Sakamoto, M. *J. Org. Chem* **2008**, *73*, 5959-5964 b. Marlett, E.M.; Park, W. S. *J. Org. Chem.* **1990**, *55*, 2968-2969
[129] Amat, M.; Lior, N.; Hidalgo, J.; Escolano, C.; Bosch, J. *J. Org. Chem.* **2003**, *68*, 1919-1928

polar amine fraction and isolated in 40% yield. To our delight, a detailed spectral analysis of this compound, established that it is indeed the tricyclic formate **101,** which was our first success towards the construction of tricyclic skeleton of the molecule.



Scheme 55 : Elementary results indicating the successful construction of the tricylcic core of the target molecule

Motivated by these very encouraging results, before optimizing this reductive cyclisation, we decided to investigate the subsequent steps in the synthesis. However, when the removal of the chiral auxiliary was executed under the classical conditions used in our laboratory, it was observed that the PMB-ether cleaved faster or at a comparable rate as that of the chiral inductor. This result thereby indicated that the PMB-group could not be used efficiently for protection of the C8 secondary alcohol.

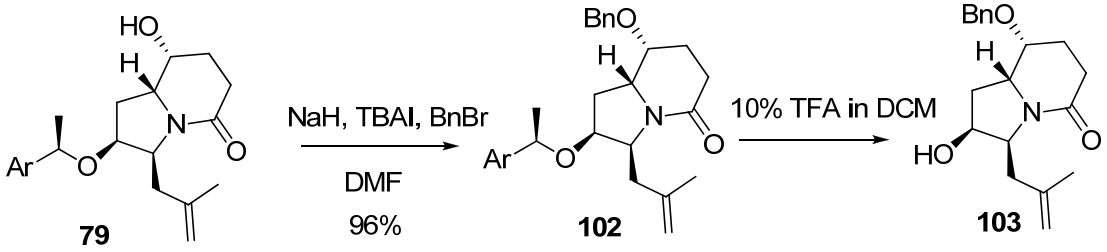


Scheme 56 : Cleavage of the PMB-group under acidic conditions

Somewhat disappointed by these results, we turned our attention towards the benzyl protecting group which is known to be more resistant to acidic conditions. The protection was realized under identical reaction conditions as described before and the desired benzyl-ether **102** was isolated in almost quantitative yield.

In order to rapidly check the compatibility of this protecting group with the removal of the chiral inductor, the bis-ether **102** was treated with 10% TFA in DCM. To our satisfaction, this preliminary test showed the chiral auxiliary had been selectively cleaved as the ^{1}H NMR of the

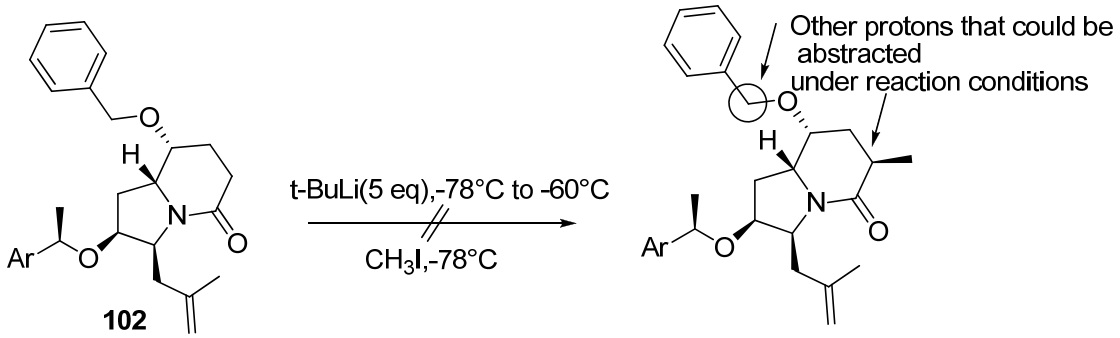
crude product of the crude product of the cleavage reaction indicated the presence of the characteristic AB-system of the benzylic protons.



Scheme 57 : Preliminary investigations into the Bn-protecting group

Having solved the problem of the orthogonal removal of the chiral inductor, we decided to attempt the methylation at C6 on this compound**.**

Unfortunately, when the benzyl ether **102** was subjected to the conditions optimized for methylation, a complex mixture of products was obtained which could not be separated by column chromatography. In addition, there was a noticeable loss of the characteristic AB-system of the benzylic protons on the ^{1}H NMR of the crude material. There is evidence in the literature that the benzylic protons could be abstracted by strong bases like *t*-BuLi even at temperatures as low as -78°C.[130] If the abstraction of this proton(s) occurred, in presence of an excess of MeI, methylation at the benzylic position could be expected as well, which in turn gives rise to the observed formation of complex mixtures. To our disappointment, this problem could not be circumvented by changing the reaction conditions and performing the reaction at lower temperature, decreasing the reaction time for enolate generation or the number of equivalents of the base.

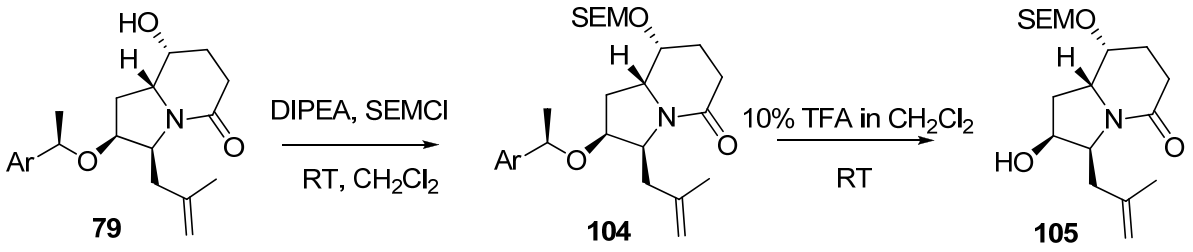


Scheme 58 : Problems encountered in methylation of the Bn-ether 102

[130] Onyeozili, E. N; Maleckza, Jr. R. E. *Tetrahedron Letters* **2006**, *47*, 6565-6568

At this stage, some other acid-resistant groups such as the MOM and the SEM ether were considered. Treatment of alcohol **79** with MOMCl gave back only starting material without any trace of the desired product.

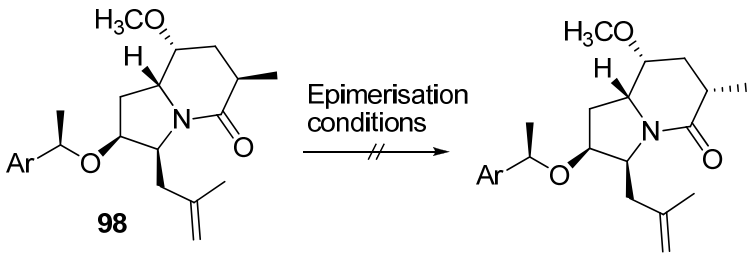
However, SEM ether **104** could be secured in 56% yield under reported conditions. Despite this moderate yield, we decided to immediately test its resistance towards the conditions for the removal of the chiral inductor and it was encouraging to observe the clean generation of the cleavage product, secondary alcohol **105.** Although this preliminary test seemed promising, the moderate yield for the protection was not very attractive to continue the synthesis with this protecting group.



Scheme 59 : Preliminary investigation of the SEM-protecting group

These observations further narrowed down the choice of the protecting group. However, to proceed further in the synthesis, we decided to use the robust Me-ether **97** in spite of the fact that its deprotection could probably be a difficult task.

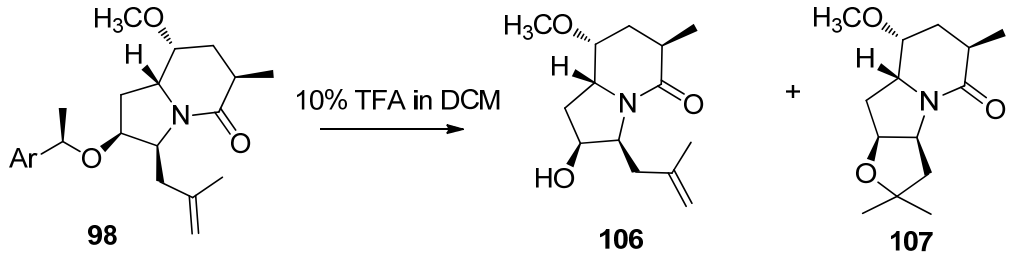
As methylation of the Me-ether **97** could be successfully reproduced (Scheme **52**), we decided to optimize the epimerisation reaction at this stage. Under the conditions previously employed on the PMB-ether **95** (Scheme **53**), the TLC indicated the formation of a new spot for epimerisation of this methyl-ether **98** also (Scheme **60**). However, the ^{1}H NMR of the crude mixture largely indicated the presence of starting material with very negligible amount of this new compound. Therefore, in order to facilitate the generation of enolate the methyl ether **98** was treated with *t*-BuLi for 1 h at a slightly higher temperature, -60°C. However, to our disappointment, complete decomposition of the starting material was observed under these conditions. This decomposition could be the consequence of an initial elimination of the methoxy anion due to the presence of the strong base. Decreasing this reaction time also gave similar results which suggested that optimizing the epimerisation protocol on this substrate could prove to be challenging.



Scheme 60 : Attempts for epimersation of the Me-ether 98

Recalling the difficulties encountered in the optimization of the aza-Prins cyclisation due to lack of reactivity with many reducing reagents (and over-reduction with others) and considering that the C8 methylation would be performed on the tricyclic intermediate, at this stage, in spite of the difficulty observed in epimerisation of methyl ether **98**, we decided to continue with this protecting group. Aware of the fact that the deprotection of the methyl group could prove to be challenging, we decided to take advantage of the fact this group is robust enough to survive the conditions for cleavage of the chiral inductor. This would allow us to study the behavior of the aza-Prins cyclisation on a substrate without the chiral inductor, a structure closer to our model studies on lactam **55**).

To rapidly test this idea, lactam **98** was treated with 10% TFA in DCM. This operation resulted in a 1:1 mixture of alcohol **106** and ether **107** in a surprisingly low 40% yield. This significant loss of material had presumably occurred during the purification of the crude product on silica gel. The formation of the ether could be explained by the protonation of the double bond in the acidic-medium giving rise to a tertiary carbocation, readily attacked by the newly formed secondary alcohol.

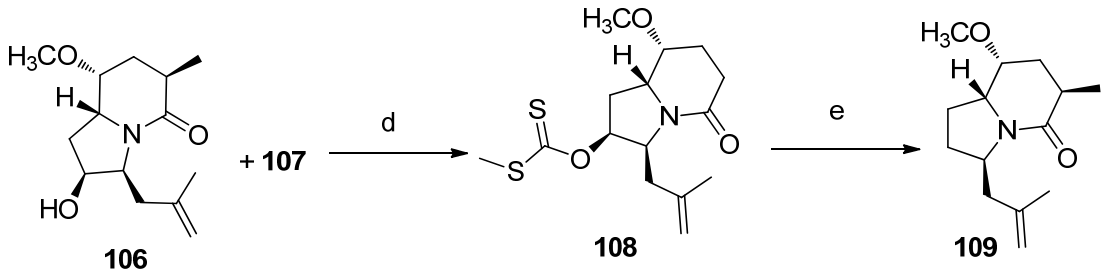


Scheme 61 : Removal of chiral inductor on methyl-ether 98

Varying the concentration of TFA in DCM, temperature conditions and solvents (only DCM, 1:1 DCM: Toluene, only Toluene) to avoid or minimize the undesired cyclisation of the terminal olefin did not prove to be useful. With a hope of limiting this undesired side-product, alternate methods with proton free reagents were tried. Disappointingly, the treatment of substrate **98** with TMSOTf in DCM, 5% $MeSO_3H$ in DCM, $MeSiCl_3$ and NaI in CH_3CN[131] also resulted in the same composition of the above mixture. General methods for removal of benzyl ethers such as reatment with BCl_3 in DCM and refluxing conditions with DDQ in presence of a phosphate buffer led to degradation of starting material.

Finally, despite the low efficiency of this reaction, with some amount of this mixture in hand, we decided proceed as far as possible in our synthetic plan. Subjecting this mixture to the classical conditions for xanthate[132] formation, gave compound **108** in a modest yield of 48% yield over 2 steps. In addition, during this purification, the unreacted compound **107** could be efficiently separated.

Subsequently, xanthate **108** smoothly underwent Barton McCombie deoxygenation[133] sequence to afford indolizidinone **109** in a nearly quantitative yield. A very accurate value is not given due to the presence of Sn-residue in the purified material.



Key : d. KH, CS_2, MeI, DCM, 48% e. AIBN, Bu_3SnH, Toluene, Reflux (quantitative)

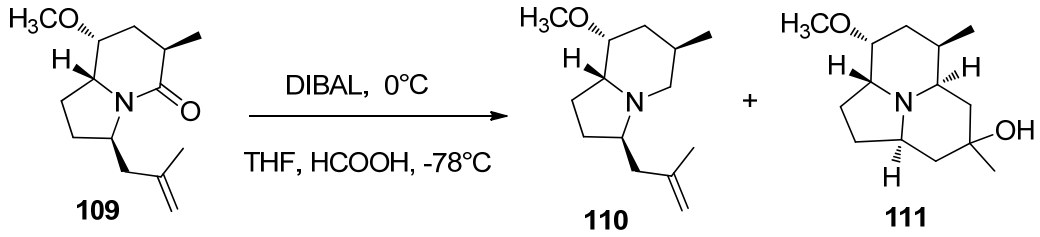
Scheme 62 : Deoxygenation of the alcohol 106

Having secured the deoxygenated product, the stage was set to attempt the epimerisation of the C6 methyl-group. With this aim, when lactam **109** was subjected to the conditions that were standardized for this reaction before (Scheme **53**), two products were observed both on the TLC

[131] Olah, G. A; Hussain, A.; Balard B. G; Narang, S. C *Angew. Chem. Int. Ed.* **1981**, *20*, 690-691
[132] Liu, J; Hsung, R. P; Peters, S. D *Org. Lett*. **2004**, *6*, 3989-3992
[133] Barton, D. H. R.; McCombie, S. W *J. Chem. Soc. Perkin Trans.1* **1975**, 1574

as well as the ^{1}H NMR. Unfortunately, the separation of these two compounds on silica gel proved to be difficult. Nevertheless, with a positive indication that this operation could indeed be executed on this substrate, we decided to attempt our much awaited goal of testing the aza-Prins cyclisation on a pure sample of the undesired epimer **109.**

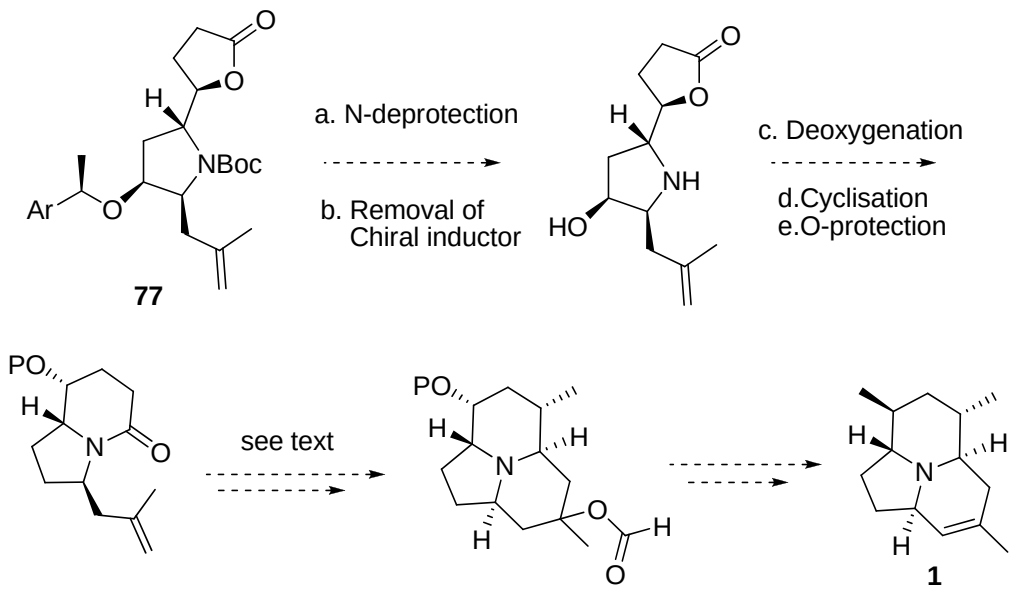
The use of DIBAL-*n*-BuLi complex in THF once again did not lead to any reaction. Also, to our disappointment, the aza-Prins reaction with a solution of DIBAL in THF at 0 °C once again resulted in complete consumption of starting material generating the tertiary amine **103** as the major product and the tricyclic amine **111** was identified as the minor one. In addition, these products could not be separated on silica gel.



Scheme 63: Preliminary investigation of the aza-Prins cyclisation on lactam 109

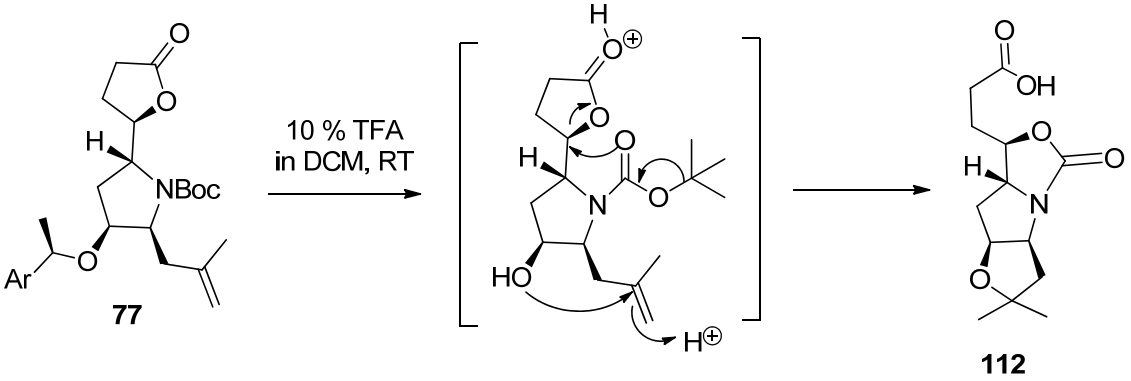
Although these were preliminary results, however they were reflective of the fact that our hypothesis that the presence of the bulky chiral inductor would have an influence on this reduction-cyclisation sequence was probably not true. Due to lack of material for thorough studies and because the synthetic sequence for obtaining lactam **109** is far from being efficient, the possibility of construction of the tricyclic structure after the removal of the chiral inductor was abandoned.

Alternatively, we made some elementary attempts to investigate the viability of removal of the chiral inductor on an intermediate even before the formation of the indolizidinone intermediate and then concentrate on formation of the ring-systems. In this event, the following strategy was proposed (Scheme 64):



Scheme 64: Proposed strategy for removal of chiral inductor before the formation of the indolizidinone system

Thus, the N-Boc lactone **77** seemed to be an appropriate intermediate to execute this operation as one could expect to achieve the deprotection of Boc-group as well as cleavage of chiral inductor in a single step. However, contrary to our expectations, when lactone **77** was subjected to the conventional conditions for cleavage of the chiral inductor, formation of the tricyclic acid **112** was observed.

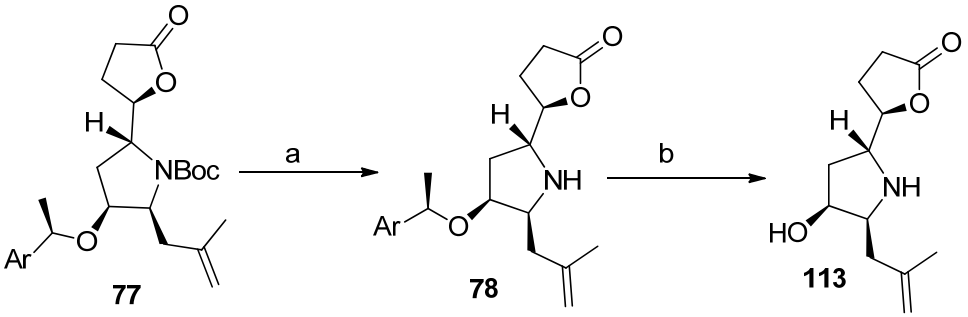


Scheme 65 : Cleavage of chiral inductor on intermediate 77

The formation of this compound could possibly be explained by successive unselective acid-catalysed events that include the inductor cleavage and activation of the double bond in the acidic medium leading to cyclisation and also, activation of the lactone moiety under the acidic conditions which could be seen as conducive for the formation of the oxazolidinone.

Nevertheless, from our prior knowledge of the fact that the Boc group could be selectively removed in presence of the inductor, we decided to cleave the Boc-group and the chiral inductor sequentially.

Pleasantly, this step-wise cleavage proceeded smoothly affording clean amino-alcohol **113** in 70% yield without disturbing the side chain olefin. This clear-cut difference in reactivity could possibly be due to the fact that the free amine in **78** is protonated in the acidic medium, thereby reducing the possibility of protonation of the double bond, thus preventing the undesired cyclisation.

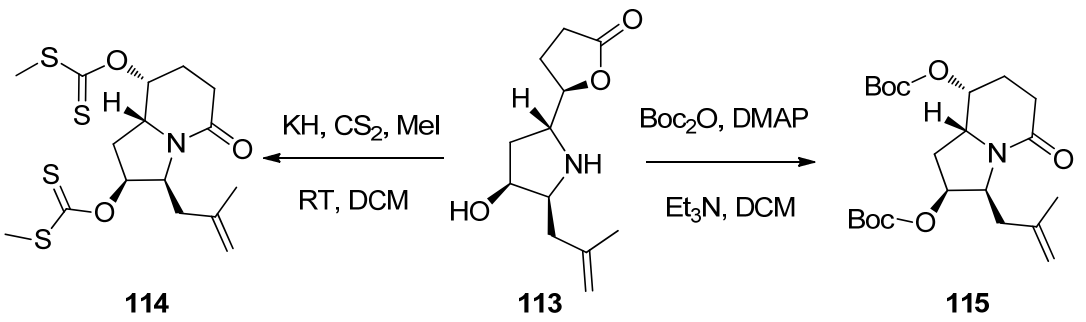


Key : a. 2,6- Lutidine, TMSOTf, CH_2Cl_2 b.10%TFA in CH_2Cl_2 (70%)

Scheme 66: Step-wise Boc-deprotection and cleavage ofthe chiral inductor on compound 77

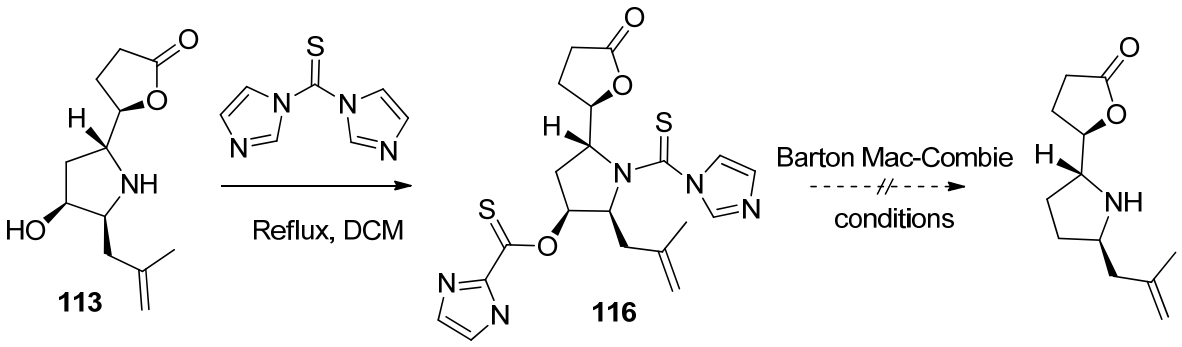
With sufficient amount of the amino-alcohol in hand, we planned to perform a Barton Mac-Combie deoxygenation sequence. However, to our surprise, while attempting to synthesize the xanthate of the secondary alcohol in compound **113,** the formation of indolizidinone bis-xanthate **114** was observed. It was believed that this could be due to the fact that the basic conditions required for the xanthate formation also facilitated the indolizidinone formation. Therefore, we decided to protect the free amine again with the Boc-group. However, under the standard conditions for Boc-protection previously employed in the synthesis, the bis-substituted indolizidinone **115** was isolated (Scheme **67**).

These results obtained strongly suggested that in basic or catalytic nucleophilic conditions the lactone is susceptible to ring opening which invariably facilitated the formation of an indolizidinone system with two secondary hydroxyl groups that were difficult to differentiate. Therefore, the formation of the xanthate in neutral conditions could be preferably used.



Scheme 67: Problems encountered in obtaining the xanthate of the secondary alcohol 113

To this end, the formation of thioimidazole xanthate **116** was attempted by refluxing the amino-alcohol **113** with 1,1'- thiocarbonyldiimidazole in DCMm[134] which resulted in the formation of the desired bis-adduct albeit in a moderate 40% yield. However, the Barton-McCombie reaction could not be performed satisfactorily as this compound surprisingly had a very poor of solubility in common solvents like toluene and benzene that are normally used for the reaction.



Scheme 68: Synthesis of the thioimidazole bis-xanthate 116

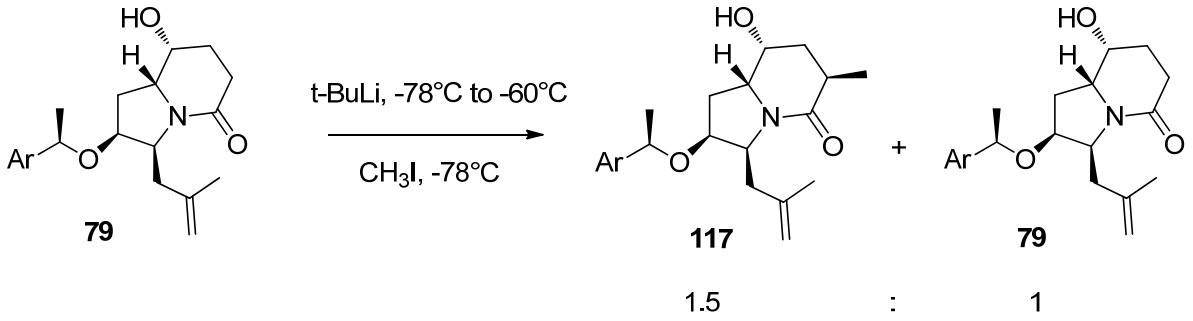
In view of these discouraging results which clearly showed that the removal of the chiral inductor before the formation of the hydroxy-indolizidinone system, led to an inefficient dead-end, we returned to our original synthetic strategy which comprised of introduction of the C6 methyl group followed by the aza-Prins cyclisation on the indolizidinone intermediate.

It was during one of our attempts to synthesize the Me-ether **97** itself that the possibility of a concomitant C-alkylation at C6 and *O*-alkylation of C8 hydroxyl in hydroxyindolizidinone **79** was discussed**.** As is observed frequently, the *O*-alkylation reactions require room temperature conditions and long reaction times for completion. Therefore, the possibility of obtaining

[134] Hanessian, S.; Dhanoa, D. S.; Beulieu, P. L. *Can. J. Chem*. **1987**, *65*, 1859-1865

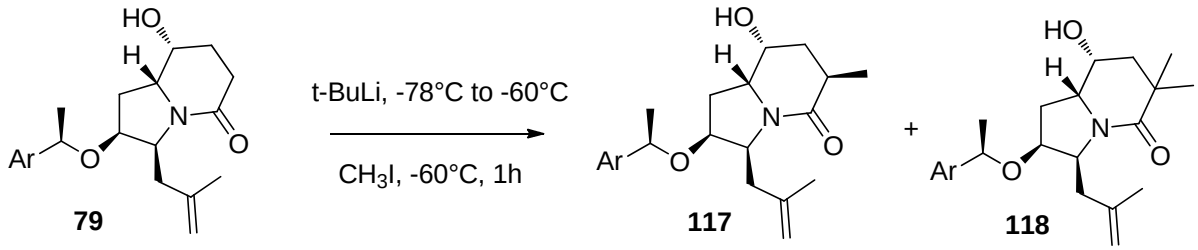
exclusively the C-alkylation product under our reaction conditions for methylation could not be neglected completely.

To our delight, when free alcohol **79** was subjected to methylation Scheme **69**, the C-alkylation product **117** was obtained exclusively, albeit with the undesired stereochemistry. This result was consistent with the fact that the size of the substituent on the *O*-atom (PMB, Me, H) has no consequence on the stereoselectivity of the reaction. In the few initial trials, considerable amount of starting material was also recovered, however *O*-alkylation product was never observed in spite of the excess of base and the alkylating agent.



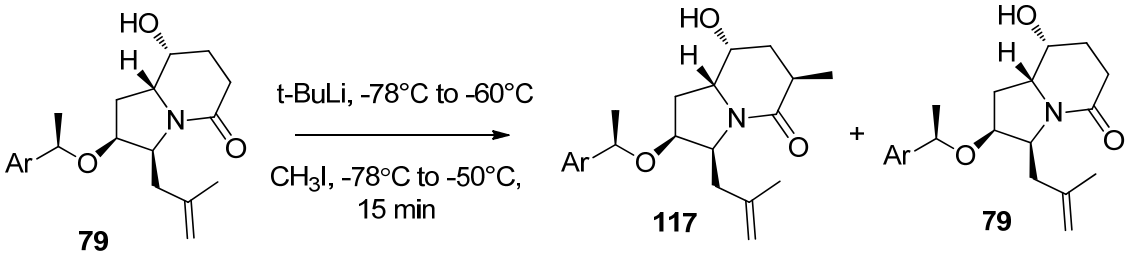
Scheme 69: Methylation of the free alcohol 79

In order to consume the starting material completely, longer reaction time was given for the alkylation step (1 h at -60°C) with larger excess of base as well as MeI. In this case, a 1: 1 mixture comprising of the mono-methylated compound **117** and the bis-methylation product at C6, compound **118** were obtained. Although, attempts to separate these compounds by column chromatography over silica gel resulted in appreciable loss of material, a small amount of compound **118** could be isolated for the purpose of analysis.



Scheme 70: Optimisation attempts of methylation of alcohol 79

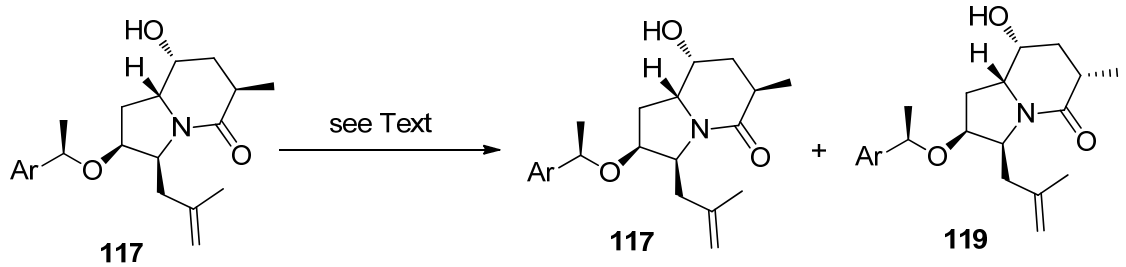
Gratifyingly, after rigorous experimentation, it was observed that increasing the temperature of the reaction mixture *rapidly* after the addition of the electrophile, furnished mono-methylated lactam **117** as the major product with less than 10% of starting material, **79** (based on ^{1}H NMR data) and negligible amount of bis-methylation product.



Scheme 71: Optimisation of the methylation of free alcohol 79

As the formation of undesired degradation products had been observed in our previous trials to optimize the epimerisation reaction on *O*-protected substrates (Me ether), lactam **117** seemed to be more appropriate to optimize the epimerisation reaction. In this case, the alkoxyanion formed by the deprotonation of the alcohol by a strong base, would have no tendency to be eliminated allowing the base to abstract selectively the proton α- to the carbonyl.

As significant loss of material was observed in our attempts to separate lactam **117** from starting alcohol **79**, we decided to engage the crude mixture itself for epimerisation by treating it with *t*-BuLi for 1 h, followed by quenching with H_2O. The presence of a new product was identified by TLC and upon purification over basic alumina, compound **119** was isolated in 30% yield.



Scheme 72: Epimerisation of compound 117

Recalling our previous exercise, NMR studies were performed to determine the stereochemistry of this new compound. To begin with, a strong nOe correlation of H_{8a} with one of the two H_7 protons allowed us to identify the H_{7axial} in the ^1H NMR spectrum of compound **119.** The coupling constants for this proton were determined to be J = 3.0 Hz, 6.0 Hz and 13.8 Hz. The biggest value obviously corresponded to its coupling with equatorial H_7 and one of the two smaller values was consistent with its coupling with H8 which is equatorial based on analogy with X-Ray data as previously discussed. Therefore, the remaining value, also corresponding to a *cis*-relationship suggested that H6 should be equatorial. Based on these data, it was concluded that compound **119** could indeed be the epimer of **117** and thus, the desired *axial diastereoisomer*.

Pleasingly, good quality crystals of this compound could be obtained by crystallizing it in EtOAc which enabled us to confirm the structure of this compound by X-Ray diffraction studies. As seen in Figure 32, the methyl substituent effectively has the appropriate stereochemistry as desired in the final molecule.

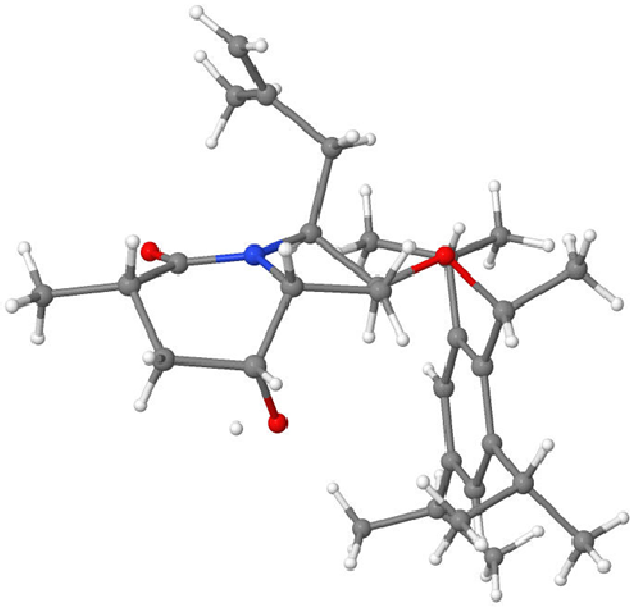


Figure 32: X-Ray Crystallographic data of compound 119

Determined to improve the ratio of the diastereoisomers in favor of the desired epimer, we planned to study the effect of the source of the proton used for quenching the reaction.

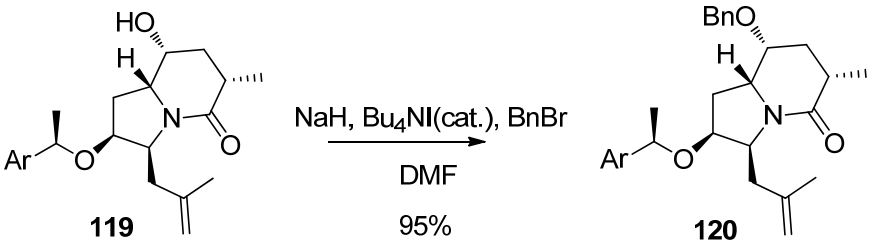
In subsequent attempts, by keeping the time for enolate generation constant at 1 h and temperature for quenching the reaction as -60°C in all cases, a range proton sources were used to quench the reaction. Use of common proton sources such as, MeOH, aqueous saturated NH_4Cl, MeOH saturated with NH_4Cl, *i*-propanol and AcOH did not bring any significant improvement in the diastereoisomeric ratio. Even bulky proton sources like 2,4,6-trimethylphenol[135] and 2,6-ditertbutyl phenol did not prove to be very useful. But, to our satisfaction, quenching the reaction with *t*-butanol and allowing the reaction mixture to warm up to room temperature furnished a 1:1 mixture of the two epimers (as calculated by ^{1}H NMR). Upon purification over basic alumina, the desired epimer was obtained in 50% yield. In addition, during this purification, the remaining unmethylated hydroxyindolizidinone **79** was also separated efficiently.

As we could not observe any conclusive trend in the ratio of the two diastereoisomers obtained based on the series of epimerisation reactions with the proton sources listed above, we decided to proceed with *t*-butanol as the quenching agent which had given us the best conversion ratio. Substrate **117** could be epimerized for as many as three cycles without any significant degradation of the recovered starting material (as observed by ^{1}H NMR) to obtain the desired epimer in 61 % yield over 3 steps based on recovered starting material. However, a limitation of the process is that the efficiency of the epimerisation was not the same in the subsequent cycles. Also, no significant improvement was observed in this ratio by increasing the time for enolate generation further (> 1h with the base) or altering the temperatures (-90°C, -78°C and -40°C) for quenching the reaction (with *t*-butanol as the quenching agent).

With this successful installation of the axial methyl group, it was again time to make the choice of the protecting group for C8 hydroxyl before embarking on the task of constructing the tricyclic skeleton of the target molecule. At this stage, the choice of the Bn-protection seemed to be the most obvious one for this C8 hydroxyl group.

[135] Hanessian, S; Buckle, R; Bayrakdarian, M *J. Org. Chem* **2002**, *67*, 3387-3397

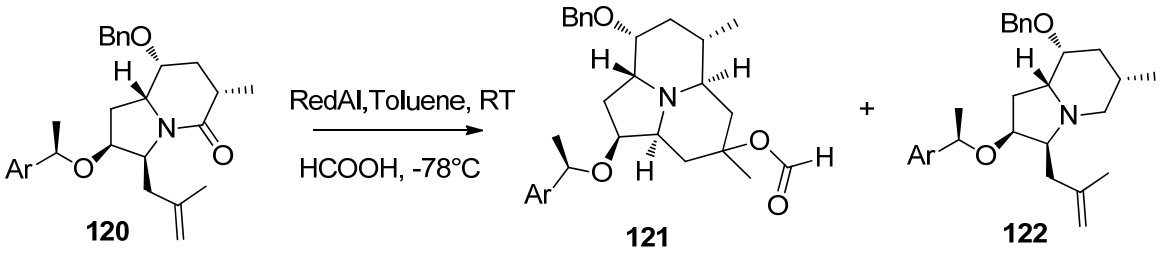
Therefore, compound **119** was uneventfully benzylated using the standard protocol to obtain the corresponding benzylated product in a quantitative yield.



Scheme 73: Benzylation of the secondary alcohol in compound 119

5.3.6 *Construction of the 8b-azaacenaphthylene ring system*

With a requisite amount of benzyl ether **120** in hand, the stage was set to study more in detail the reduction-cyclisation sequence. Based on our previous studies with PMB-ether**,** the partial reduction of RedAl in toluene at room temperature, followed by acid-quenching at low temperature, again provided a mixture comprising of tricyclic formate **121** and amine **122.** On purification, the tricyclic formate was recovered in a modest yield of 42% yield, which was fairly consistent with the results obtained with the PMB-protected epimer, **95**, while amine **122** was obtained in 38% yield. In order to help the characterization, we synthesized an authentic sample of the amine by treating lactam **120** with large excess of $LiAlH_4$.



Scheme 74: The aza-Prins cyclisation with Bn-ether 120

In spite of these encouraging results, a major challenge at this stage was to avoid or at least, limit the complete reduction of the lactam to amine **122**. While numerous optimization attempts to perform the reaction below 0°C led to recovery of clean staring material, a complex mixture of the starting material **120**, formate **121** and amine **122** was recovered at 0°C. Nevertheless, in all the trials, at and above 0°C, the complete reduction of hemiaminal intermediate to the amine **115** appeared to be very fast. This observation was based on the fact that the more polar spot (corresponding to the amine) appeared on the TLC from the beginning of the reaction even in presence of the starting material.

Undeterred, we continued our trials to limit this over-reduction by sequentially considering other factors such as the strength and size of the reducing agent, the effect of the solvent in which the reaction is performed and the efficiency of hydrolysis of the reducing agent in the reaction solvent by the quenching agent.

Owing to experimental limitations such as viscosity of the reagent and the scale of the reaction, at least 5eq of RedAl had been used for all the reactions so far, which means that there is always an excess of reducing agent in the reaction mixture which could lead to the over-reduced product. In order to avoid this excess, commercially available reagent (65% w/v RedAl solution in toluene) was diluted for easier handling. When 1 eq of this 1.0 M solution of RedAl was used for the reaction, clean starting material was recovered. In addition, it was observed that the hydrolysis of RedAl with HCOOH was very slow in toluene. This could also be crucial because if the hydrolysis of the reducing agent is not rapid, it would allow time for the excess of reducing agent present in the reaction mixture to completely reduce the lactam even after the addition of HCOOH is complete.

In order to eliminate this possibility also, it was decided that the HCOOH shall be added at a higher temperature as one could expect a faster hydrolysis. Also, a reverse-quenching procedure by addition of the reaction mixture to a large excess of HCOOH was also considered. Unfortunately, these modifications did not help our situation as the hydrolysis continued to be slow due to the heterogeneity of the medium.

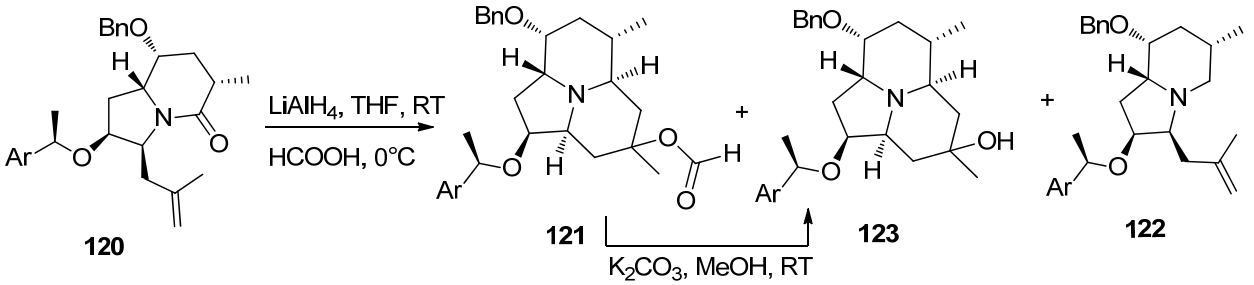
Undauntedly, we decided to replace RedAl with $LiAlH_4$[136] that it is a powerful reducing agent, a relatively less bulky source of hydride and would undergo rapid acidolysis in usual solvents because of their miscibility with HCOOH.

The treatment of benzyl ether **120** with a controlled amount of LAH, a 1.0 M solution in THF at 0°C, also led to a mixture of compounds from which the formate could be separated in 40% yield from the more polar fraction. Performing the reaction at lower temperatures (-40°C) gave back the starting material whereas at temperatures higher than 0°C, the same ratio of products was obtained except that the reaction was faster (30 min). The formation of the over-reduced amine **122** could still not be eliminated even with the reverse-quenching technique and efficient hydrolysis procedure, supporting our previous observation that perhaps this over reduction proceeds to a large extent, even before the addition of HCOOH.

Interestingly, at this stage, a careful analysis of the ^1H NMR spectrum of the more polar (amine) fraction as mentioned above showed that it was in fact a 1:1 mixture of two compounds. On

[136] Conolly, P. J.; Heathcock, C.H. *J. Org.Chem* **1985**, *50*, 4135-4144

further, purification over silica gel, the new compound was isolated and identified as the tricyclic tertiary alcohol **123.** This compound can be formed either by the hydrolysis of the formate during the basic workup of the reaction mixture (10% NaOH solution) or by the water present in HCOOH used to quench the reaction. Subsequently, by subjecting the crude mixture obtained for the cyclisation to hydrolysis with K_2CO_3 in methanol, the tertiary alcohol **123** could be obtained in a yield of 65%.



Scheme 75 : Construction of the tricyclic azaacenaphthylene ring system

The reaction behaved similarly in diethyl ether with 1 eq. of LAH with consistently reproducible results. Unfortunately, complete reduction of the lactam to amine **122** could not be avoided.

At this stage, we performed a nOe-experiment (500 MHz, $CDCl_3$) on formate **121**, which supported the fact that the tricyclic intermediate indeed possessed the stereochemistry as desired in the target molecule at all the four stereocentres introduced so far.

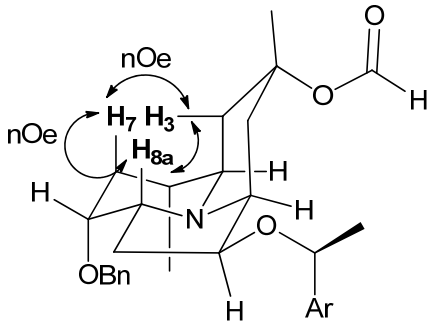
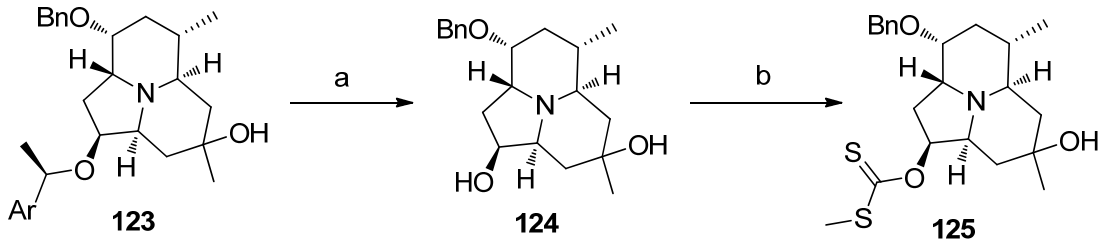


Figure 33: nOe experiments to establish the stereochemistry of the tricyclic formate 121

Thus, the success of this crucial transformation infested the confidence in us to explore the final stages of the synthesis.

5.3.7 *Towards Alkaloid (-)-205B*

In order to proceed further in the synthesis, the first task was the removal of the chiral auxiliary. As expected from the results obtained on the model substrate (Scheme 57), treatment of the bis-benzylic ether **123** with 10% TFA in DCM proceeded uneventfully to selectively cleave the chiral auxiliary to afford diol **124** in 75% yield. At this stage, a Barton-McCombie deoxgenation sequence was attempted. To this end, diol **124** was treated sequentially with KH, CS_2 and MeI at low temperature with short reaction times in order to selectively synthesize the corresponding xanthate of the secondary alcohol.[137] Upon purification on silica gel, the desired xanthate **125** was recovered in 67% yield. This unexpectedly modest yield could presumably be due to the possibile formation of a quaternary ammonium ion as a consequence of N-methylation by excess MeI.

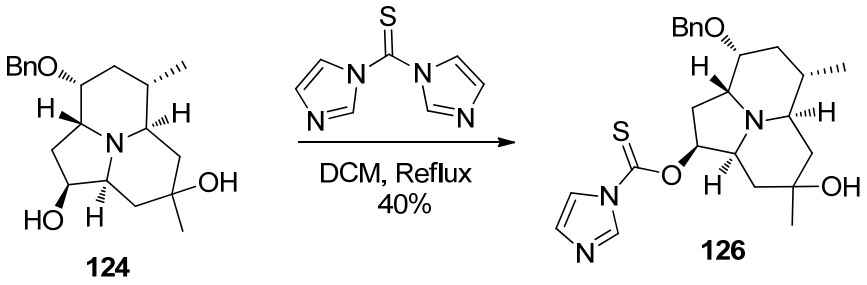


Key : a.10% TFA in DCM, 75% b. KH, CS_2, MeI, DCM, 67%

Scheme 76 : Selective synthesis of the xanthate of secondary alcohol

Alternatively, in order to improve this yield, based on our previous knowledge (Scheme 67), we attempted the formation of bis-thioimidazole xanthate by treating diol **124** with 1,1'-bisdithiocarbonyldiimidazole[134] at room temperature. Disappointingly, the yield of the recovered xanthate **126** was even lower. Due to limited amount of substrate and time available, no more optimization of this transformation was attended.

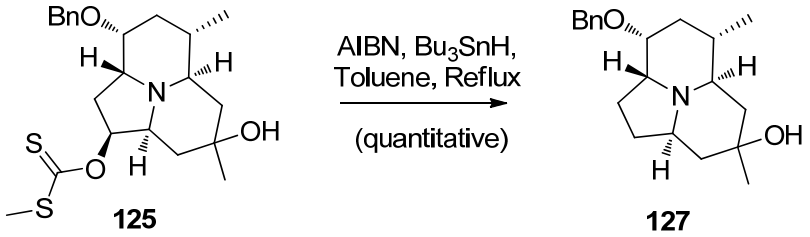
[137] Tiwari, D. K.; Gumuste, V. K.; Rakeeb, A.; Deshmukh, A. S. *Synthesis* **2006**, 115-122



124 126

Scheme 77: Alternate method for synthesis od xanthate

Nevertheless, we surged ahead in the synthesis by subjecting xanthate **125** to the classical Barton-MacCombie conditions, which pleasingly generated the deoxygenated product **127**, in almost quantitative yield after purification.[138]



125 127

Scheme 78 : Synthesis of the advanced tricyclic intermediate

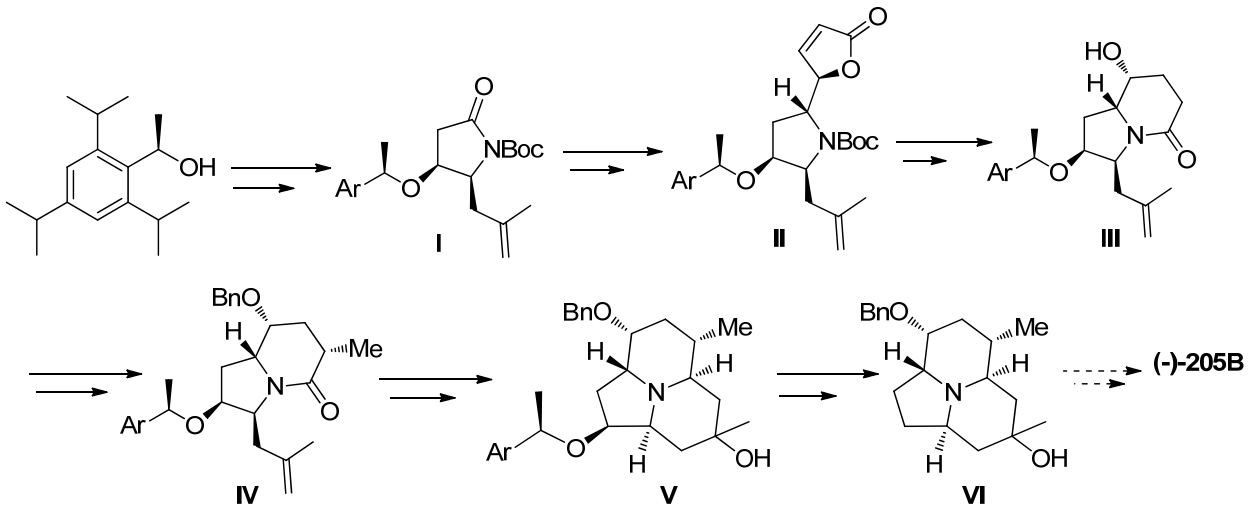
We have therefore, succeeded in obtaining the advanced tricyclic intermediate **127**, possessing the carbon skeleton of our target molecule except for the C8 Me-group. The target molecule should thus be accessible by dehydration of the tertiary alcohol group, after the installation of the equatorial methyl group.

[138] Some Sn-residue is still present.

Conclusions and Perspectives

Conclusions:

In summary, through the work done in this thesis, we wish to disclose the successful synthesis of an advanced tricyclic intermediate (Scheme **79**) which possesses the architecturally complex and rare 8b-azaacenaphthylene ring system of alkaloid (-)-**205B**. This new route is characterized by three major chemical transformations. First of all, the asymmetric thermal [2 + 2] cycloaddition - Beckmann ring expansion strategy developed in our laboratory which gives access to pyrolizidinone **I,** our first key intermediate. An efficient and highly stereoselective vinylogous Mannich reaction leads to the indolizidinone **III** through the butenolide intermediate **II**. After the successful installation of the C6 axial methyl group by an alkylation-methylation sequence, the tricyclic intermediate **V** was obtained via the key aza-Prins cyclisation reaction of indolizidinone **IV.** A facile removal of the chiral auxiliary and subsequent deoxygenation sequence, delightfully generated the advanced tricyclic intermediate towards the alkaloid (-)-**205B.** Thus, with an efficient control of 4 stereogenic centres, the advanced intermediate **VI** was obtained with an overall yield of 3.7 % in the longest linear sequence comprising of 20 steps.

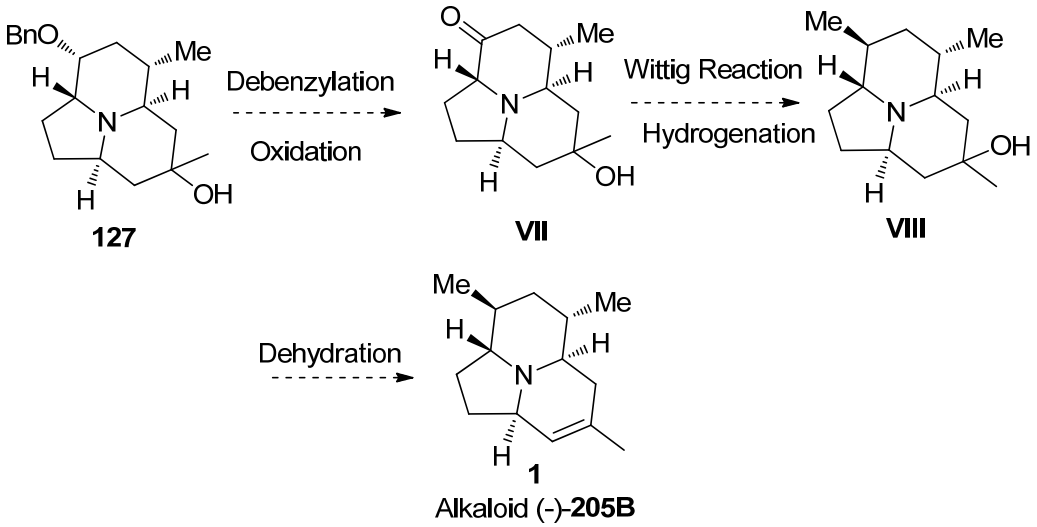


Scheme 79: Summary for the studies directed towards synthesis of (-)-205B

Perspectives:

Our principal focus at this stage is to optimize the final steps leading to the target molecule, which includes the installation of the C8 equatorial methyl group. We envisage that this aim could be achieved by the sequence depicted in Scheme **80,** which would allow us to obtain the (±)-**205B.**

Subsequently, we expect to perform the optically active series, which would enable us to generate enantiopure form this alkaloid for performing studies to determine the pharmacological activity of this unexplored natural product.

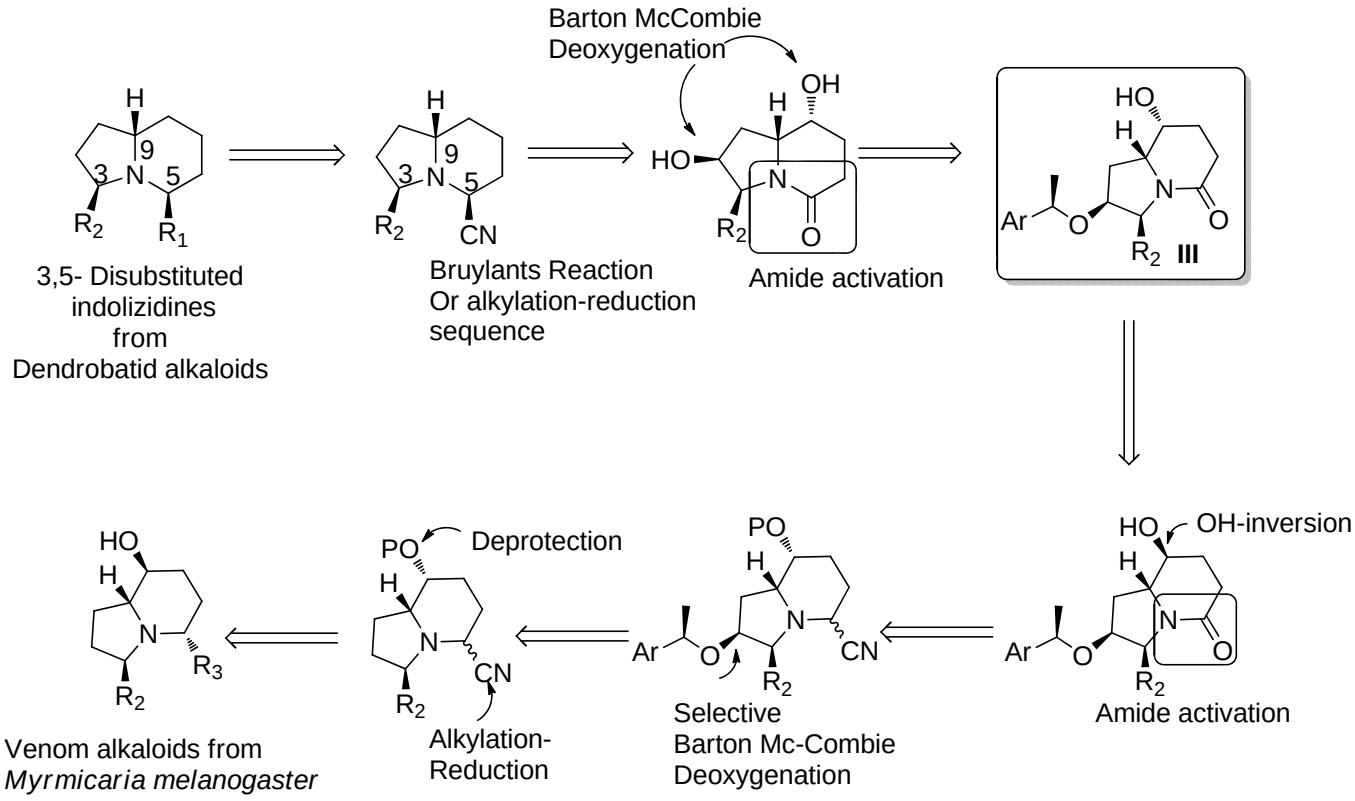


Scheme 80: Proposed completion of the total synthesis of (-)-205B

In addition, hydroxyindolizidinone **III** could prove to be a valuable synthetic intermediate for the total synthesis of other indolizidine natural products[139] as illustrated in Scheme **81**. For example: the 3,5- substituted indolizidines of the Dendrobatid family are expected to be accessible from this bicyclic intermediate via activation of the amide group and a subsequent Bruylant's reaction or a alkylation-reduction sequence.

[139] a. Toyooka, N.; Zhou, D.; Nemeto, H.; Tezuka, Y.; Kadota, S.; Jones, T. H.; Garraffo, H. M.; Spande, T. F.; Daly, J. W. *Synlett* **2008,** 12, 1894-1896 b. Jones, T. P.; Voegtle, H. L., Miras, H. M.; Weatherford, r. G.; Spande, T. F.; Garraffo, H. M.; Daly, J. W.; Davidson, D. W.; Snelling, R. R. *J. Nat. Prod***. 2007**, *70*, 160-168

Interestingly, it been noted that this hydroxyindolizidine skeleton is also a key structural entity found in the venom alkaloids recently extracted from the ant *Myrmicaria melanogaster* from Brunei in the Indonesian archipelago.



Scheme 81: Scope of the synthetic strategy for total synthesis of indolizidine natural products

Thus, it is envisioned that this effective strategy would be useful in approaching the total synthesis of molecules belonging to other families of alkaloids also.

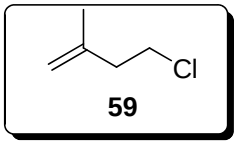
Experimental Section

General Procedure

All experiments were carried out under argon atmosphere unless otherwise stated. THF and Et_2O were distilled over Na-benzophenone. DCM, DMSO, DIPEA, di-isopropyl amine, HMPA, Et_3N, acetonitrile, 2,6-lutidine, pyridine, NMP, toluene and triethylamine were distilled over CaH_2. Trichloroacetyl chloride, benzyl bromide, *p*-methoxybenzyl chloride and oxalyl chloride were distilled over $CaCl_2$. Ethylene diamine and methanol were distilled over Na. DMF was distilled over $CaSO_4$. All other products were directly used as received from commercial sources without any purification.

NMR spectra were recorded on Bruker Avance 300, Bruker Avance 400 or Varian U^+ 500 spectrometers and in chloroform-d_1 unless otherwise stated. All coupling constants have been calculated using the methods described by Hoye *et al*.[140] All melting points were recorded on Buchi- Tottoli apparatus. IR measurements have been performed on Nicolet 397 spectrometer and were recorded as neat samples or in DCM solution placed between NaCl pellets. The mass spectra were recorded on a Nermag R10 mass spectrometer in ESI mode (Ionisation voltage = 70 eV).

[140] Hoye, T. R.; Hanson, P. R.; Vyvyan, J. R. *J. Org. Chem*. **1994**, *59*, 4096-4103
Hoye, T. R.; Zhao, H. *J. Org. Chem*. **2002**, *67*, 4014-4016

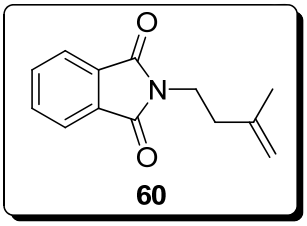


59

4-chloro-2-methylbut-1-ene

To a solution of commercially available alcohol **58** (10.0 mL, 100.0 mmol), in dry diethyl ether (26.0 mL) was added nBu$_3$N (24.0 mL, 100.0 mmol). The flask was cooled down to 0°C and $SOCl_2$ (7.4 mL, 102.0 mmol) was added slowly over 2 h by using a syringe-pump. After the addition was complete, the reaction mixture was hydrolyzed by adding 80.0 mL of water and diluted in diethyl ether. The organic phase was washed once with water and two times with a 10% solution of NaOH, separated and dried over Na_2SO_4. The ether was removed by distillation at 50 °C using a Vigreux column. The residue was further purified by distilling at P = 500 mbar/ 80°C to recover 4.2 g of chloroalkene **59** in 65% yield.

^{1}H NMR (300 MHz): δ 1.75 (s, 3H), 2.36-2.53 (t, J = 7.0 Hz, 2H), 3.47-3.66 (t, J = 7.5 Hz, 2H), 4.78 (s, 1H), 4.85 (s, 1H).

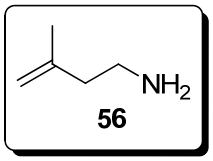


60

2-(3-methylbut-3-enyl)isoindoline-1,3-dione

To a suspension of commercially available potassium phthalimide (8.5 g, 45 mmol) in dry DMF (20.0 mL) was added compound **59** (4.2 g, 40 mmol), drop wise at room temperature. The reaction mixture was stirred at 120°C for 1 h and then, refluxed at 160°C for an additional 1 h. Formation of a white precipitate was observed as the reaction progressed. At the end of 2 h, it was cooled down to room temperature, diluted in ether and washed thoroughly with water. The organic phase was separated and dried over Na_2SO_4 and the solvent was evaporated *in vacuo* to obtain 14.2 g of crude N-alkyl phthalimide **60** as a white solid.

^{1}H NMR (300 MHz): δ 1.81 (s, 3H), 2.39 (t, J = 7.5 Hz, 2H), 3.82 (t, J = 7.0 Hz, 2H), 4.67 (s, 1H), 4.73 (s, 1H), 7.67-7.73 (m, J = 3.0 Hz, 2H), 7.80-7.85 (m, J = 3.0 Hz, 2H).

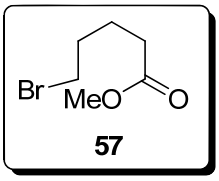


56

3-methylbut-3-en-1-amine

To a solution of N-alkyl phthalimide **60** (6.3 g, 29.0 mmol) in ethanol (100 mL), $N_2H_4.H_2O$ (1.6 mL, 32.0 mmol) was added and the resultant suspension was refluxed at 80°C for 1 h. As formation of a white precipitate was observed within the first 10 min of the reaction, an additional 100 mL of ethanol was added. At the end of 1 h, the reaction mixture was cooled down to room temperature and HCl (4.1 mL) was added. The reaction mixture was filtered over Celite and the filtrate was concentrated under vacuum. This process was repeated until no more precipitation was observed and a clear yellow solution was obtained. Evaporation of this solution to dryness gave 4.5 g of a white solid, which was again diluted in ether and neutralized with a 10% solution of NaOH. The ether was distilled off at P = 760 mm Hg/ 50 °C) to obtain the primary amine **56** (2.0 g) as a colorless liquid.

^{1}H NMR (300 MHz): δ 1.73 (s, 3H), 2.17-2.41 (m, 4H), 2.82-2.88 (t, *J* = 7.0 Hz, 2H), 4.74 (s, 1H), 4.82 (s, 1H).

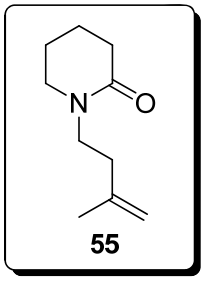


57

Methyl 5-bromopentanoate

A solution of commercially available **61** δ-valerolactone (5.0 mL, 53.8 mmol) in 33% HBr in glacial acetic acid (15.0 mL, 25.1 mmol) was stirred at 75 °C for 5 h. The resultant dark brown liquid was stirred at room temperature overnight. After 16 h of stirring, 20.0 mL of dry MeOH was added and the reaction mixture was refluxed for another 2 h. The reaction mixture was then cooled down to room temperature and concentrated by evaporating the solvent under vacuum. The residue was diluted in EtOAc and washed with saturated $NaHCO_3$ solution, followed with brine. The organic phase was separated, dried over Na_2SO_4 and the solvent was evaporated to obtain 8.8 g of the crude δ-bromo ester **57** as a pale yellow solid.

^{1}H NMR (300 MHz): δ 1.72-1.95 (m, 4H), 2.34 (t, *J* = 7.0 Hz, 2H), 3.41 (t, *J* = 7.0 Hz, 2H), 3.67 (s, 3H)

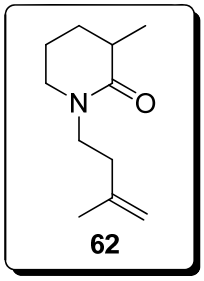


55

1-(3-methylbut-3-enyl)piperidin-2-one

60% NaH (4.1g, 102.5 mmol) was weighed out in a clean, dry, argon-flushed flask and washed thoroughly with pentane. A solution of amine **56** (2.0 g, 23.0 mmol) in dry DMF (10.0 mL) was added dropwise over 20 min. After the addition was complete, the reaction mixture was heated to 50 °C and a solution of the bromo-ester **57** (5.5 g, 28.5 mmol) in DMF (10.0 mL) was added drop wise using a syringe-pump over 1 h. After the addition was complete, the reaction mixture was quenched with MeOH, diluted in 100.0 mL of ether and washed thoroughly with water. The organic phase was dried over Na_2SO_4 and the solvent was evaporated under vacuum to obtain 1.36 g of the crude lactam **55**. Purification of the crude product over silica gel (40% EtOAc in pentane, 2% AcOH) furnished 0.796 g the purified lactam in 4.7 % yield over 5 steps from alcohol **58** as a yellow oil.

^{1}H NMR (300 MHz): δ 1.71-1.82 (m, 7H), 2.24 (t, *J* = 7.0 Hz, 2H), 2.38 (t, *J* = 7.0 Hz, 2H), 3.27 (t, *J* = 7.0 Hz, 2H), 3.47 (t, *J* = 7.0 Hz, 2H), 4.69 (s, 1H), 4.75 (s, 1H)

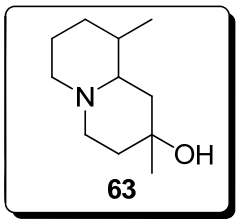


62

3-methyl-1-(3-methylbut-3-enyl)piperidin-2-one

To a solution of (*i*-Pr)$_2$NH (0.070 mL, 0.492 mmol) in THF (0.4 mL) at -50 °C was added *n*-BuLi (0.180 mL, 0.451 mmol) and the solution was stirred for 30 min during which the temperature was allowed to increase to -30 °C. This solution of LDA was added dropwise to a solution of lactam **55** (0.069 mg, 0.410 mmol) in THF (0.400 mL) pre-cooled to -15°C. The reaction mixture was stirred for 30 min at this temperature and MeI (0.250 mL, 4.0 mmol) was added. After stirring at room temperature for 2 h, it was quenched with saturated NH_4Cl and diluted in ether. The organic phase was washed with saturated NH_4Cl, dried over Na_2SO_4 and the solvent was evaporated *in vacuo* to obtain 0.079 g of the crude methylated lactam. After filteration over silica gel (40% EtOAc/ pentane), 0.032 g of the pure methylated lactam **62** and 0.027 mg of starting material, lactam **55** was recovered as a yellow oil. (Yield: 70% for lactam **62**, brsm)

^{1}H NMR (300 MHz): δ 1.21 (d, *J* = 7.0 Hz, 3H), 1.63-1.98 (m, 7H), 2.17-2.28 (t, *J* = 7.0 Hz, 2H), 2.36 (m, 1H), 3.17-3.33 (t, *J* = 7.0 Hz, 2H), 3.38-3.50 (t, *J* = 7.0 Hz, 2H), 4.68 (s, 1H), 4.74 (s, 1H).



63

2,9-dimethyloctahydro-1*H*-quinolizin-2-ol

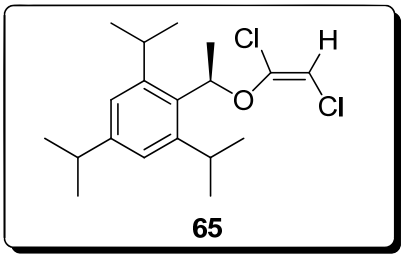
To a solution of DIBAL-H (0.271 ml, 0.260 mmol) in THF (0.150 mL) was added *n*-BuLi (0.108 mL, 0.260 mmol) in THF and stirred at 0 °C for 1.5 h. The resulting ate-complex was added dropwise to a solution of lactam **62** (10 mg, 0.050 mmol) in THF (0.200 mL) and stirred at 0 °C

with constant monitoring with TLC. At the end of 3 h, no more starting material was observed on TLC, so the reaction mixture was cooled down to -78 °C and HCOOH (0.100 mL) was added and allowed to warm up to room temperature overnight. It was diluted in ether washed with 10% NaOH solution until the pH was alkaline. The organic phase was dried over Na_2SO_4 and evaporation of the solvent under vacuum gave the crude quinolizidine **63**. Purification of the crude product over silica-gel provided 8 mg of the two isomeric alcohols in 85% yield as a yellow oil.

IR (film): 3364, 2928, 2807, 2764, 1650, 1469, 1373, 1285, 1163 cm^{-1}.

^{1}H NMR (300 MHz): δ 0.85 (d, *J* = 6.5 Hz, 3H, minor isomer), 0.99 (d, *J* = 7.0 Hz, 3H, major isomer), 1.24 (s, 3H, minor isomer), 1.26 (s, 3H, major isomer), 1.18-2.18 (m, 10H), 2.77-2.90 (m, 2H), 3.41-3.46 (m, 1H, minor diastereoisomer), 3.61-3.66 (m, 1H, major diastereoisomer).

MS (DCI, NH_3 + isobutane): *m/z* 184 (MH^+), 166.



65

(*R*,*E*)-2-(1-(1,2-dichlorovinyloxy)ethyl)-1,3,5-triisopropylbenzene

35% suspension of potassium hydride in mineral oil (15.0 g, 126.0 mmol) was suspended in an argon flushed flask. The mineral oil was removed by washing repeatedly with pentane. To this suspension of KH in of 100 mL of dry THF, (±)-1-(2, 4, 6-triisopropylphenyl)ethanol (15.0 g, 60.0 mmol) was slowly added as a solution in THF (200 mL). The reaction mixture was stirred at 0 °C until hydrogen evolution was complete (approx.2 h). It was then cooled to -50 °C and treated dropwise with trichloroethylene (5.7 mL, 66.0 mmol) over 30 min. After the addition was complete, the reaction mixture was allowed to warm up to room temperature over 4 h and carefully quenched with MeOH at 0°C. It was diluted in pentane and washed with saturated NH_4Cl. The organic phase was separated, dried over Na_2SO_4 and the solvent was evaporated *in vacuo* to obtain the crude product. Purification of the crude material by filtration over silica gel

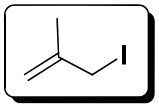
(pre-treated with 2.5% Et_3N v/v) with pentane afforded 15.9 g of dichloroenol ether **65** in 76% yield as a colorless oil, which solidified upon storage at -30 °C.

Mp: 38-41°C (pentane)

IR (film): 3087, 1624, 1612, 1081, 1045 cm^{-1}

^{1}H NMR (300 MHz): δ 1.20-1.35 (m, 18H), 1.70 (d, *J* = 6.9 Hz, 3H), 2.90 (sept, *J* = 6.9 Hz, 1H), 3.15-3.75 (m, 2H), 5.60 (s, 1H), 6.00 (q, *J* = 6.8 Hz, 1H), 7.05 (s, 2H).

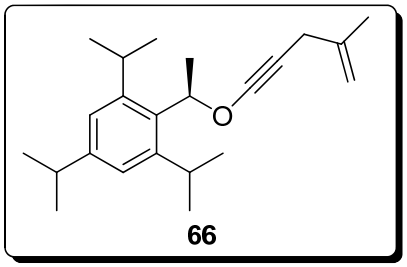
MS (ESI): *m/z* 343 and 341 (M^+), 248, 231 (100%)



3-iodo-2-methylprop-1-ene

Commercially available allyl chloride (15.00 mL, 0.160 mmol), sodium iodide (29.00 g, 193 mmol) and acetone (30 mL) was refluxed during 3 h. The mixture was then poured into water (145 mL). The organic layer was separated, washed with a 1 M solution of sodium bisulfite solution, followed by water. The residue was directly distilled at (P = 75 Torr / 53 °C). The distillate was dried over sodium sulphate (and stored over copper turnings) to yield 32 g of pure 2-methyl allyl iodide. (Yield: 73 %).

^{1}H NMR (400 MHz): δ 1.90 (dd, *J* = 1.4, 0.8 Hz, 3H), 3.91 (d, *J* = 0.8 Hz, 2H), 4.89 (m, 1H), 5.19 (m, 1H).



66

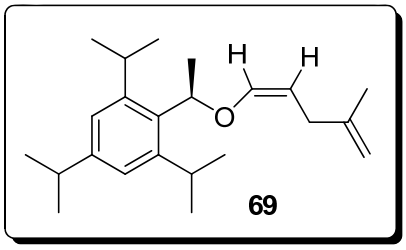
(*R*)-1,3,5-triisopropyl-2-(1-(4-methylpent-4-en-1-ynyloxy)ethyl)benzene

To a solution of dichloro enol ether **65** (16.00 g, 46.64 mmol) in dry THF (340 mL) at -90 °C, *n*-BuLi (46.50 mL, 133.59 mmol) was added drop wise. The reaction mixture was allowed to warm

to -40°C and treated dropwise with 3-iodo-2-methyl-pro-1-ene (14.50 mL, 133.06 mmol), followed by HMPA (37 mL, 223 mmol). The resulting solution was allowed to warm to 0 °C over 3 h and then poured into cold saturated NH_4Cl solution. The aqueous layer was extracted 3 times with cold pentane. The combined organic phase was washed with cold water, dried over Na_2SO_4 and concentrated under reduced pressure to give 21.38 g of acetylenic enol ether as brown oil which was used directly without any purification.

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

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



69

(*R*,*Z*)-1,3,5-triisopropyl-2-(1-(4-methylpenta-1,4-dienyloxy)ethyl)benzene

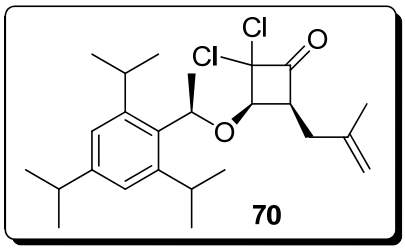
To a solution of crude ynol ether **66** (20.0 g, 61.25 mmol) in dry DMF (92 mL) at 0 °C was flushed repeatedly with Ar. 10% Pd/Ba_2SO_4 (5.8 g, 5.14 mmol) and ethylene diamine (2.10 mL, 30 mmol) were added sequentially and the reaction mixture was vigorously stirred at 0 °C under a hydrogen atmosphere for 10 min, after which 1-hexene (20.00 mL, 160 mmol) was added dropwise. At the end of 9 h (the reaction was followed by IR), the mixture was diluted with cold pentane and filtered over Celite. The filtrate was thoroughly washed with cold water and brine, dried over Na_2SO_4 and concentrated under reduced pressure to obtain enol ether (15.79 g) as a yellow oil (5 – 7 % of saturated product is also present). It was filtered through (deactivated silica gel) with pentane very rapidly to yield 11.6 g of pure enol ether **69** (72% over 2 steps).

IR (film): 2960, 2929, 2869, 1661, 1608, 1460, 1384, 1255 cm^{-1}

^{1}H NMR (400 MHz): δ 1.20-1.27 (m, 18H), 1.61 (d, *J* = 6.8 Hz, 3H), 1.74 (s, 3H), 2.71-2.96 (m, 3H), 3.20-3.64 (m, 2H), 4.33 (q, *J* = 6.9 Hz, 1H), 4.68 (br s, 1H), 4.72 (br s, 1H), 5.34 (q, *J* = 6.8

Hz, 1H), 6.03 (d, *J* = 6.9 Hz, 1H), 7.01 (s, 2H).

^{13}C NMR (400 MHz): δ 22.7 (CH_3), 24.2 (CH_3), 24.8 (CH_3), 29.2 (CH_3), 32.7(CH_2), 34.1 (CH), 75.5 (CH), 103.8 (CH), 109.6 (CH_2), 120.6 (CH_3), 133.2 (CH), 144.8 (C), 145.6 (C), 147.7 (C).



70

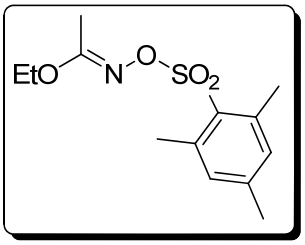
(3*R*,4*S*)-2,2-dichloro-4-(2-methylallyl)-3-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)cyclobutanone

To a stirred suspension of crude enol ether **69** (11.6 g, 35.6 mmol) and Zn-Cu couple (11.6 g, 177.5 mmol) in dry ether (310 mL) was added dropwise neat trichloroacetyl chloride (4.8 mL, 427.96 mmol) at room temperature. During this addition, the mixture was sonicated 3-4 times. The mixture was vigorously stirred for an additional 1 h, after which the ethereal mixture was filtered over Celite and diluted with a large volume of pentane. The resulting suspension was partially concentrated under reduced pressure, filtered over Celite and diluted with pentane again. This sequence was repeated until the removal of the zinc chloride was complete. The filtrate was then washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4 and concentrated *in vacuo* to give cyclobutanone **70** (14.75 g), which was used without further purification.

IR (film): 2961, 2922, 2870, 1808, 1608, 1460 cm^{-1}

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

^{13}C NMR (400 MHz): δ 22.5 (CH_3), 23.9 (CH_3), 24.1 (CH_3), 25.4 (CH_3), 28.5 (CH_3), 28.6 (CH_3), 33.2 (CH_2), 34.2 (CH_2), 57.5 (CH_3), 73.7 (CH_3), 77.5 (CH_3), 112.8 (CH_2), 120.9 (CH_3), 123.5 (CH_3), 130.8 (C), 141.8 (C), 147.2 (C), 148.4 (C), 149.2 (C), 195.9 (C)

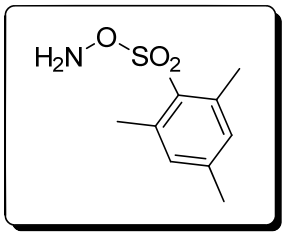


Ethyl *O*-(mesitylenesulfonyl)-acetohydroxamate

To a solution of ethyl N-hydroxyacetimidate (14.0 g, 135.0 mmol) and triethylamine (18.3 mL, 131.0 mmol) in DMF (35mL) at 0°C was added portion wise 2-mesitylenesulfonyl chloride (28.9 g, 133 mmol). A white precipitate was formed instantly. The reaction mixture was stirred for an additional 1 h, diluted in ether and washed thoroughly with water and dried over Na_2SO_4. Evaporation of solvent under reduced pressure gave 34.0g of ethyl O-(mesitylenesulfonyl)-acetohydroxamate as yellow oil which was used without purification.

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

^{1}H NMR (400 MHz): δ 1.15 (t, *J* =7.0 Hz, 3H), 2.00 (s, 3H), 2.27 (s, 3H), 2.61 (s, 6H), 3.87 (q, *J* = 7.0 Hz, 2H), 6.93 (s, 2H)



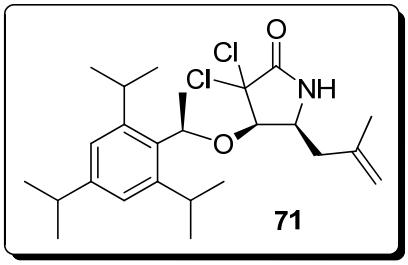
O-Mesitylenesulfonylhydroxylamine

70% perchloric acid (10.5 mL, 173 mmol) was added to a solution of crude ethyl O-(mesitylenesulfonyl)-acetohydroxamate (34.0 g, 112 mmol) in dioxane at 0°C. The resulting mixture was stirred for 10 min and then poured into a large volume of ice during which formation of a white precipitate (MSH) was observed. The solid was filtered rapidly and washed with cold water, followed by pentane to furnish 32.0 g of MSH.[141]

IR (film): 3339, 2979, 2940, 1610 cm^{-1}

[141] *Note:* 1) *This compound contains considerable amount of water and pentane.* 2) *It decomposes* ***violently*** *at RT when totally dry but it can be stored at -30°C for several months without degradation.*

^{1}H NMR (400 MHz): δ 2.30 (s, 3H), 2.60 (s, 6H), 5.06 (br, s, >>2H), 6.97 (s, 2H)



71

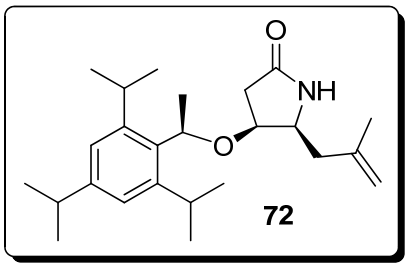
(4*R*,5*S*)-3,3-dichloro-5-(2-methylallyl)-4-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)pyrrolidin-2-one

A solution of crude cyclobutanone **70** (14.75 g, 33.56 mmol) in dry dichloromethane (310 mL) at room temperature was treated with *O*-mesitylenesulfonylhydroxylamine (11.0 g, 50.92 mmol) and a small amount of sodium sulfate and stirred for 7 h. Additional 1.0-g portions of *O*-mesitylenesulfonylhydroxylamine were added at two hour intervals. After filtration of the mixture over Celite, the solvent was removed under reduced pressure and the resulting residue was dissolved in toluene (200 mL) and placed on a column of basic alumina (650 mL), which was eluted with methanol. The fractions were combined and concentrated under reduced pressure. The resulting residue was triturated with dichloromethane and the suspension was filtered through Celite. Evaporation of the solvent gave the crude dichloro lactam **71** (15.43 g) as a pale yellow solid.

IR (film): 2961, 2869, 1731, 1606, 1562, 1454 cm^{-1}

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

^{13}C NMR (400 MHz): δ 20.8 (CH_3), 20.9 (CH_3), 21.1 (CH_3), 21.8 (CH_3), 22.8 (CH_3), 24.8 (CH_3), 25.4 (CH_3), 28.4 (CH), 34.4 (CH), 38.8 (CH_2), 53.1 (CH_2), 53.1 (CH), 82.1 (CH), 114.34 (CH), 120.9 (CH), 123.7 (CH), 130.9 (CH), 146.5 (C), 148.1 (C), 148.8 (C), 167.5 (C)



72

(4*S*,5*S*)-5-(2-methylallyl)-4-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)pyrrolidin-2-one

A suspension of the crude dichloro lactam **71** (15.4 g, 35.0 mmol) and Zn-Cu couple (11.2 g, 175.0 mmol) in methanol saturated with NH_4Cl (310 mL) was stirred at room temperature for 1 h and then was refluxed for an additional 3 h. The resulting mixture was filtered over Celite and the filtrate was concentrated under reduced pressure. The residue was dissolved in dichloromethane and was washed with water and brine. The organic phase was dried over Na_2SO_4 and evaporation of the solvent gave the crude product, which was purified by silica gel chromatography (63 – 200 μ : 200 mL) with 0 - 5 % methanol saturated with ammonia in dichloromethane to provide lactam **72** as a pale yellow solid. (7.7 g, 72 % over 3 steps from the enol ether **69**)

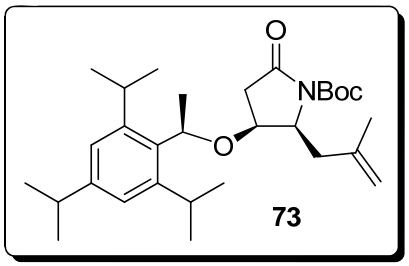
Mp: 114.7°C

IR (film) : 3225, 2960, 2869, 1698, 1608, 1461 cm^{-1}

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

^{13}C NMR (400 MHz): δ 22.4 (CH_3), 23.2 (CH_3), 25.1 (CH_3), 28.1 (CH_3), 29.3 (CH_3), 34.1 (CH_3), 36.7 (CH_2), 38.2 (CH_2), 55.4 (CH), 71.2 (CH), 72.5 (CH), 113.3 (CH_2), 120.8 (CH), 123.4 (CH), 132.2 (C), 142.2 (C), 146.2 (C), 147.9 (C), 148.9 (C), 174.8 (C)

MS (ESI): *m/z* 408 (MNa^+, 100%), 386 (MH^+)



(2*S*,3*S*)-*tert*-butyl 2-(2-methylallyl)-5-oxo-3-((*R*)-1-(2,4,6-triisopropylphenyl) ethoxy)pyrrolidine-1-carboxylate

To a solution of lactam **72** (7.7 g, 20 mmol) in dry methylene chloride (50 mL) were added triethylamine (2.8 mL, 20.02 mmol) and di-tert-butyl dicarbonate (8.72 g, 40 mmol) at room temperature. The reaction mixture was cooled to 0 °C and DMAP (2.45 g, 20.0 mmol) was added in portions. The reaction mixture was then stirred for 2 h at room temperature, quenched with saturated NH_4Cl and diluted with dichloromethane. The organic layer was washed with saturated NH_4Cl and dried over Na_2SO_4. Evaporation of the solvent provided the crude product, which was purified by silica gel (40 – 60 μ : 90 mL) chromatography with 10 % AcOEt in pentane to provide N-protected-lactam **73** (10.24 g, 81 %) as a white solid.

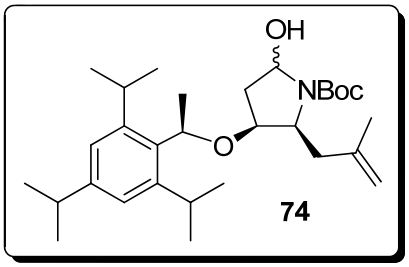
Mp : 141.7°C

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

^{1}H NMR (400 MHz): δ 1.16-1.30 (m, 18H), 1.46-1.57 (m, 12H), 1.79 (s, 3H), 2.23 (dd, *J* = 13.8, 8.3 Hz, 1H), 2.55 (dd, *J* = 13.8, 4.2 Hz, 1H), 2.62-2.70 (m, 2H), 2.86 (sept, *J* = 6.9 Hz, 1H), 3.05-3.20 (br m, 1H), 3.87 (br m, 1H), 4.05-4.13 (m, 1H), 4.37 (td, *J* = 7.9, 4.6 Hz, 1H), 4.80 (s, 2H), 5.05 (q, *J* = 6.8 Hz, 1H), 6.95 (s, 1H), 7.06 (s, 1H).

^{13}C NMR (100 MHz): δ 22.8 (CH_3), 23.2 (CH_3), 24.0 (CH_3), 25.1 (CH_3), 27.9 (CH_3), 28.0 (CH_3), 34.1 (CH_3), 37.2 (CH_2), 38.1 (CH_2), 58.5 (CH), 69.8 (CH), 71.7 (CH), 83.1 (C), 114.7 (CH_2), 120.8 (CH), 123.5 (CH), 132.1 (C), 141.8 (C), 145.9 (C), 148.8 (C), 149.8 (C), 170.8 (C).

MS (ESI): *m/z* 508 (MNa^+, 100%), 231.



(2*S*,3*S*)-*tert*-butyl 5-hydroxy-2-(2-methylallyl)-3-((*R*)-1-(2,4,6-triisopropylphenyl) ethoxy)pyrrolidine-1-carboxylate

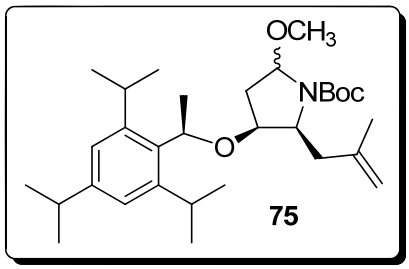
To a solution of N-protected-lactam **73** (10.4 g, 21.4 mmol) in dry THF (42 mL) was added a solution of 1 M $LiBHEt_3$ in THF (Super-Hydride) (26.0 mL, 25.1 mmol) at -78 °C. The reaction mixture was stirred for 30 min at this temperature and was then quenched with saturated aqueous $NaHCO_3$ solution (55 mL), and the mixture was allowed to stand until the temperature reached 0 °C. H_2O_2 (5.0 mL) was added and the mixture was stirred for 30 min. The aqueous layer was extracted 3 times with ether. The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure to obtain the hemiaminal **74** (10.3 g) as a yellow oil which was used in the following step without any further purification.

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

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

^{13}C NMR (100 MHz): δ 22.8 (CH_3), 23.3 (CH_3), 24.9 (CH_3), 27.9 (CH_3), 28.2 (CH_3), 34.1 (CH_3), 36.4 (CH_2), 38.4 (CH_2), 56.9 (CH), 71.9 (CH), 74.3 (CH), 80.2 (CH), 80.3 (C), 113.6 (CH_2), 120.6 (CH), 123.4 (CH), 133.3 (C), 142.5 (C), 145.5 (C), 147.6 (C), 148.9 (C), 155.0 (C).

MS (DCI, NH_3 + isobutane): *m/z* 472 (M-16), 372, 358, 231.



75

(2*S*,3*S*)-*tert*-butyl 5-methoxy-2-(2-methylallyl)-3-((*R*)-1-(2,4,6-triisopropylphenyl) ethoxy)pyrrolidine-1-carboxylate

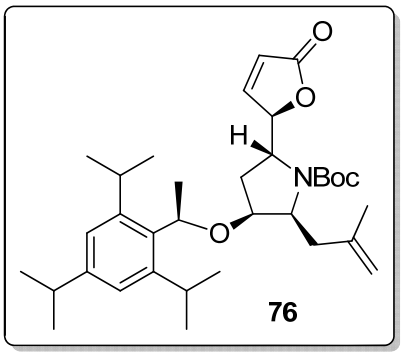
To a solution of the crude hemiaminal **74** (10.3 g, 21.3 mmol) in 2,2-dimethoxypropane (15.0 mL, 106 mmol) at 0°C, catalytic amount of CSA (900 mg, 4.2 mmol) was added and the reaction mixture was stirred at the same temperature for 1 h, then it was quenched with saturated $NaHCO_3$ and diluted in ether. The organic layer was washed with saturated $NaHCO_3$ thoroughly and dried over Na_2SO_4. Upon evaporation of the solvent, 10.4 g of aminal **75** was isolated as pale yellow oil which was used without purification.

IR (film): 2962, 2869, 1702, 1607, 1456, 1390, 1367, 1167, 1098 cm^{-1}

^{1}H NMR (400 MHz): δ 1.18-1.32 (m, 18H), 1.39-1.43 (m, 9H), 1.48-1.53 (m, 3H), 1.73 (br s, 3H), 2.28-2.31 (m, 2H), 2.56-2.70 (m, 2H), 2.86 (sept, *J* = 6.9 Hz, 1H), 3.10-3.30 (br m, 1H), 3.35-3.39 (m, 3H), 3.79-3.92 (br m, 3H), 4.72 (br s, 1H), 4.75 (br s, 1H), 5.03 (q, *J* = 6.8 Hz, 1H), 5.05-5.20 (m, 1H), 6.95 (s, 1H), 7.04 (s, 1H).

^{13}C NMR (100 MHz): δ 24.0 (CH_3), 24.9 (CH_3), 28.2 (CH_3), 28.5(CH_3), 29.3 (CH_3), 34.1 (CH), 37.3 (CH_2), 37.6 (CH_2), 56.7 (CH), 57.6 (CH), 72.2 (CH), 75.2 (CH_2), 80.1 (C), 87.3 (CH), 113.3 (CH_2), 120.6 (CH), 123.5 (CH), 133.4 (C), 142.9 (C), 145.5 (C), 147.5 (C), 148.9 (C).

MS (DCI, NH_3 + isobutane): *m/z* 502 (MH^+), 472, 431, 372, 231.



(2*S*, 3*S*, 5*R*)-*tert*-butyl 2-(2-methylallyl)-5-((*R*)-5-oxo-2,5-dihydrofuran-2-yl)-3-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)pyrrolidine-1-carboxylate

$BF_3.Et_2O$ (1.8 mL, 14.2 mmol) was slowly added to a solution of **75** (4.8 g, 9.6 mmol) and 2-(trimethylsiloxy) furan (3.1 mL, 18.9 mmol) in dry DCM (135 mL) and the temperature was maintained between -90°C and -78°C during 1.5 h, after which saturated $NaHCO_3$ (80 mL) was added and the organic layer was separated. The aqueous phase was extracted 3 times with DCM and the combined organic phase were dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the residue by silica gel (40 – 60 μ) chromatography with 10 % AcOEt in pentane provided a yellow oil, the *threo* butenolide diastereoisomer **76(a)** (3.8 g, 72 % from **73**) as the major product. Another fraction corresponding to the *erythro* diastereoisomer **76(b)** (1.39 g, 26.5 % from **75**) was also isolated.

Major diastereoisomer **76(a)** *(threo)*:

IR (film): 2961, 2926, 2868, 2869, 1762, 1692, 1611, 1457, 1387, 1367 cm^{-1}

^{1}H NMR (**400 MHz**, from a mixture of rotamers): δ 1.10-1.31 (m, 18H), 1.41-1.45 (m, 9H), 1.49 (d, *J* = 6.7 Hz, 3H), 1.74-1.85 (m, 4H), 1.91-1.98 (m, 1H), 2.07-2.22 (m, 1H), 2.39-2.56 (m, 1H), 2.85 (sept, *J* = 6.9 Hz, 1H), 3.00-3.15 (br m, 1H), 3.74-3.90 (m, 2H), 3.97 (q, *J* = 6.7 Hz, 1H), 4.32-4.41 (m, 1H), 4.75 (s, 2H), 4.98 (q, *J* = 6.8 Hz, 1H), 5.50-5.90 (m, 2H), 6.94 (s, 1H), 7.03 (s, 1H), 7.09-7.23 (m, 1H).

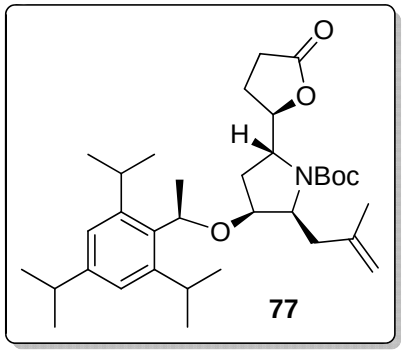
^{13}C NMR (100 MHz): δ 23.1(CH_3), 24.8 (CH_3), 25.2 (CH_3), 26.5 (CH_3), 27.9 (CH_3), 28.1 (CH_3), 28.1 (CH), 28.6 (CH_2), 28.7 (CH_2), 34.0 (CH), 36.9 (CH), 54.9 (CH), 59.1 (CH), 71.2 (CH), 74.8 (CH), 81.7 (CH_2), 82.2 (CH_2), 113.7 (CH_2), 121.9 (CH), 123.1(CH), 125.1 (CH), 132.5 (C), 142.8 (C), 145.6 (C), 148.7 (C), 152.6 (C), 153.3(C).

MS (ESI): *m/z* 576.4 (MNa^+, 100%)

Minor diastereoisomer **76(b)** *(erythro):*

^{1}H NMR (400 MHz, from a mixture of rotamers**) : δ** 1.13-1.31 (m, 18H), 1.41-1.50 (m. 12H), 1.52-1.8 (m, 3H), 2.43 (m, 1H), 2.85 (sept, *J* = 6.5 Hz, 1H), 3.10-3.22 (m, 1H), .71-3.92 (m, 1H), 3.97-4.32 (m, 3H), 4.61-4.8 (m, 2H), 5.0 (q, *J* = 6.5 Hz,1H), 5.8 (m, 1H), 6.25 (m, 1H), 6.93 (s, 1H), 7.02 (s, 1H), 7.31-7.55 (m, 1H)

^{13}C NMR (100 MHz): δ 19.5 (CH_3), 23.1 (CH_3), 24.3 (CH_3), 25.0 (CH_3), 25.1 (CH_3), 28.3 (CH_3), 34.1 (CH), 37.2 (CH_2), 55.8 CH), 57.9 (CH), 69.9 (CH), 75.2 (CH), 80.8 (CH_2), 82.1 (CH), 88.2 (CH), 113.6 (CH_2), 120.6 (C), 122.5 (C), 123.5 (C), 133.5 (C), 143.1 (C), 147.7 (C), 154.8 (C).



77

(2*S*, 3*S*, 5*R*)-*tert*-butyl 2-(2-methylallyl)-5-((*R*)-5-oxotetrahydrofuran-2-yl)-3-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)pyrrolidine-1-carboxylate

A solution of butenolide **76(a)** (6.7 g, 12.1 mmol) in methanol (150 mL) was cooled to 0 °C to which $CuCl_2 \cdot 2H_2O$ (1.62 g, 12.1 mmol) was added. The resulting mixture was stirred at the same temperature for 5 min before the addition of $NaBH_4$ (0.460 g, 12.1 mmol). After every 10 min, further portions of $NaBH_4$ (1 or 2 eq) were added slowly (H_2 evolution when $NaBH_4$ is added). At the end of 1 h (approx. 7 eq of $NaBH_4$), no more strating material was observed on the TLC. The reaction was quenched with saturated NH_4Cl solution and extracted 3 times with CH_2Cl_2. The combined organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Filtration over silica gel with dichloromethane afforded 6.4 g of the pure lactone **77** as a white solid in 87 % yield.

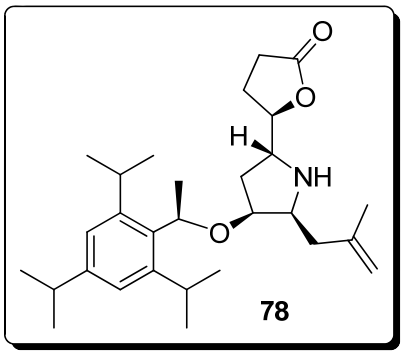
Mp: 113-115°C

IR (film): 3063, 2962, 2922, 2868, 1783, 1694, 1607, 1458, 1392, 1369 cm^{-1}

^{1}H NMR (400 MHz): δ 1.15-1.30 (m, 18H), 1.40-1.45 (m, 9H), 1.53 (d, *J* = 6.4 Hz, 3H), 1.77 (br s, 3H), 1.88-2.60 (m, 8H), 2.85 (sept, *J* = 6.8 Hz, 1H), 3.10-3.25 (br m, 1H), 3.80-4.40 (m, 4H), 4.76 (s, 2H), 5.07 (q, *J* = 6.8 Hz, 1H), 5.20-5.30 (m, 1H), 6.94 (s, 1H), 7.05 (s, 1H).

^{13}C NMR (100 MHz): **δ** 23.9 (CH_3), 24.2 (CH_3), 28.5 (CH_3), 24.2 (CH_2), 28.6 (CH_2), 37.0 (CH_2), 34.1 (CH), 55.3 (CH), 58.8 (CH), 71.2 (CH), 74.4 (CH), 78.6 (CH), 80.5 (C), 113.7 (CH_2), 120.6 (CH), 123.5 (CH), 131.9 (C), 142.8 (C), 145.8 (C), 147.8 (C), 149.1 (C), 176.7 (C).

MS (ESI): *m/z* 578.4 (MNa^+, 100%)



78

(*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

To the crude lactone **78** (6.5 g, 11.69 mmol) in dry methylene chloride (30 mL) at 0 °C was sequentially added 2,6-lutidine (5.5 mL, 46.8 mmol) and TMSOTf (6.38 mL, 35.1 mmol). The reaction mixture was stirred for 1 h at 0°C and saturated NH_4Cl was added. It was allowed to warm up to room temperature and diluted with methylene chloride. The organic layer was separated and the aqueous phase was extracted 2 times with methylene chloride. The combined organic phase was washed 2 times with saturated aqueous $NaHCO_3$ solution, dried over Na_2SO_4, and concentrated under reduced pressure to give 6.4 g of the amine **78** as a yellow oil which was used directly without any purification.

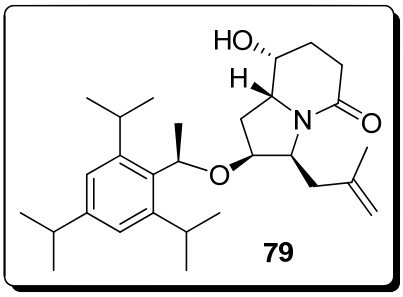
IR (film): 2961, 2930, 2868, 1777, 1608, 1459, 1382, 1176 cm^{-1}

^{1}H NMR (400 MHz): δ 1.16-1.30 (m, 18H), 1.52 (d, *J* = 6.8 Hz, 3H), 1.64 (s, 3H), 1.76-2.32 (m, 6H), 2.42-2.70 (m, 2H), 2.85 (sept, *J* = 6.9 Hz, 1H), 3.15-3.30 (m, 1H), 3.51 (td, *J* = 7.7, 5.6 Hz,

1H), 3.70-3.98 (m, 3H), 4.41 (td, *J* = 7.1, 5.6 Hz, 1H), 4.66 (s, 1H), 4.74 (s, 1H), 5.07 (q, *J* = 6.8 Hz, 1H), 6.94 (s, 1H), 7.04 (s, 1H).

^{13}C NMR (100 MHz): δ 21.2 (CH_3), 22.4 (CH_3), 24.1 (CH_3), 24.2 (CH_3), 24.5(CH_3), 27.5 (CH_3), 27.8 (CH_2), 28.3 (CH_3), 32.4 (CH_2), 33.1 (CH_3), 36.7 (CH_2), 57.9 (CH), 58.4 (CH), 70.5 (CH), 77.6 (CH), 82.7 (CH), 111.1 (CH_2), 122.3 (C), 132.8 (C), 142.8 (C), 144.4 (C), 146.5 (C), 156.8 (C), 176.7 (C).

MS (DCI, NH_3 + isobutane): *m/z* 456 (MH^+), 400, 231



79

(2*S*,3*S*,8*R*,8a*R*)-8-hydroxy-3-(2-methylallyl)-2-((*R*)-1-(2,4,6-triisopropylphenyl) ethoxy)hexahydroindolizin-5(1*H*)-one

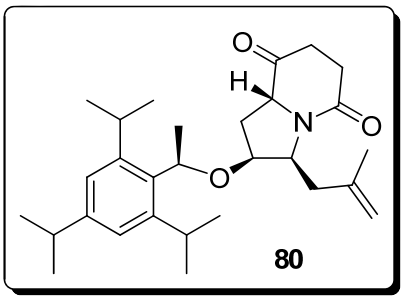
To a solution of amine **78** (6.0 g, 13.1 mmol) in dry methanol (35.0 mL) was added a solution of sodium methoxide in methanol (15.0 mL, 14.4 mmol) under argon at room temperature. After 1 h, the reaction was quenched with brine, extracted 3 times with Et_2O. The combined organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to obtain 8.6 g of the crude product as yellow oil. Re-crystallisation in diethyl ether gave 3.1 g of the desired product as a white solid. Purification of the mother liquor (5.5 g) over silica gel chromatography (40-100% AcOEt in pentane) furnished 1.1 g of the hydroxyindolizidinone **79** (4.2 g, 76 % from **76(a)** as a white solid.

IR (film): 3348, 3074, 2961, 2922, 2869, 1614, 1461, 1410, 1370, 1326, 1210 cm^{-1}

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

^{13}C NMR (400 MHz): δ 22.7 (CH_3), 23.1 (CH_3), 24.2 (CH_3), 24.3 (CH_3), 24.4 (CH_3), 25.1 (CH_3), 25.2 (CH_3), 25.4 (CH_3), 26.2 (CH_2), 27.9 (CH_2), 28.8 (CH), 29.3 (CH), 33.2 (CH_2), 34.1 (CH), 35.4 (CH_2), 56.9 (CH), 58.9 (CH), 64.5 (CH), 72.9 (CH), 74.8 (CH), 111.7 (CH_2), 120.5, 123.3 (2CH), 133.8 (C), 143.8 (C), 145.2 (C), 147.4 (C), 148.5 (C), 168.5 (C).

MS (DCI, NH_3 + isobutane): *m/z* 456 (MH^+), 400, 371, 231.



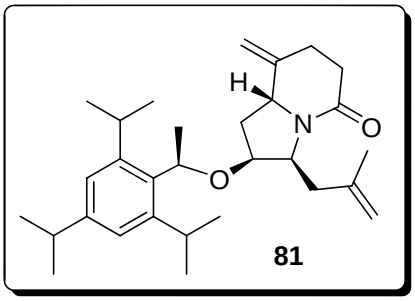
80

(2*S*,3*S*,8a*R*)-3-(2-methylallyl)-2-((*R*)-1-(2,4,6-triisopropylphenyl) ethoxy)hexahydroindolizine-5,8-dione

Oxalyl chloride (0.016 mL, 0.18 mmol) in dry methylene chloride (0.55 mL) was cooled at -78 °C and treated dropwise with DMSO (0.013 mL, 0.18 mmol) in dry methylene chloride (0.029 mL), the internal temperature was maintained below at -70 °C. After stirring for 1 h at below -70 °C, the mixture was re-cooled to -78 °C and hydroxyindolizidinone **79** (0.04 g, 0.09 mmol) was added slowly as a solution in dry methylene chloride (0.450 mL). As the temperature of the reaction mixture approached to -55 to -60 °C, triethylamine (0.062 mL, 0.44 mmol) was injected slowly. The cooling bath was removed and the mixture was stirred for 1 h until the temperature reached room temperature. The reaction mixture was diluted in dichloromethane and quenched with H_2O. The organic layer was separated, washed 2 times with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure to give the indolizidinone **80** (38 mg) which was used directly without any purification.

IR (film): 3073, 2963, 2930, 2869, 1732, 1663, 1607, 1431, 1374, 1314 cm^{-1}

^{1}H NMR (400 MHz): δ 1.15-1.30 (m, 18H), 1.53 (d, *J* = 6.8 Hz, 3H), 1.81 (s, 3H), 2.12-2.26 (m, 2H), 2.33-2.76 (m, 6H), 2.85 (sept, *J* = 6.8 Hz, 1H), 3.05-3.24 (m, 1H), 3.75-3.90 (m, 2H), 3.70-3.82 (m, 2H), 4.20 (dd, *J* = 3.6, 10.0 Hz, 1H), 4.64 (s, 1H), 4.73 (s, 1H), 5.06 (q, *J* = 6.7 Hz, 1H), 6.94 (s, 1H), 7.04 (s, 1H).

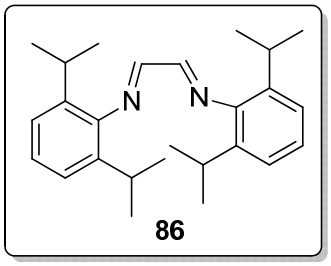


81

(2*S*,3*S*,8a*R*)-3-(2-methylallyl)-8-methylene-2-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)hexahydroindolizin-5(1*H*)-one

n-BuLi (0.087 mL, 0.22 mmol) was injected slowly to a stirred suspension of methyltriphenylphosphonium bromide (100 mg, 0.25 mmol) in dry THF (0.46 mL) at 0 °C. After 15 min at this temperature, the yellow solution was placed at -30 °C and a solution of ketone **80** (14 mg, 0.03 mmol) in THF (0.2 mL) was added. The mixture solution was stirred 30 min at -30 °C and then 1 h 30 at 0 °C and quenched with H_2O. The cooling bath was removed and the reaction mixture was allowed to reach room temperature. It was diluted with Et_2O and the organic layer was separated. The aqueous layer was extracted 3 times with Et_2O, the combined organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the residue by silica gel (40 – 60 μ) chromatography (10 to 30 % AcOEt in pentane) gave 3.0 mg of the methylene compound **81** in 21 % yield.

^{1}H NMR (400 MHz): δ 1.15-1.29 (m, 18H), 1.54 (d, *J* = 6.8 Hz, 3H), 1.68 (s, 3H), 1.97-2.07 (m, 2H), 2.18-2.48 (m, 6H), 2.85 (sept, *J* = 6.8 Hz, 1H), 3.10-3.20 (m, 1H), 3.80-3.90 (m, 1H), 3.99 (td, *J* = 6.9, 4.1 Hz, 1H), 4.31-4.39 (m, 1H), 4.55-4.62 (m, 2H), 4.67 (br s, 1H), 4.91 (s, 1H), 4.97 (s, 1H), 5.04 (q, *J* = 6.6 Hz, 1H), 6.93 (s, 1H), 7.04 (s, 1H).



86

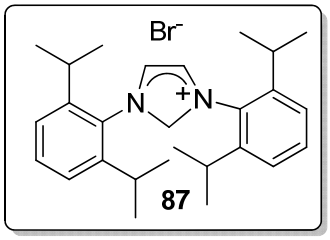
N,*N*'-(ethane-1,2-diylidene)bis(2,6-diisopropylaniline)

To a solution of 2,6-diisopropylphenyl amine (4.9 g, 27.76 mmol) in *n*-propanol (20.0 mL) was added a pre-mixed solution of 40% aqueous solution of glyoxal (1.82 g, 13.85 mmol), 5.0 ml of *n*-propanol and 5.0 mL of distilled water. After 1 h of stirring at 70 °C, the reaction mixture was cooled to room temperature and 200 mL of water was added to it. The resulting precipitate was collected by filtration and dried *in vacuo* to obtain 3.66 g of the diamine **86** as a white solid.

Mp: 90.8 °C (reported: 71-73 °C)

^{1}H NMR (400 MHz, acetone): δ 1.22 (d, *J* = 7.01 Hz, 24 H), 2.87-3.02 (sept, *J* = 6.5 Hz, 4H), 7.13-7.22 (m, 6 H), 8.1 (s, 2H)

^{13}C NMR (100 MHz): δ 23.5, 28.1, 123.3, 125.3, 136.8, 148.2, 163.3

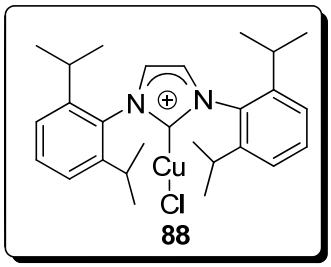


87

1,3-bis(2,6-diisopropylphenyl)imidazolium chloride

In a 25 mL flask, a solution of bromomethyl ethyl ether (0.550 mL, 6.6 mmol) in THF (1.5 mL) was prepared. A solution of diimine **86** (3.0 g, 7.95 mmol) in THF (4.0 mL) was added drop wise to this colorless solution, followed by addition of 4-5 drops of water using a Pasteur-pipette. The reaction mixture was sealed under Argon and stirred at 40 °C for 16 h. At the end of 16 h, it was cooled to room temperature and the solid obtained was collected by filtration. Amount: 3.0 g, brown flakes.

^{1}H NMR (400 MHz): δ 1.25 (d, *J* = 6.51 Hz, 12 H), 1.30 (d, *J* = 6.51 Hz, 12 H), 2.45 (sept, *J* = 6.5 Hz, 4H), 7.36 (d, *J* = 1.5 Hz, 4 H), 7.58 (t, 2H), 8.12 (d, *J* = 1.5 Hz, 2H), 10.0 (s, 1H)

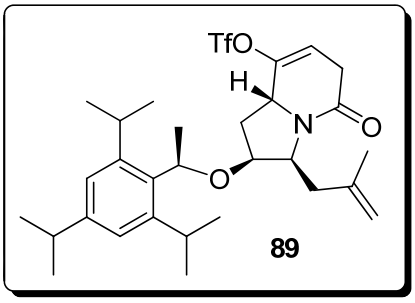


88

(1,3-bis(2-isopropylphenyl)imidazolidin-2-yl)copper(I) chloride

In a dry, argon flushed flask was charged with copper (I) chloride (0.107 mg, 1.65 mmol) 1,3-bis(2,6-di-isopropylphenyl)imidazolium bromide **87** (0.500 g, 1.1 mmol) and potassium *t*-butoxide (0.125 g, 1.1 mmol) and dry THF (10.0 mL) was introduced into the flask. The resultant suspension was stirred at room temperature for 24 h. After filtering the reaction mixture through a plug of Celite, the solvent was evaporated to obtain 370 mg of the copper-salt as a white solid.

^{1}H NMR (400 MHz): δ 1.25 (d, *J* = 7.0 Hz, 12H), 1.31 (d, *J* = 7.0 Hz, 12H), 2.59-2.81 (sept, *J* = 6.5 Hz, 4H), 7.41 (d, *J* = 1.5 Hz, 4H), 7.50-7.59 (m, 2H), 7.71 (s, 2H).



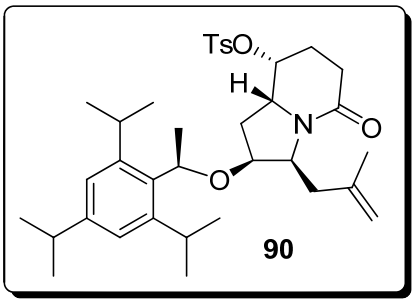
89

(2*S*,3*S*,8a*R*)-3-(2-methylallyl)-5-oxo-2-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)-1,2,3,5,6,8a-hexahydroindolizin-8-yl trifluoromethanesulfonate

To a solution of ketone **80** (25 mg, 0.055 mmol) in dry THF (0.250 mL) at -90°C, was added drop wise, NaHMDS (0.085 mL, 0.11 mmol). After stirring the reaction mixture at this temperature for 10 min, commercially available Comin's triflating agent (43 mg, 0.0825 mmol) was added as a solution of THF (0.100 mL) over 5 minutes while maintaining the temperature below -80°C. The reaction mixture acquired a deep orange coloration during this addition. After

the addition was complete, the reaction mixture was allowed to warm up to room temperature and quenched with saturated $NaHCO_3$ solution. It was diluted in ether and the organic phase was washed with saturated $NaHCO_3$ solution, followed by brine and dried over Na_2SO_4. Upon evaporation of solvent, 60 mg the crude triflate was obtained, which was purified by passing it over a short column of fluorisil which gave 47 mg of the purified product in 74% yield.

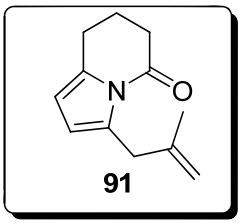
^{1}H NMR (300 MHz): δ 1.1-1.34 (m, 18H), 1.56 (d, *J* = 5.6 Hz, 3H), 1.81 (s, 3H), 1.98-2.18 (m, 3H), 2.30-2.48 (m, 4H), 2.85 (sept, *J* = 6.7 Hz, 1H), 3.05-3.23 (m, 2H), 3.72-3.90 (m, 1H), 4.2 (m, 1H), 4.41-4.82 (m, 3H), 5.05 (q, *J* = 6.7 Hz, 1H), 6.93 (s, 1H), 7.03 (s, 1H).



(8*R*,8a*R*)-3-(2-methylallyl)-5-oxo-2-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy) octahydroindolizin-8-yl 4-methylbenzenesulfonate

To a solution of hydroxyindolizidinone **79** (50 mg, 0.109 mmol) in dry DCM (0.5 mL) at 0°C was added triethylamine (0.075 mL, 0.5475 mmol) and DMAP (50 mg, 0.408 mmol) sequentially, followed by *p*-toluenesulfonyl chloride (65mg, 0.3410), purified by crystallisation. The reaction mixture was allowed to stir at room temperature overnight. It was diluted in DCM and the organic phase was washed with saturated NH_4Cl solution. The combined organic phase was dried over Na_2SO_4 and the crude product was obtained by evaporation of solvent. Purification of the crude product over silica gel (50% EtOAc in pentane) gave 43 mg of the desired tosylate **90** in 89% yield.

^{1}H NMR (400 MHz): δ 1.11-1.36 (m, 18H), 1.52 (d, *J* = 6.8 Hz, 3H), 1.65 (s, 3H), 1.72-1.90 (m, 1H), 1.93-2.09 (m, 2H), 2.11-2.32 (m, 5H), 2.46 (s, 3H), 2.85 (sept, *J* =7.2 Hz, 1H), 3.10-3.20 (m, 1H), 3.73-3.85 (m, 1H), 3.91-4.00 (m, 2H), 4.48-4.58 (m, 2H), 4.61 (s, 1H), 4.80 (br, s, 1H), 4.94-5.05 (m, 2H), 6.93 (s, 1H), 7.02 (s, 1H), 7.27-7.37 (m, 2H), 7.65-7.84 (m, 2H)



91

3-(2-methylallyl)-7,8-dihydroindolizin-5(6*H*)-one

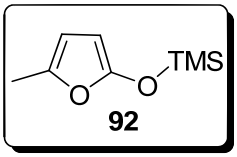
To a solution of tosylate **90** (11.0 mg, 0.018 mmol) in HMPA (0.150 ml) was added NaCN (5.0 mg. 0.0632 mmol) at room temperature. The reaction mixture was stirred overnight and was diluted in ether. The ethereal solution was washed with water repeatedly. The organic phase was dried over Na_2SO_4 and evaporation of the solvent was removed under reduced pressure to provide 22 mg compound **91** as a yellow oil. (Note: HMPA is present).

IR (film): 3477, 2924, 2846, 2804, 1672, 1459, 1297, 1200, 985, 747 cm^{-1}

^{1}H NMR (400 MHz): δ 1.79 (s, 3H), 1.94-2.05 (m, 3H), 2.62-2.69 (m, 2H), 2.78-2.87 (m, 3H), 4.56 (s, 1H), 4.79 (s, 1H), 5.87 (d, *J* = 3.3 Hz. 1H), 5.93 (d, *J* = 3.2 Hz, 1H)

^{13}C NMR (400 MHz): δ 22.9 (CH_3), 24.0 (CH_2), 29.8 (CH_2), 35.2 (CH_2), 37.2 (CH_2), 107.5 (CH), 111.1 (CH_2), 112.5 (CH), 133.1 (C), 136.03 (C), 144.4 (C), 147.8 (C), 167.2 (C).

MS spectra (ESI): *m/z* 190 (MH^+), 212 (MNa^+)

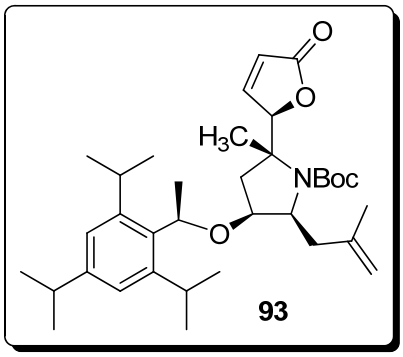


92

trimethyl(5-methylfuran-2-yloxy)silane

To a equimolar mixture of triethylamine (0.710 ml, 5.1 mmol) and trimethylchlorosilane (0.660 ml, 5.1 mmol) was added pre-cooled commercially available neat, α-angeliclactone (0.457 ml, 5.1 mmol). After stirring at room temperature for 6 h, distillation under reduced pressure (T = 85 °C/ 10 torr P) gave 5-methyl-2-trimethylsilyloxyfuran in quantitative yield which was stored and used at low temperatures.

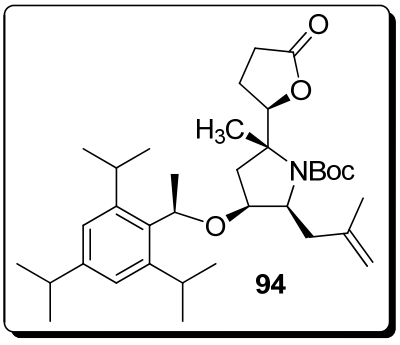
^{1}H NMR (400 MHz): δ 0.28 (s, 9H), 1.52 (s, 3H), 4.95 (m, 1H), 5.75 (m, 1H)



(2*R*)-*tert*-butyl 2-methyl-5-(2-methylallyl)-2-((*R*)-5-oxo-2,5-dihydrofuran-2-yl)-4-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)pyrrolidine-1-carboxylate

$BF_3.Et_2O$ (0.020 mL, 0.169 mmol) was slowly added to a solution of aminal **75** (0.045 g, 0.091 mmol) and 5-methyl-2-(trimethylsiloxy) furan **92** (0.150 mL, 0.546 mmol) in dry DCM (0.650 mL) and the reaction temperature was allowed to rise slowly. After 2 h (T = - 40°C) when no more starting material was observed on the TLC, saturated aqueous $NaHCO_3$ (1.0 mL) was added, and the rreaction mixture was diluted in methylene chloride. The organic layer was separated and the aqueous phase was extracted 3 times with methylene chloride. The combined organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the residue by silica gel (40 – 60 μ) chromatography (10 % AcOEt in pentane) provided 23.1 mg of butenolide **93** in 45 % over 3 steps.

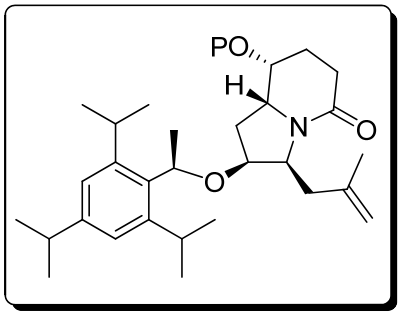
^{1}H NMR (400 MHz): δ 1.13-1.34 (m, 21H), 1.36-1.45 (m, 9H), 1.50 (d, *J* = 7.0 Hz, 3H), 1.58 (s, 3H), 1.69-1.83 (m, 2H), 1.87-2.17 (m, 3H), 2.29-2.4 (m, 2H), 2.85 (sept, *J* = 6.7 Hz, 1H), 3.06-3.2 (m, 1H), 3.77-3.92 (m, 2H), 4.01-4.18 (m, 1H), 4.7 (s, 1H), 4.74 (s, 1H), 5.02 (q, *J* = 6.7 Hz, 1H), 6.94 (s, 1H), 7.04 (s, 1H).



(2*R*,4*S*,5*S*)-*tert*-butyl 2-methyl-5-(2-methylallyl)-2-((*R*)-5-oxotetrahydrofuran-2-yl)-4-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)pyrrolidine-1-carboxylate

A solution of butenolide **93** (21.0 mg, 0.036 mmol) in methanol (0.200 mL) was cooled to 0°C and treated with $CuCl_2 \cdot 2H_2O$ (5 mg, 0.036 mmol). The resulting mixture was stirred for 5 min before the addition of $NaBH_4$ (0.076 g, 1.99 mmol). After 10 min, further portions of $NaBH_4$ (1 or 2 eq was added slowly, H_2 evolution was observed) every 10 min until a complete conversion is observed on TLC The reaction was quenched with saturated NH_4Cl solution and extracted 3 times with CH_2Cl_2. The combined organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Filtration over silica gel with methylene chloride provided 18.6 mg of the lactone in 87% yield.

^{1}H NMR (400 MHz): δ 1.13-1.28 (m, 21H), 1.40-1.46 (m, 9H), 1.48 (s, 3H), 1.53 (d, *J* = 6.5 Hz, 3H), 1.91-2.1 (m, 2H), 2.36-2.6 (m, 2H), 2.85 (m, 1H), 3.17 (m, 1H), 3.77-3.96 (m, 2H), 3.98-4.1 (m, 1H), 4.62-4.68 (m, 1H), 4.73 (m, 1H), 5.06 (q, *J* = 6.9 Hz), 6.93 (s, 1H), 7.03 (s, 1H).



P = *p*-methoxy benzyl, **95**

= methyl, **97**

= benzyl, **102**

General procedure for O-protection of hydroxyindolizidinone:

60% NaH (4.0 eq) was weighed out in an argon flushed flask and washed thoroughly with pentane at 0 °C. A solution of alcohol (1.0 eq) in dry DMF was introduced drop wise and the reaction mixture was allowed to stir at 0 °C for 1 h. At the end of 1 h, the corresponding electrophile (1.5 eq, PMBCl/ BnBr/ MeI) was added, followed by 0.1 eq of TBAI[142] and stirred at RT overnight. The reaction mixture was quenched carefully with MeOH and diluted in EtOAc. The organic layer was washed thoroughly with a 5% solution of LiCl, followed by brine. The combined organic phase was dried over Na_2SO_4 and evaporation under vacuum gave the crude

[142] Note: TBAI was not added for methylation.

product which was purified by silica gel chromatography (10-30% EtOAc in pentane) to obtain the purified product in all the cases.

(2*S*,3*S*,8*R*,8a*R*)-8-((4-methoxybenzyl)oxy)-3-(2-methylallyl)-2-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)hexahydroindolizin-5(1*H*)-one, **95**

Yield: 95%; white solid

^{1}H NMR (400 MHz): δ 1.14-1.29 (m, 18H), 1.52 (d, *J* = 6.6Hz, 3H), 1.64-1.75 (m, 4H), *1.87-1.97* (ddd, *J* = 6.3, 8.4, 12.1 Hz, 1H), 2.10-2.45 (m, 6H), 2.85 (sept, *J* = 7.0 Hz, 1H), 3.07-3.21 (m, 1H), 3.69 (ddd, *J* = 2.4 Hz, 1H), 3.77-3.89 (m, 5H), 3.97 (q, *J* = 6.9 Hz, 1H), 4.35 (d, AB system, *J* = 11.8 Hz, 1H), 4.50-4.61 (m, 3H), 4.65 (s, 1H), 5.00 (q, *J* = 7.1 Hz, 1H), 6.85 (s, 1H), 6.88 (s, 1H), 6.90 (s, 1H), 7.02 (s, 1H), 7.19 (s, 1H), 7.21 (s, 1H).

^{13}C NMR (400 MHz): δ 22.5 (CH_3) 22.9 (CH_3), 23.6 (CH_2), 24.0 (CH_3),, 24.2 (CH_3), 24.9 (CH_3), 25.2 (CH_3), 26.5 (CH_2), 28.8 (CH_2), 29.2 (CH_2), 33.1(CH_2), 34.1 (CH), 35.4 (CH_2), 55.4 (CH), 56.5 (CH_3),58.6 (CH), 70.0 (CH_2), 70.3 (CH), 70.5 (CH), 72.5 (CH), 72.6 (CH), 111.7 (C), 113.8 (CH_2), 120.4 (CH), 123.3 (CH), 129.2 (CH), 129.4 (C), 130.2 (C), 133.9 (C), 143.9 (C), 145.0 (C), 147.4 (C), 148.5 (C), 159.3 (C), 168.3 (C).

MS (ESI): *m/z* 576.4 (MH^+, 100%), 598 (MNa^+).

(2*S*,3*S*,8*R*,8a*R*)-8-methoxy-3-(2-methylallyl)-2-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)

hexahydroindolizin-5(1*H*)-one, **97**

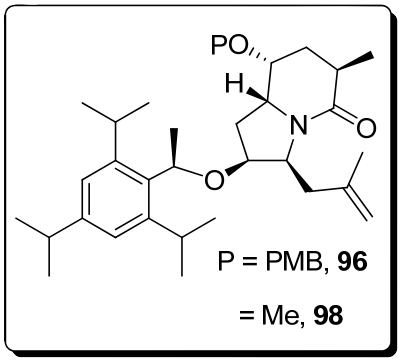
Yield: 98%; Yellow oil

^{1}H NMR (400 MHz): δ 1.14-1.36 (m, 18H), 1.52 (d, *J* = 7.0 Hz, 3H), 1.70 (m, 1H), 1.72 (s, 3H), 1.90-2.01 (m, 1H), 2.13-2.30 (m, 6H), 2.40 (m, 1H), 2.85 (sept, *J* = 6.9 Hz, 1H), 3.09-3.22 (m, 1H), 3.28 (s, 3H), 3.49 (ddd, *J* = 2.4 Hz, 1H), 3.78-3.95 (m, 3H), 4.51-4.58 (m, 2H), 4.66 (s, 1H), 5.00 (q, *J* = 6.9 Hz, 1H), 6.93 (s, 1H), 7.02 (s, 1H)

(2*S*,3*S*,8*R*,8a*R*)-8-(benzyloxy)-3-(2-methylallyl)-2-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)hexahydroindolizin-5(1*H*)-one, **102**

Yield: 98%, yellow oil

^{1}H NMR (400 MHz): δ 1.13-1.29 (m, 18H), 1.52 (d, *J* = 6.6 Hz, 3H), 1.70 (s, 3H), 1.90-1.98 (m, 1H), 2.15-2.47 (m, 6H), 2.85 (sept, *J* = 6.75 Hz, 1H), 3.08-3.19 (m, 1H), 3.73 (ddd, *J* = 2.4 Hz, 1H), 3.78-3.91 (m, 2H), 3.99 (q, *J* = 6.7 Hz, 1H), 4.4 (d, AB system, *J* = 12.1 Hz, 1H), 4.51-4.68 (m, 5H), 5.00 (q, *J* = 6.9 Hz, 1H), 6.90 (s, 1H), 7.02 (s, 1H), 7.25-7.38 (m, 5H).



General procedure for the methylation of the protected hydroxyl-indolizidinone 95 and 97

To a solution of the ether (1.0 eq) in dry THF at -90 °C, *t*-BuLi (5.0 eq) was added drop wise, which imparted a deep yellow color to the reaction mixture. It was stirred for 15 minutes during which the temperature was allowed to increase to -60 °C. The reaction mixture was again cooled down to -78 °C and an excess of MeI (10 eq) was added. It was stirred for another 15 min at this temperature, quenched with saturated NH_4Cl and diluted in ether. The organic phase was washed with saturated NH_4Cl, dried over Na_2SO_4 and evaporation of solvent under reduced pressure gave the corresponding crude methylated lactam which was purified over silica gel (12-15% EtOAc in pentane) to recover the pure methylated lactam.

(2*S*,3*S*,6*R*,8*R*,8a*R*)-8-((4-methoxybenzyl)oxy)-6-methyl-3-(2-methylallyl)-2-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)hexahydroindolizin-5(1*H*)-one, **96**

Yield: 96%, Yellow oil

IR (film): 2958, 2928, 2867, 1643, 1612, 1513, 1462, 1247 cm^{-1}

^{1}H NMR (400 MHz): δ 1.13 -1.32 (m, 21H), 1.40 (ddd, *J* = 1.2, 6.7, 11.5 Hz, 1H), 1.52 (d, *J* = 6.8 Hz, 3H), 1.69 (s, 3H), 1.85-1.93 (m, 1H), 2.11-2.47 (m, 5H), 2.85 (sept, *J* = 6.9 Hz, 1H), 3.08-3.20 (m, 1H), 3.66 (ddd, *J* = 2.4 Hz, 1H), 3.78-3.91 (m, 5H), 3.96 (q, *J* = 6.7 Hz, 1H), 4.34 (d, AB system, *J* = 11.6 Hz, 1H), 4.48-4.58 (m, 3H), 4.64 (s, 1H), 5.00 (q, *J* = 6.5 Hz, 1H), 6.85 (s, 1H), 6.87 (s, 1H), 6.90 (s, 1H), 7.02 (s, 1H), 7.18 (s, 1H), 7.20 (s, 1H).

^{13}C NMR (100 MHz): δ 18.7 (CH_3), 22.7 (CH_3), 22.9 (CH_2), 24.0 (CH_3), 24.1 (CH_3), 24.3 (CH_3), 24.9 (CH_3), 25.2 (CH_3), 28.2 (CH), 29.3 (CH), 30.5 (CH), 31.6 (CH), 32.3 (CH_2), 32.9 (CH_2), 34.1 (CH), 35.4 (CH_2), 55.4 (CH), 56.4 (CH), 58.9 (CH_3), 70.0 (CH_2), 70.4 (CH), 72.8 (CH), 74.9 (CH), 111.5 (CH_2), 113.9, 120.5 (CH), 123.3 (CH), 129.2 (CH), 130.3 (CH), 133.9 (CH), 143.9(C), 145.1 (C), 147.4 (C), 148.6 (C), 159.3 (C), 171.8 (C).

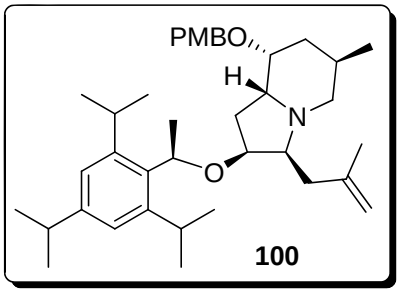
MS (ESI): *m/z* 590.4 (MH^+, 100%), 612.4 (MNa^+)

(2*S*,3*S*,6*R*,8*R*,8a*R*)-8-methoxy-6-methyl-3-(2-methylallyl)-2-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)hexahydroindolizin-5(1H)-one, **98**

Yield: 98%, Yellow oil

^{1}H NMR (400 MHz): δ 1.14-1.33 (m, 18H), 1.38 (t, *J* = 7.6 Hz, 1H), 1.52 (d, *J* = 6.6 Hz, 3H), 1.71 (s, 3H), 1.84-1.97 (m, 1H), 2.07-2.44 (m, 5H), 2.85 (sept, *J* = 7.2 Hz, 1H), 3.11-3.23 (m, 3H), 3.28 (s, 3H), 3.45 (ddd, *J* = 2.5 Hz, 1H), 3.78-3.96 (m, 2H), 4.49-4.57 (m, 2H), 4.65 (s, 1H), 5.00 (q, *J* = 6.3 Hz, 1H), 6.91 (s, 1H), 7.02 (s,1H).

MS (ESI): *m/z* 570.3 (MH^+, 100%)



100

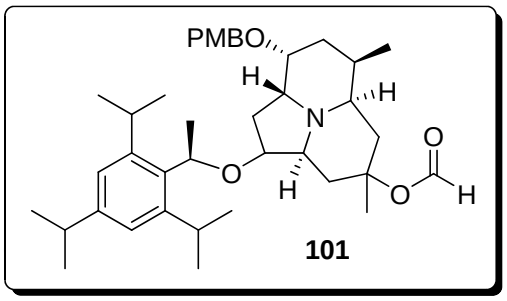
(2*S*,3*S*,6*R*,8*R*,8a*R*)-8-(4-methoxybenzyloxy)-6-methyl-3-(2-methylallyl)-2-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)octahydroindolizine

To a solution of α-methylated lactam **96** (11.1 mg, 0.019 mmol) in dry THF (0.250 mL) was added a solution of 1.0 M DIBAL-H in THF (0.093 mL, 0.093 mmol) at 0 °C and the reaction mixture was stirred at this temperature for 3 h. It was quenched with saturated NH_4Cl solution and diluted in DCM. The organic phase was washed with saturated NH_4Cl solution, separated and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure gave 10.0 mg of the crude tertiary amine **100**.

IR (film): 3382, 2958, 2927, 2867, 1611, 1513, 1459, 1247 cm^{-1}

^{1}H NMR (400 MHz): δ 0.78 (d, *J* = 7.0 Hz, 3H), 1.13-1.35 (m, 18H), 1.48 (s, 3H), 1.69 (d, *J* = 12.5 Hz, 3H), 1.78-2.34 (m, 7H), 2.35-2.45 (m, 1H), 2.85 (sept, *J* = 6.6 Hz, 1H), 3.08-3.25 (m, 2H), 3.40 (m, 1H), 3.45 (m, 1H), 3.65 (ddd, *J* = 2.5 Hz, 1H), 3.75-4.07 (m, 5H), 4.44 (d, AB system, *J* = 11.7 Hz, 1H), 4.55 (d, AB system, *J* = 12 Hz, 1H), 4.63 (s, 1H), 4.71 (s, 1H) 5.02 (q, *J* = 6.7 Hz, 1H), 6.73-6.95 (m, 3H), 6.97-7.03 (m, 1H), 7.10-7.22 (m, 2H).

MS (ESI): *m/z* 576 (MH^+, 100)



101

(2a*S*,6a*R*,7*R*,9*R*,9a*R*)-9-(4-methoxybenzyloxy)-5,7-dimethyl-2-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)decahydro-1*H*-pyrrolo[2,1,5-*de*]quinolizin-5-yl formate

To a solution of the α-methylated lactam **96** (10 mg, 0.0169 mmol) in dry toluene (0.300 mL), was added at 0°C, RedAl, a 65% (w/v) in toluene, (0.025 mL, 0.0845 mmol). The reaction mixture was allowed to stir for 30 min. It was cooled down to -78 °C, HCOOH (0.065 mL) was added. It was allowed to warm up to room temperature overnight, diluted in ether and washed with 10% NaOH solution until the pH was alkaline. The combined organic phase was dried over Na_2SO_4 and the solvent was evaporated to obtain the crude mixture of formate **101** and amine **100** as a yellow oil. Upon purification over silica gel, 3.8 mg of formate **101** (1 % MeoH saturated with ammonia) was isolated in 40% yield and 4.5 mg of amine **100** (5% MeOH

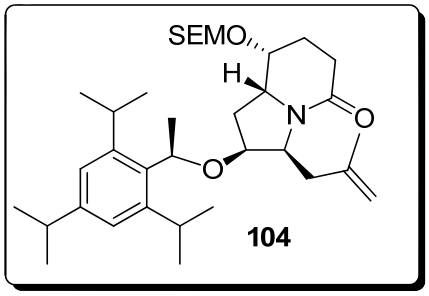
saturated with ammonia) was obtained in 46% yield from the crude material.

IR (film): 2958, 2927, 2869, 1721, 1610, 1513, 1460, 1247, 1175, 1079 cm^{-1}

^{1}H NMR (400 MHz): δ 0.81 (d, *J* = 7.0 Hz, 3H), 1.05(t, *J* = 13.7 Hz, 1H), 1.18-1.37 (m, 18H), 1.48 (d, *J* = 6.5 Hz, 3H), 1.52 (s, 3H), 1.57-1.70 (m, 2H), 1.77 (ddd, *J* = 3.6, 6.5, 10.1 Hz, 1H), 1.89-2.07 (m, 2H), 2.07-2.19 (m, 2H), 2.24-2.34 (m, 1H), 2.85 (sept, *J* = 6.7 Hz, 1H), 3.00 (ddd, *J* = 3.3, 5.2, 13.1 Hz, 1H), 3.11-3.22 (m, 2H), 3.24-3.33 (ddd, *J* = 3.5, 6.6, 11.9 Hz, 1H), 3.45 (ddd, *J* = 2.5, 1H), 3.75-3.91 (m, 4H), 3.96-4.03 (ddd, *J* = 3.8, 6.8, 13.0 Hz, 1H), 4.32 (d, AB system, *J* = 12.0 Hz, 1H), 4.56 (d, AB system, *J* = 12.0 Hz, 1H), 4.98 (q, *J* = 7.03 Hz, 1H), 6.81-6.86 (m, 2H), 6.90 (s, 1H), 6.99 (s, 1H), 7.19-7.24 (m, 2H). 8.05 (s, 1H)

^{13}C NMR (100 MHz): δ 17.9 (CH_3), 23.1 (CH_3), 23.2 (CH_3), 24.1 (CH_3), 24.2 (CH_3), 24.5 (CH_3), 24.8 (CH_3), 24.9 (CH_3), 25.4 (CH_3), 27.5 (CH), 27.7 (CH_2), 28.0 (CH), 29.8 (CH_2), 30.5 (CH), 30.8 (CH_2), 31.5 (CH_2), 34.2 (CH), 53.6 (CH), 55.4 (CH), 59.9 (CH), 70.7 (CH_2), 71.0 (CH), 71.5 (CH), 74.4 (CH), 84.2 (C), 112.7 (CH_2), 120.3 (CH), 123.2 (CH), 125.7 (CH), 129.7 (CH), 131.1 (C), 133.1 (C), 144.3 (C), 146.1 (C), 147.5 (C)

MS (ESI): *m/z* 620 (MH^+, 100%)

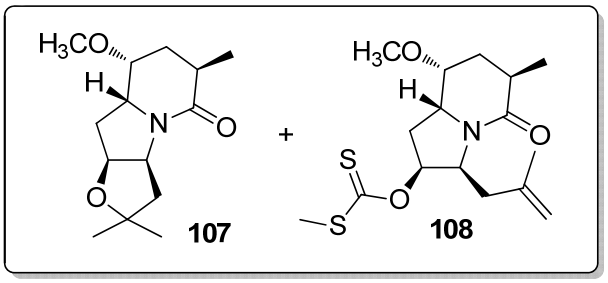


104

(2*S*,3*S*,8*R*,8a*R*)-3-(2-methylallyl)-2-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)-8-((2-(trimethylsilyl)ethoxy)methoxy)hexahydroindolizin-5(1*H*)-one

To a solution of hydroxyindolizidinone **79** (20 mg, 0.0438 mmol) and DIPEA (0.075 mL, 0.438) in dry DCM (0.250 mL), was added SEMCl (0.040 mL, 0.219 mmol) at room temperature. The reaction mixture was refluxed for 2 h, then quenched with water and diluted in DCM. The organic phase was washed with water, separated and dried over Na_2SO_4. Evaporation of the solvent gave the 22.0 mg of crude SEM-ether, which was purified over silica gel (10% EtOAc in pentane) to recover 12.0 mg of purified product **104** as yellow oil in 56% yield.

^{1}H NMR (400 MHz): δ 0.03 (d, *J* = 2.01 Hz, 9H), 0.81-0.99 (m, 4H), 1.13-1.34 (m, 18 H), 1.52 (d, *J* = 6.9 Hz, 3H), 1.70 (s, 3H), 1.92-2.0 (m, 1H), 2.11-2.25 (m, 2H), 2.27-2.38 (m, 3H), 2.85 (sept, *J* = 7.0 Hz, 1H), 3.08-3.31 (m, 1H), 3.60-3.66 (m, 2H), 3.77-3.99 (m, 4H), 4.49-4.83 (m, 5H), 5.03 (q, *J* = 7.0 Hz, 1H), 6.92 (s, 1H), 7.02 (s, 1H).



To a solution of Me-ether **98** (110 mg, 0.234 mmol) in 0.750 mL of DCM at 0°C, was added neat TFA (0.075 ml) drop wise with vigorous stirring. The reaction mixture was stirred for 45 min at room temperature, after which it was placed at 0 °C again and quenched slowly with MeOH saturated with NH_3. The addition of MeOH saturated with NH_3 was continued until the formation of white fumes ceased. The resultant solution was concentrated *in vacuo* and diluted in 1.0 mL of DCM. The white precipitate formed was filtered and this process was repeated until no more salt formation was observed. The organic layer was evaporated to obtain the crude product which upon purification over silica gel (1.0% MeOH saturated with NH_3 in DCM), gave 75.0 mg of an inseparable mixture of the secondary alcohol **106** and the cyclised product **107**.

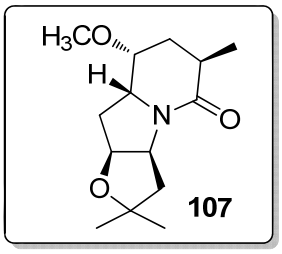
In a dry, Ar-flushed flask, 30% KH in mineral oil (100.0 mg, 0.729 mmol) was weighed out and washed 3 times with pentane. A solution of the above mentioned mixture (75.0 mg, 0.313 mmol) was prepared in 1.0 mL of dry THF and introduced dropwise into the flask at 0 °C. The suspension was stirred for an additional 30 min at room temperature after the addition was complete. The flask was re-cooled to 0°C and CS_2 (0.131 mL, 2.18 mmol) was added. The cooling bath was removed and stirring was continued for 15 min, after which MeI (0.250 mL, 0.3.64 mmol) was added at 0 °C. At the end of 15 min, the reaction mixture was quenched with saturated NH_4Cl and diluted in ether. The aqueous phase was extracted with ether and the combined organic phase was dried over Na_2SO_4 and evaporated *in vacuo* to obtain the crude product. At this stage, purification over silica gel (70% EtOAc in pentane) led to the separation of 46.0 mg of pure xanthate **108** (53% yield over 2 steps) and 16.0 mg of compound **107**.

O-(2S,3S,6R,8R,8aR)-8-methoxy-6-methyl-3-(2-methylallyl)-5-oxooctahydroindolizin-2-yl-S-methyl carbonodithioate, **108**:

IR (film): 3400**,** 2955, 2923, 2846, 1641, 1441, 1408, 1209 cm^{-1}

^{1}H NMR (400 MHz): δ 1.34(s, 3H), 1.43-1.45 (m, 1H), 1.78 (s, 3H), 1.99-2.07(m, 1H), 2.23-2.39 (m, 4H), 2.57 (s, 3H), 2.97 (dd, *J* = 4.5, 13.5 Hz, 1H), 3.31 (s, 3H), 3.55-3.60 (ddd, *J* = 2.0 Hz, 1H), 3.81-3.87 (ddd, *J* = 2.8, 5.4, 11.5 Hz, 1H), 4.45-4.51 (ddd, 1H), 4.69 (s, 1H), 4.73 (s, 1H), 5.96-6.01 (ddd, J = 1.5, 5.0, 9.0 Hz, 1H)

^{13}C NMR (100 MHz): δ 18.1 (CH_3), 19.1 (CH_3), 22.7 (CH_3), 31.4 (CH), 31.5 (CH_2), 32.2 (CH_2), 33.3 (CH_2), 35.3 (CH_2), 56.2 (CH), 59.8 (CH), 61.0 (CH), 71.8 (CH), 81.5 (CH), 112.1 (CH_2), 142.0 (C), 173.1 (C).



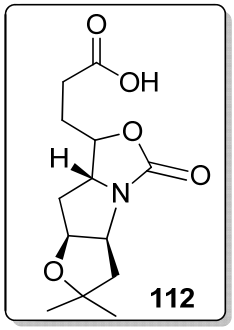
(1a*S*,4a*S*,6*R*,8*R*,8a*S*)-8-methoxy-5-oxo-3,3,6-trimethyloctahydro(4*H*)furano[2,3-*b*]indolizine

Alternate procedure for removal of chiral inductor during which compound **107** was obtained:

To a solution of Me-ether **98** (10 mg, 0.0213 mmol) in CH_3CN (0.100 mL) was added NaI (8 mg, 0.051 mmol) and trichloromethylsilane (0.010 mL, 0.051 mmol). The reaction mixture was stirred for 30 min and then it was diluted in DCM, quenched and washed 3 times with 10% $Na_2S_2O_3$ solution. The organic phase was dried over Na_2SO_4 and evaporated *in vacuo* to obtain the crude product. Purification over silica gel (10% MeOH saturated with NH_3 in DCM), furnished 3.0 mg of compound **107** in 76% yield.

^{1}H NMR (400 MHz): δ 1.20 (s, 3H), 1.26 (s, 3H), 1.29 (s, 3H), 1.48 (ddd, *J* = 1.2, 11.7, 13.7 Hz, 1H), 1.63-1.70 (m, 1H), 1.88-1.95 (m, 1H), 2.08 (ddd, *J* = 4.5, 11.2, 13.2 Hz), 2.32-2.48 (m, 3H), 3.34 (s, 3H), 3.54-3.58 (m, 1H), 3.88 (ddd, *J* = 3.1, 5.6, 11.7 Hz, 1H), 4.50-4.54 (m, 1H), 4.56-4.62 (m, 1H).

^{13}C NMR (100 MHz): δ 17.6 (CH_3), 27.1 (CH), 28.7 (CH), 29.8 (CH_2), 30.8 (CH), 33.1 (CH_2), 47.0 (CH_2), 56.5 (CH), 60.4 (CH), 63.4 (CH_3), 72.2 (CH), 78.9 (CH), 82.4 (C), 171.4 (C).



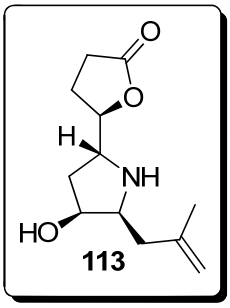
3-((3a*S*,7a*R*,8a*S*)-2,2-dimethyl-5-oxooctahydrofuro[2',3':4,5]pyrrolo[1,2-*c*]oxazol-7-yl)propanoic acid

To a solution of N-protected lactone **77** (42.0 mg, 0.075 mmol) in dry DCM (0.250 mL) at 0 °C, was added dropwise neat TFA (0.025 mL) with vigorous stirring. The reaction mixture was stirred for 25 min at room temperature, after which it was placed at 0 °C and quenched slowly with MeOH saturated with NH_3 until the formation of white fumes ceased. The resultant solution was concentrated *in vacuo* (without heating the water bath) and diluted in 1.0 mL of DCM. The white precipitate formed was filtered and this process was repeated until no more salt formation was observed. The organic layer was evaporated to obtain 70 mg of crude product from which 15.0 mg (60%) of the above compound was recovered by purification over silica gel (5.0 % MeOH saturated with NH_3 in DCM) as a yellow oil.

^{1}H NMR (400 MHz): δ 1.35 (s, 3H), 1.45 (s, 3H), 1.74-1.86 (m, 2H), 2.15-2.21 (m, 3H), 2.43-2.61 (m, 4H), 3.58-3.68 (ddd, J = 2.9, 6.0, 11.5 Hz, 1H), 4.22 (q, J = 2.5 Hz, 1H), 4.53-4.61 (ddd, J = 1.9, 8.6, 9.1 Hz, 1H), 4.65-4.72 (ddd, J = 1.8, 5.2, 9.7 Hz, 1H).

^{13}C NMR (100 MHz): δ 24.35 (CH_2), 24.5 (CH_3), 28.4 (CH_2), 29.7 (CH_3), 32.2 (CH_2), 36.7 (CH_2), 58.6 (CH), 60.6 (CH), 71.4 (CH), 82.4 (CH), 155.3 (C), 177.3 (C).

MS (ESI): *m/z* 292 (MNa^+, 100%)



113

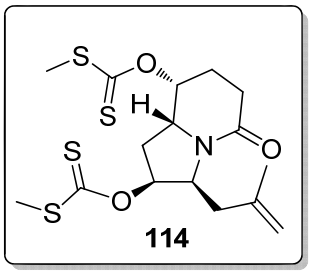
(*R*)-5-((2*R*,4*S*,5*S*)-4-hydroxy-5-(2-methylallyl)pyrrolidin-2-yl)dihydrofuran-2(3*H*)-one

To a solution of aminolactone **78** (70 mg, 0.158 mmol) in 0.450 mL of DCM at 0C, 0.050 ml of TFA (neat) was added dropwise with vigorous stirring. The reaction mixture was stirred for 45 min at room temperature, after which it was placed at 0 °C and quenched slowly with MeOH saturated with NH_3 until the formation of white fumes ceased. The resultant solution was concentrated *in vacuo* and diluted in 1.0 mL of DCM. The white precipitate formed was filtered and this process was repeated until no more salt formation was observed. The organic layer was evaporated to obtain 77 mg of crude product from which 20.0 mg (62 %) of the pure secondary alcohol **113** was recovered by purification over silica gel (10% MeOH saturated with NH_3 in DCM).

^{1}H NMR (400 MHz): δ 1.73-1.96 (m, 5H), 1.99-2.14 (m, 2H), 2.26-2.54 (m, 3H), 3.0 (m, 1H), 3.87 (ddd, *J* = 2.3, 5.2, 10.9 Hz, 1H), 4.08-4.13 (m, 1H), 4.18-4.29 (m, 1H), 4.37-4.44 (m, 1H), 4.82 (s, 2H).

^{13}C NMR (100 MHz): δ 22.8 (CH_3), 26.6 (CH_2), 27.0 (CH_2), 35.3 (CH_2), 35.7 (CH_2), 58.9 (CH), 59.4 (CH), 63.9 (CH), 71.6 (CH), 111.6 (CH), 144.8 (C), 169.6 (C).

MS (ESI): *m/z* 226 (MH^+, 100%)



114

S,*S*'-dimethyl *O*,*O*'-((2*S*,3*S*,8*R*,8a*R*)-3-(2-methylallyl)-5-oxooctahydroindolizine-2,8-diyl) dicarbonodithioate

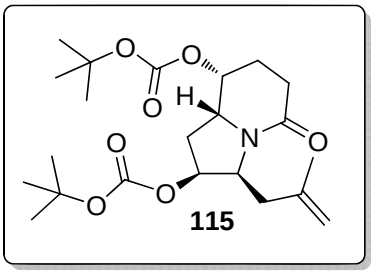
In a dry, Ar-flushed flask, was weighed out 30% KH in mineral oil (10.0 mg, 0.179 mmol) and washed 3 times with pentane. A solution of alcohol **113** (9.0 mg, 0.119 mmol) was prepared in dry THF (0.200 mL) and introduced dropwise into the flask at 0 °C. After warming to room temperature, the suspension was stirred for an additional 30 min. The flask was then recooled to 0 °C and CS_2 (0.005 mL, 0.238 mmol) was added. The cooling bath was removed and stirring was continued for 15 min, after which MeI (0.002 mL, 0.119 mmol) was added at 0 °C. At the end of 15 min, the reaction mixture was quenched with saturated NH_4Cl and diluted in ether. The aqueous phase was extracted with ether and the combined organic phase was dried over Na_2SO_4 and evaporated *in vacuo* to obtain the crude product which was purified over silica gel (3% MeOH saturated with NH_3 in DCM) to recover 5.0 mg of pure compound 114.

IR (film): 2957, 2924, 2850, 1644, 1455, 1441, 1409, 1209 cm^{-1}

^{1}H NMR (300 MHz): δ 1.80 (s, 3H), 1.89-2.13 (m, 3H), 2.18-2.53 (m, 6H), 2.55 (s, 3H), 2.58 (s, 4H), 3.00 (m, 1H), 4.03-4.12 (ddd, *J* = 2.4, 5.2, 11.1 Hz, 1H), 4.52-4.61 (m, 1H), 4.70(s, 1H), 4.72 (s, 1H), 6.0 (m, 1H), 6.2 (m, 1H)

^{13}C NMR (100 MHz)[143]: δ 19.4 (CH_3), 22.9 (CH_3), 24.8 (CH_2), 27.2 (CH_2), 29.8 (CH_2), 34.1 (CH_2), 35.3 (CH_2), 59.8 (CH_3), 59.83 (CH_3), 74.7 (CH), 80.2 (CH), 112.5 (CH_2), 140.1 (C).

MS (ESI): *m/z* 406.2 (MH^+, 100%)



115

di-*tert*-butyl ((2*S*,3*S*,8*R*,8a*R*)-3-(2-methylallyl)-5-oxooctahydroindolizine-2,8-diyl) dicarbonate

To a solution of compound **113** (20.0 mg, 0.088 mmol) in dry DCM (0.500 mL) were added at room temperature triethylamine (0.015 mL, 0.088 mmol), di-tert-butyl dicarbonate (40.0 mg, 0.177 mmol) sequentially. The reaction mixture was cooled to 0 °C and DMAP (10 mg, 0.088 mmol) was added. It was then stirred for 2 h at room temperature, quenched with saturated

[143] Due to availability of scarce amount of pure material, the C-quartenary in the xanthate **114** could not be detected

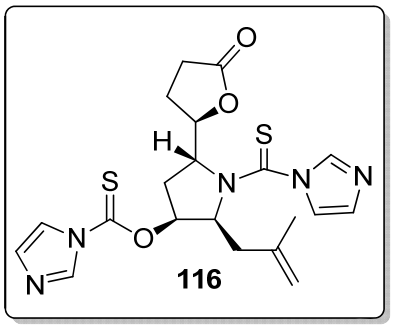
NH_4Cl, diluted with dichloromethane, dried over sodium sulfate and filtered. Evaporation of the solvent gave the crude product, which was purified by silica gel chromatography (5.0% MeOH saturated with NH_3 in DCM) to obtain compound **115** (10.24 mg, 30%) as a white solid.

IR (film): 2982, 2932, 2920, 1740. 1643, 1455, 1369, 1280, 1156 cm^{-1}

^{1}H NMR (400 MHz): δ 1.46 (s, 18H), 1.8 (s, 3H), 1.83-2.08 (m, 3H), 2.18-2.30 (m, 2H), 2.38-2.48 (m, 2H), 3.0 (m, 1H), 4.00 (ddd, *J* = 2.8, 5.0, 11.2 Hz, 1H), 4.34-4.45 (m, 1H), 4.72 (s, 1H), 4.75 (s, 1H), 5.05 (m, 1H), 5.23 (m, 1H).

^{13}C NMR (100 MHz)[144]: δ 22.3 (CH_3), 25.4 (CH_2), 26.9 (CH_2), 27.9 (CH_3), 35.3 (CH_2), 35.4 (CH_2), 59.5 (CH), 68.6 (CH), 73.6 (CH), 88.7 (C), 82.8 (C), 112.4 (CH_2), 142.4 (C), 152.8 (C), 153.0 (C), 168.6 (C).

MS (ESI): *m/z* 448 (MNa^+, 100%)



O-(5*R*)-1-(1*H*-imidazole-1-carbonothioyl)-2-(2-methylallyl)-5-((*R*)-5-oxotetrahydrofuran-2-yl)pyrrolidin-3-yl 1*H*-imidazole-1-carbothioate

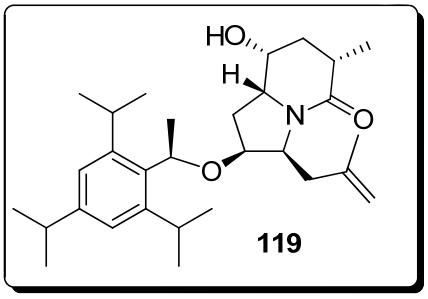
To a solution of alcohol **113** (10.0 mg, 0.044 mmol) in DCM (0.100 mL), was added 1,1'-bis thiocarbonylimidazole (20.0 mg, 0.222 mmol) and heated in a sealed tube overnight at 40 °C. After 12 h, the reaction mixture was cooled to room temperature, quenched with saturated NH_4Cl and diluted in DCM. The organic phase was washed 3 times with saturated NH_4Cl and dried over Na_2SO_4. The crude product was obtained by evaporation of solvent *in vacuo* and purified over silica gel (1.0 % MeOH saturated with NH_3 in DCM) to obtain 11 mg of the pure compound **116** in 55 % yield.

IR (film): 2381, 2389, 1661, 1650, 1407, 1275 cm^{-1}

[144] Due to availability of scarce amount of pure material, the C-quartenary in compound **115** could not be detected

^{1}H NMR (400 MHz): δ 1.71 (s, 3H), 1.94-2.49 (m, 6H), 2.60 (m, 1H), 3.00 (m, 1H), 3.8-3.90 (br, 2H), 4.10-4.16 (ddd, *J* = 2.5, 5.3, 11.1 Hz), 4.51 (s, 1H), 4.59-4.66 (m, 1H), 4.67 (s, 1H), 5.95 (m, 1H), 6.03-6.07 (m, 1H), 7.00 (s, 2H), 7.05 (s, 2H), 8.24 (s, 1H), 8.27 (s, 1H)

MS (ESI): *m/z* 446 (MH^+, 100%)



119

(2*S*,3*S*,6*S*,8*R*,8a*R*)-8-hydroxy-6-methyl-3-(2-methylallyl)-2-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)hexahydroindolizin-5(1*H*)-one

To a solution of the hydroxyindolizidinone **79** (500 mg, 1.1 mmol) in dry THF (20.0 mL) at -90 °C, was added drop wise *t*-BuLi (5.6 mL, 5.5 mmol), which imparted a deep yellow color to the reaction mixture. It was stirred for 15 minutes during which the temperature was allowed to increase to -60°C. The reaction mixture was then cooled down to -78°C and MeI (1.0 mL, 20.0 mmol) was added. The temperature was rapidly increased to -40°C over 20 minutes after which the reaction mixture was quenched with saturated NH_4Cl and diluted in ether. The organic phase was washed with saturated NH_4Cl and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure provided a mixture (520 mg) of the crude mono-methylated lactam **117** and < 10% starting hydroxyindolizidinone **79**, which was engaged directly in the epimerisation reaction.

To a solution of the above crude mixture (520 mg, 1.1 mmol) in dry THF (10.0 mL), was added drop wise *t*-BuLi (5.6 ml, 5.5 mmol) at -90 °C. The temperature was raised -60 °C and the reaction mixture was stirred at this temperature for 1 h and was quenched with a solution of *t*-BuOH (1.0 ml) in THF (2.0 mL) followed by warming up to room temperature over 30 min. It was diluted in ether and washed 3 times with saturated NH_4Cl. The organic phase was separated and dried over Na_2SO_4. Evaporation of solvent under reduced pressure gave a mixture of the two epimers (and < 10% of hydroxyindolizidinone **79**) as a yellow oil. This mixture was purified over basic alumina to obtain 155 mg of the axial epimer **119** (30-60% EtOAc in pentane, pale

yellow solid), 162 mg of the equatorial epimer **117** (80% EtOAc in pentane – EtOAc only, pale yellow solid) and 57 mg of hydroxyindolizidinone **79** (MeOH, yellow oil).

Treatment of the recovered starting material **117** under the above mentioned reaction conditions two more times, provided 115 mg more of compound **119.**

Axial diastereoisomer, **119**: Yield: (61% brsm)

Mp: 162.6 °C

IR (film): 3387, 2961, 2927, 2869, 1613, 1461, 1384, 1106, 1078 cm^{-1}

^{1}H NMR (400 MHz): δ 1.12-1.34 (m, 21H), 1.45 (ddd, *J* = 2.6, 5.6, 13.0 Hz, 1H), 1.52 (d, *J* = 6.7 Hz, 3H), 1.77 (s, 3H), 2.06-2.16 (m, 2H), 2.26-2.24 (m, 4H), 2.85 (sept, *J* = 7.0 Hz, 1H), 3.11-3.22 (m, 1H), 3.77-3.91 (m, 2H), 3.96-4.07 (m, 2H), 4.52 (ddd, *J* = 4.4, 6.5,13.8 Hz, 1H), 4.56 (s, 1H), 4.65 (s, 1H), 5.02 (q, *J* = 6.7 Hz, 1H), 6.91 (s, 1H), 7.03 (s, 1H).

^{13}C NMR (100 MHz): δ 17.9 (CH_3), 22.5 (CH_3), 23.0 (CH_3), 23.1 (CH_3), 24.0 (CH_3), 24.2 (CH_3), 25.0 (CH_3), 25.3 (CH_3), 28.7 (CH), 29.4 (CH), 32.7 (CH), 33.0 (CH_2), 34.2 (CH), 36.8 (CH_2), 38.0 (CH_2), 56.3 (CH), 58.2 (CH), 67.1 (CH), 72.3 (CH), 74.8 (CH), 112.2 (CH_2), 120.5 (CH), 123.4 (CH), 133.6 (C), 144.1 (C), 147.5 (C), 172. 1 (C).

MS (ESI): *m/z* 470 (MH^+, 100 %)

Equatorial diastereoisomer, **117**:

Mp: 55°C (pentane)

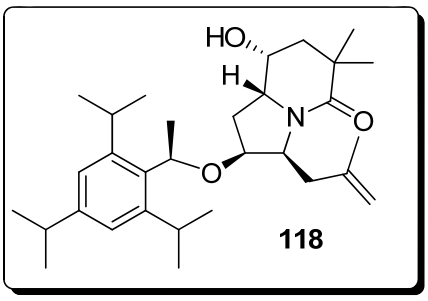
IR (film): 3387, 2961, 2927, 2869, 1613, 1461, 1384, 1328, 1106, 1078 cm^{-1}

^{1}H NMR (400 MHz): δ 1.1 (d, *J* = 7.02 Hz, 3H), 1.13-1.32 (m, 18H), 1.44-1.59 (m, 1H), 1.52 (d, *J* = 6.7 Hz, 3H), 1.69 (s, 3H), 1.93-2.02 (ddd, *J* = 6.5, 8.5, 12.5 Hz, 1H), 2.06-2.31 (m, 3H), 2.34-2.46 (m, 2H), 2.85 (sept, *J* = 6.7 Hz, 1H), 3.1-3.2 (m, 1H), 3.79-3.89 (m, 2H), 3.91-4.0 (m, 2H), 4.48-4.58 (m, 2H), 4.64 (s, 1H), 5.02 (q, *J* = 6.7 Hz, 1H), 6.91 (s, 1H), 7.02 (s, 1H)

^{13}C NMR (100 MHz): δ 18.9 (CH_3), 22.6 (CH_3), 23.0 (CH_3), 23.9 (CH_3), 24.1 (CH_3), 24.3 (CH_3), 24.9 (CH_3), 25.2 (CH_3), 28.7 (CH), 29.2 (CH), 29.4 (CH), 31.2 (CH), 33.2 (CH_2), 34.1

(CH), 35.5 (CH_2), 36.9 (CH_2), 56.6 (CH), 59.2 (CH), 64.4 (CH), 72.7 (CH), 74.7 (CH), 111.6 (CH_2), 120.5 (CH), 123.2 (CH), 133.8 (C), 143.6 (C), 147.3 (C), 172.1 (C).

MS (ESI): *m/z* 470 (MH^+, 100%)



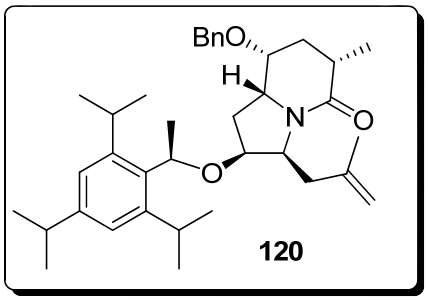
118

(3*S*,8*R*,8a*R*)-8-hydroxy-6,6-dimethyl-3-(2-methylallyl)-2-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)hexahydroindolizin-5(1*H*)-one

Note: During the methylation of the hydroxyindolizidinone **79,** *if the reaction mixture is stirred at -60 °C for 1 h after the addition of* MeI*, it leads to the formation of the bis-methylation product* **118,** *which can be separated in small amount from the α- methylated lactam* **117** *by purification over silica gel (30% EtOAc in pentane).*

^{1}H NMR (400 MHz): δ 1.10-1.36 (m, 24H), 1.52 (d, *J* = 6.7 Hz, 3H), 1.74 (s, 3H), 1.79-1.86 (m , 1H), 1.88-1.97 (m, 1H), 2.02-2.18 (m, 2H), 2.21-2.45 (m, 3H), 2.85 (sept, *J* = 7.0 Hz, 1H), 3.15 (m, 1H), 3.78-3.94 (m, 2H), 3.94-4.04 (m, 2H), 4.49-4.69 (m, 3H), 5.04 (q, *J* = 7.0 Hz, 1H), 6.92 (s, 1H), 7.03 (s, 1H).

MS (ESI): *m/z* 484 (MH^+, 100%)



120

(3*S*,6*S*,8*R*,8a*R*)-8-(benzyloxy)-6-methyl-3-(2-methylallyl)-2-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)hexahydroindolizin-5(1*H*)-one

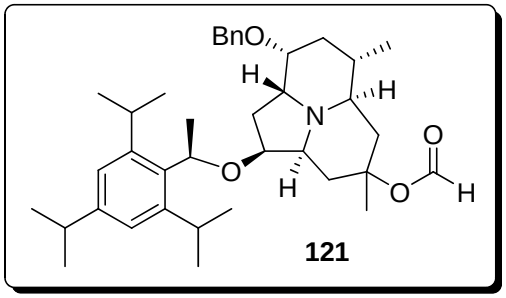
An argon flushed flask at 0°C was charged with NaH 60% suspension in mineral oil, (100 mg, 2.38 mmol), then washed 3 times with pentane. A solution of compound **119** (280 mg, 0.597 mmol) in dry DMF (10.0 mL) was added dropwise to the suspension and allowed to stir at 0 °C for 1 h, after which benzyl bromide (0.100 mL, 0.895 mmol) was added dropwise, followed by addition of TBAI(10.0 mg). The reaction mixture was allowed to stir at room temperature overnight, cooled to 0 °C and quenched carefully with MeOH and diluted in EtOAc. The organic layer was washed 2 times with 5% solution of LiCl, followed by brine. The organic phase was dried over Na_2SO_4 and evaporated under vacuum to obtain the crude product which was purified by silica gel chromatography (10-20% EtOAc in pentane) to afford 280 mg of the pure benzyl ether **120**. (83% yield).

IR (film): 2934, 2929, 2868, 1647, 1454, 1359, 1111 cm^{-1}

^{1}H NMR (400 MHz): δ 1.13-1.29 (m, 21H), 1.52 (d, *J* = 7.0 Hz, 3H), 1.76 (s, 3H), 1.78-1.86 (ddd, *J* = 3.5, 5.6, 14.6 Hz, 1H), 1.99-2.15 (m, 3H), 2.26 (dd, *J* = 4.6, 13.5 Hz, 1H), 2.31-2.41 (m, 2H), 2.85 (sept, *J* = 7.03 Hz, 1H), 3.06-3.20 (m, 1H), 3.69 (q, *J* = 3.5 Hz, 1H), 3.80-3.93 (m, 2H), 4.11 (q, *J* = 7.5 Hz, 1H), 4.36 (d, AB system, *J* = 11.6 Hz, 1H), 4.51-4.65 (m, 4H), 5.02 (q, *J* = 7.0 Hz, 1H), 6.89 (s, 1H), 7.03 (s, 1H), 7.22-7.35 (m, 5H)

^{13}C NMR (100 MHz): δ 18.6 (CH_3), 22.5, 22.9, 24.0, 24.1, 24.9, 25.3 (CH_3), 28.8, 29.4 (CH_3), 29.8 (CH_2), 32.2 (CH_2), 33.3 (CH_2), 34.1 (CH_2), 36.5 (CH_2), 56.3 (CH), 58.1 (CH), 70.5 (CH_2), 72.6 (CH_2), 72.7 (CH_2), 74.9 (CH_2), 109.0 (C), 111.9 (CH_2), 120.5 (CH), 123.5 (CH), 127.7 (CH), 120.0 (CH), 133.9 (C), 138.1 (C), 144.1 (C), 147.4 (C), 172.1 (C).

MS (ESI): *m/z* 560.4 (MH^+, 100%)



121

(2*S*,2a*S*,6a*R*,7*S*,9*R*,9a*R*)-9-(benzyloxy)-5,7-dimethyl-2-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy) decahydro-1*H*-pyrrolo[2,1,5-*de*]quinolizin-5-yl formate

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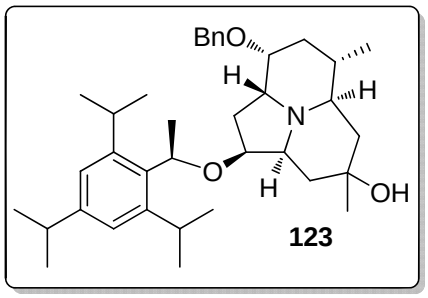
To a solution of the benzyl ether **120** (45.0 mg, 0.080 mmol) in dry THF (1.00 mL) at room temperature was added drop wise, a 1.0 M solution of $LiAlH_4$ in THF (0.120 mL, 0.120 mmol). The reaction mixture was stirred at this temperature until the TLC indicated complete consumption of starting material (approx. 20 min). After this, HCOOH (0.500 mL) was added rapidly to the reaction mixture and the cooling bath was removed. It was stirred at room temperature for an additional 1 h and the resultant solution was diluted in ether and washed with sat. K_2CO_3 solution until the pH was alkaline. The combined organic phase was dried over Na_2SO_4 and evaporation of solvent under reduced pressure furnished the crude mixture of products as a yellow oil. Upon purification of the above mixture on silica gel (1% MeOH saturated with ammonia), 20.0 mg of the pure formate **121** was isolated in 42% yield.

IR (film): 2958, 2926, 2869, 1721, 1605, 1454, 1382, 1176, 1079 cm^{-1}

^{1}H NMR (400 MHz): δ 0.83 (d, *J* = 7.2 Hz, 3H), 1.07-1.36 (m, 19H), 1.49 (d, *J* = 7.4 Hz, 3H), 1.54 (s, 3H), 1.56-1.86 (m, 4H), 1.89-2.08 (m, 2H), 2.10-2.26 (m, 1H), 2.26-2.36 (m, 1H), 2.83 (sept, *J* = 7.0 Hz, 1H), 3.02 (ddd, *J* = 3.2, 5.4, 13.1 Hz, 1H), 3.08-3.3.25 (m, 2H), 3.25-3.35 (ddd, *J* = 3.8, 7.0, 12.1 Hz, 1H), 3.48 (ddd, *J* = 2.4 Hz, 1H), 3.96-4.0 (m, 1H), 4.03 (ddd, *J* = 4.0, 7.0, 13.2 Hz. 1H), 4.39 (d, AB system, *J* = 12.0 Hz, 1H), 4.62 (d, AB system, *J* = 12.0 Hz, 1H), 5.00 (q, *J* = 7.0 Hz, 1H), 6.92 (s, 1H), 7.03 (s, 1H), 7.20-7.39 (m, 5H), 8.05 (s, 1H)

^{13}C NMR (100 MHz): δ 17.9 (CH_3), 24.5 (CH_3), 24.8 (CH_3), 24.9 (CH_3), 25.4 (CH_3), 27.5 (CH_3), 27.7 (CH_2), 28.0 (CH), 29.2 (CH), 29.4 (CH_2), 29.5 (CH_2), 30.9 (CH_2), 34.2 (CH_3), 53.6 (CH), 55.4 (CH), 59.9 (CH), 71.0 (CH), 71.1 (CH_2), 72.0 (CH), 74.4 (CH), 85.6 (C), 120.4 (CH), 123.1 (CH), 127.6 (CH), 128.3 (CH), 128.5 (CH), 133.2 (C), 138.9 (C), 147.5 (C), 148.9 (C), 160.5 (C).

MS (ESI): *m/z* 590 (MH^+, 100%)



123

(2*S*,2a*S*,5a*R*,6*S*,8*R*,8a*R*)-8-(benzyloxy)-4,6-dimethyl-2-((*R*)-1-(2,4,6-triisopropylphenyl) ethoxy)decahydro-pyrrolo[2,1,5-*de*]quinolizin-4-ol

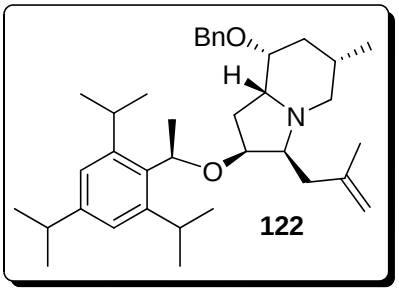
A solution of benzyl ether **120** (18 mg, 0.032 mmol) was processed as above to obtain 15 mg of a mixture of formate **121**, tertiary amine **122** and alcohol **123.** To a methanolic solution of this mixture, was added solid K_2CO_3 (50.0 mg, 0.362 mmol) and the resultant suspension was stirred at room temperature for 30 min. The reaction mixture was diluted in a large excess of DCM and washed repeatedly with brine. The combined organic phase was dried over Na_2SO_4 and evaporation of solvent under reduced pressure gave the crude tertiary alcohol **123**, which was purified on silica gel chromatography (pure EtOAc) to furnish 11.0 mg of the pure product of **123.** (65% yield over 2 steps).

IR (film): 3398, 2960, 2929, 2869, 1603, 1454, 1265, 1081 cm^{-1}

^{1}H NMR (400 MHz): δ 0.83 (d, *J* = 7.03 Hz, 3H), 1.12-1.39 (m, 21H), 1.43 (s, 3H), 1.48 (d, *J* = 6.7 Hz, 3H), 1.50-1.85 (m, 4H), 2.13-2.25 (m, 1H), 2.26-2.40 (m, 1H), 2.85 (sept, *J* = 6.7 Hz, 1H), 2.96 (ddd, *J* = 3.2, 4.7, 13.0 Hz, 1H), 3.09-3.22 (m, 2H), 3.22-3.30 (ddd, *J* = 4.0, 6.8, 12.4 Hz, 1H), 3.46 (q, J = 2.5 Hz, 1H), 3.83-3.96 (m, 1H), 4.02 (ddd, *J* = 4.0, 7.4, 13.3 Hz, 1H), 4.39 (d, AB system, *J* = 12.0 Hz, 1H), 4.63 (d, AB system, *J* = 12.0 Hz, 1H), 5.00 (q, *J* = 7.2 Hz, 1H), 6.91 (s, 1H), 6.99 (s, 1H), 7.26-7.33 (m, 5H)

^{13}C NMR (100 MHz): δ 17.9 (CH_3), 23.1(CH_3), 24.1 (CH_3), 24.2 (CH_3), 24.5 (CH_3), 24.9(CH_3), 25.3 (CH_3), 25.9 (CH_3), 27.4 (CH_3), 28.0 (CH_3), 29.2 (CH), 29.8 (CH), 30.8 (CH_2), 31.0 (CH_2), 31.6 (CH_2), 33.2 (CH_2), 34.2(CH_3), 53.4 (CH), 56.2 (CH), 60.7 (CH), 70.9 (CH), 71.1 (CH_2), 72.2 (CH), 74.4 (CH), 120.4(C), 123.2 (C), 127.6 (C), 128.2 (C), 128.3 (C), 133.3 (C), 139.0 (C), 146.1 (C), 147.4 (C), 148.9 (C).

MS (ESI): *m/z* 562.4 (MH^+, 100%)



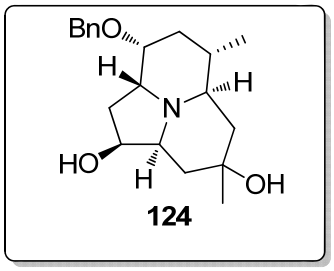
122

(6*R*,8*R*,8a*R*)-8-(benzyloxy)-6-methyl-3-(2-methylallyl)-2-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)octahydroindolizine

^{1}H NMR (400 MHz): δ 0.77 (d, *J* = 6.6 Hz, 3H), 0.91 (t, *J* = 7.5 Hz, 1H), 1.04-1.17 (m, 18H), 1.52 (d, *J* = 6.7 Hz, 3H), 1.61-1.75 (m, 5H), 1.83 (t, *J* = 10.6 Hz, 1H), 1.94 (q, *J* = 7.4 Hz, 1H), 1.99-2.12 (m, 2H), 2.27 (m, 1H), 2.42 (m, 1H), 2.85 (sept, *J* = 7.0 Hz, 1H), 3.05-3.17 (m , 2H), 3.47-3.59 (m, 1H), 3.75 (m, 1H), 3.87 (sept, *J* = 6.7 Hz, 1H), 4.1 (ddd, *J* = 2.5, 2.5, 7.8 Hz, 1H), 4.49 (d, AB system, *J* = 12.7 Hz, 1H), 4.55 (d, AB system, *J* = 12.7 Hz, 1H), 4.61 (s, 1H), 4.65 (s, 1H), 4.96 (q, *J* = 7.01 Hz, 1H), 6.86 (s, 1H), 6.96 (s, 1H), 7.19-7.31 (m, 5H)

^{13}C NMR (100 MHz): δ 19.5 (CH_3), 23.1 (CH_3), 23.4 (CH_3), 24.0 (CH_3), 24.4 (CH_3), 24.8 (CH_3), 25.0 (CH_3), 25.3 (CH_3), 28.0 (CH_3), 29.1 (CH_2), 33.4 (CH_2), 33.9 (CH), 34.9 (CH_2), 57.8 (CH_2), 58.0 (CH), 67.6 (CH), 70.7 (CH_2), 70.9 (CH), 75.6 (CH), 75.9 (CH), 110.3 (CH_2), 120.4 (CH), 123.1 (CH), 127.4 (CH), 127.6 (CH), 133.3(C), 138.9 (C), 145.5 (C), 146.0 (C), 147.1 (C), 147.1 (C), 148.9 (C).

MS (ESI): *m/z* 546.4 (MH^+, 100%)



124

(1*S*,2a*R*,3*R*,5*S*,5a*R*,8a*S*)-3-(benzyloxy)-5,7-dimethyldecahydro-pyrrolo[2,1,5-*de*]quinolizine-1,7-diol

To a solution of the tertiary alcohol **123** (106 mg, 0.188 mmol) in 0.800 mL of DCM at 0 °C, was added neat TFA (0.070 ml) dropwise with vigorous stirring. The reaction mixture was

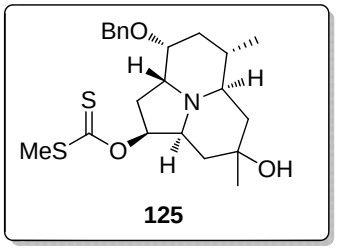
stirred for another 1 h at room temperature, after which it was placed at 0 °C again and quenched with 10% NaOH solution and diluted in DCM. The resultant organic phase was washed with 10% NaOH solution and dried over Na_2SO_4. The solvent was evaporated *in vacuo* to obtain the crude product which upon purification over silica gel (2.0% MeOH saturated with NH_3 in DCM), furnished 54.0 mg of diol **124** a yellow oil in 86% yield.

IR (film): 3371, 2955, 2925, 2865, 1458 cm^{-1}

^{1}H NMR (400 MHz): δ 0.85 (d, *J* = 7.03 Hz, 3H), 1.09-1.43 (m, 7H), 1.51-1.64 (m, 2H), 1.81 (ddd, *J* = 3.5, 3.5, 14.0 Hz, 1H), 2.26-2.45 (m, 2H), 3.01 (ddd, *J* = 3.0, 5.0, 13.0 Hz, 1H), 3.1(ddd, *J* = 2.1, 7.7, 11.2 Hz, 1H), 3.30-3.40 (ddd, *J* = 3.6, 6.8, 12.6 Hz, 1H), 3.47 (ddd, *J* = 2.5 Hz, 1H), 4.02 (ddd, J = 3.9, 7.4, 13.0 Hz, 1H), 4.42 (AB system, d, *J* = 12.0 Hz, 1H), 4.52-4.59 (ddd, *J* = 3.2, 6.5, 13.0 Hz, 1H), 4.64 (AB, d, *J* = 12.7 Hz, 1H), 7.26-7.36 (m, 5H)

^{13}C NMR (100 MHz): δ 17.9 (CH_3), 26.1 (CH_3), 27.5 (CH), 31.3 (CH_2), 31.6 (CH_2), 33.2 (CH_2), 33.9 (CH_2), 53.2 (CH), 56.2 (CH), 61.5 (CH), 70.7 (CH), 71.3 (CH_2), 71.4 (C), 72.2 (CH), 127.7 (CH), 128.2, 128.4 (CH), 138.9 (C).

MS (ESI): *m/z* 332.2 (MH^+, 100%)



125

O-((1*S*,2a*R*,3*R*,5*S*,5a*R*,8a*S*)-3-(benzyloxy)-7-hydroxy-5,7-dimethyldecahydro-pyrrolo[2,1,5-*de*]quinolizin-1-yl) *S*-methyl carbonodithioate

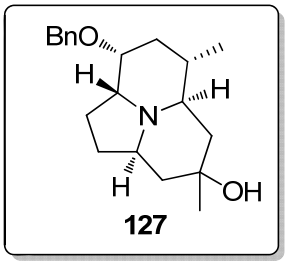
In a dry, Ar-flushed flask, was weighed out 30% KH in mineral oil (40.0 mg, 0.302 mmol) and washed 3 times with pentane. A solution of alcohol **124** (50.0 mg, 0.151 mmol) was prepared in dry THF (1.0 mL) and added dropwise at 0 °C. The suspension was stirred for an additional 30 min at room temperature after the addition was complete. The flask was re-cooled to 0 °C and CS_2 (0.025 mL, 0.453 mmol) and MeI (0.028 mL, 0.453 mmol) were added sequentially at 0°C with stirring at room temperature for 15 min in between additions. Finally, the reaction mixture was quenched with 10% NaOH solution and diluted in ether. The aqueous phase was extracted

with ether and the combined organic phase was dried over Na_2SO_4 and evaporated *in vacuo* to obtain the crude product which was purified over silica gel (2.0% MeOH saturated with NH_3 in DCM) to recover 38.0 mg of pure xanthate **125.**

^{1}H NMR (400 MHz): δ 0.89 (d, *J* = 7.0 Hz, 3H), 1.13-1.38 (m, 6H), 1.50-1.76 (m, 3H), 1.79-1.82 (ddd, *J* = 3.5, 3.5, 14.0Hz, 1H), 2.36-2.46 (m, 1H), 2.51-2.62 (m, 4H), 3.07 (ddd, *J* = 3.2, 5.8, 13.0 Hz, 1H), 3.15-3.22 (ddd, *J* = 1.6, 6.9, 12.0.8 Hz, 1H), 3.5 (ddd, *J* = 2.5 Hz, 1H), 3.75-3.82 (ddd, *J* = 3.6, 6.5, 12.4 Hz, 1H), 4.47 (d, AB system , *J* = 12.5 Hz, 1H), 4.67 (d, AB system, *J* = 12.5 Hz, 1H), 5.96 (ddd, *J* = 2.6, 6.6, 10.1 Hz, 1H), 7.28-7.39 (m, 5H)

^{13}C NMR (100 MHz): δ 17.9 (CH_3), 19.2 (CH_3), 25.9 (CH), 27.3 (CH), 30.9 (CH_2), 31.4 (CH_2), 32.9 (CH_2), 53.1 (CH), 56.2 (CH), 59.8 (CH), 71.3 (CH_2), 71.6 (CH), 82.3 (CH), 127.8 (CH), 128.3 (CH), 128.5 (CH), 138.6 (CH), 215.3 (C).

MS (ESI): *m/z* 422.2 (MH^+, 100%).



127

(2a*R*,5a*R*,6*S*,8*R*,8a*R*)-8-(benzyloxy)-4,6-dimethyldecahydro-pyrrolo[2,1,5-*de*]quinolizin-4-ol

To a solution of Bu_3SnH (0.025 ml, 0.031 mmol) in dry toluene (0.450 mL), was added AIBN (2.0 mg) and the contents were heated upto 70°C. At this temperature, a solution of xanthate **125** (0.015 mg, 0.0309 mmol) in dry toluene (0.500 mL) was added drop wise over 45 min. The resultant reaction mixture was refluxed for 3.5 h after which it was allowed to cool down to room temperature. Purification of the crude reaction mixture over silica gel (2% MeOH saturated with NH_3 in DCM) gave the pure deoxygenated product **127** (5.0 mg).

Note: Sample contaminated with some Sn-residue

^{1}H NMR (400 MHz): δ 0.86 (d, *J* = 7.0 Hz, 3H), 1.05-1.69 (m, 10 H), 1.79 (ddd, *J* = 3.5. 3.5, 14.0 Hz, 1H), 1.87-1.98 (m, 1H), 2.00-2.14 (m, 1H), 2.35-2.46 (m,1H), 2.86 (ddd, *J* = 1.5, 6.5,

9.0 Hz, 1H), 3.10 (ddd, *J* = 3.2, 5.5, 13.1 Hz, 1H), 3.30 (ddd, *J* = 3.8, 7.3, 11.9 Hz, 1H), 3.5 (q, *J* = 2.5 Hz, 1H), 4.45 (AB, d, *J* = 12.3 Hz, 1H), 4.64 (AB, d, *J* = 12.4 Hz, 1H), 7.27-7.36 (m, 5H)

^{13}C NMR (100 MHz): δ 13.8 (CH_3), 15.7 (CH_2), 18.0 (CH_3), 23.2 (CH_2), 27.2 (CH), 27.4 (CH_2), 30.8 (CH_2), 31.8 (CH_2), 40.8 (C), 54.3 (CH), 55.5 (CH), 56.9 (CH), 71.3 (CH_2), 72.3 (CH), 127.6 (CH), 128.3 (CH), 128.2 (CH), 137.0 (C)

MS (ESI): *m/z* 316.2 (MH^+, 100%)