Total Synthesis of Alstolactine A & Synthetic Studies Towards Members of Akuammiline Alkaloids

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ÉCOLE POLYTECHNIQUE
FÉDÉRALE DE LAUSANNE

À mon père.

« Le succès c'est d'aller d'échec en échec

sans perdre son enthousiasme. »

Winston Churchill.

« La vie est courte, mais un sourire

ne prend qu'une seconde. »

Proverbe Cubain.

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Abstract

The work presented in this thesis focuses on the synthesis of monoterpene indole alkaloids.

The first part describes the development of a general methodology to provide an enantioenriched platform, useful for the convergent synthesis of Akuammiline alkaloids. Despite a series of attempts using chiral phosphoric acids, the enantioselective desymmetrization of meso-1,3-diones turned out to be complex and was unfortunately unsuccessful. The second part details our first approach toward the total synthesis of (±)-alstolactine A, (±)-alstolactine B and (±)-alstolactine C. A robust eighteen-step sequence was developed, however, the numerous issues we encountered while attempting to complete the synthesis led us to re-evaluate our strategy.

The third part of this thesis details the 22 steps synthesis of (±)-alstolactine A from commercially available starting materials. Our approach involves: a) creation of a quaternary stereocenter C7 at an early stage; b) rapid build–up of the first γ-lactone; c) diastereoselective azidolactonization; d) [Ni(cod)2]-mediated intramolecular cyclization to construct the azabicyclo[3.3.1]nonane bridged system and e) formation of the last γ-lactone via epoxide opening. Finally, the fourth and fifth parts describe the synthetic studies toward various members of the Akuammiline family: (±)-alstolactine B and (±)-alstolactine C and the possibilities to reach (±)-scholarisine K, (±)-scholarisine L and (±)-scholarisine M starting from an advanced intermediate from our strategy.

Keywords

Total synthesis, indole alkaloids, alstolactine A, alstolactine B, alstolactine C, scholarisine K, scholarisine L, scholarisine M, enantioselective desymmetrization, heteroannulation, diastereoselective azidolactonization, nickel-mediated cyclization

Résumé

Ce travail de thèse porte sur la synthèse d'alcaloïdes indoliques monoterpéniques.

Le premier chapitre décrit le développement d'une méthodologie permettant l'obtention d'une plateforme énantio-enrichie utile pour la synthèse convergente d'alcaloïdes appartenant à la famille des *Akuammilines*. Malgré de nombreuses tentatives impliquant l'utilisation d'acides phosphoriques chiraux, la désymétrisation de composés méso-1,3 dicétones s'est avérée complexe et n'a malheureusement pas abouti. Le deuxième chapitre décrit la première approche adoptée afin de réaliser la synthèse racémique de l'(±)-alstolactine A, (±)-alstolactine B et (±)-alstolactine C. Une séquence robuste de 18 étapes a ainsi été développée, malheureusement, les nombreux problèmes rencontrés pour terminer cette synthèse nous ont amené à reconsidérer notre stratégie initiale.

Le troisième chapitre de cette thèse détaille la synthèse totale de l'astolactine A en 22 étapes à partir de la 1,3-cyclohexanedione. Notre approche comprend : a) la création d'un stéréocentre quaternaire à un stade précoce; b) la construction rapide de la première γ-lactone; c) une azidolactonisation diastéréosélective; d) une cyclisation intramoléculaire induite par du [Ni(cod)$_2$] permettant la formation d'un système ponté de type azabicyclo[3.3.1]nonane et e) la construction de la dernière γ-lactone via l'ouverture d'un époxyde. Enfin, les quatrième et cinquième parties décrivent les études synthétiques portant sur différents membres de la famille des *Akuammiline*: (±)-alstolactine B et (±)-alstolactine C et les possibilités de parvenir aux (±)-scholarisine K, (±)- scholarisine L et (±)-scholarisine M à partir d'un intermédiaire avancé de notre stratégie.

Mots-clés :

Synthèse totale, alcaloïdes indoliques, alstolactine A, alstolactine B, alstolactine C, scholarisine K, scholarisine L, scholarisine M, désymétrisation énantiosélective, hétéroannulation, azidolactonisation diastéréosélective, addition-1,4 catalysée au nickel.

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List of Abbreviations

AAC	Azide-Alkyne cycloaddition
Ac	Acetyl
AD	Asymmetric dihydroxylation
Aq.	Aqueous
Ar	Aryl
atm	Atmosphere
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
brsm	Based on recovery of starting material
Bu	Butyl
cacld	Calculated
Cat.	Catalytic
Conc.	Concentrated
COSY	Correlation spectroscopy
Cy	Cyclohexyl
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	Dichloroethane
DCM	Dichloromethane
DEAD	Diethyl azidocarboxylate
DEPT	Distortionless enhancement by polarization transfer
DFT	Density functional theory
DIBAL	Diisobutylaluminium hydride

DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMF	Dimethylformamide
DMP	Dess-Martin periodinane
DMSO	Dimethylsulfoxide
DPPA	Diphenyl phosphoryl azide
dppp	1,3-Bis(diphenylphosphino)propane
d.r.	Diastereomeric ratio
EDC	*N*-Ethyl-*N*'-(3-dimethylaminopropyl)carbodiimide hydrochloride
ee	Enantiomeric excess
equiv.	Equivalents
ESI	Electron-spray ionization
Et	Ethyl
FCC	Flash column chromatography
GPP	Geranyl pyrophosphate
HFIP	Hexafluoroisopropanol
HMBC	Heteronuclear multiple bond correlation
HMDS	Hexamethyldisilazane
HMPA	Hexamethylphosphoramide
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single quantum coherence
HWE	Horner-Wadsworth-Emmons
***i*Pr**	Isopropyl
IR	Infrared

LDA	Lithium diisopropylamide
mCPBA	*meta*-Chloroperbenzoic acid
Me	Methyl
m.p.	Melting point
Ms	Mesyl
MS	Molecular sieves
NBS	*N*-Bromosuccinimide
NMO	*N*-Methylmorpholine oxide
NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser Spectroscopy
Nu	Nucleophile
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
PE	Petroleum ether
Ph	Phenyl
Phen	Phenantroline
Pin	Pinacol
Rf.	Retention factor
rt	Room temperature
IR	Infrared
LDA	Lithium diisopropylamide
mCPBA	*meta*-Chloroperbenzoic acid
Me	Methyl
m.p.	Melting point

Ms	Mesyl
MS	Molecular sieves
NBS	*N*-Bromosuccinimide
NMO	*N*-Methylmorpholine oxide
NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser Spectroscopy
Nu	Nucleophile
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
PE	Petroleum ether
Ph	Phenyl
Phen	Phenantroline
Pin	Pinacol
Rf.	Retention factor
rt	Room temperature
S_N	Nucleophilic substitution
***t*Bu**	*tert*-Butyl
TBA	Tetrabutylammonium
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
THF	Tetrahydrofuran
Tf	Triflate
TFA	Trifluoroacetic acid
TLC	Thin-layer chromatography

TMS	Trimethylsilyl
Tol	Tolyl
Ts	Tosylate

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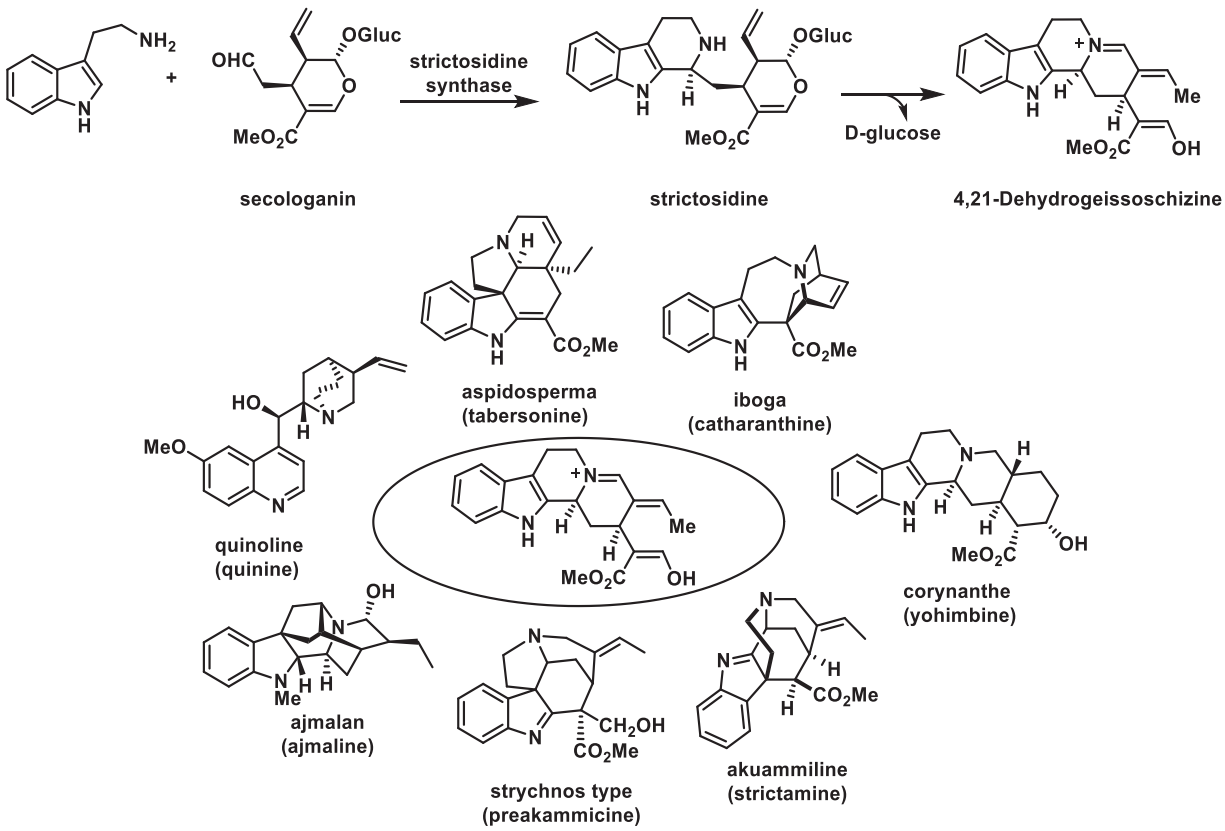
CHAPTER 1 - Introduction

For ages plants and fungi were used to treat and cure different diseases. Constant development in isolation and structure elucidation allowed chemists to identify myriad of bioactive compounds. The poor biomass of natural products in Nature motivates chemists to design strategy and methodology to achieve their synthesis. One of the main classes of these natural products is the monoterpene indole alkaloids. Due to their elegant polycyclic molecular architectures, their structural diversity and their biological activities, indole alkaloids have been investigated by chemists and biologists over the last century and are of primary interest in our laboratory.

Monoterpene indole alkaloids can be classified in many different families which are related to their structural diversity. Despite this vast diversity, these alkaloids are all biosynthesized from the same starting point: a Pictet-Spengler reaction between tryptamine and secologanin to give strictosidine. This reaction is catalyzed by an enzyme called strictosidine synthase and marks the beginning of the biosynthetic pathway. The biosynthetic power of strictosidine is revealed after the deglucosylation. Subsequent hydrolysis of acetal and iminium formation afford 4,21-dehydrogeissoschizine. This primarily formed aglucon cannot be isolated and undergoes subsequent cyclizations, leading to diverse skeletons of polycyclic natural products: monoterpene indol alkaloid.[1]

[1] a)O'Connor, S. E.; Marech, J. J. *Nat. Prod. Rep.*, **2006**, *23*, 532. b) Saxton, E. J. *Nat. Prod. Rep.* **1997**, *14*, 559.c) Szabo, L. F. *Molecules* **2008**, *13*, 1875. d)Bandini, M.; Eichholzer, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 9608.



Scheme 1: Major classes of terpene indole alkaloids derived from geissoschizine

Among this family, akuammiline, represented in scheme 1 by strictamine, showed an interesting and complex molecular architecture. Over 30 members of this family with different ring connectivities have been isolated to date.

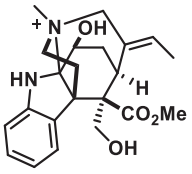
I. Akuammiline Alkaloids

I.1. History & structure

Akuamma, one of the native names of the tree *Picralima klaineana* found in tropical Africa (Ghana, Benin, Ivory Coast, Nigeria etc), serves as the etymological origin of the akuammiline alkaloid group.[2] The dried seeds from this plant are used in traditional medicine throughout West Africa, particularly in Ghana, Ivory Coast and Nigeria. The seeds are crushed or powdered and taken orally. They are mainly used for the treatment of both malaria and diarrhea and also as a painkiller.

[2] Henry, T. A.; Sharp, T. M. *J. Chem. Soc.* **1927**, 1950.

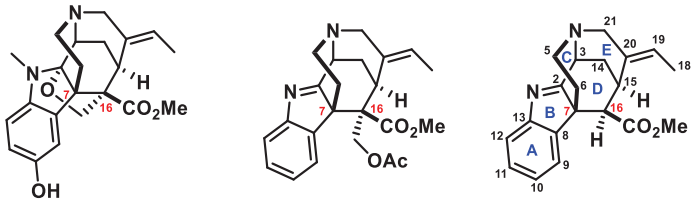
Echitamine was the first akuammiline alkaloid to be isolated by Gorup-Besanz[3] in 1875 and described by Hesse[4] in 1879, although, the first reliable data on this alkaloid were provided by Goodson and Henry in 1925.[5] Indeed, they prepared and analyzed several crystalline derivatives and furnished evidence of the presence of an indole ring and a carbomethoxy group. Tremendous upsurge of interest on the structure of echitamine led chemists to be interested on this exceptional structure.



echitamine

Scheme 2: Echitamine: first isolated akuammiline alkaloid

Two years later, in 1927, Henry and Sharp isolated and characterized four different alkaloids from akuamma seeds and named the first structure they elucidated akuammine, referring to the akuamma tree.[6] From these seeds, the second indole alkaloid akuammilineserved as an eponym of a whole natural product family: the akuammiline alkaloids.[7] Nevertheless, the class of akuammiline alkaloids is best represented by strictamine which was isolated from the plant *Rhazya stricta* in 1966.[8] A structural feature of this class of monoterpene indole alkaloids is the presence of a C7-C16 bond that creates a rigid and cage-like framework made of three six-membered rings and one eight-membered ring (scheme 3). Moreover, this C7-C16 connection generates two six-membered rings (C and E) in a boat conformation. The central system also exhibits an *E*-configured ethylidene substituent at C20 and a methyl ester at C16 which are common in all akuammiline compounds.[9]



akuammine akuammiline strictamine

Scheme 3: Isolation of 3 new alkaloids in 1927, akuammine, akuammiline and strictamine.

[3] Gorup-Besanez, v. Justus Liebigs Ann. Chem. **1875**, 176, 88.
[4] Hesse, O. *Ber. Dtsch. Chem. Ges.* **1879**, *11*, 1546.
[5] Goodson, J. A.; Henry, T. A. *J. Chem. Soc.*, *Trans*. **1925**, *127*, 1640.
[6] Henry, T. A.; Sharp, T. M. *J. Chem. Soc*. **1927**, 1950.
[7] Henry, T. A. *J. Chem. Soc*. **1932**, 2759.
[8] Schnoes, H. K.; Biemann, K.; Mokry, J.; Kompis, I.; Chatterjee, A.; Ganguli, G. *J. Org. Chem*. **1966**, *31*, 1641.
[9] Eckermann, R.; Gaich, T.; *Synthesis*, **2013**, *45*, 2813.

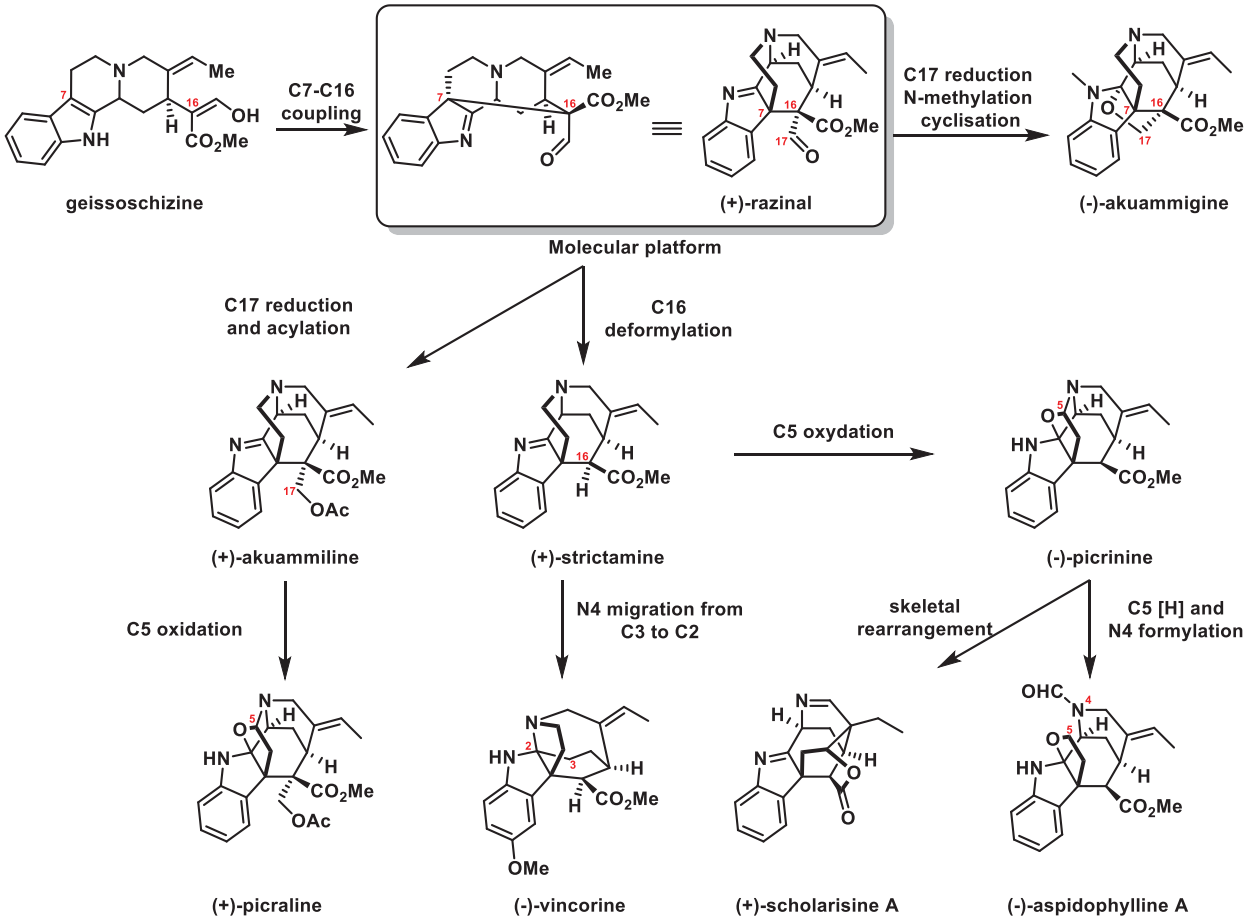
Apart from their unique and intriguing structure, akuammiline alkaloids interested scientific community due to their broad range of biological activities including anticancer, anti-inflammatory and anti-malarial activities.

I.2. Biosynthesis

As previously mentioned, akuammiline alkaloids derive from geissoschizine.[10] Indeed, (+)-razinal is generated by the oxidative coupling of C7 and C16 of geissoschizine. This compound is a platform for the biosynthesis of all the other alkaloids from akuammiline family.[11,12]

As shown in scheme 4, when razinal undergoes a C16 deformylation (+)-strictamine is generated. Whereas reduction/acylation of the aldehyde moiety (C17) of razinal affords (+)-akuammiline. At this stage, in both transformations the indolenine remains untouched. However, starting from strictamine, a C5 oxidation leads to (-)-picrinine whereas a N4 migration from C3 to C2 leads to (-)-vincorine. This time, in both cases, the indolenine moiety reacted to give the indoline. As for strictamine, picrinine is a platform for the biosynthesis of different akuammiline alkaloids. On one hand, after imine formation, indolenine regeneration and construction of the lactone moiety, picrinine can be converted into scholarisine A. On the other hand, a C5 reduction and a N4 formylation of picrinine leads to aspidophylline A.

[10] O'Connor, S. E.; Marech. J. J.; *Nat. Prod. Rep.*, 2006, **23**, 532-547.
[11] Eckermann, R.; Gaich, T.; *Synthesis*, **2013**, *45*, 2813.
[12] Smith, J. M.; Moreno, J.; Boal, B. W.; Garg, N. K.; *Angew. Chem. Int. Ed.* **2014**, *53*, 2.



Scheme 4: Biosynthesis of Akuammiline family starting from geissoschizine

As shown in scheme 4, the akuammiline framework, characterized by a C-C bond between carbons C7 and C16, leads to very complex molecular architectures. It can explain why the first total synthesis of an akuammiline alkaloid was not completed until 2009, when the group of Qin synthesized vincorine, while the first akuammiline alkaloid was isolated in 1875.

I.3. Synthesis of akuammiline indole alkaloids

Since the first synthesis of vincorine reported by Qin *et all* in 2009[13], efforts from different research groups led to the development of synthetic strategies. These progresses allowed the racemic and/or enantioselective synthesis of vincorine (by Ma and MacMillan[14]), scholarisine A (by Smith and Snyder),

[13] Zhang, M.; Huang, X.; Shen, L.; Qin, Y. *J. Am. Chem. Soc.* **2009**, *131*, 6013.
[14] Horning, B. D.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2013**, *135*, 6442.

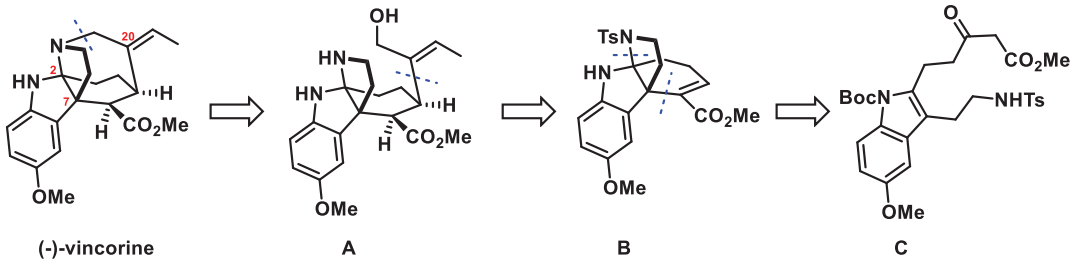
strictamine (by Zhu and Garg and many other), calophyline A (by Zu[15]), cathafoline (Garg[16]), picrinine (by Garg) and finally aspidophylline A (by Garg, Ma, Zhu and Yang). Some strategies are presented below.

I.3.1. **Synthesis of vincorine**

Vincorine consists of a pentacyclic structure with 4 stereogenic centers including a quaternary center at C7 position and a *N,N*-aminal moiety. Moreover, a methoxy group is present at C10 position.

Qin's synthesis

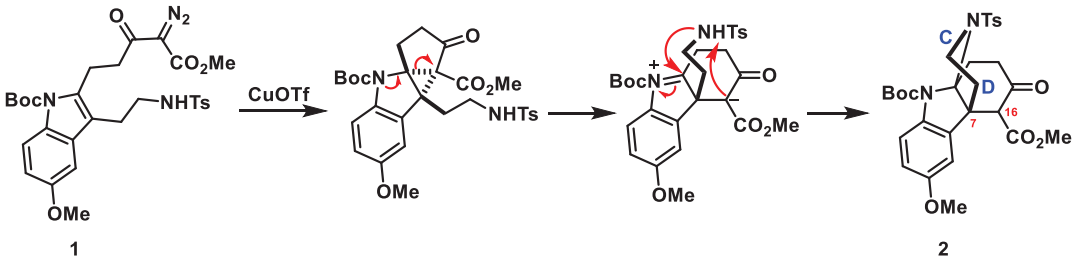
The first racemic synthesis of vincorine was achieved by Qin and co-workers in 2009 with an overall yield of 1% over 31 steps.[13] As shown in the retrosynthetic plan (scheme 5), the target was obtained *via* a ring closing from the secondary amine and the primary alcohol. The *E*-configured alkene substituent at C20 can be generated starting from the α,β-unsaturated ester **B**. The formation of C7 quaternary center and the pyrolidinoindoline scaffold were achieved via a three-step one-pot cascade reaction starting from **C**.



Scheme 5: Retrosynthesis of (-)-vincorine by Qin.

This three-step one-pot cascade reaction consists of a copper-catalyzed intramolecular cyclopropanation, a ring opening and a ring closure. As described in scheme 6, starting from diazo compound **1**, the indole cyclopropanation was initiated by CuOTf. Fragmentation of the unstable ring generated an indolinium and a 1,3 dicarbonyl fonctions. Subsequent trapping of the iminium by tosyl amine led to the desired product **2** in 52% yield. This cascade reaction allowed the formation of rings C and D in a single step. Further carbonyl reduction, mesylation and elimination led to α,β-unsaturated ester **B**.

[15] Li, G.; Zu, L. *Angew. Chem. Int. Ed.* **2016**, *55*, 1.
[16] Picazo, E.; Morrill, L.; Garg, N. K. *J. Am .Chem. Soc.* **2018**, *140*, 6483.

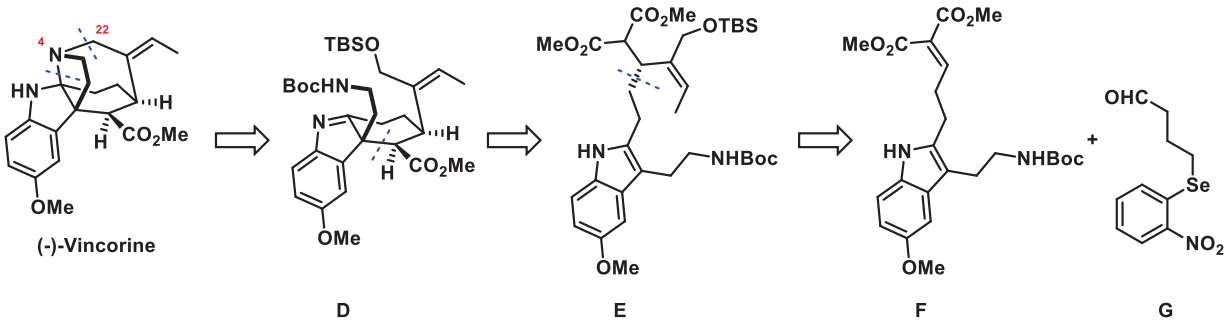


1 2

Scheme 6: Key three-step one-pot cascade reaction.

Ma's synthesis

In 2012, Ma and co-workers reported the first asymmetric synthesis of (-)-vincorine in 5% overall yield over 18 steps starting from 5-methoxytryptamine.[17] As shown in the retrosynthetic plan (scheme 7), first disconnection of N4-C21 and subsequent disconnection of C2-N4 of vincorine could provide tricyclic compound **D**. This latter could be generated from **E** *via* intramolecular oxidative coupling between indole and malonate moieties. Olefin **E** could be prepared by organocatalytic Michael addition of aldehyde **G** to **F**.

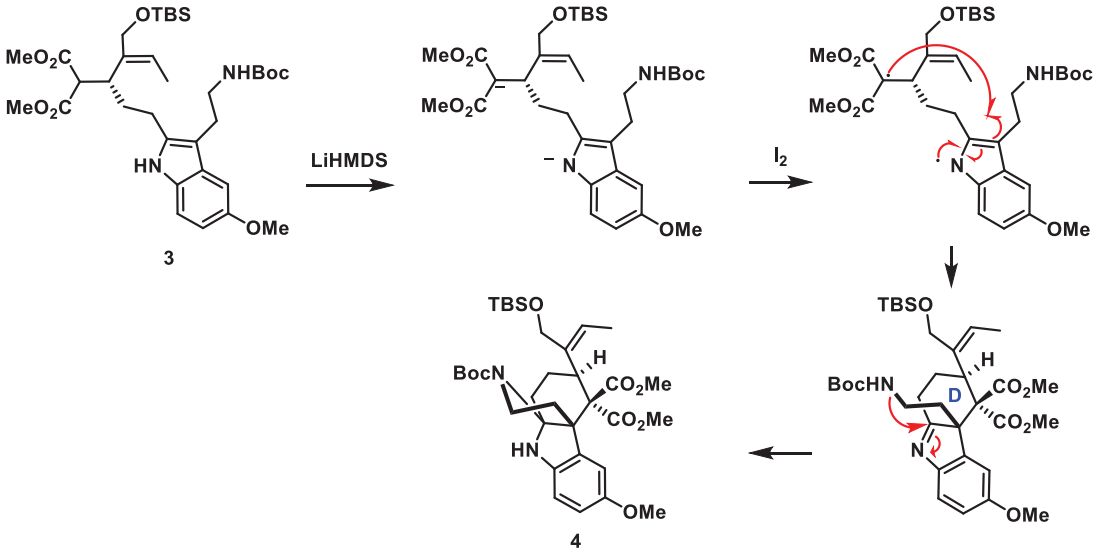


D E F G

Scheme 7: Ma's retrosynthetic pathway for (-)-vincorine.

As shown in scheme 8, the key step of this sequence is the intramolecular oxidative coupling. The dianion is generated using LiHMDS. After addition of iodine the dianion is presumably oxidized into a diradical. Generation of indolenine allowed the formation of the C7 radical which recombines with the dicarbonyl radical to form cycle D. Finally, addition of the tryptamine nitrogen to the previously generated imine allowed the formation of the C ring.

[17] Zi, W.; Xie, W.; Ma, D. *J. Am. Chem. Soc.* **2012**, *134*, 9126.



Scheme 8: Ma's intramolecular oxidative coupling.

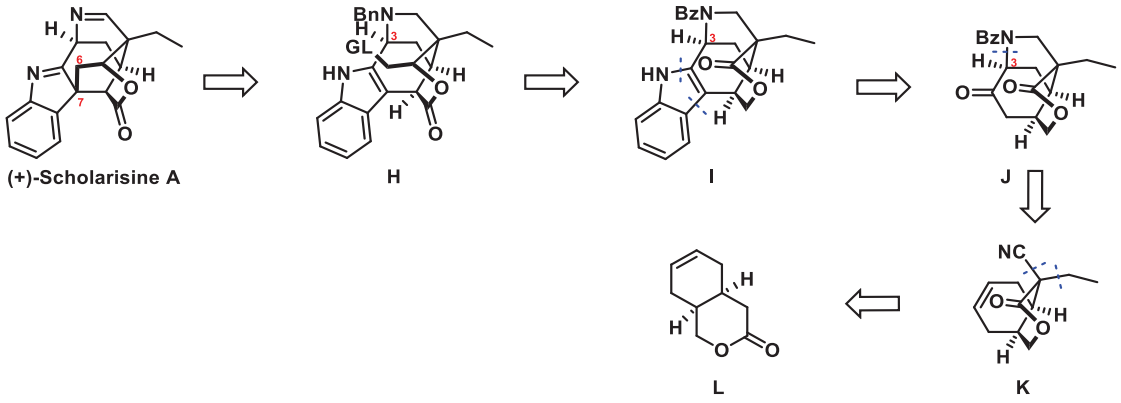
I.3.2. **Synthesis of scholarisine A**

As described in the biosynthesis, scholarisine A is generated via a skeletal rearrangement of picrinine. This alkoaloid contains 6 fused rings and six stereogenic centers, including two quaternary centers. This scaffold also contains a bridged lactone, an aliphatic imine, and an indolenine core.

Smith's synthesis:

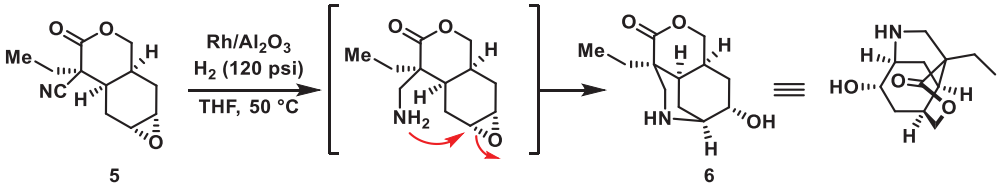
In 2012, Amos B. Smith and co-workers reported the first enantioselective total synthesis of (+)-scholarisine A.[18] This work was achieved in a 21 steps sequence with an overall yield of 5.6%. As shown in the retrosynthetic plan below (scheme 9), C7-C6 carbon bond could be generated via intramolecular alkylation reaction starting from intermediate **H**. This latter could be obtained from lactone **I** via functional group modifications. The indole moiety can be generated via Fischer indole synthesis from tricyclic fused ring **J**. The latter could be formed *via* a reductive cyclization cascade from intermediate **K** which might be itself formed starting from bicyclic lactone intermediate **L**.

[18] Adams, G. L.; Carroll, P. J.; Smith, A. B. *J. Am. Chem. Soc.* **2013**, *135*, 519.



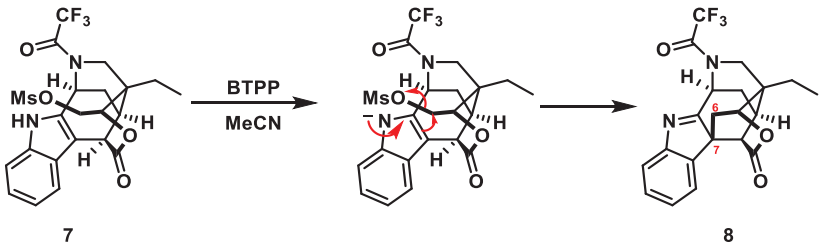
Scheme 9: Smith's retrosynthetic pathway for (+)-scholarisine A

The first key step of this total synthesis is the reductive cyclization cascade using rhodium on alumina to form the N-C3 bond with concomitant generation of the right part of this complex scaffold. As shown in scheme 10, after nitrile reduction, the newly generated amine undergoes intramolecular epoxide opening resulting in the formation of tricyclic compound **6** in 64% yield. Moreover, the epoxide opening allowed the formation of the secondary alcohol, which could be used later for the installation of the indole moiety.



Scheme 10: Smith reductive cyclization cascade.

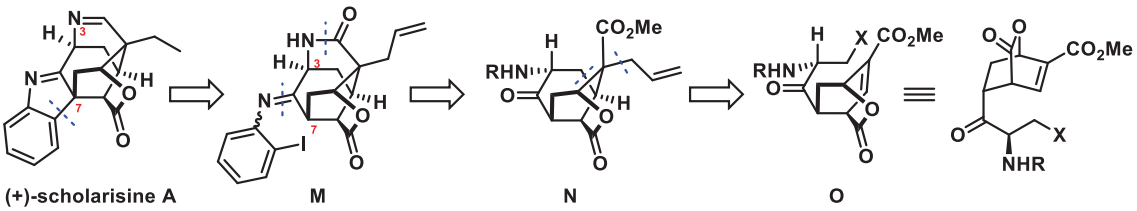
The second key step, leading to the complete scaffold of (+)-scholarisine A, was achieved *via* an intramolecular alkylation. As shown in scheme 11, treating intermediate **7** with *tert*-butyliminotri(pyrrolidino)phosphorene (BTPP), which acted as base, allowed a selective deprotonation of the indole nitrogen. Formation of the indolenine moiety via delocalization of the electron density led to the substitution of the mesyl group and to the generation of the desired quaternary center (C7).



Scheme 11: Smith C7 quaternary stereocenter formation.

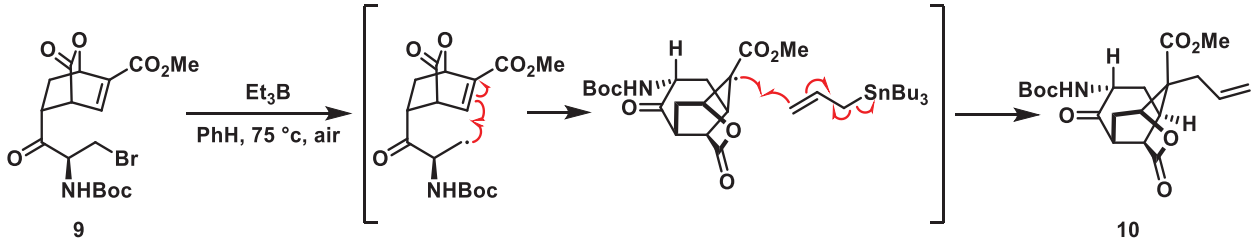
Snyder's synthesis:

The second asymmetric synthesis of (+)-scholarisine was reported in 2013 by Snyder *et al*.[19] The synthesis was achieved in 14 steps from a known α,β-unsaturated ester (15 steps from commercially available material). As shown in the retrosynthetic plan (scheme 12), the target alkaloid could be formed *via* a C-H arylation to attach the indolenine fragment directly to a near fully functionalized core. The N-C3 bond could be generated *via* epimerization/lactamization sequence starting from **N**. Finally, intermediate **N** could be generated starting from **O** *via* a tandem radical cyclization/keck allylation.



Scheme 12: retrosynthetic pathway of (+)-scholarisine A by Snyder.

As shown in scheme 13, the first key step of this sequence involves radical chemistry to build the tetracyclic lactam. The use of air and Et_3B as radical initiator allowed the homolysis of the carbon-bromide bond. The resulting primary radical underwent a 6-*exo*-trig cyclization affording a more stable tri-substituted α-carbonyl radical, which was then trapped in situ with allyltributylstannane to give tricycle **10** with full diastereoselectivity.

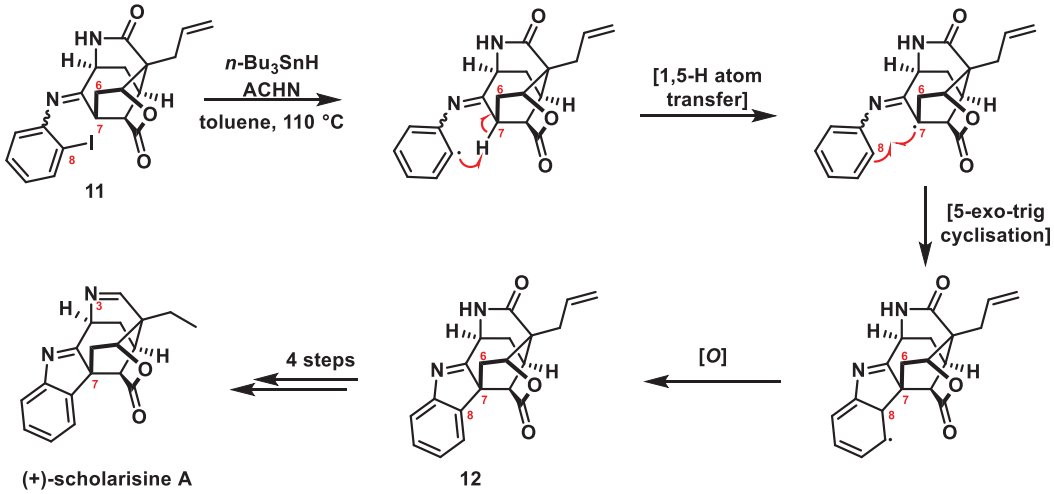


Scheme 13:Snyder tandem radical cyclization/keck allylation.

Further functionalization of intermediate **10** through C3-epimerization, intramolecular lactamization, and iodoaniline condensation provided imine **11** (scheme 14). This latter was used without further purification for next step.

[19] Smith, M. W.; Snyder, S. A. *J. Am. Chem. Soc.***2013**, *135*, 12964.

The second key step of this total synthesis consists of a C-H arylation which involves a second radical cascade to forge the polycyclic core. The use of tributyltin hydride allowed the generation of the aryl radical which underwent a 1,5-hydrogen transfer. The resulting tertiary radical underwent a 5-*exo*-trig cyclization to form a C7-C8 linkage. Finally, oxidation followed by aromatization led to desired spiroindolenine **12**.



Scheme 14: Snyder late stage C-H arylation.

Subsequent reactions (4 steps) allowed the generation of the ethyl group and the imine to provide desired (+)-scholarisine A.

I.3.3. **Synthesis of picrinine**

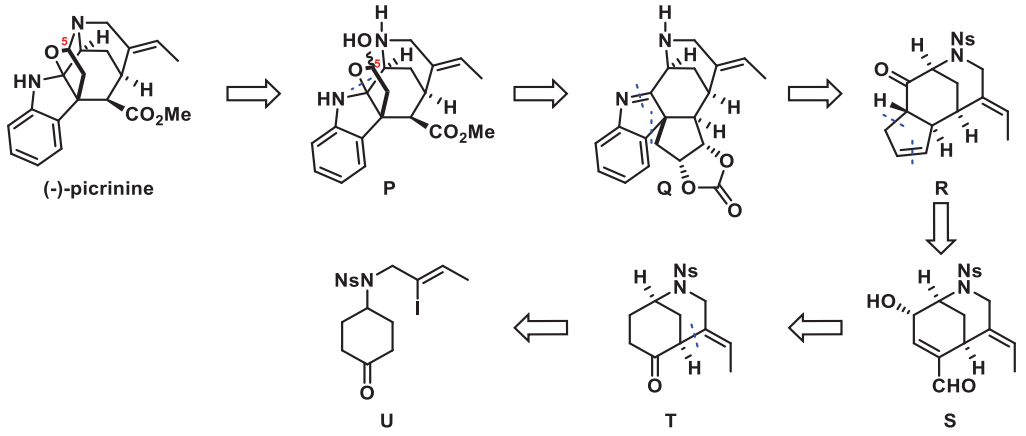
Picrinine is a highly complex cage like molecule which contains a furoindoline core fused to a densely functionalized cyclohexyl ring. This alkaloid possesses six stereogenic centers, five of them are contiguous, and contains two *N,O*-acetal linkages within its polycyclic skeleton. To the best of our knowledge, the only synthesis reported so far was developed by Garg and co-workers in 2014.[20]

Garg's synthesis:

As shown in scheme 15, Garg and co-workers envisaged to install the bis(*N,O*-acetal) linkage at the late stage of the synthesis starting from **Q**. The latter could be formed via a Fischer indolization reaction between phenylhydrazine and tricyclic ketone **R**. Compound **R** could be generated from enal **S**, which could be in turn

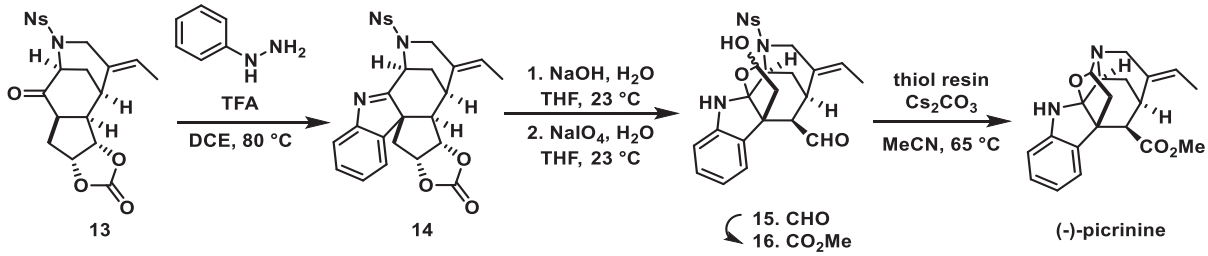
[20] Smith, J. M.; Moreno, J.; Boal, B. W.; Garg, N. K. *J. Am. Chem. Soc.***2014**, *136*, 4504.

generated from **T**. Finally, the bridged bicycle could be formed via a Pd-catalyzed enolate cyclization starting from **U**.



Scheme 15: retrosynthetic pathway of picrinine by Garg.

The first key step of this sequence is the Fischer indolization reaction in order to forge the natural product skeleton. As shown in scheme 16, when carbonate intermediate **13** was treated with phenylhydrazine and TFA at 80 °C, the desired hexacyclic indolenine product was obtained in 69% yield with complete diastereoselectivity. After hydrolysis of the carbamate moiety, oxidative cleavage allowed the formation of lactol **15** in 81% yield over 2 steps. A series of delicate late-stage transformations allowed the conversion of the aldehyde moiety into the corresponding methyl ester **16** without affecting the lactol. Finally, treating the lactol/methyl ester with a solid supported thiol resin led to the bis(*N,O*-acetal) formation and provided desired (-)-picrinine, via cyclization of the presumed aminolactol.



Scheme 16: Garg late stage sequence using Fischer indolization.

The so-called “interrupted Fisher indolization” was then applied to the synthesis of various natural products of the Akuammiline family. In 2017, Garg and *all* provided an overview of this key reaction from a methodological standpoint and their efforts to apply it to the synthesis of aspidophylline, pricrinine and strictamine.[21]

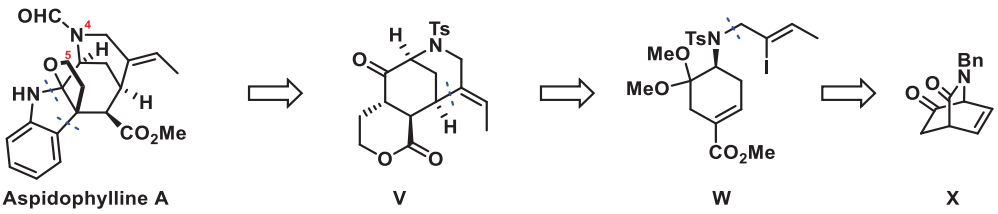
[21] Susick, R.; Morrill, L. A.; Garg, N. K. *Synlett*, **2017**, *28*, 1.

I.3.4. **Synthesis of aspidophylline A**

As described in the biosynthesis, aspidophylline A is generated from picrinine *via* a C5 reduction and a N4 formylation. This cage-like pentacyclic compound includes a highly substituted cyclohexane with 5 contiguous stereocenters and a furoindoline moiety. This alkaloid was the target of different groups during the last 5 years. In 2011, the first total synthesis of aspidophylline A was achieved by Garg and co-workers. In 2014, our laboratory reported another strategy to synthesize this naturel product. Several months later, Ma and co-worker reported a third strategy to generate this complex scaffold.

Garg's synthesis:

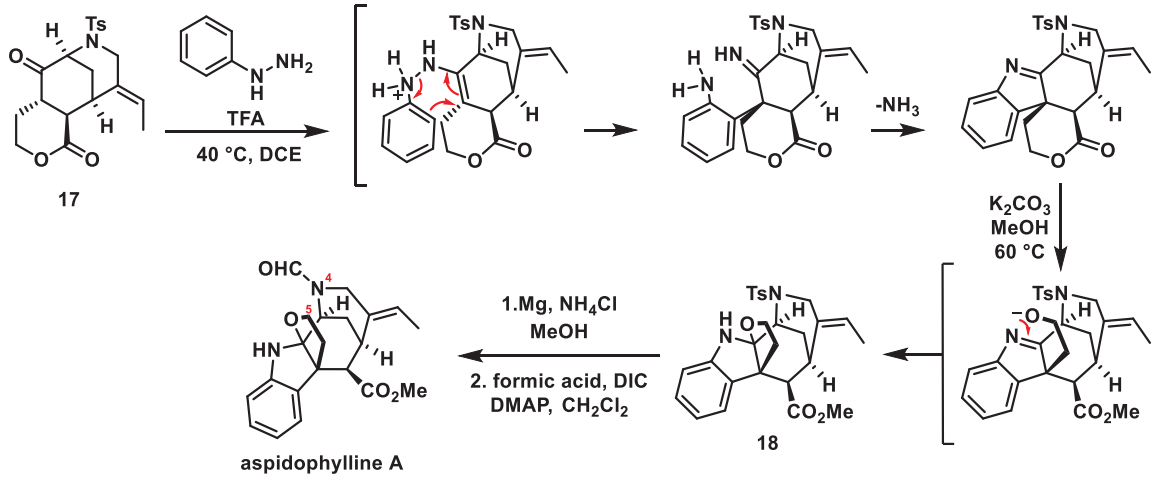
The total synthesis of aspidophylline A was reported in 2011 by Garg and co-workers *via* an 18 steps sequence and with an overall yield of 5.2%.[22] As shown in scheme 17, aspidophylline A could be generated from key intermediate **V** via an interrupted Fischer indole synthesis as a key step. This latter key intermediate could be generated via a regioselective Heck cyclization and a series of transformations starting from vinyl iodide **W**. This vinyl iodide could be in turn generated from bicyclic lactam **X** in 5 steps.



Scheme 17: Retrosynthetic pathway of aspidophylline A by Garg.

The key step of this total synthesis is presented below (scheme 18). The Fischer indolization was conducted starting from key intermediate **17,** and phenylhydrazine. [3,3]-Sigmatropic rearrangement and subsequent elimination of ammonia provided indolenine moiety which was subjected to potassium carbonate at 60 °C. One-pot lactone methanolysis followed by subsequent cyclization allowed the generation of desired furoindoline intermediate **18**. The whole process afforded the desired product in 70% yield. Further removal of the tosyl protecting group and N-formylation afforded aspidophylline A.

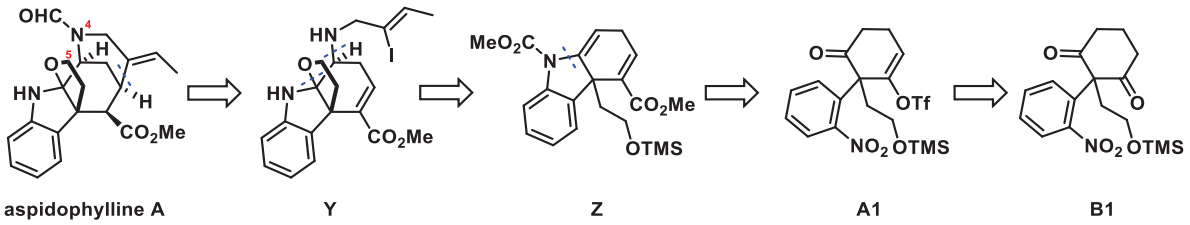
[22] Zu, L.; Boal, B. W.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, *133*, 8877.



Scheme 18: Garg key step: one-pot Fischer indolization/lactone opening/furoindoline generation.

Zhu's Synthesis:

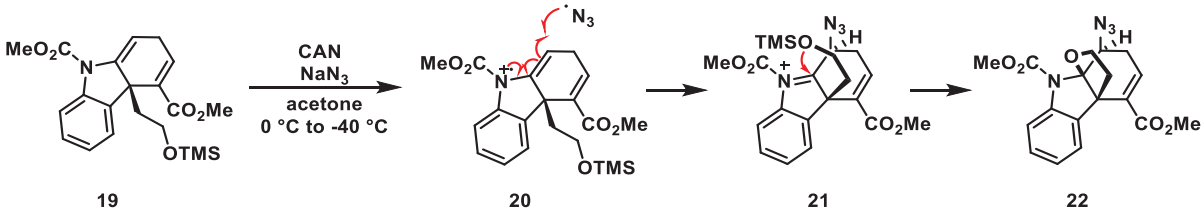
In 2014, our laboratory reported the synthesis of aspidophylline A.[23] As shown in the retrosynthetic plan, the target molecule could be generated via a 1,4-addition starting from the corresponding vinyl iodide (scheme 19). This latter could be obtained via intramolecular azidoalkoxylation from enecarbamate **Z**. This tricyclic compound could be prepared from **A1**, which could be in turn be prepared via desymmetrization of known cyclohexane-1,3-dione **B1**.



Scheme 19: Retrosynthetic pathway of aspidophylline A by Zhu.

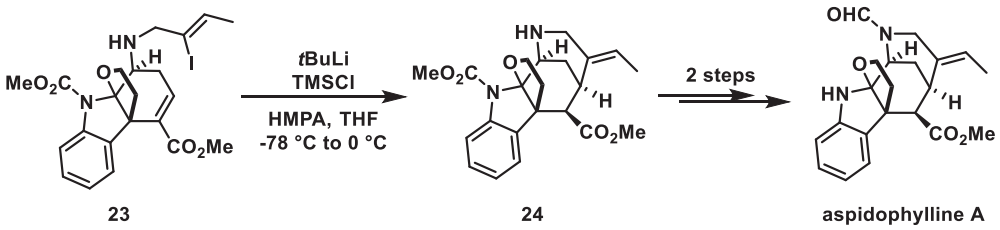
The first key step of the total synthesis is a CAN-mediated azidoalkoxylation which allows the efficient formation of the tetracyclic furoindoline core of the natural product (scheme 20). This cascade reaction allows to successfully install three contiguous stereocenters and an azido group at C3 position.[24] The reaction was performed using ceric ammonium nitrate which acted as a mild oxidant to promote the formation of radical cation **20** *via* single electron transfer. Then, this radical cation is trapped by azide, with tandem loss of another electron, to afford an indoleninium species **21**, which finally undergoes in situ cyclization to generate desired tetracyclic furoindoline core **22**.

[23] Ren, W.; Wang, Q.; Zhu, J. *Angew.Chem. Int. Ed.* **2014**, *53*, 1818.
[24] Li, Q.; Li, G.; Shi, Y. *Org. Lett.*, **2013**, *15*, 2601.



Scheme 20: Snyder tandem radical cyclization/keck allylation.

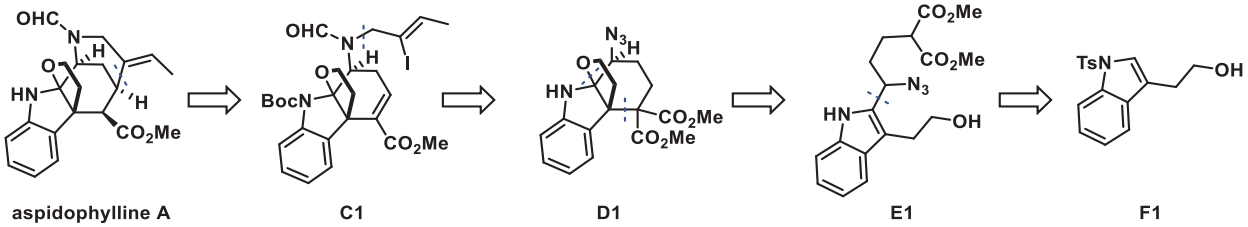
Further azide reduction under Staudinger conditions and N-monoallylation with (Z)-1-bromo-2-iodobut-2-ene provided desired intermediate **23** for the challenging intramolecular Michael addition. After intense investigations, treatment of **23** with *t*BuLi delivered pentacyclic intermediate **24** in 51% yield (scheme 21). Subsequent formylation and cleavage of the methyl carbamate afforded Aspidophylline A.



Scheme 21: Zhu intramolecular Michael addition via lithium-halogen exchange.

Ma's synthesis

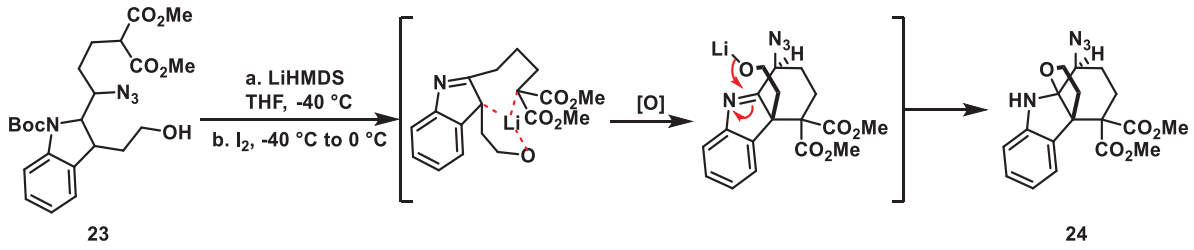
Several months after Zhu's synthesis, Ma and co-workers reported their successful approach for the synthesis of aspidophylline A.[25] They decided to build the pentacyclic ring via a Michael addition from vinyl iodide intermediate **C1** which could be obtained starting from azide **D1** (scheme 22). Similarly to vincorine, they decided to build the tetracyclic core via an intramolecular oxidative coupling. Substrate **E1** could be prepared in several steps from indol **F1**.



Scheme 22: Retrosynthetic pathway of aspidophylline A by Ma.

[25] Teng, M.; Zi, W.; Ma, D. *Angew.Chem. Int. Ed.* **2014**, *53*, 1814.

The key oxidative coupling was performed using LiHMDS as base, I_2 as oxidant and afforded compound **24** with a furoindoline moiety in 36% yield (scheme 23).



23 24

Scheme 23: Ma oxidative coupling step.

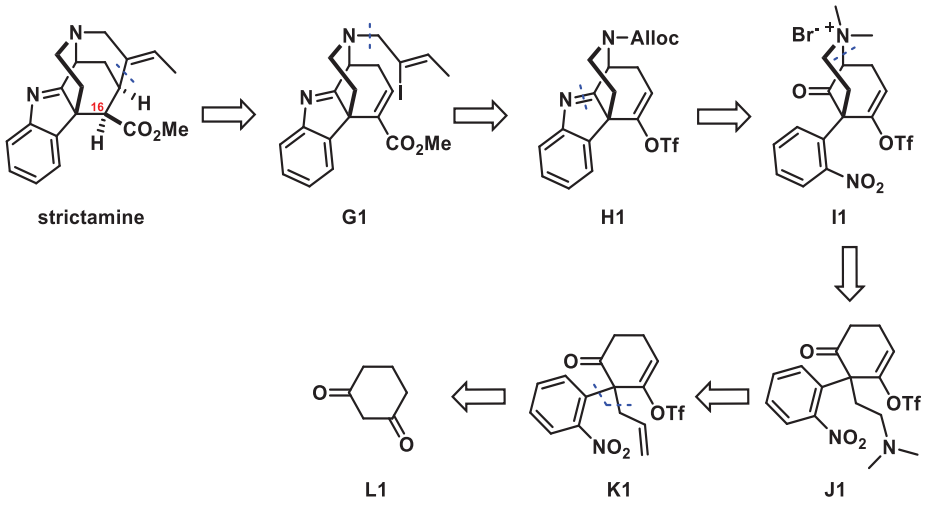
I.3.5. **Synthesis of strictamine**

Strictamine was isolated in 1965 from flowers of *Alstonis scholaris.* Its absolute configuration was determined by X-ray crystallographic analysis in 1977. Biosynthetically, it is generated via C16 deformylation starting from razinal. Strictamine bears the least functionalized carbon skeleton of all akuammiline alkaloids without lacking the signature structural motifs. This compound possesses an indolenine motif, four stereocenters and shows two parallel 1,3-bridged [3,3,1]-bicycles built from the central cyclohexane core. The total synthesis of strictamine was a challenge for many groups since its structural elucidation. Despite many syntheses of strictamine are reported in literature, only few of them will be presented bellow.

Zhu's synthesis

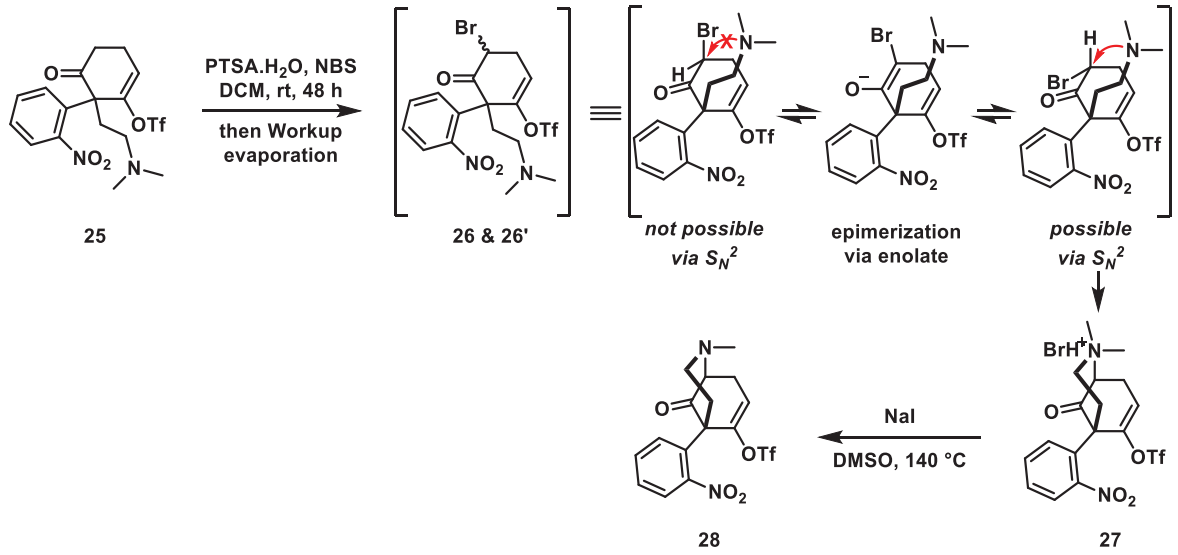
In 2016 our laboratory reported the total synthesis of strictamine in nine steps from a known enol triflate.[26] As shown in the retrosynthetic plan (scheme 24), the target molecule could be obtained via a 1,4-addition starting from the vinyl iodide **G1** which could be in turn prepared from enol triflate **H1**. This latter could be generated from **I1,** under reductive conditions, via *N*-demethylation and indolenine formation. Key quaternary ammonium salt could be prepared from tertiary amine **J1** which can be formed in multi-gram scale, according to a reported procedure, from 1,3-cyclohexanedione **L1**.

[26] Ren, W.; Wang, Q.; Zhu, J. *Angew.Chem. Int. Ed.* **2016**, *55*, 3500.



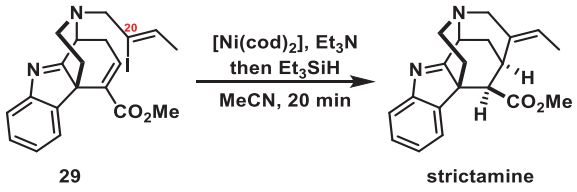
Scheme 24: Retrosynthetic pathway of strictamine by Zhu.

The first key step of this short total synthesis was the formation of the crucial 2-azabicyclo[3,3,1]non-6-en-9-one. Submission of tertiary amine **25** to PTSA and NBS allowed the formation of the α-bromo ketone as a mixture of two diastereoisomers (scheme 25). Subsequent basic workup allowed a complete cyclization via S_N2, in quantitative yield, via epimerization of one of the diastereoisomers through the enolate intermediate. *N*-demethylation of quaternary ammonium salt **27** was performed using NaI in DMSO at 140 °C for 1 hour. This first key sequence allowed the preparation of compound **28** in 40% yield over 2 steps.



Scheme 25: Zhu 2-azabicyclo[3,3,1]non-6-en-9-one formation.

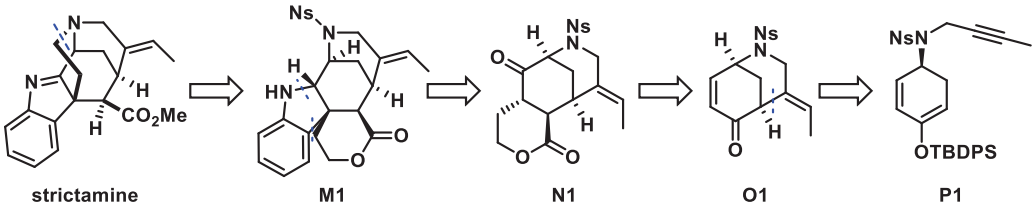
The final step of the total synthesis of strictamine consisted in an intramolecular Michael addition (scheme 26). This last step turned out to be extremely challenging. Despite a myriad of optimizations, the desired alkaloid was obtained in only 5-10% yield using $[Ni(COD)_2]$, Et_3N and triethylsilanne in MeCN.



Scheme 26: Zhu intramolecular Michael addition.

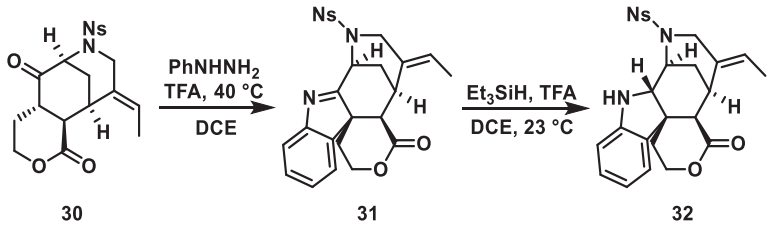
Garg's synthesis

In parallel, Garg and co-workers reported the enantioselective synthesis of strictamine.[27] As shown in the retrosynthetic plan (scheme 27), the target molecule could be obtained *via* a late stage C-N bond formation from **M1**. The indoline moiety could be generated via a reductive interrupted Fischer indolization. Ketolactone **N1** could be obtained from enone **O1** which can be generated via a gold-catalyzed reaction starting from enantioenriched amine **P1**.



Scheme 27: Retrosynthetic pathway of (+)-strictamine by Garg.

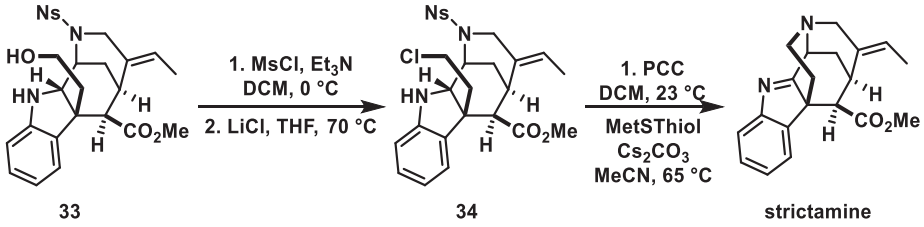
In a similar manner to the synthesis of Aspidophylline A and Picrinine, an interrupted Fischer indolization reaction was conducted in order to introduce the key C7 quaternary stereocenter. As shown in scheme 28, ketolactone **30** was exposed to phenylhydrazine and TFA at 40 °C to generate indolenine **31**. This intermediate was directly reduced using Et_3SiH to generate the indoline compound **32** in high yield and complete control of stereochemistry.



Scheme 28: Garg reductive interrupted Fischer indolization.

[27] Moreno, J.; Picazo, E.; Morrill, L. A.; Garg, N. K.; *J. Am. Chem. Soc.***2016**, *138*, 1162.

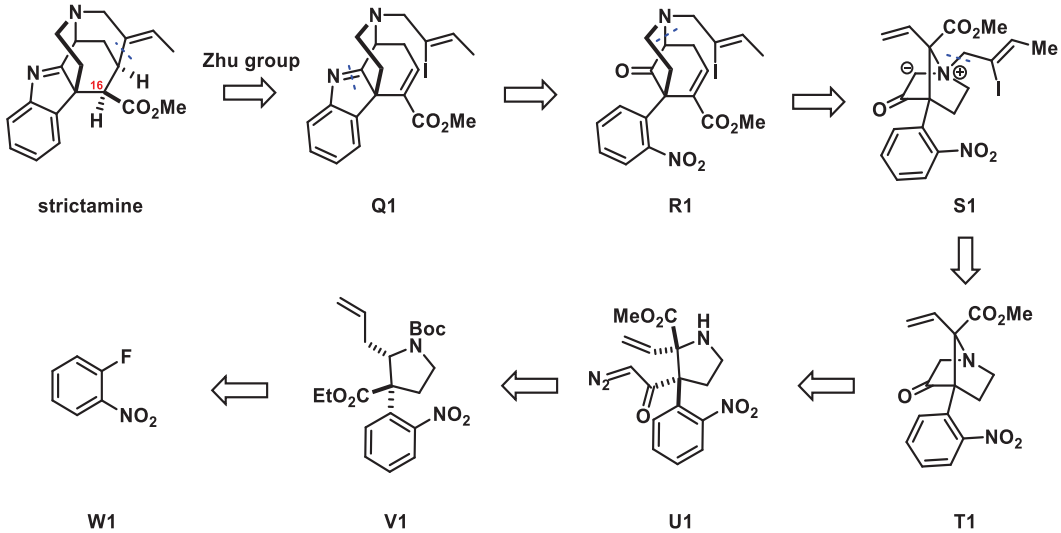
Lactone opening afforded compound **33**, its primary alcohol was then converted to chloride to afford compound **34** in 77% yield (scheme 29). Oxidation of indoline to indolenine followed by denosylation and subsequent cyclization furnished strictamine in quantitative yield over two steps.



Scheme 29: Garg late stage reactions to reach strictamine.

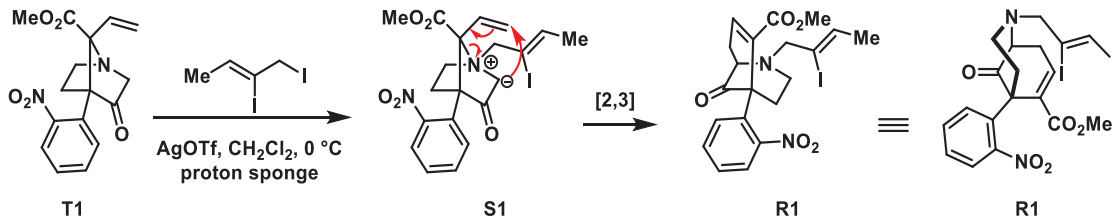
Gaich 's synthesis

In 2017, Pr. Tanja Gaich reported a formal total synthesis of strictamine in 21 isolated steps (34 chemical tranformations). As shown in scheme 30, the indolenine moiety can be generated through nitro reduction and condensation from intermediate **R1**. The key transformation of this synthesis is the Stevens [2,3]-sigmatropic rearrangement where ammonium ylide **S1** rearranges in a [2,3]-sigmatropic fashion to form the bridge bicycle **R1**. Intermediate **S1** could be easily formed via quaternarization of amine **T1**. Bridged tertiary amine **T1** could be generated though N-H insertion reaction starting from α-diazo ketone **U1**. This latter could be obtained *via* functional group interchange and [2,3]-sigmatropic rearrangement of compound **V1**. Finally, **V1** could be prepared in 6 steps starting from commercially available fluoronitrobenzene **W1**.



Scheme 30: Retrosynthetic pathway of (+)-strictamine by Gaich

As shown in scheme 31, Stevens [2,3]-rearrangement, involved in the preparation of bicycle **R1,** was conducted using a freshly prepared allyl-iodide mixed with silver(I) triflate in DCM at 0 °C followed by the addition of a mixture of proton sponge and tertiary amine **T1**. These reaction conditions forced the formation of ylide **S1** which directly rearranged into desired product **R1** in 42% yield.

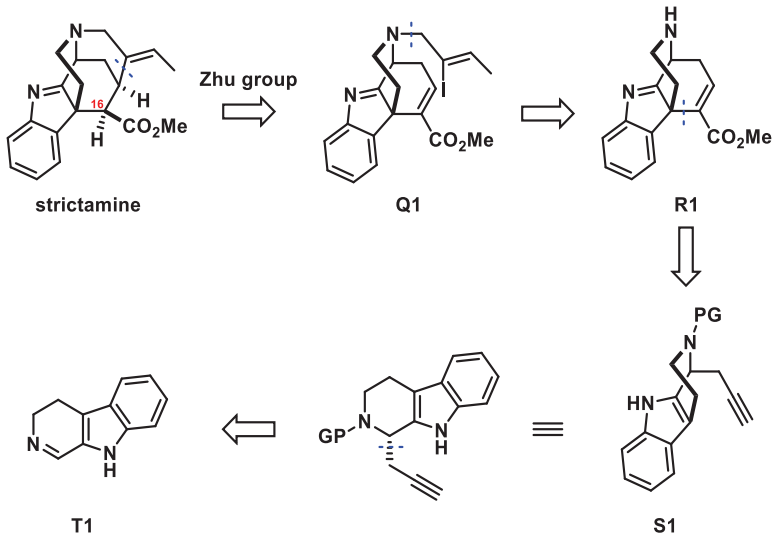


Scheme 31: Stevens [2,3]-rearrangement to form the bridge bicycle R1

A two steps sequence was then needed to reach intermediate **Q1** reported to provide strictamine after 1,4-addition cyclisation using bis(1,5-cyclooctadiene)nickel(0).

Snyder 's synthesis

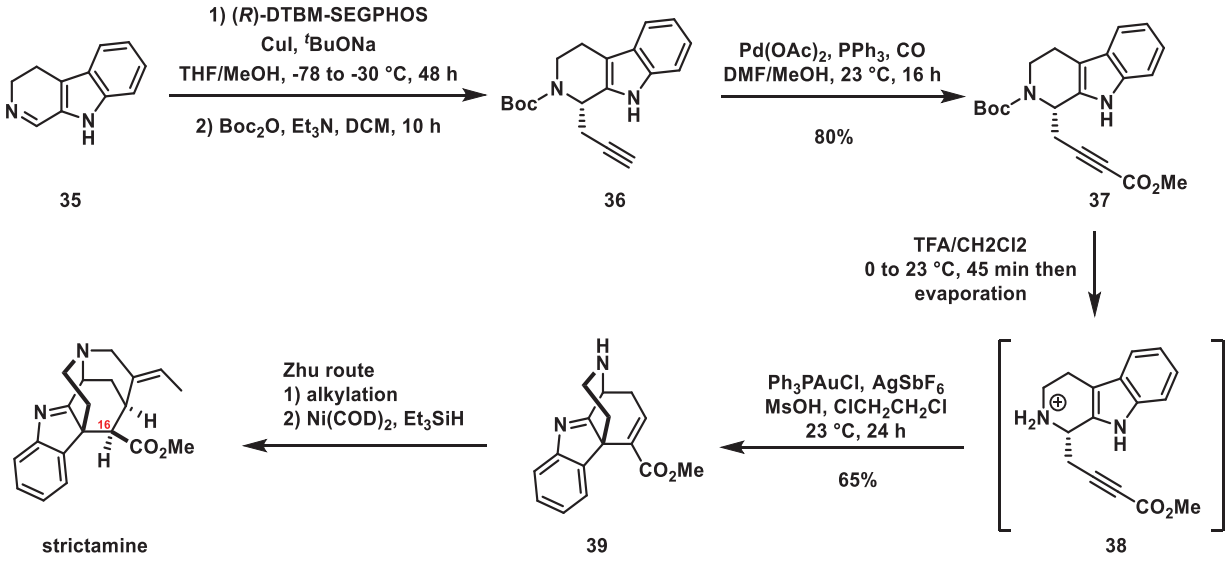
A 7-step formal synthesis of strictamine was reported in 2017 by Snyder *et al*.[28] As shown in scheme 32 intermediate **Q1** could be obtained *via N*-alkylation of compound **R1**. The later could be generated *via* a key 6-*endo*-dig cyclization starting from indole **S1**. Finally, compound **S1** could be generated *via* a novel asymmetric propargylation of 3,4-dihydro-β-carboline **T1**.



Scheme 32: Retrosynthetic pathway of (+)-strictamine by Snyder

[28] Smith, M. W.; Zhou, Z.; Gao, A. X.; Snyder, A. S. *Org. Lett*. **2017**, *19*, 1004.

As described in scheme 33 the use of asymmetric allenylboronate-mediated propargylation, followed by Boc protection provided intermediate **36** in 63% yield and 86% *ee*. The newly generated intermediate **36** was then converted into methyl ester **37** in 80% yield *via* Pd-catalyzed oxidative carbonylation. The key 6-*endo*-dig cyclization was then performed with a treatment of **37** with TFA and DCM to generate the ammonium salt **38**. This salt was then exposed to stoichiometric $AgSbF_6$, catalytic amount of Ph_3AuCl, stoichiometric MsOH and afforded the desired cyclized product **39** in 65% yield. The two remaining steps to reach the natural product was already reported by our group.



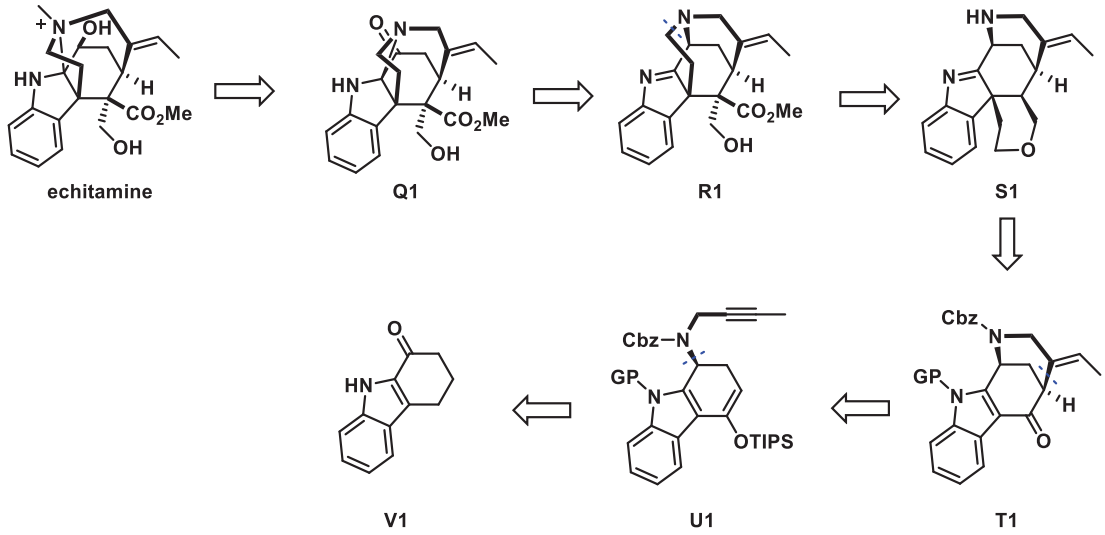
Scheme 33: 7-steps formal synthesis of strictamine

I.3.6. **Synthesis of echitamine**

As previously mentioned, echitamine was the first akuammiline alkaloid to be isolated by Gorup-Besanz in 1875[29] and described by Hesse in 1879.[30] However, first reliable data on this alkaloid were provided by Goodson and Henry in 1925.[31] It is interesting to note that despite its early isolation, the first synthesis of this natural product was only reported this year by Ang Li group.[32] As shown in the retrosynthetic plan (scheme 34), the target molecule could be obtained *via* a late stage reduction/methylation sequence from **Q1**. Indoline moiety could be generated *via* a Polonovski-Potier reaction followed by formal N-4 migration starting from **R1**. The construction of the azabicyclo [3.3.1]noname motif of **R1** could be obtained from **S1** through a one-pot halogenation/amination approach followed by a late stage aldol reaction. Fonctional

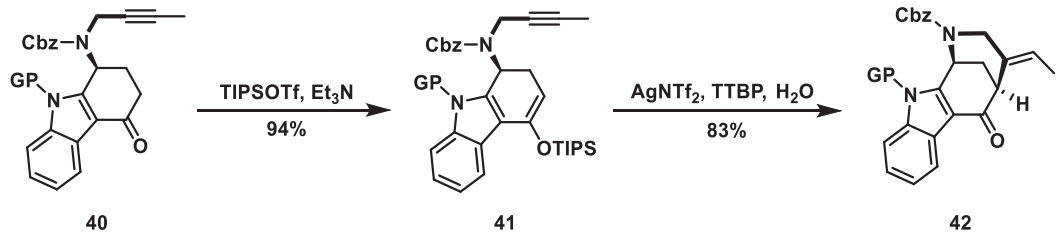
[29] Gorup-Besanez, v. Justus Liebigs Ann. Chem. **1875**, 176, 88.
[30] Hesse, O. *Ber. Dtsch. Chem. Ges.* **1879**, *11*, 1546.
[31] Goodson, J. A.; Henry, T. A. *J. Chem. Soc., Trans.* **1925**, *127*, 1640.
[32] Zhang, X.; Kakde, B. N.; Li, A. *Ang. Chem. Int. Ed.* **2019**, *58*, 6053.

group interchange of **S1** led to tetracyclic ketone **T1**. This latter could be generated though a silver-catalyzed cyclization of the terminal alkyne of **U1**.



Scheme 34: Retrosynthetic pathway of (+)-echitamine by Ang Li

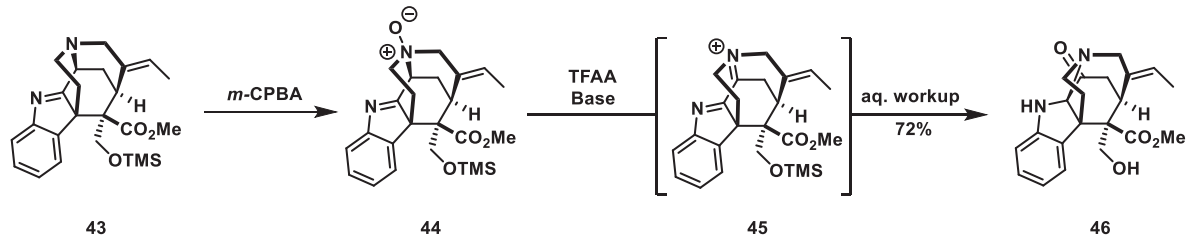
As shown in scheme 35, conversion of compound **40** into the corresponding silyl enol ether **41** allowed the set-up required for the first key step of the synthesis. The use of catalytic amount of silver provided the 6-exo-dig cyclization product in 83% yield even on a decagram scale. It is worthy to note that a similar cyclization was previously reported using gold in the synthesis of Strictamine by Garg.[33] However, the use of silver turned out to be more efficient since only one isomer of the desired product **42** was obtained under optimized conditions.



Scheme 35: Silver catalysed 6-exo-dig cyclization in the formation of 37

The second key sequence of the strategy was achieved though generation of *N*-oxide **44** (scheme 36). The use of 2,6-di-tert-butylpyridine in addition of TFAA afforded the more substituted iminium indicating an excellent selectivity of the Polonovski-Potier reaction. Addition of water allowed the formation of ketone **46** with the concomitant amine migration providing the hemi-aminal intermediate.

[33] Moreno, J.; Picazo, E.; Garg, N. K. *J. Am. Chem. Soc.* **2016**, *138*, 1162.



Scheme 36: Formation of the indolenine moiety via Polonovski-Potier and formal N-4 migration

II. Alstolactine A-C

II.1. History & structure

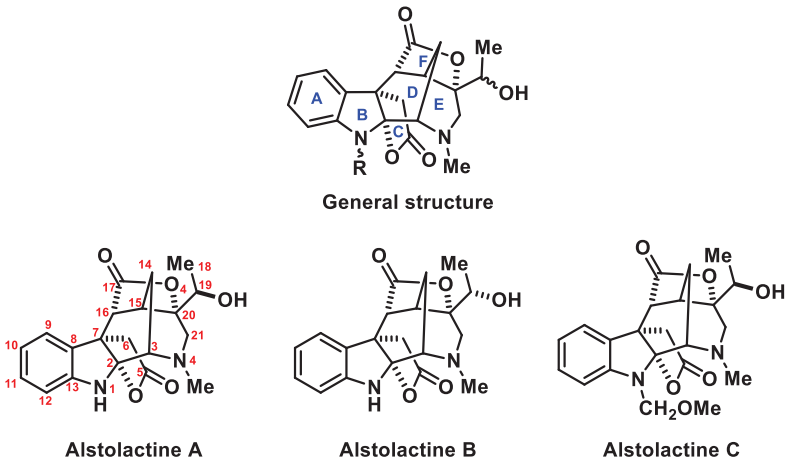
Alstolactine A-C were isolated in 2014 from the long-term stored leaves of *Alstonia scholaris* by Xiao-Dong Luo, Ya-Ping Liu and coworkers.[34] The leaves of *Alstonia scholaris* have been used to treat chronic respiratory diseases in "dai" ethnopharmacy since 100 years in Yunnan province, in China. Its crude extract, developed as traditional Chinese medecine, has also been prescribed in hospitals and sold over the counter in drug stores. Stimulated by the clinical efficiency, Liu, Luo and co-workers decided to carry on the phytochemical and pharmacological research on this plant.

In previous evaluations[35], they isolated a series of monoterpenoid indole alkaloids ((E/Z)-alstoscholarine, scholarisine A, and picrinine) from different parts of the plant. Moreover, evaluation of the crude extract from *Alstonia scholaris* leaf was carried out both in vitro and in vivo and resulted in significant anti-tussive efficiency. From other previous pharmacological evaluations, it was proved that picrinine, the main compound in the total alkaloids, was the bioactive constituent of the anti-tussive effect.

During quality control of this medicinal plant, it was noticed that the amount of picrinine decreased and additional compounds appeared in HPLC fingerprint profile of leaves of *Alstonia scholaris* that have been stored for 7 years. Correspondingly, the anti-tussive efficacy reduced significantly. Intrigued by this phenomenon, Liu, Luo and co-workers decided to conduct a phytochemical study of the total alkaloids of long-term stored leaves. After purification, they were able to isolate three new monoterpenoid indole alkaloids, alstolactine A, B and C. As shown in scheme 37, similarly to other akuammiline alkaloids,

[34] Yang, X. W.; Qin, X. J. ; Zhao, Y. L.; Lunga, P. K.; Li, X. N.; Jiang, S. Z.; Cheng, G. G.; Liu, Y. P.; Luo, X. D.; *Tetrahedron letters*, **2014**, *55*, 4593.
[35] (a) Cai, X. H.; Du, Z. Z.; Luo, X. D. *Org. Lett*. **2007**, *9*, 1817. (b) Cai, X. H.;Tan, Q. G.; Liu, Y. P.; Feng, T.; Du, Z.Z.; Li, W. Q.; Luo, X. D. *Org. Lett*. **2008**, *10*,577; (c) Feng, T.; Cai, X. H.; Zhao, P. J.; Du, Z. Z.; Li, W. Q.; Luo, X. D. *PlantaMed*. **2009**, *75*, 153. (d) Cai, X. H.; Liu, Y. P.; Feng, T.; Luo, X. D. Chin. *J.Nat. Med.* **2008**, *6*, 20.

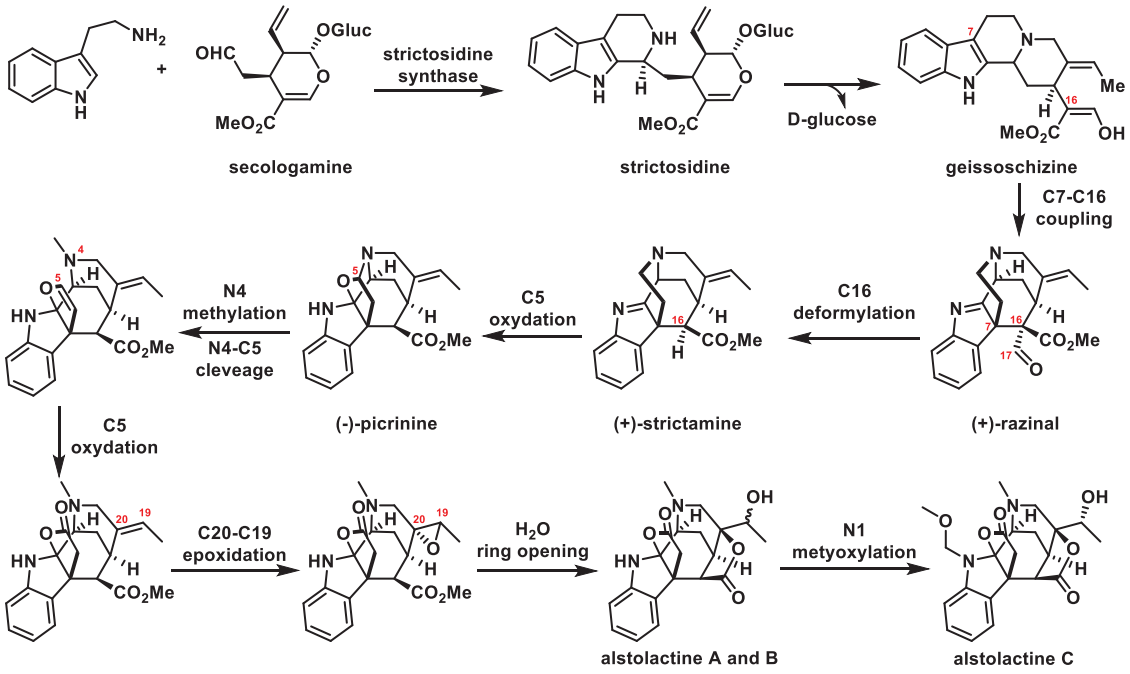
alstolactine A, B and C possess a C7-C16 connection leading to a very compact cagelike structure, containing two highly substituted fused-hexacyclic rings (E and D) with 6 contiguous stereocenters. Moreover, each alkaloid possesses two lactonic rings fused in their rigid structures leading to the formation of three quaternary centers at C2 and C7 (lactone C) and C20 (lactone F). Additional secondary alcohol at C19, in α-position to quaternary carbon C20 increases the structure complexity of those three alkaloids. The (*R*) configuration at C19 belongs to alstolactine A whereas the (*S*) configuration belongs to alstolactine B. On the other hand, alstolactine C possesses the (19*R*) configuration with N1 being methoxymethylated.



Scheme 37: Alstolactine A, B and C with their corresponding carbon number.

II.2. Biosynthesis

According to observations, these compounds might be derived from picrinine via oxidation and cyclization. As previously described, all akuammiline alkaloids derived from razinal. C16 deformylation and subsequent C5 oxidation led to picrinine (scheme 38). It was proposed that N4 methylation induced the N4-C5 cleavage leading to furan derivative. A C5 oxidation led to the formation of the first lactone of this complex compound. Epoxidation at C20-C19 and subsequent ring open afforded the second lactone and led to alstolactine A or B. Finally, N1 methyoxylation led to alstolactine C.

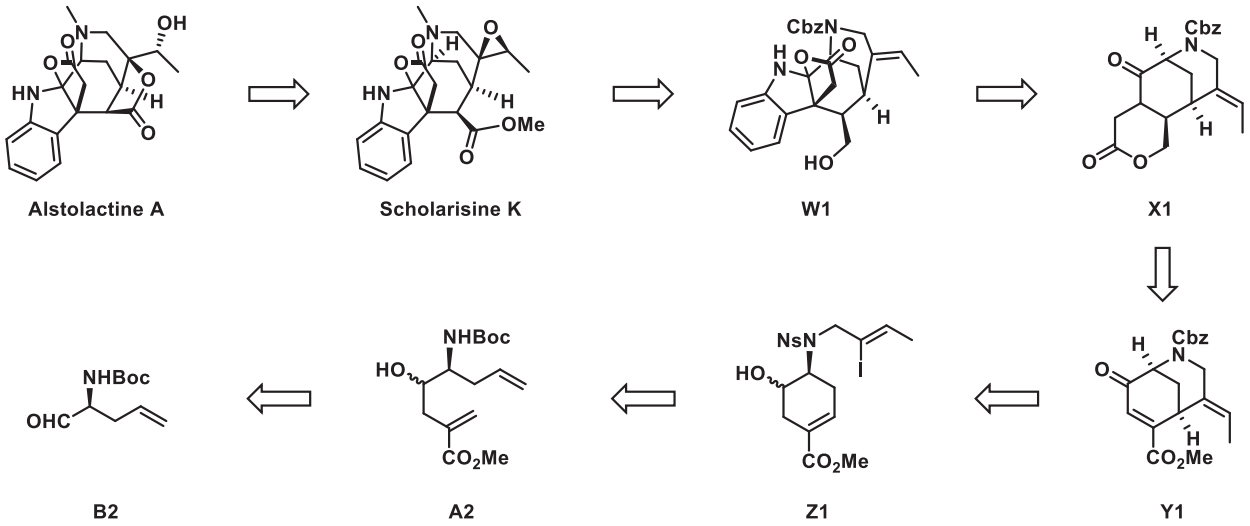


Scheme 38: Complete biosynthesis of alstolactines alkaloids starting from secologanin.

II.3. Previous synthesis of astolactine A

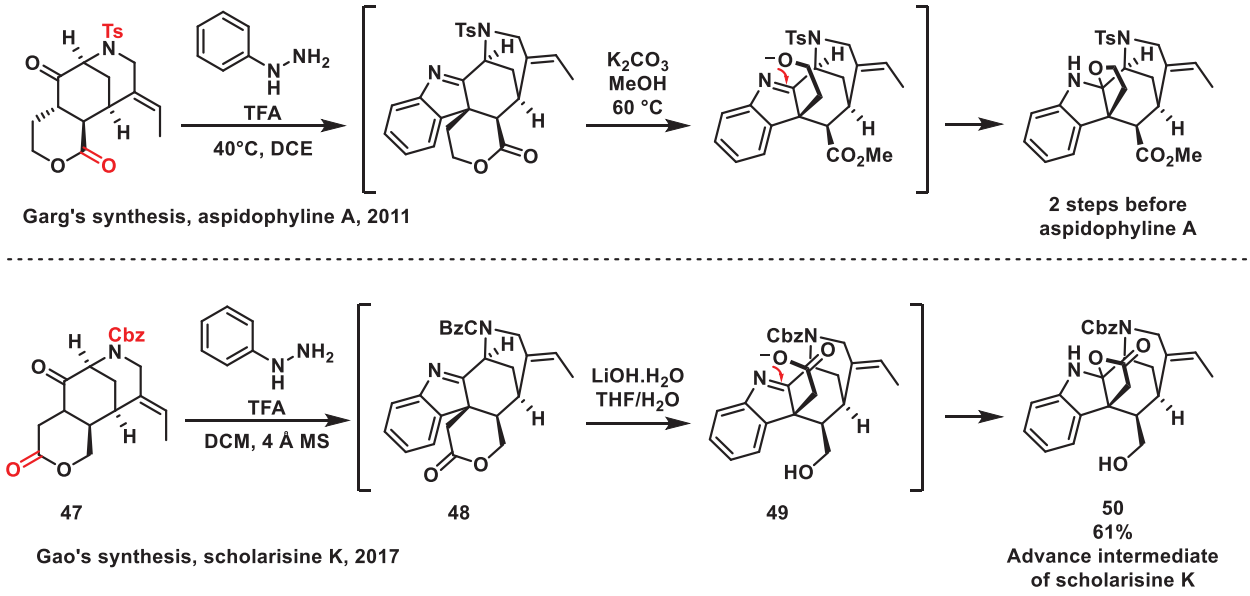
Since the isolation of alstolactine in 2014, only one synthesis of the natural product was reported. In 2017, the group of Gao reported the total synthesis of alstolactine A *via* acid-promoted epoxide opening/lactonization starting from scholarisine K.[36] As described in scheme 39, scholarisine K could be obtained from **W1** after epoxidation and oxidation of the primary alcohol. Compound **W1** could be formed *via* Fisher indolization and base promoted lactone opening starting from intermediate **X1**. The 6-member ring lactone of compound **X1** could be obtained after functional group interchange of the bicyclic-compound **Y1**. The later could be easily generated *via* intramolecular Heck reaction starting from compound **Z1**. Cyclized intermediate **Z1** could be formed after alkylation and ring-closing metathesis of amino alcohol **A2**. Finally, the amino alcohol could be generated in a single step starting from **B2**.

[36] Wang, D.; Hou, M.; Ji, Y.; Gao, S. *Org. Lett.* **2017**, *19*, 1922.



Scheme 39: Retrosynthetic pathway of Alstolactine by Gao

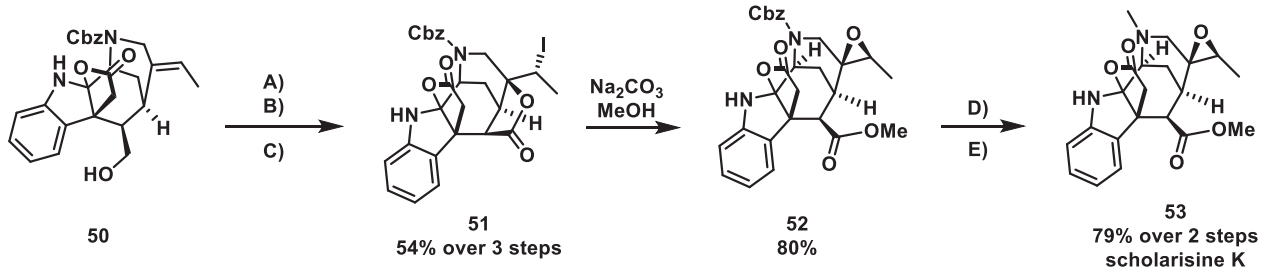
As described in scheme 40, the strategy was similar to the work of Garg for the synthesis of aspidophyline A and strictamine. Indeed, the lactone was transformed *via* Fischer indolization to indolenine **48**, which bears an all-carbon quaternary stereocenter on C-7. Subsequently, a base promoted lactone opening and recyclization generated the desired indoline **50** in 61% yield.



Scheme 40: Similarities of Garg and Gao strategies

The synthesis of scholarisine K was achieved *via* oxidation of the alcohol to the corresponding carboxylic acid followed by iodolactonization to produce the intermediate **51** (scheme 41). Lactone opening and epoxide formation under basic conditions in MeOH generated compound **52** in 80% yield. Cbz-removal followed by reductive amination finally afforded scholarisine K in 79% yield. It is interesting to note that epoxide **52** was generated *via* a two steps sequence: iodolactonization & lactone opening. The single-step generation of the epoxide was attempted without success using various reagents: *m*-CPBA, H_2O_2, oxone etc. They hypothesized

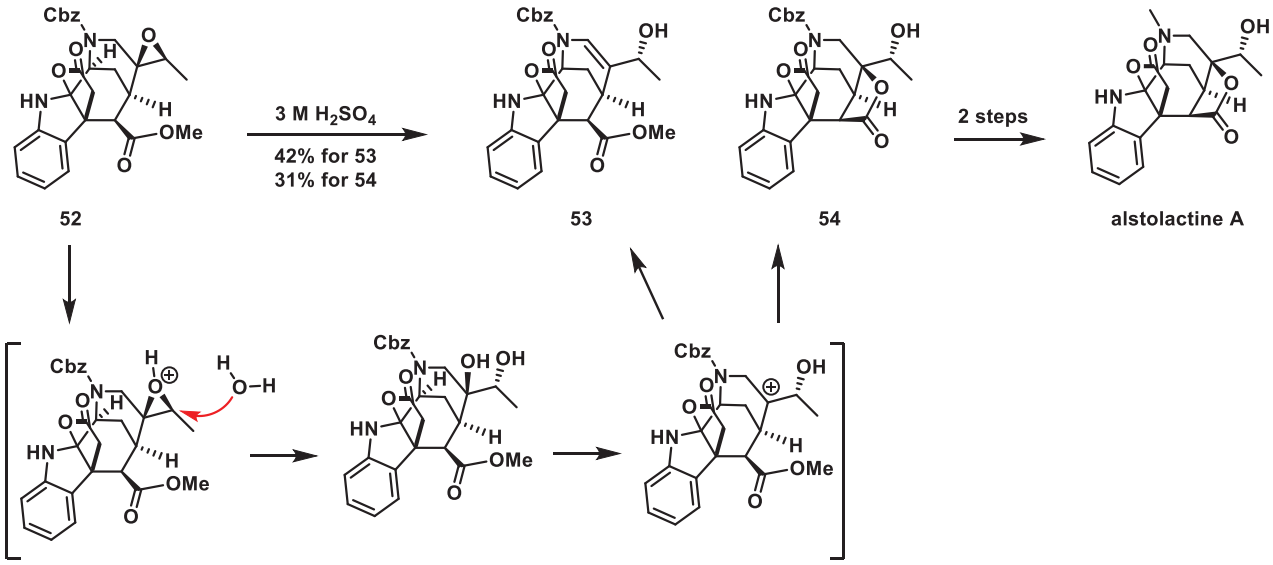
that the unprotected amino group of the indoline might participate in the oxidation, giving rise to side reactions. We also face such issues toward the synthesis of alstolactine A (describe in chapters 3 & 4).



Conditions:
A) DMP, DCM. B) $NaClO_2$, NaH_2PO_4, ^tBuOH, Isoamylene. C) KI, I_2, $NaHCO_3$, THF/H_2O.
D) $Pd(OH)_2/C$, H_2, MeOH, 40 °C. E) CH_2O, $NaBH_3CN$, MeOH, 40 °C

Scheme 41: Last sequence toward scholarisine K

The synthesis of alstolactine A was first attempted using scholarisine K. Unfortunately, exposing this natural product to acidic conditions led to its decomposition. The Gao group finally achieved the total synthesis of alstolactine A with treatment of the epoxide **52** with 3 M H_2SO_4 in acetone (scheme 42). They proposed that epoxide **52** was first activated by protonic acid, followed by intramolecular S_N2 addition by water to produce the diol intermediate, which gave the cationic species under acidic conditions. Finally, an intramolecular lactonization generated compound **54** in 31% yield, and a second dehydratation afforded conjugated diene **53**. As a final point, the desired natural product was abtained by replacing the Cbz with a methyl group in 79% yield over 2 steps.



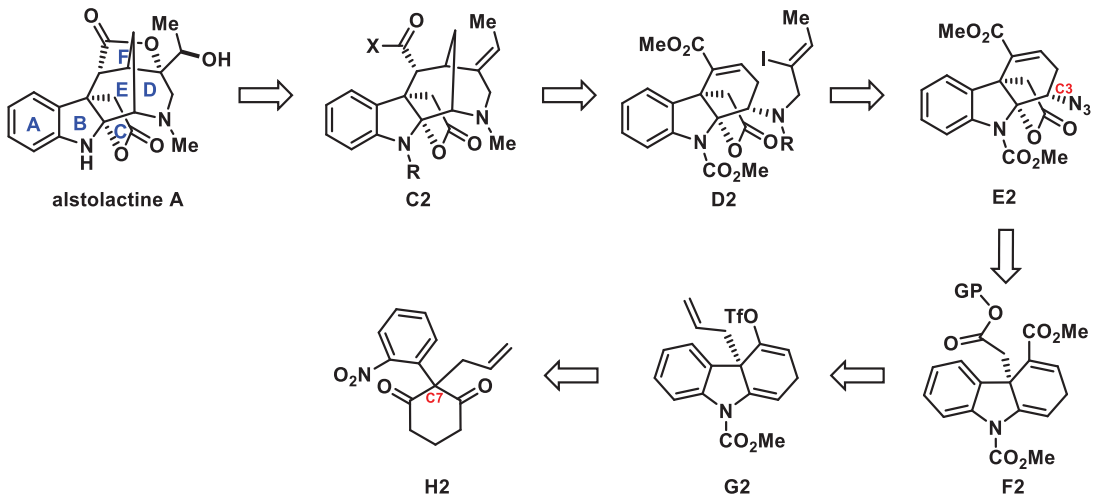
Scheme 42: Last sequence toward alstolactine A

In summary, the Gao group achieved the asymmetric synthesis of alstolactine in 26 linear steps from commercial material.

CHAPTER 2 - Enantioselective approach

I. Retrosynthesis

After having accomplished the total syntheses of aspidophylline A and strictamine, we became interested in alstolactines, other members of the akuammiline alkaloids family. The principle strategic consideration of our synthetic design towards alstolactine is based on the early-stage creation of the C7 quaternary center. The retrosynthetic analysis is shown in scheme 43. We planned to form the lactone ring F by iodolactonization or an epoxidation/ring opening sequence starting from compound **C2**. The 2-azabicyclo[3.3.1]nonane ring system would be built from vinyl iodide **D2** by an intramolecular Michael addition. The tertiary amine could be generated though functional group interconversion starting from the *cis* azide **E2**. The latter could be obtained *via* a one-pot azidolactonization cascade allowing the C3-N bond formation with the concurrent construction of the γ-lactone ring C. Tricyclic indoline **F2** could be obtained after oxidation of the double bond and carbonylation of the enol triflate starting from **G2**. Finally, intermediate **G2** could be generated *via* desymmetrization of the readily available 2-allyl-2-(*o*-nitrophenyl)cyclohexane-1,3-dione (**H2**).



Scheme 43: Alstolactine A retrosynthetic pathway.

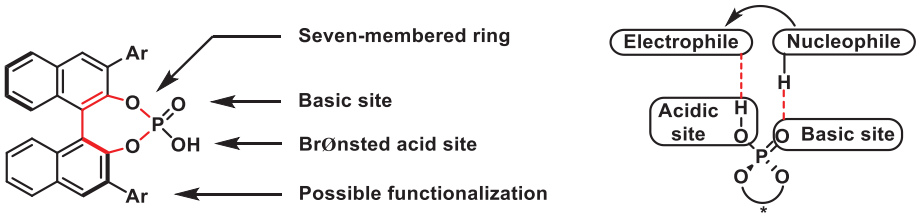
In order to target an enantioselective synthesis of alstolactine, the first part of my PhD focused on the desymmetrization of compound **V1** using chiral phosphoric acid.

II. Desymmetrization of prochiral 1,3-cyclohexanediones

II.1. Chiral phosphoric acid presentation

For years, two classes of efficient asymmetric catalyst, enzymes and synthetic metal complexes were mainly used. In the past decades the appearance of organocatalysis emerged as a third class of powerful asymmetric catalysis.[37]

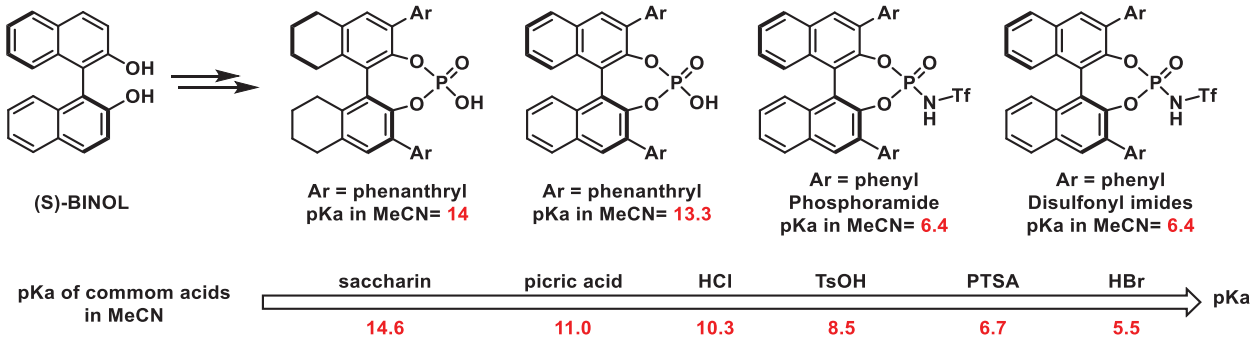
The use of BINOL-derived phosphoric acids has been known for over 40 years in organic synthesis. Nevertheless, their usage as catalyst started only 15 years ago. Akiyama and Terada were pioneers in the field with the reports in 2004 on the chiral Brønsted-acid catalyzed Mannich reaction.[38,39] Those catalysts are highly versatile and have been shown to catalyze a plethora of asymmetric transformations under simple and mild reaction conditions. As described in scheme 44, these BINOL-derived phosphoric acids possess an axial chirality. The phosphorus atom is embedded in a seven-membered ring which prevents free rotation and therefore fixes the configuration of the Brønsted acid. Since the phosphoryl oxygen atom provides an additional Lewis basic site, chiral phosphoric acid might act as bifunctional catalyst in which both of these sites are involved in the stabilization of a transition state.



Scheme 44: BINOL-derived phosphoric acid.

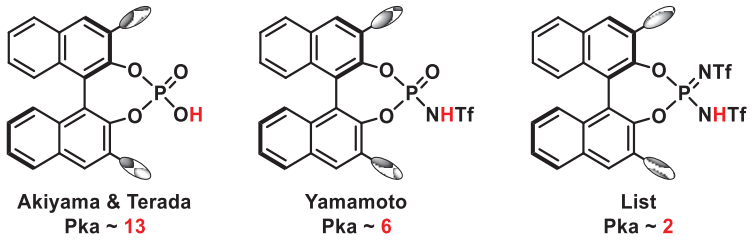
When phosphoric acids are not acidic enough to activate a particular substrate, they could be replaced by *N*-triflyl phosphoramides (prepared in one step from the corresponding phosphoric acid) which shows higher acidity.[40] In 2013, Rueping and Leito reported a full study on establishing an acidity scale in MeCN for the commonly used Brønsted acid catalyst.[41] As described in scheme 45, the acidity scale for BINOL-derived Brønsted acids is quite broad, from 14 for the less acidic to 6.4 for the more common catalyst.

[37] List, B.; Yang, W. *Science* **2006**, *313,* 1584.
[38] Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem; Int. Ed.* **2004**, *43*, 1566.
[39] Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126,* 5356.
[40] Nakashima, D.; Yamamoto, H. *J. Am. Che. Soc.* **2006**, *128*, 9626.
[41] Kaupmess, K.; Tolstoluzhsky, N.; Raja, S.; Rueping, M.; Leito, I. *Angew. Chem; Int. Ed.* **2013**, *52*, 11569.



Scheme 45: Acidity scale of BINOL-derived BrØnsted acids and comparison with common acid in MeCN.

Others variant were then described by List with the use of phosphoramidimidate brønsted acid catalyst allowing the reduction of pka until ~2 (scheme 46).[42]

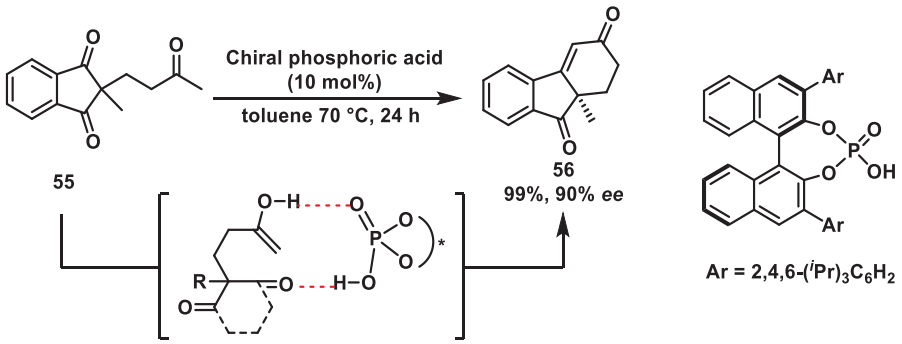


Scheme 46: Acidity scale of BINOL-derived BrØnsted acids, introduction of phosphoramidimidate.

During the expansion of those organocatalysts, various intramolecular asymmetric desymmetrization have been developed.[43] However, only few examples were reported on meso-1,3-diones. One example is presented below.

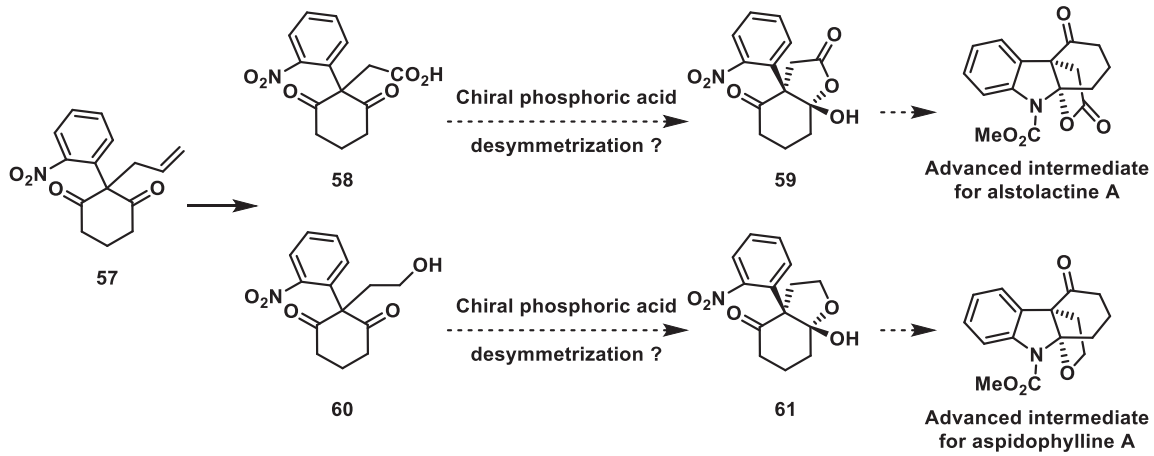
In 2009, Akiyama and co-workers reported a chiral phosphoric acid catalyzed desymmetrization of *meso*-1,3-diones.[44] As presented in scheme 47, the desymmetrization of 1,3-diones **55** followed by dehydration was accomplished in a single step to afford chiral cyclohexenones. Mechanistically, it is thought that the acidic organocatalyst promotes an intramolecular aldol condensation involving two hydrogen bonds. In one hand, the chiral phosphoric acid activates the carbonyl moiety. On the other hand, the Lewis basic part activated the enol. This reaction allowed the formation of cyclohexanone **56** in excellent yield and high enantioselectivity.

[42] A) Kaib, P. S. J.; List, B. *Synlett*, **2016**, *27*, 156. B) Kaib, P. S. J.; List, B. *Angew.Chem.Int.Ed.***2016**,*55*,13200.
[43] Gualtierotti, J-B.; Pasche, D.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2014**, *53*, 9926.
[44] Mori, K.; Katoch, T.; Suzuki, T.; Noji, T.; Yamanaka, M.; Akiyama, T.; *Angew. Chem. Int. Ed*, **2009**, *48*, 9652.



Scheme 47: Akiyama desymmetrization of 1,3-dione derivatives.

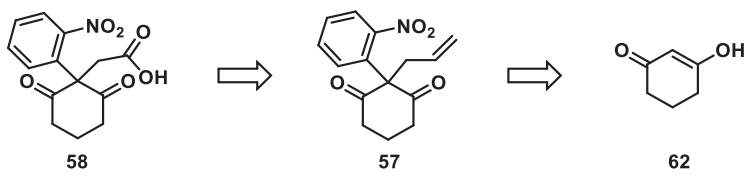
As compound **57** was identified as a possible platform for skeletal diversity, we thought to develop a desymmetrization process using chiral phosphoric acid. Starting from carboxylic acid **58** or alcohol **60**, an enantioselective desymmetrization was envisaged in order to prepare an advanced intermediate of alstolactine A or aspidophylline A, respectively (scheme 48).



Scheme 48: Desymmetrization for the enantioselective preparation of advanced intermediates of akuammiline family.

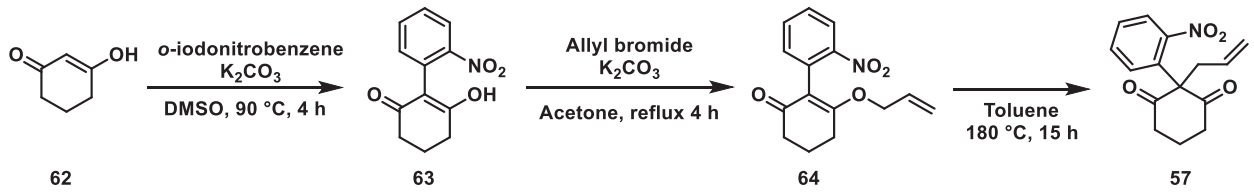
II.2. Desymmetrization of carboxylic acid derivative

The initial attempt for the desymmetrization, using chiral phosphoric acid was undertaken using acid **58** as starting material. This desired intermediate could be prepared following the sequence shown below.



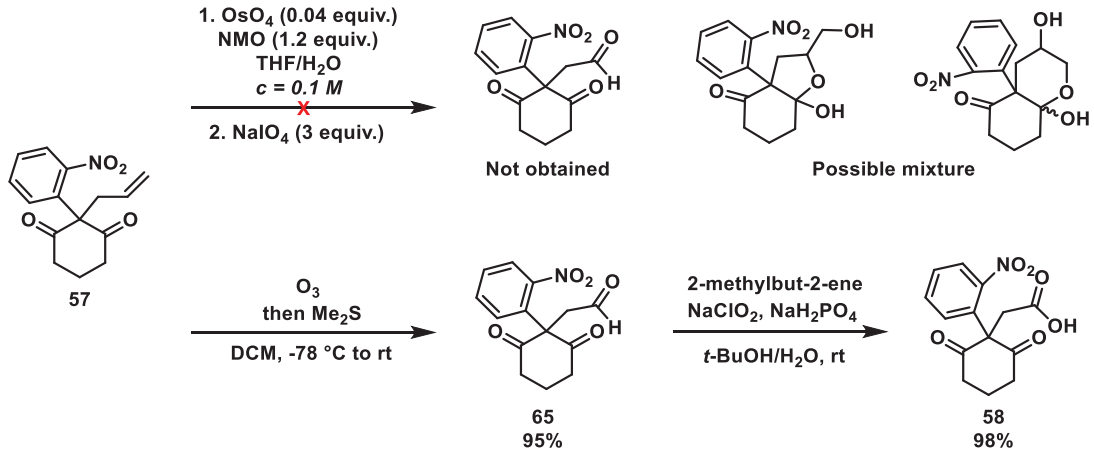
Scheme 49: Retrosynthesis of cyclohexanedione derivatives.

Intermediate **57** was obtained *via* a 3-step sequence developed by Bonjoch *et al* (scheme 50).[45] The first step involves direct arylation of dione **62** *via* a nucleophilic aromatic substitution reaction using *o*-iodonitrobenzene, potassium carbonate as base in dimethyl sulfoxide. This reaction was scaled in up to 60 g and afforded desired product **63** in 70% yield. This arylation was then followed by an *O*-allylation (89% yield). Subsequent Claisen rearrangement allowed the generation of the all-carbon quaternary center of compound **57** in 79% yield.



Scheme 50: Synthesis of meso 1,3-diketone 39.

This prochiral compound underwent first dihydroxylation using catalytic amount of OsO_4 and NMO as co-oxidant (scheme 51). Subsequent oxidative cleavage using sodium *meta*-periodate was conducted. Unfortunately, the reaction turned out to be unsuccessful. A messy reaction mixture was obtained, probably due to the reaction of the diol intermediate with ketones affording a mixture of acetal and diastereoisomers. Desired carboxylic acid **58** was finally cleanly obtained through ozonolysis followed by oxidation of the aldehyde **65** using Pinnick oxidation. Starting from **62** the overall yield of the sequence was 46% over 5 steps.

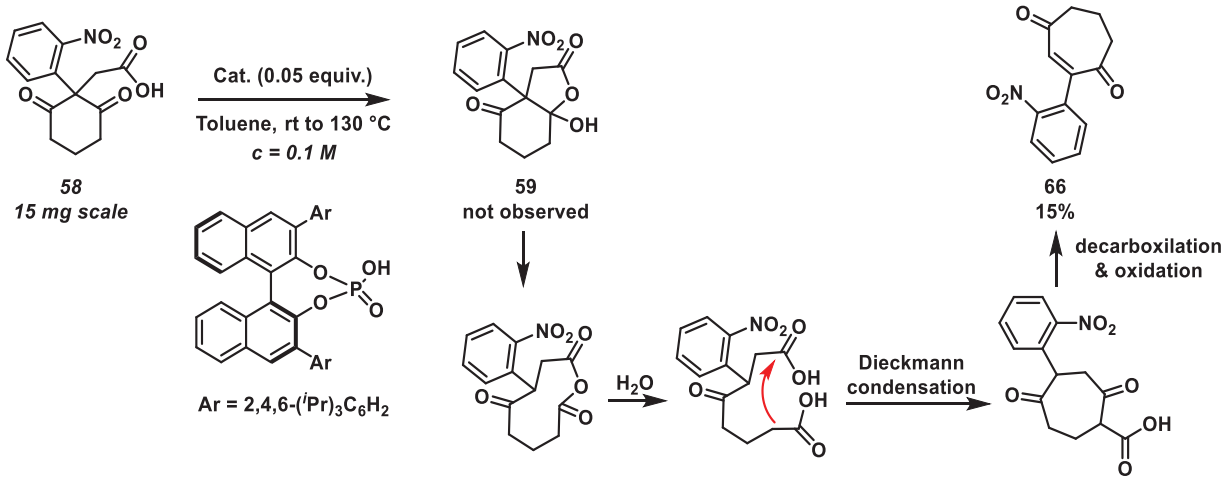


Scheme 51: Synthesis of desired acid intermediate 40 for the desymmetrization process.

With the desired acid **58** in hands, we turned our attention towards its desymmetrization using chiral phosphoric acid. As shown in scheme 52, the first attempt was conducted using CPA in toluene. Unfortunately, the starting material was not soluble at room temperature and no reaction occurred. In fact, even when the temperature was increased from 25 °C to 50 °C (for 12 hours), from 50 °C to 80 °C (12 hours)

[45] Solé, D.; Bosch, J.; Bonjoch, J. *Tetrahedron* **1996**, *52*, 4013.

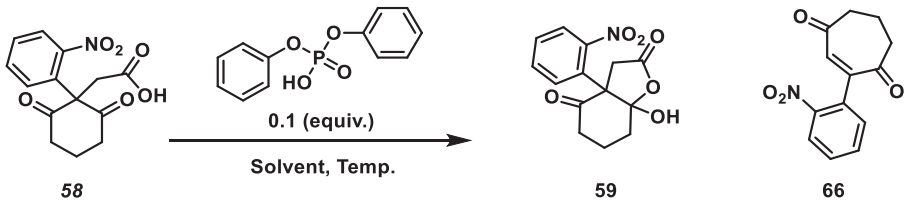
and from 80 °C to 130 °C, both solubility and reactivity of the starting material were disappointing. Nevertheless, after 2 days at 130 °C compound **66** was isolated in 15% yield.



Scheme 52: First desymmetrization attempted using CPA.

Different solvents and temperature were then examined in the presence of achiral diphenyl phosphate (table 1). Unfortunately, desired acetal **59** was never observed. Despite the screening of different solvents, the starting material remained insoluble at room temperature (except in MeCN) and required harsher conditions to react.

Table 1: Solvent screening for desymmetrization using acid intermediate.



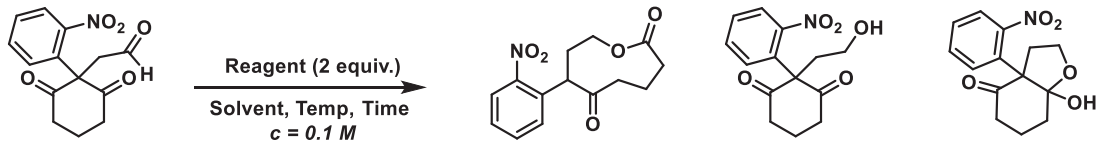
Entry	Solvent	Comments
1	dioxane	rt 12h, 50 °C all night, 80 °C 12h, 100 °C overnight, 130 °C 24h. Starting material & decomposition
2	MeCN	rt 12h, 50 °C all night, 80 °C 12h, 100 °C overnight, 130 °C 24h. Starting material & decomposition
3	DCE	rt 12h, 50 °C overnight, 80 °C 12h, 100 °C overnight: compound 49 formed, 130 °C 24h no evolution
4	$CHCl_3$	rt 12h, 50 °C overnight, 80 °C 12h, 100 °C overnight: compound 49 formed, 130 °C 24h no evolution.

Because of low nucleophilicity of the carboxylic acid function and solubility issues, we turned our attention toward the desymmetrization of alcohol substrate.

II.3. Desymmetrization of alcohol derivative

As previously described, aldehyde **65** was generated *via* ozonolysis in excellent yield. Subsequent reduction would afford the alcohol. Therefore, the first experiment for the chemoselective reduction of aldehyde in the presence of ketone was performed using $NaBH_4$ at -78 °C. Interestingly, a macrolactone product **67** was obtained in 22% yield (table 2). Different solvents and temperatures were examined (entries 1 to 6), however, no desired alcohol was observed. Neither the use of $LiBH_4$ nor DIBAL-H were successful. Surprisingly, using $NaBH_4$ in MeOH at -20 °C afforded macrolactone **67** in 44% yield (entry 6). Finally, the use of $LiAlH(O^tBu)_3$ at -78 °C increased the yield up to 60% (entry 9).

Table 2: Screening conditions for the chemo-selective reduction of aldehyde 65.

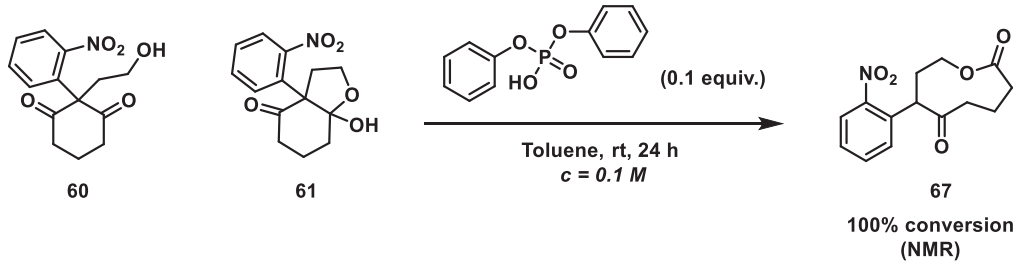


65 67 60 61

Entry	Reagent	Solvent	Temp	time	comments
1	$NaBH_4$	DCM/EtOH 7:3	-78 °C	6h	22% of 67
2	$NaBH_4$	MeOH	-78 °C	2h30	not clean 3 new aldehydes observed on crude NMR
3	$NaBH_4$	DCM/EtOH 7:3	0 °C	2h	One major product but entry 4 more clean
4	$NaBH_4$	MeOH	0 °C	1h20	29% of 67
5	$NaBH_4$	MeOH	rt	2h	67 not observed many spots, probably degradation
6	$NaBH_4$	MeOH	-20 °C	1h20	44% of 67
7	$LiBH_4$	THF/MeOH 10:1	0 °C	1h	13% of 67
8	DIBAL-H	DCM	-78 °C	7h	Messy
9	$LiAlH(O^tBu)_3$	THF	-78 °C	1h30	1 equiv, after 1 hour 0.1 equiv more. After column, 60% compound 67
10	$NaBH_3CN$	THF/AcOH 10:1	0 °C	1h	Perfectly clean. Mix of 60 and 61. Column: lead to macrolactone 67

As basic conditions afforded the macrolactone by-product in variable yields, we turned our attention toward a reduction in acidic media. Therefore, the aldehyde **65** was treated with sodium cyanoborohydride at 0 °C in a mixture of THF/acetic acid (10:1). To our delight, this reduction resulted in a clean mixture of alcohol **60** and acetal **61** in a 1:1 ratio (entry 10). Unfortunately, those compounds were unstable and were converted into macrolactone **67** on silica gel. Moreover, after 2 days in $CDCl_3$, the same by-product **67** was generated. Those observations confirmed the instability of the mixture in acidic media.

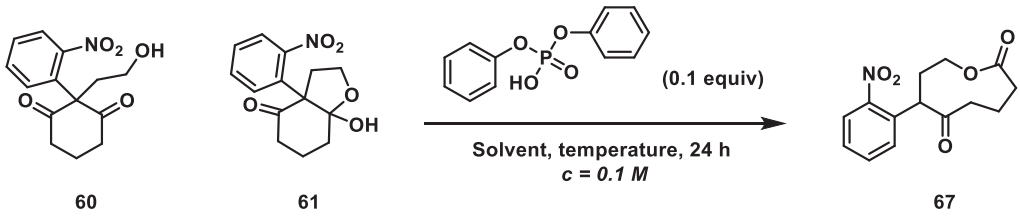
The crude mixture was therefore used directly without further purification. First experiment consisted in submitting the mixture to diphenyl phosphate (0.1 equivalent) in toluene (scheme 53). After 24 hours at room temperature, full and clean conversion into the macrolactone **67** was observed.



Scheme 53: First attempt using diphenyl phosphate.

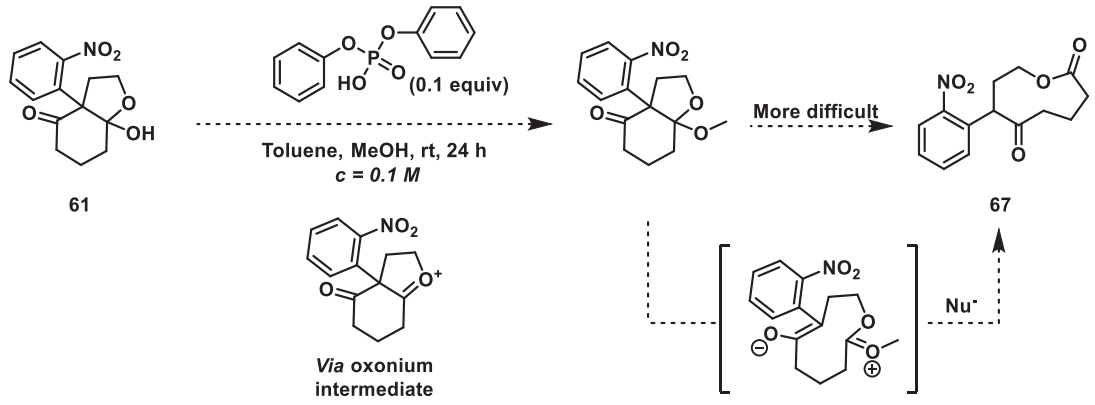
Changing the solvent (MeCN, THF and DCM) did not influence the outcome of the reaction and the same result was obtained after 24 hours. When the reaction was performed at lower temperature, as described in table 3, the macrolactone by-product was formed exclusively.

Table 3: Solvents/temperatures optimizations.



Entry	Solvent	Temperature	Conversion
1	toluene	rt	100%
2	toluene	-78 °C	100%
3	MeCN	0 °C	100%
4	THF	-78 °C	100%
5	CH_2Cl_2	-78 °C	100%

It was thought that the use of MeOH could prevent the formation of the macrolactone by the formation of a mixed acetal (scheme 54). Unfortunately, only the macrolactone was obtained.

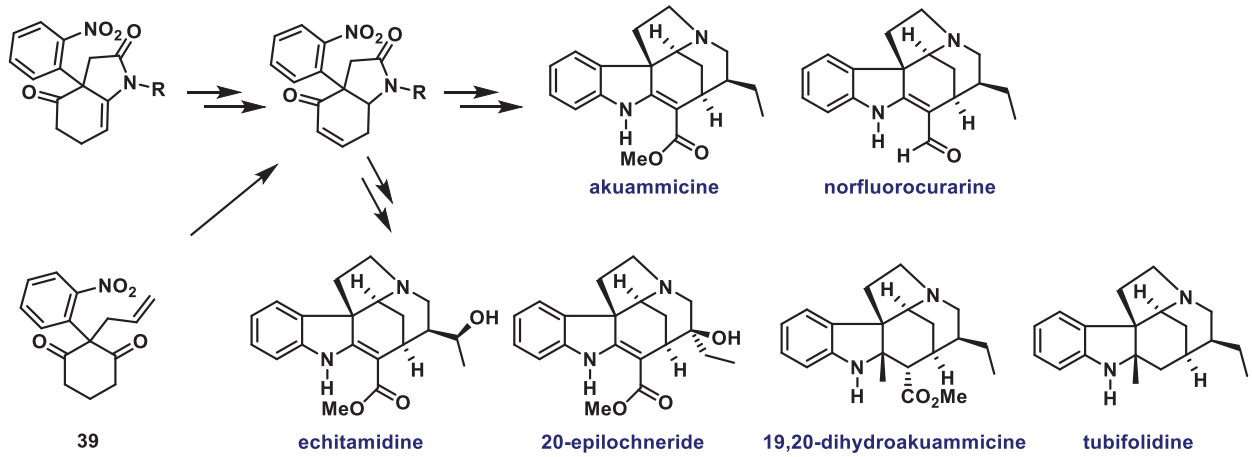


Scheme 54: Attempt for the mixed-acetal formation.

Because of the constant formation of the macrolactone and the impossibility to control the ratio alcohol/ acetal, we therefore turned our attention to another functional group.

II.4. Desymmetrization of amide derivative

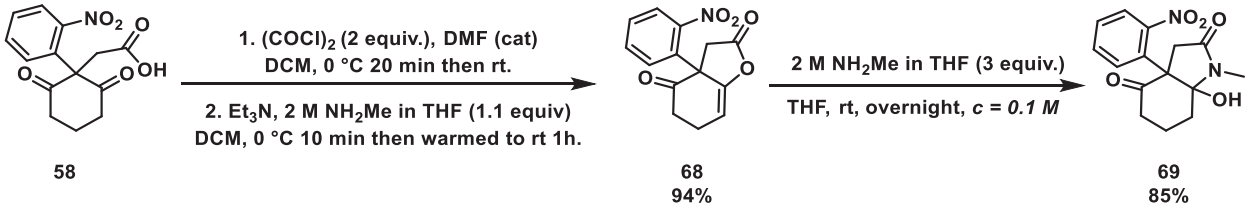
The amide moiety was envisaged as it would be a compromise between low reactivity of acid **58** and uncontrolled equilibrium between alcohol and acetal. Despite those attempts were not related to the synthesis of alstolactine, it could open the door to a large number of *strychnos* natural products. Some examples are shown below.[46]



Scheme 55: Possible general synthesis of strychnos alkaloids.

[46] Bosch, J; Solé, D.; Garcia-Rubio, S.; Bonjoch, J. *J. Am. Chem. Soc*. **1997**, *119*, 7230.

First experiments were planned using *N*-methyl-amide as starting material. Surprisingly, addition of methylamine on the acyl chloride intermediate did not provide the desired product (scheme 56). Lactone **68** was isolated in 94% yield. Addition of methylamine (3 equiv.) in THF afforded compound **69** in 85% yield. The desired *N*-methyl-amide in its opened-form was not detected.

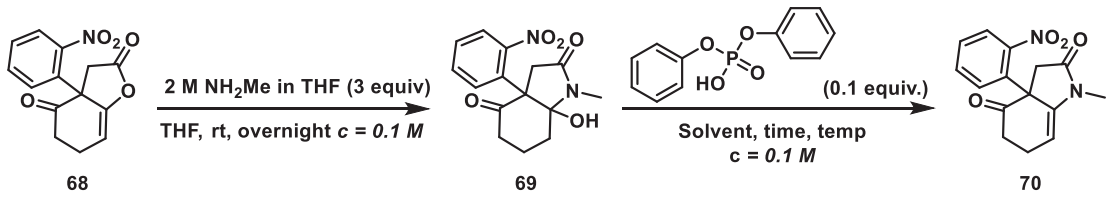


Scheme 56: Attempt for methyl amide formation.

The reaction was also performed at 0 °C using methylamine, DIPEA, HOBT and EDC hydrochloride, but the desired amide was never observed even after neutral work-up.

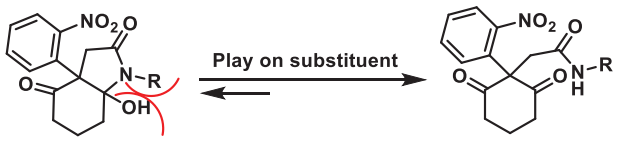
Unfortunately, this hemiaminal **69** turned out to be extremely stable and insoluble in many different solvents including MeOH. Nevertheless, compound **69** was treated with phosphoric acid. Despite the use of different solvents and temperatures, the open form was never detected neither by TLC nor NMR analysis. As presented below (table 4), starting material **69** remained insoluble at room temperature in either toluene, MeCN or dioxane. Increasing the temperature allowed a better solubilization and led to the formation of compound **70** in excellent yield.

Table 4: Solvent/temperature screening of intermediate 69 with racemic phosphoric acid.



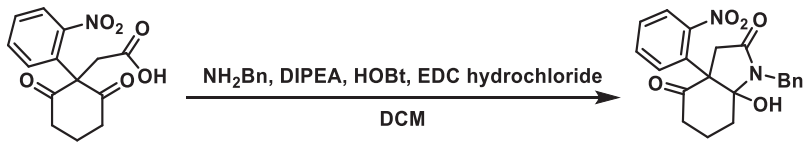
Entry	Solvent	Time	Comments	Yield
1	Toluene	2 days	rt SM not soluble, 50 °C: Suspension. After 24 h almost full conversion. 80 °C overnight.	Quantitative
2	MeCN	16 h	rt SM not soluble, 50 °C: Solubilisation. After 16 h, reaction complete.	Quantitative
3	Dioxane	2 days	rt SM not soluble, 50 °C: Suspension. After 24 h almost full conversion. 80 °C overnight not complete. 100 °C 4 h, reaction complete.	96%

It was then supposed that the *N*-acyl hemiaminal equilibrium could be modified by changing the substituent on the nitrogen of the amide moiety (scheme 57).



Scheme 57: General proposition to "control" the N-acyl hemiaminal equilibrium.

However, when benzylamine was used, similar results were obtained. As previously observed, the hemiaminal was formed exclusively and the open form of the amide was not observed (scheme 58).

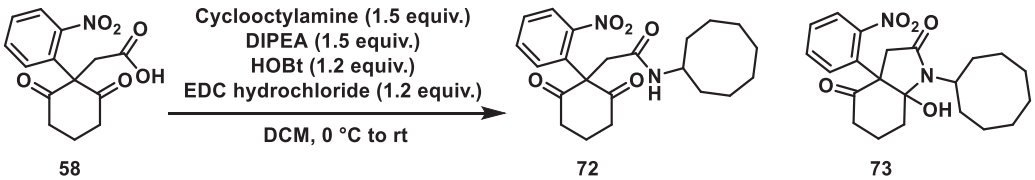


58 71

Scheme 58: Amide coupling leading to exclusive formation of the N-acyl hemiaminal.

We then turned our attention to a more sterically hindered substituent: a cyclooctyl group. The coupling reaction using this cyclooctylamine was performed in DCM from 0 °C to room temperature (table 5). NMR analysis was conducted in order to better understand the evolution of the **72**/**73** ratio. The first experiment (entry 1) was performed on small scale and after 24 hours, a mixture of **72**/**73** was obtained in favor of compound **73**. The same experiment was repeated (entry 2) and after 5 hours NMR of an aliquot showed a ratio of 94:6 in favor of **72**. After 24 hours, the same **72**/**73** ratio as entry 1 was obtained. These two experiments confirmed that the open form could be obtained as major product within a short reaction time. Therefore, when the reaction was repeated and quenched after 3 hours (entry 3) an excellent ratio of 97:3 in favor of **72** was obtained. However, this ratio slightly decreased after purification on silica gel. The mixture of the two products was isolated in only 46% yield with a good ratio **72**/**73** of 92:8.

Table 5: Attempts to control the amide/hemiaminal ratio.



58 72 73

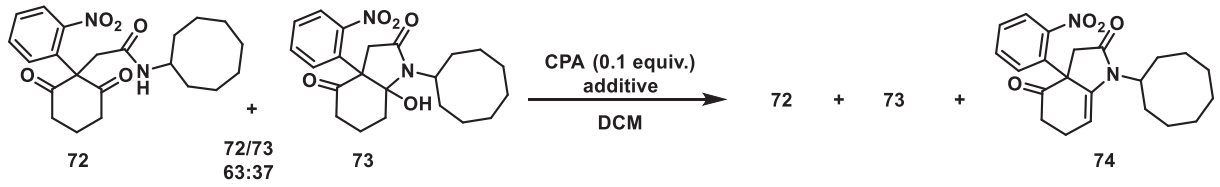
Entry	NMR time	NMR ratio 72/73	Isolated yield	ratio 72/73 after column
1	24 h	44:56	-	-
2	5 h	94:6		
	24 h	44:56	-	-
3	3 h	97:3	46%	92:8
4	24 h	-	70%	63:37

In order to optimize the reaction conditions for the desymmetrization using CPA, it was decided to favor a good yield instead of a good ratio **72**/**73**. Therefore, the coupling reaction was repeated in larger scale (entry 4) and after 24 hours the desired mixture was isolated in 70% yield with a 63:37 ratio of **72**/**73**.

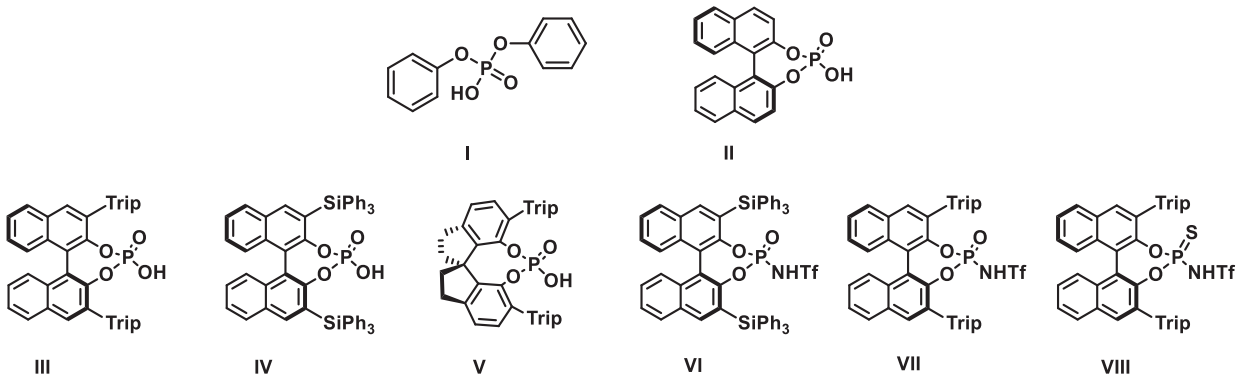
As shown in table 6, first attempts (entries 1 & 2) were conducted using racemic phosphoric acid in dichloromethane at room temperature. In both cases, after 24 hours the hemiaminal **73** was converted to **74**. Surprisingly, compound **72** seemed to be unreactive. As previously mentioned, during the coupling reaction (table 5) the ratio **72**/**73** changed after purification on silica gel (entry 3). Assuming that silica was responsible for promoting the formation of **73**, it was decided to add a small amount of silica directly in the reaction mixture (entry 3 table 6). Unfortunately, after 24 hours, amide **72** did not cyclized.

Despite disappointing preliminary results using achiral phosphoric acid (entry 1 to 3), it was decided to screen different chiral phosphoric acids. As described in table 6, using chiral phosphoric acid III, IV and V (entries 4 to 6) no reaction was observed. Surprisingly, even when the temperature was increased up to 60 °C the **72**/**73** ratio remained unchanged and compound **74** was not formed. The low reactivity in presence of the chiral phosphoric acids in comparison with the achiral one was probably due to steric hindrance. It was then decided to move to more active Brønsted acids. When the reaction was performed using *N*-triflyl phosphoramides such as CPA VI as catalyst (entry 7) similar results were obtained. Despite higher acidity, the steric hindrance probably remained problematic. However, using CPA VII and VIII (entries 8 & 9), hemiaminal **73** was consumed and the desired product **74** was generated in approximately 30% yield. Unfortunately, the product was obtained as a racemic mixture.

Table 6: Racemic and enantioselective attempts for the desymmetrization process



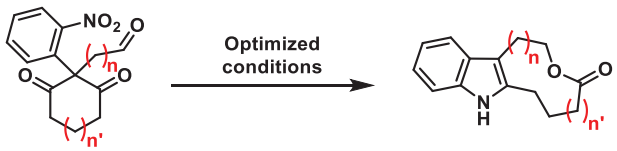
Entry	CPA	Additive	72/73/74 ratio after 4 hours	72/73/74 ratio after 16 hours	72/73/74 ratio after 24 hours	Comments
1	I	-	-	-	68:2:30	-
2	II	-	61:22:17	60:0:40	60:0:40	-
3	II	SiOH	-	-	62:0:38	-
4	III	-	63:37:0	63:37:0	63:37:0	up to 40 °C for 10 hours, no reaction.
5	IV	-	63:37:0	63:37:0	63:37:0	up to 40 °C for 10 hours, no reaction.
6	V	-	63:37:0	63:37:0	63:37:0	up to 60 °C for 10 hours, no reaction.
7	VI	-	63:37:0	63:37:0	63:37:0	up to 40 °C for 10 hours, no reaction.
8	VII	-	63:10:27	62:0:38	62:0:38	*ee* = 0%
9	VIII	-	-	63:0:37	63:0:37	*ee* = 0%



Despite being different than acid **58** or alcohol **60** the cyclization of **72** into **73** turned out to be difficult. However, achiral phosphoric acid I and II, chiral *N*-triflyl phosphoramides VII and VIII could catalyzed the reaction to provide the desired product **74**, though without enantioinduction.

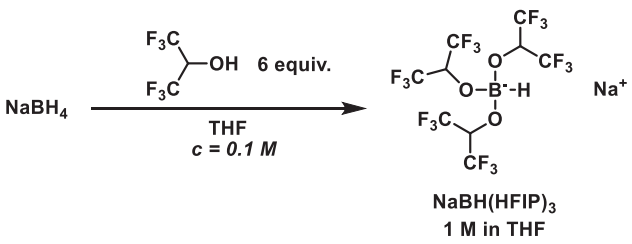
III. Synthesis of indole-fused macrolactone

As previously noticed, macrolactone **67** could be obtained in reasonable yield under specific conditions. It was thought that this reaction was worthy to be developed and applied in due course through a one pot sequence to generate indole skeleton.



Scheme 59: Possible general methodology for the one-pot synthesis of macrolactone.

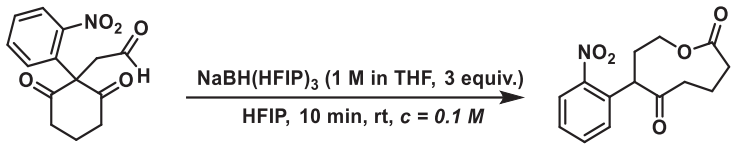
In 1975, Charles S. Sell[47] reported that degree of selectivity of the reducing agents decreased in the following order: $LiAlH(O^tBu)_3$ > $NaBH_4$ > $LiBH_4$ > $LiAlH_4$. We noticed that the use of $NaBH_4$ in MeOH at -20 °C afforded macrolactone **67** in 44% yield. Moreover, the use of a mono hydride source, $LiAlH(O^tBu)_3$ at -78 °C improved the yield up to 60%. According to those results, we turned our attention to mono-hydride reducing agents which would allow chemoselective reduction of aldehydes over ketones. In 2008, Toshima and coworkers reported chemoselective reduction of aldehydes over ketones using sodium tris(hexafluoroisopropoxy)borohydride (scheme 60).[48]



Scheme 60: Synthesis of $NaBH(HFIP)_3$.

This reducing agent proved to be far superior to others previously screened reductant in terms of both selectivity and efficiency (scheme 61), even at room temperature.

[47] Sell,C. S. *Aust. J. Chem.* **1975**, *28*, 1383.
[48] Toshima, K; Matsumura, S; Kuoiwa, Y. *SYNLETT,* **2008**, *16*, 2523.



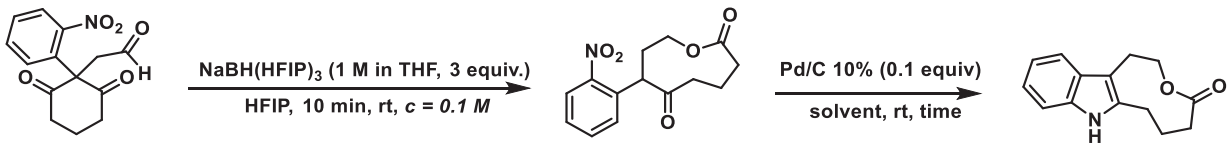
47 50 86%

Scheme 61: First attempt for macrolactone formation using $NaBH(HFIP)_3$.

As shown in scheme 61, using $NaBH(HFIP)_3$ (1 M in THF) afforded full reaction in only 10 minutes. Despite the slight excess of hydride, at room temperature, both lactone and ketone remained untouched. The same yield was obtained when increasing the reaction time from 10 minutes to 7 hours, proving the chemo-selectivity of the reagent. The reduction of the nitro group was then performed.

As shown in table 7, the first attempt was performed though hydrogenation using Pd/C and H_2 in THF (entry 1). Despite compound **75** being obtained in 93% yield, the reduction was very slow and reached full conversion only after 4 days. When the reaction was conducted without purification of the intermediate **67**, the desired macrolactone **75** was obtained in 82% yield over two steps (entry 2). In order to reduce the reaction time, a mixture of THF/^{t}BuOH was envisaged. This solvent system allowed the reduction of the reaction time from 4 days to 24 hours (entry 3). A one-pot process was conducted using HFIP as solvent, but no reaction occurred and intermediate **67** was fully recovered (entry 4).

Table 7: Attempts for the sequential macrolactonization/ nitro reduction.



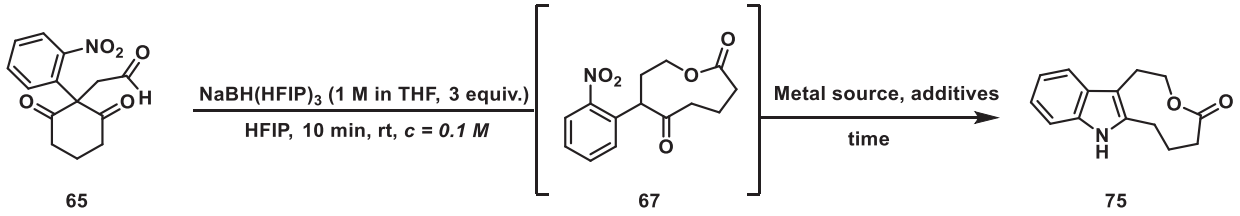
65 67 75

Entry	Intermediate 67	Solvent	Time	Yield product 75	Comments
1	column. 86% yield	THF	4 days	93%	-
2	Only Work-up	THF	4 days	82% over two steps	-
3	column. 88% yield	THF/^{t}BuOH	24 hours	87%	-
4	one pot-process	HFIP	2 days	0%	Compound 67 recovered

Despite palladium-mediated hydrogenation affording the desired product in good yield, we turned our attention to other metals such as titanium, zinc and iron. Results of the two steps one-pot process are presented in table 8. Attempts using titanium (III) chloride (2 M in HCl) were unsucessfull due to the biphasic mixture in HFIP (entry 1). Even when acetone was used as co-solvent, a single phase reaction was not obtained. However, zinc in combination with a saturated solution of ammonium chloride led to full conversion in only 10 minutes at room temperature (entry 2). Unfortunately, the desired product was

obtained in only 40%. Reducing the equivalent of zinc from 100 to 20 (entry 3) afforded **75** in 38% yield within 3 hours. Additionally, a side product was extracted from the aqueous layer (after acidification) corresponding to the hydrolyzed lactone. Attempt using iron powder at 80 °C for 12 hours did not afford any reduction of the nitro group (entry 4). Addition of ammonium chloride to the reaction mixture gave also disappointing results (entry 5). However, addition of acetic acid allowed a clean and fast reduction of the nitro group and provided the desired product **75** in 88% yield in a one-pot process from **65** (entry 6).

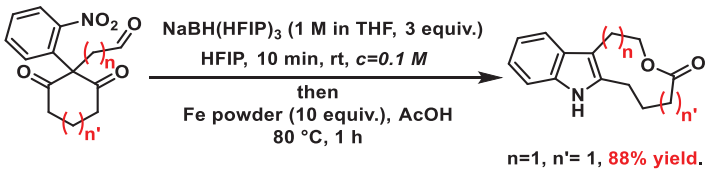
Table 8: Attempts for the one-pot macrolactonization process.



65 67 75

Entry	Metal (equiv.)	Additives	Temp.	Time	Yield	Comments
1	$TiCl_3$, 2 M in HCl (8 equiv.)		rt	-	0%	Even with acetone, titanium miror
2	Zn dust (100 equiv.)	NH_4Cl	rt	10 min	40%	Full conversion
3	Zn dust (2*10 equiv.)	NH_4Cl	rt	3 hours	38%	hydrolized by-product in aqueous phase
4	Fe powder (10 equiv.)	-	80 °C	12 hours	0%	Intermediate recover
5	Fe powder (10 equiv.)	NH_4Cl	80 °C	12 hours	10%	Intermediate recover
6	Fe powder (10 equiv.)	AcOH	80 °C	1 hour	88%	reaction performed in sealed tube

Finally, the best conditions starting from aldehyde **65** for an efficient one-pot reaction is summarized in scheme 62. In connection with our laboratory's interest on indole alkaloids, it could be interesting to explore the reaction scope and apply this one-pot reaction to a more valuable project.



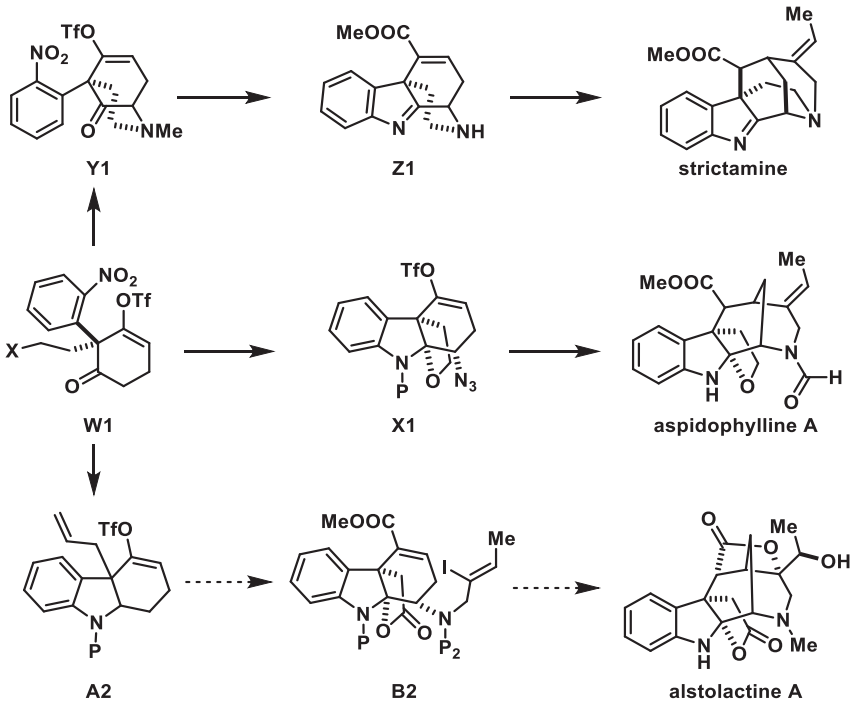
Scheme 62: Efficient one-pot reaction for the synthesis of indole-fused macrolactones

It is noteworthy that regioselective access to 9-membered lactones with a fused indole unit was recently reported from 2-nitrophenyl-1,3-cyclohexanediones.[49] At this point in time it was then decided to undertake the synthetic study of alstolactine A, B & C. Attempts toward those targets will be discussed in chapter III.

[49] Loya, D. R.; Paolis, M. *Chem. Eur. J.***2018**, *24*, 2080.

CHAPTER 3 - Synthetic studies of alstolactine A-C: 1st strategy

Due to its elegant polycyclic molecular architecture, the akuammiline family is of primary interest in our group. As shown in scheme 63, a synthetic strategy was developed for the preparation of akuammiline alkaloids using compound **W1** as a possible platform to generate skeletal diversity. The efficiency of this strategy allowed the recent total synthesis of aspidophylline A and strictamine.



Scheme 63: Platform to provide skeletal diversity of Akuammiline family.

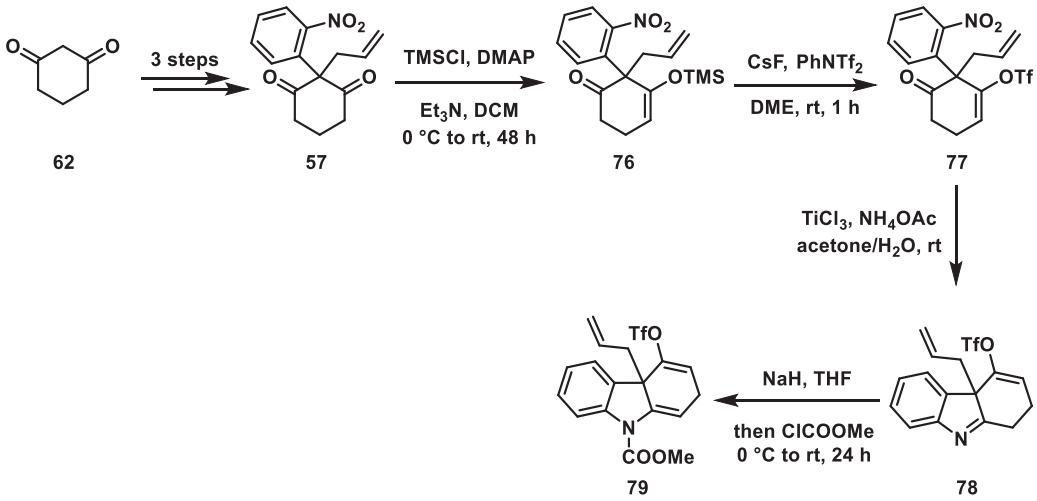
I. Based on literature precedent

The synthesis starts with the elaboration of intermediate **57** which can be prepared in three steps (as shown in scheme 50, p. 33) according to the procedure developed by Bonjoch, Bosch and co-workers.[50] The first part of the synthesis consisted of a nucleophilic aromatic substitution followed by an *O*-allylation and a Claisen rearrangement. This three steps sequence allowed the preparation of the desired intermediate **57** on a multigram scale. Indeed, the sequence was conducted on a 60 grams scale and the final product **57** was obtained *via* recrystallization in EtOAc.

[50] Solé, D.; Bosch, J.; Bonjoch, J. *Tetrahedron* **1996**, *52*, 4013.

Dione **57** was converted to silyl enol ether **76** by treatment with chlorotrimethylsilane, triethylamine and 4-dimethylaminopyridine in DCM. At room temperature, a long reaction time (48 hours) was required to reach full conversion albeit stoichiometric amount of DMAP was used (scheme 64). Due to the acid sensitivity of silyl enol ether, compound **76** was used without further purification and converted into the corresponding enol triflate **77** in 57% yield over two steps. This transformation was first reported in 2002 by Corey and co-workers and consisted of stirring silyl enol ether in the presence of vacuum-dried CsF (3 equiv) and *N*-phenyltrifluoromethanesulfonimide (2 equiv) in freshly distilled DME. [51] It resulted in the in-situ generation of trifluoromethanesulfonyl fluoride gas which trapped the enolate. It is worthy to note that the instantaneous generation of this very toxic gas required to work under extreme caution; nevertheless, this 2 steps sequence was perfomed up to 20 grams scale with a 57% isolated yield of compound **77**.

Due to the presence of both the enol triflate and allyl groups, hydrogenation of the nitro- moiety was not viable. In 1904 Sachs and Sichel reported the reduction of nitroarenes using titanium (III).[52] Later on, Wong and co- workersextended the scope.[53] Since then, this reducing agent has continued to be attractive for chemists eager to develop new synthetic methods.[54] Using these conditions, the nitro group of compound **77** was reduced. Spontaneous condensation of the resulting aniline with the carbonyl group led to the formation of the desired indolenine **78** in 76% yield. Methyl carbamate **79** was then prepared in 77% yield using sodium hydride and methyl chloroformate in THF.

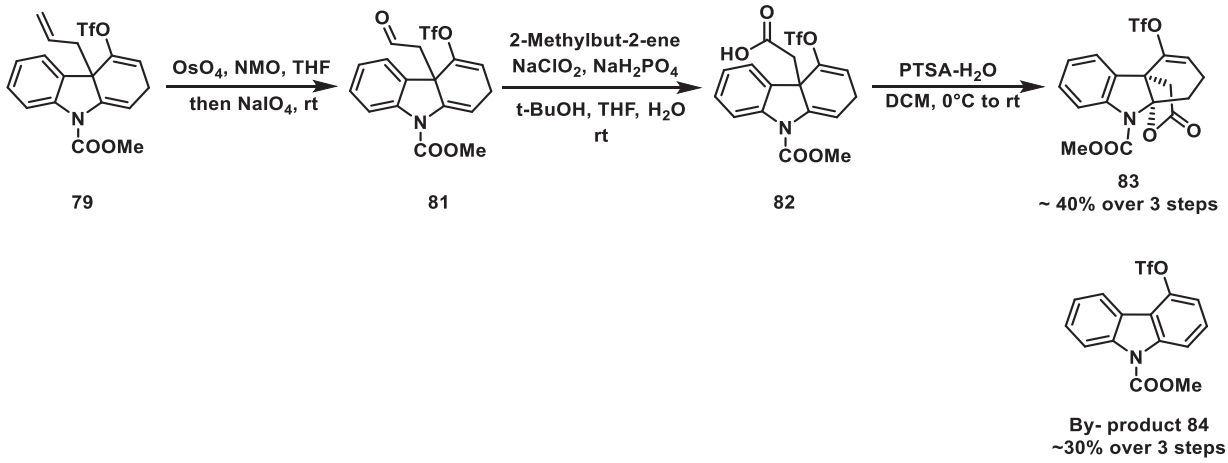


Scheme 64: Synthesis of tricyclic intermediate 79 based on literature antecedent.

[51] Mi, Y. ; Schreiber, J. V. ; Corey, E. J. *J. Am. Chem. Soc.***2002**, *124*, 11290.
[52] Sachs, F. ; Sichel, E. ; *Ber. dtsch. chem. Ges.***1904**, *37*, 1861.
[53] Ho, T, L. ; Wong, C. M.; *Synthesis*, **1974**, *1*, 45.
[54] Tong, S.; Xu, Z.; Mamboury, M.; Wang, Q.; Zhu, J.; *Angew. Chem. Int. Ed.* **2015**, *54*, 11809.

II. Lactone & enone formation

As developed by Dr. Weiwu Ren, lactone **83** was generated in a 3 steps sequence (scheme 65). Aldehyde **81** was prepared *via* dihydroxylation of the allyl group in the presence of catalytic amount of OsO_4 and NMO as co-oxidant[55] followed by a one-pot oxidative cleavage using sodium meta-periodate. The resulting aldehyde was used without further purification in a Pinnick oxidation affording acid **82**. The last lactonization step was performed using PTSA-H_2O in DCM providing the desired lactone **83** in 40% yield over 3 steps. A carbazole by-product **84** was also obtained in 30% yield.

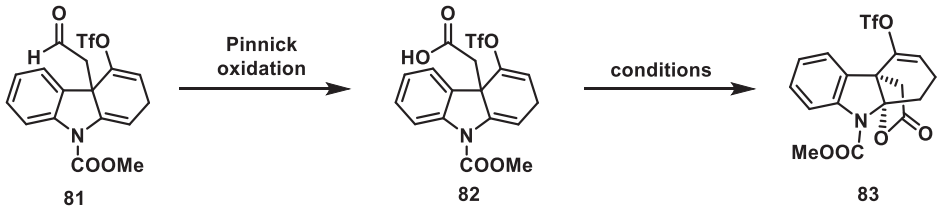


Scheme 65: Synthesis of lactone 83 and formation of carbazole.

As shown in table 9, different acids were examined to promote the formation of desired lactone **83**. When a solution of HCl (1M) in THF was employed no desired product was observed (entry 1). However, a more concentrated HCl solution allowed the formation of the desired product in 50% yield over two steps (entry 2). No reaction was observed when acetic acid in DCM was used (entry 3). Others acidic reagents were then screened such as TFA and TfOH. However, none of them led to satisfactory results (entry 4 and 6). Finally, the best conditions obtained were using PTSA monohydrate in DCM and the desired product **83** was isolated in 67% yield over two steps.

[55] VanRheenen, V.; Kelly, R. C.; Cha, D. Y.; *Tetrahedron Letters*, **1976**, *23*, 1973.

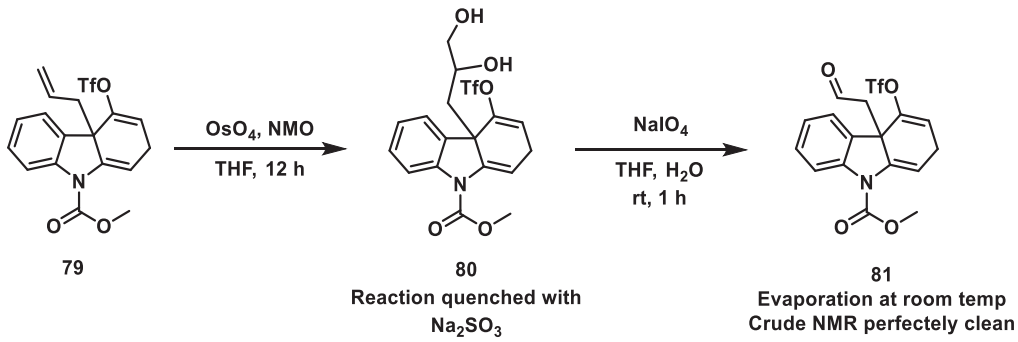
Table 9: Optimization of the lactone formation.



Entry	Conditions	Results
1	HCl (1.0 M), THF, rt	no reaction
2	HCl (4.0 M), THF, rt	50% over 2 steps
3	AcOH, DCM, rt	no reaction
4	TFA, DCM, rt	52% over 2 steps
5	PTSA.H_2O, DCM, rt	67% over 2 steps
6	TfOH, DCM, 0 °C	30% over 2 steps

Although the desired lactone **83** was obtained, the formation of aromatized by-product **84** dramatically reduced the yield of this sequence (scheme 65).

It had also been observed that, during aldehyde formation, carbazole **84** was obtained in 7 to 10% NMR yield. It was suggested that the presence of trace amounts of OsO_4 or NMO in the crude product might lead to oxidation of the cyclohexadiene intermediate. Thus, compound **81** was synthesized *via* a two-steps sequence. After dihydroxylation reaction with OsO_4 and NMO, the reaction mixture was quenched with sodium sulfite. Finally, oxidative cleavage of the crude diol **80** using $NaIO_4$ in water/THF afforded aldehyde **81** without contamination of the carbazole **84** (scheme 66).



Scheme 66: Diol quenched with Na_2SO_3 lead to a constantly clean aldehyde.

Subsequently, aldehyde **81** was converted to carboxylic acid **82** *via* a Pinnick oxidation. Initial studies showed that a large amount of carbazole **84** was formed during the oxidation step based on NMR analysis (Figure 1).

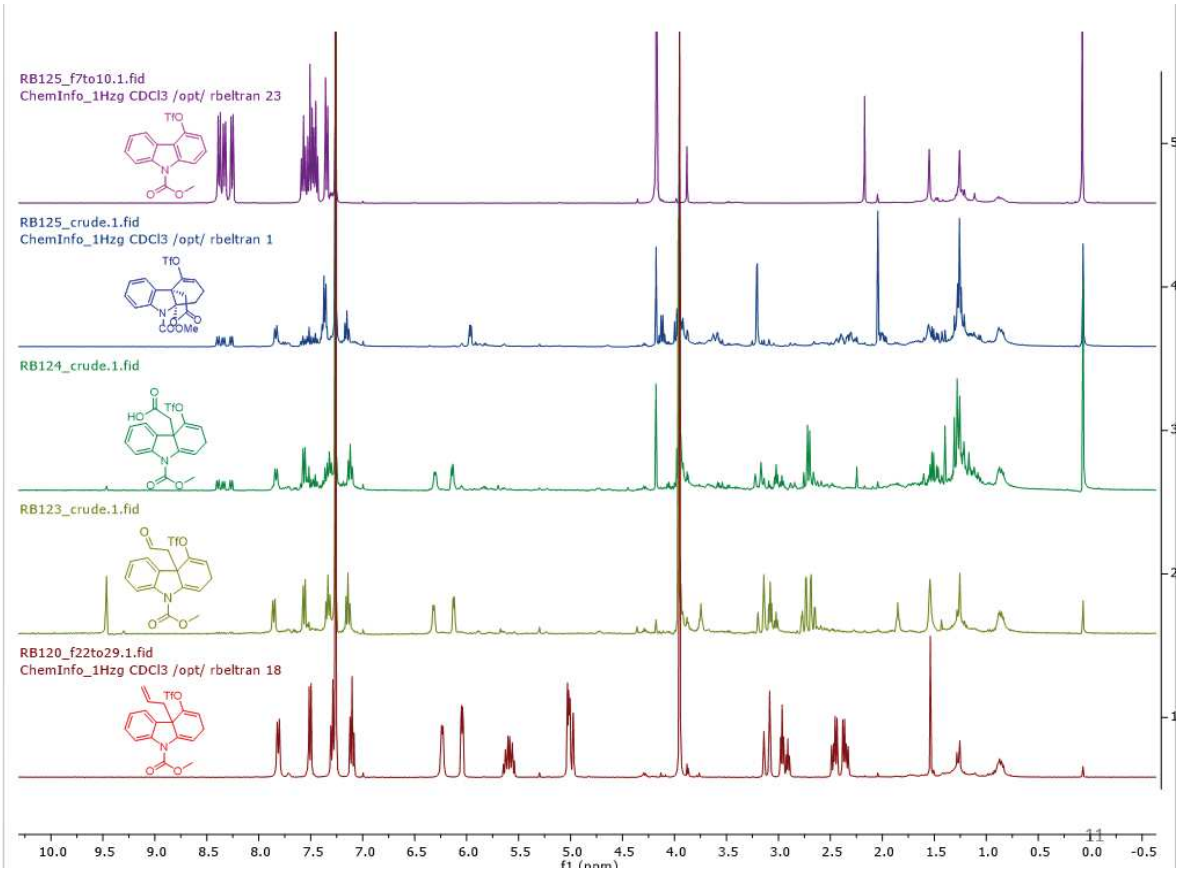


Figure 1: ^{1}H NMR of the crude mixture - Carbazole formed during Pinnick oxidation.

A series of conditions were then screened in order to decrease the amount of aromatized side product **84** formed during the oxidation step (table 10).

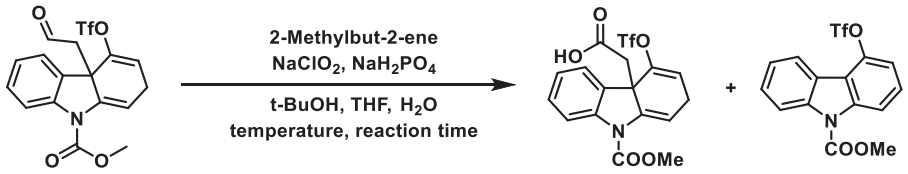
When the reaction time was prolonged to 60 min, a disappointing 1:1 ratio of **82**/**84** was obtained after work-up (entry 1). It was first thought that the acidic pH could be responsible for this retro-mannich type reaction. Thus, the pH was monitored carefully, however it remained neutral during the whole oxidation process. It was then suggested that radical side reactions could be responsible for the formation of the aromatized by-product. Therefore, oxygen was removed via a Freeze-Pump-Thaw sequence (entry 2) but a similar ratio (~1:1) was obtained. The reaction time was then reduced to 40 minutes allowing an enhanced 1:0.15 ratio of **82**/**84** (entry 3). Conducting the reaction at 0 °C did not improve the crude ratio **82**/**84** (entry 4). However, after 30 min, NMR of an aliquot showed only small amount of aromatized product (only 5%).

It was suspected that a part of carbazole **84** could be formed during the work-up or the evaporation. Therefore, it was decided to extract the aqueous layer using DCM instead of EtOAc which would permit a faster evaporation (entry 5). However, similar results to entry 3 were obtained. It was then thought that trace amount of remaining oxidant in the organic layer could be responsible for the aromatization during the evaporation. The work-up was therefore performed using a saturated solution of Na_2SO_3 but the crude

mixture was less clean (entry 6). When the reaction was repeated using a diluted solution of Na_2SO_3 no improvement of the crude ratio was observed (entry 7).

Based on those results, it was concluded that the formation of aromatized by-product could be limited using short reaction time and fast evaporation after work-up. Consequently, with a reaction time of 25 minutes, an extraction using DCM, and an evaporation at 20 °C, the aromatized by-product **84** was generated in only 12% (entry 7).

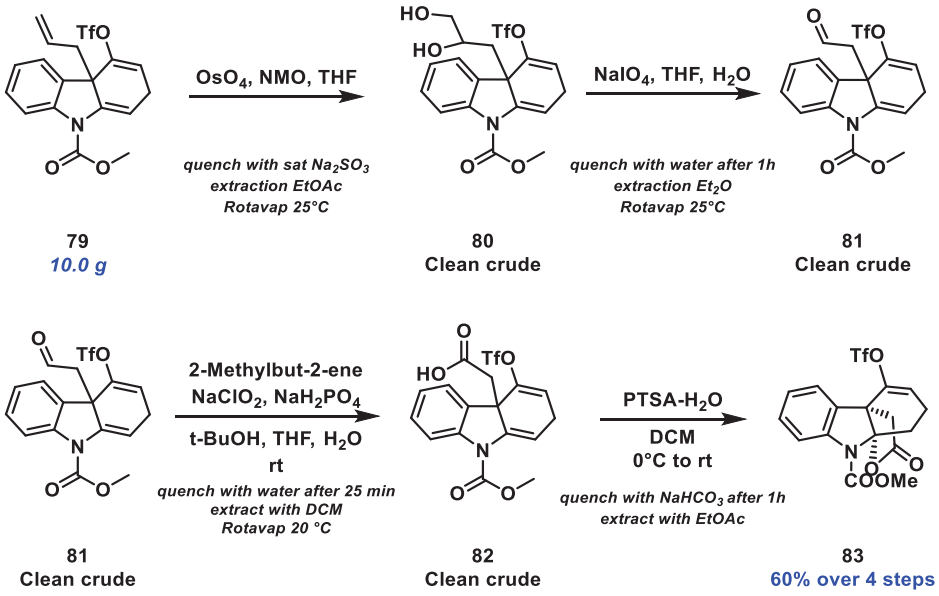
Table 10: Improvement of the Pinnick oxidation, attempts to reduce the amount of 84.



81 82 84

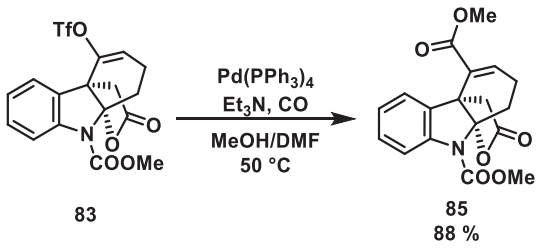
Entry	Pump freeze	Temperature	Reaction time	NMR ratio at 30 min 82/84	Quench and extraction	NMR ratio after work-up 82/84	Comment
1	-	0 °C to rt	60 min	-	quench water extract EtOAc	~1:1	
2	Yes	0 °C to rt	60 min	-	quench water extract EtOAc	~1:1	
3	-	0 °C to rt	40 min	-	quench water extract EtOAc	1:0.15	
4	-	0 °C	40 min	1:0.05	quench water extract EtOAc	1:0.15	
5	-	rt	40 min	1:0.09	quench water extract DCM	1:0.16	
6	-	rt	40 min	1:0.06	quench Na_2SO_3 sat extract DCM	1:0.07	less clean
7	-	rt	40 min	1:0.09	quench water extract DCM wash with 0.1 M Na_2SO_3	1:0.17	
8	-	rt	25 min	-	quench water extract DCM	1:0.12	evaporation at 20 °C

Finally, with the optimized conditions in hand, the four-step sequence provided the desired lactone **83** with an overall yield of 60% (scheme 67). This sequence was repeated several times, up to 10 grams and exhibits high reproducibility.



Scheme 67: Optimized 4 steps sequence for lactone formation.

Starting from previously synthesized lactone **83**, palladium catalyzed methoxycarbonylation was performed in the presence of catalytic amounts of tetrakis(triphenylphosphine)palladium(0), triethylamine and carbon monoxide. The reaction was conducted in MeOH/DMF at 50 °C for 1 h affording the desired α,β-unsaturated ester in 88% yield (scheme 68).



Scheme 68: Palladium catalyzed methoxycarbonylation.

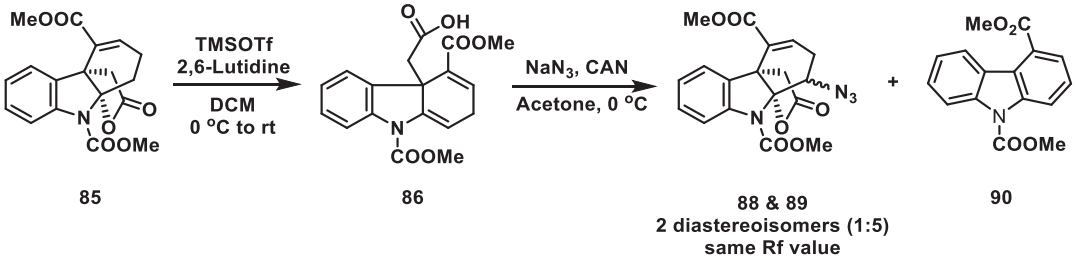
With an efficient route for the preparation of intermediate **85** in hand, we turned our attention to the introduction of the C3-N bond.

III. Synthesis of the azide intermediate

Dr. Weiwu Ren conducted a series of optimization in order to form the C-N bond. Based on the Aspidophylline A total synthesis achieved in our group, it was thought that an azidolactonization cascade could efficiently create the tetracyclic lactone core of the natural product.

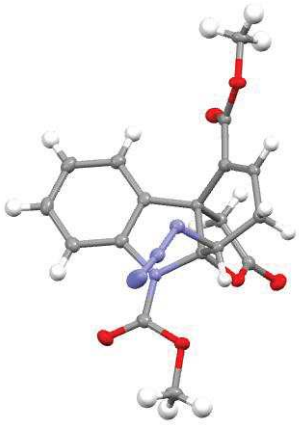
Initial attempts focused on the lactone opening using TMSOTf and 2,6-lutidine as a weak and non-nucleophilic base. Unfortunately, the desired silyl ester was not obtained. In fact, the silyl group was cleaved

during the work-up leading to free carboxylic acid **86**. The azidolactonization was then performed in acetone, at 0 °C, via the dropwise addition of a ceric ammonium nitrate solution into a mixture of the starting material and sodium azide. A mixture of desired products (**88** & **89**) and aromatized product **90** was observed (scheme 69).



Scheme 69: Lactone opening/azidolactonization sequence.

Unfortunately, according to X-Ray analysis, the diastereoselectivity was in favor of the undesired *beta*-isomer.



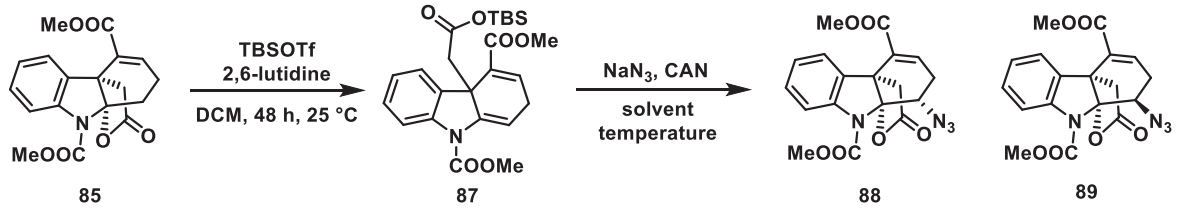
Scheme 70: X-Ray of the trans-isomer.

The second attempt was performed in DCM using TBSOTf instead of TMSOTf in the presence of 2,6-lutidine. Desired silyl ester **87** (table 11) was generated with concomitant formation of the ene-carbamate moiety. Then, intermediate **87** underwent azidolactonization under the conditions described in table 11.

Surprisingly, the desired diastereoisomer was obtained in a 1.1:1 mixture in favor of the desired *cis* product (entry 1). Further optimizations were conducted and the effect of both the temperature and the solvent were examined. When a solution of CAN was added dropwise into a solution of silyl ester and sodium azide at room temperature, the desired diastereoisomer was obtained with a d.r. of 2.5:1 (entry 2). When the reaction was performed at -20 °C, the d.r. decreased dramatically to 1:5 in favor of the *trans* undesired isomer (entry 3). However, increasing the temperature from -20 °C to 20 °C completely reversed the diastereoselectivity to afford a good d.r. of 5:1 in favor of the desired *cis* isomer (entry 4). Additionally, when the reaction was performed at higher temperature, the same d.r. of 5:1 was obtained albeit the crude mixture

was not as clean as for entry 4. Finally, using MeCN instead of acetone as solvent led to a poor d.r. of 1:1 (entry 6).

Table 11: Dr. Weiwu Ren silyl ester 87 formation and d.r. optimizations.



85 87 88 89

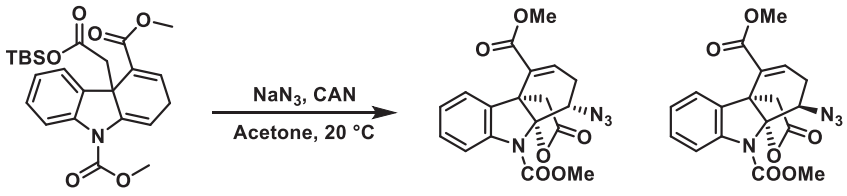
Entry	Conditions	d.r. results 88/ 89
1	acetone 0 °C	1.1:1
2	acetone 0 °C (CAN solution at rt)	2.5:1
3	acetone -20 °C	1:5
4	acetone 20 °C	5:1
5	acetone 40 °C	5:1 (not as clean as 20 °C)
6	acetonitrile 20 °C	1:1

According to these results, it was concluded that conducting the reaction at room temperature in combination with the use of a tert-butyldimethylsilyl protecting group was required to obtain a good d.r. in favor of the desired diastereoisomer.

However, as it was previously observed, the major issue encountered during the azidolactonization cascade was the generation of the aromatized side product **90** in almost 30% yield. Moreover, the optimized conditions which afforded the best 5:1 d.r. were unfortunately not reproducible on larger scale. Therefore, some attempts were dedicated to reduce the amount of aromatized by-product **90** and to improve the diastereoselectivity of the reaction.

As shown in table 12, it was noticed that when the addition of CAN was conducted relatively fast, a reproductible d.r. of 1:1 was obtained (entry 1). However, slower addition resulted in the increase of the d.r. in favor of the desired *cis* isomer. In fact, when the addition was performed with a rate of approximately 1 drop per second (entry 2), comparable to entry 3 (using syringe pump, 0.2 mL/min), the same d.r. of 2.5:1 in favor of the *cis* isomer was obtained. Similar d.r. was observed when 3Å MS were added to the reaction mixture. Interestingly, when the addition rate decreased to 0.1 mL/min (addition over 10 min), the d.r. of 5:1 was obtained (entry 5). On the other hand, performing the addition over 20 minutes decreased the d.r. to 1.5:1 (entry 6).

Table 12: Diastereomeric ratio evolution based on the rate of CAN addition.



87
10 mg scale

88

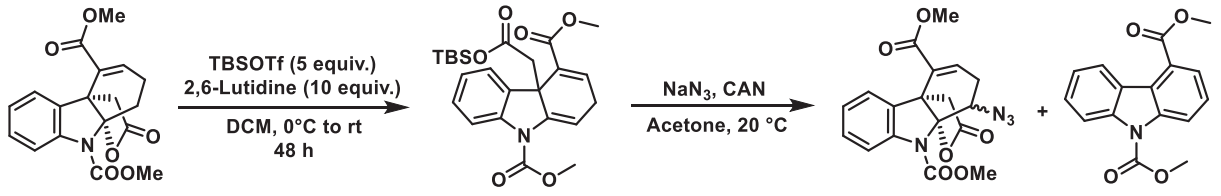
89

Entry	Rate of CAN addition (C = 0.075 M)	d.r. 88/89	Comments
1	Fast addition by hand	1:1	repeated 3 times
2	Slow addition by hand ~1 drop/sec	2.5:1	addition over 5 min
3	syringe pump 0.2 ml/min	2.5:1	addition over 5 min
4	syringe pump 0.2 ml/min	2.5:1	dry acetone with MS
5	syringe pump 0.1 ml/min	5:1	addition over 10 min
6	syringe pump 0.05 ml/min	1.5:1	addition over 20 min
7	syringe pump 0.1 ml/min	2.5:1	control exp entry 5

Unfortunately, when the reaction conditions shown in entry 5 were repeated (entry 7) a d.r. of 2.5:1 was obtained indicating that the addition rate was not the only parameter having an influence on the diasteroselectivity of the reaction. Nevertheless, according to table 12, it was concluded that reducing the addition rate of CAN solution, in general led to the increase of the desired diastereoisomer.

Having obtained both a good yield and a good d.r., it was decided to gradually increase the scale of the reaction (table 13). From 10 mg (entries 1 and 2), the reaction scale was increased to 30 mg with an addition rate of 0.2 mL/min (entry 3). It resulted in a good d.r. of 5.8:1 in favor of the desired isomer. Unfortunately, the same addition rate on a 50 mg scale led to a poor d.r. of 1.5:1 (entry 4).

Table 13: Influence of the addition rate and the reaction scale on the yield and the diastereoselectivity



85 | 87 crude | 88/89 | 90

Entry	Scale	Rate of CAN addition	d.r. 88/89	Crude NMR ratio 88/89/90	Isolated yield	Comments
1	10 mg	0.1 ml/min	5:1	-	-	-
2	10 mg	0.1 ml/min	2.5:1	52/21/27	60%	-
3	30 mg	0.2 ml/min	5.8:1	63/11/26	55%	
4	50 mg	0.2 ml/min	1.5:1	45/30/25	-	
5	50 mg	0.3 ml/min	1.8:1	29/16/45	41%	90 major product
6	50 mg	0.3 ml/min	2:1	57/29/14	73%	Get rid of lutidine
7	100 mg	0.6 ml/min	2:1	28/14/58	-	90 major product
8	200 mg	1.2 ml/min	2.5:1	50/20/30	55%	-
9	100 mg	0.6 ml/min	1.5:1	56/37/7	93%	No traces of lutidine

So far, the best d.r. was obtained with a rate of 0.2 ml/min on a 30 mg scale reaction. Therefore, on a 50 mg scale reaction, the estimated rate should be 0.33 ml/min. When a 0.33 ml/min rate was used for a 50 mg scale reaction (entry 5), the diastereoselectivity slightly increased from 1.5:1 (entry 4) to 1.8:1. However, the mixture of the two diastereoisomers was isolated in only 41% yield (over two steps). This lower yield was attributed to the formation of aromatized by-product **90** in large amount. It was then decided to repeat the same experiment in order to obtain a more reliable yield. In fact, the desired mixture of the two diastereisomers was obtained in 73% yield with a 2:1 d.r. (entry 6) confirming that on a 50 mg scale reaction, a rate of 0.3 ml/min seemed to be more appropriate. The reaction scale was then doubled as well as the rate of the CAN addition. On a 100 mg of scale reaction, using a rate of 0.6 ml/min, the desired product was obtained with a 2:1 d.r. (entry 7). Finally, conducting the reaction on 200 mg scale with a rate of 1.2 ml/min afforded the azide **88/89** in 55% yield with a 2.5:1 d.r. (entry 8).

According to tables 11, 12 and 13, general comments can be made on the diastereoselectivity of the azidolactonization reaction. First of all, the OTBS group is required to favor the desired diastereoisomer. Using the free acid as starting material, the *trans* isomer was major with a 5:1 ratio. In addition, it was noticed that the temperature played a crucial role in the diasteroselectivity of the reaction. Indeed, from -20 °C to 20 °C a reversed diastereoselectivity was observed (table 11, entries 3 and 4). However, it was found that 20 °C was the best compromise between a reasonable diastereoselectivity and a low generation of the aromatized by-product. Moreover, additional experiments showed the importance of the concentration of the reaction

mixture. In fact, the best rate for the addition of the CAN solution seemed to be around 0.6 ml/min on a 100 mg scale reaction.

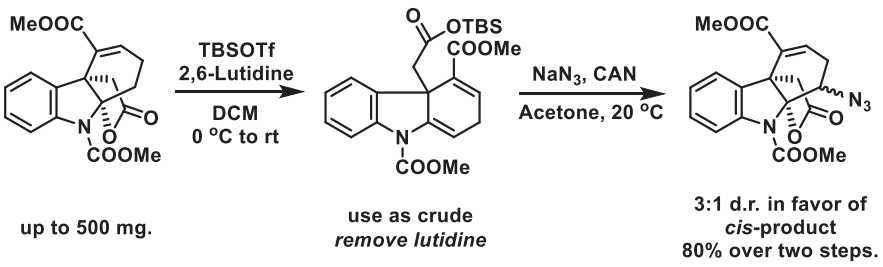
Despite a series of experiments in order to improve the diastereoselectivity on larger scale, the global yield of the azidolactonization cascade remained very fluctuating (table 13). As shown in entries 2 to 8, the desired product was always obtained as a mixture with aromatized by-product **90**. In some cases, this side product was generated as a major product (entries 5 and 7). After careful analysis of crude NMR spectra of the lactone opening reaction, it was noticed that the amount of 2,6-lutidine for entries 5 and 7 was superior to the amount observed for the other experiments.

Although the reaction was very clean, crude compound **87** was always obtained with some remaining 2,6-lutidine. Indeed, elimination of 2,6-lutidine via standard work-up never allowed its complete removal. Moreover, acidic work-up was excluded due to the sensitivity of the silyl ester moiety.

The whole sequence was then repeated (entry 6) and the maximum amount of 2,6-lutidine was removed. Surprisingly, desired product **88/89** was isolated in 73% yield. Control experiments were conducted in order to reproduce this result. The sequence was repeated on 100 mg scale and intermediate **87** was washed several times with brine, allowed to dry on the rotavap (30 °C, ~ 15 mbar) half a day and finally allowed to dry on the oil pump for 12 hours in order to remove all traces of 2,6-lutidine. To our delight, the desired product **88/89** was obtained with an excellent yield of 93% over 2 steps (entry 9). However, the diastereoselectivity decreased to 1.5:1 in favor of the desired product.

According to entry 6 and 9, it was noticed that 2,6-lutidine had an influence on the outcome of the reaction. It was therefore concluded that 2,6-lutidine had to be completely removed from the crude before the azidolactonization cascade reaction.

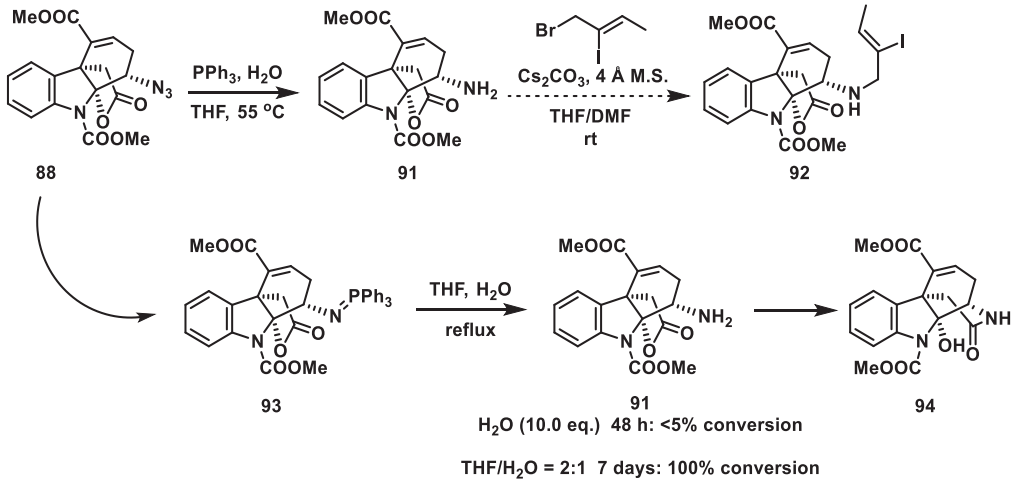
Having all this information in hand, this two steps sequence was performed on a 200 mg scale and was finally repeted regularly on a 500 mg scale. The diastereoselectivirty remained around 3:1 d.r in favor of the *cis*-product with an isolated yield of 75/80% over 2 steps (See scheme 71).



Scheme 71: Two steps sequence for lactone opening & azidolactonization

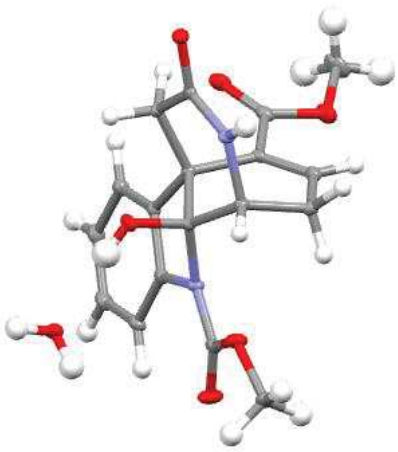
IV. Reduction of azide and *N*-allylation

Our strategy consisted of the reduction of azide **88** *via* a Staudinger reaction followed by nucleophilic substitution with allyl bromide to provide desired product **92**. Unfortunately, as shown in scheme 72, amine **74** was not isolated. Iminophosphorane intermediate **93**, generated during the Staudinger reaction was found to be unusually stable. In order to form the amine, compound **93** was refluxed in THF in the presence of 10 equivalents of water. Surprisingly, after 48 hours, only 5% conversion was observed. It was then decided to increase the THF/H_2O ratio up to 2:1, after 7 days under reflux, the reaction finally reached full conversion.



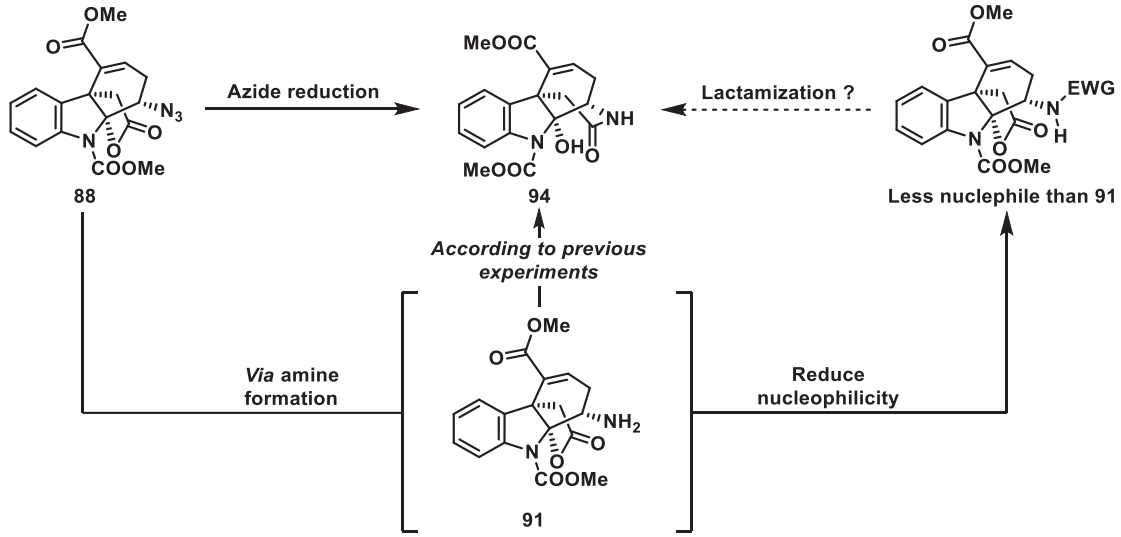
Scheme 72: Attempts for azide reduction/allylation.

Unfortunately, desired amine **91** was not obtained. As shown in scheme 72, lactam **94** was generated as the only product. The translactamization product was confirmed by X-Ray analysis (sheme 73).



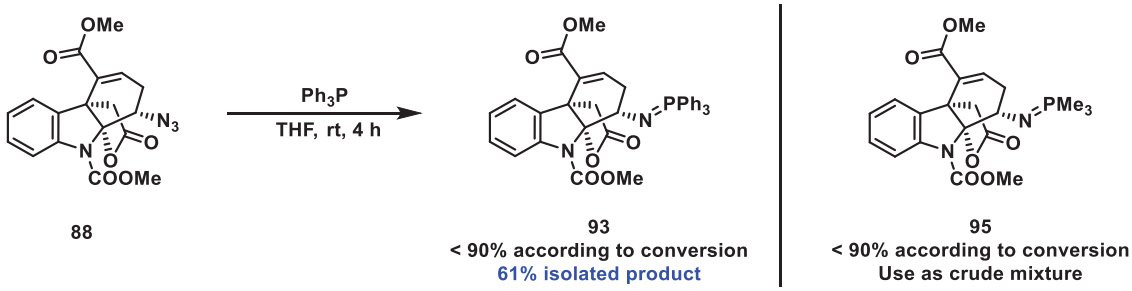
Scheme 73: X-Ray lactam

It was thought that reducing the nucleophilicity of the amine could avoid trans-lactamization (scheme 74). Therefore, attempts for the preparation of carbamates starting from azide **88** were conducted. Because of the double bond of the enone, the reduction was required to be chemoselective.



Scheme 74: Avoid translactamization via direct conversion of azide to t-butyl carbamate.

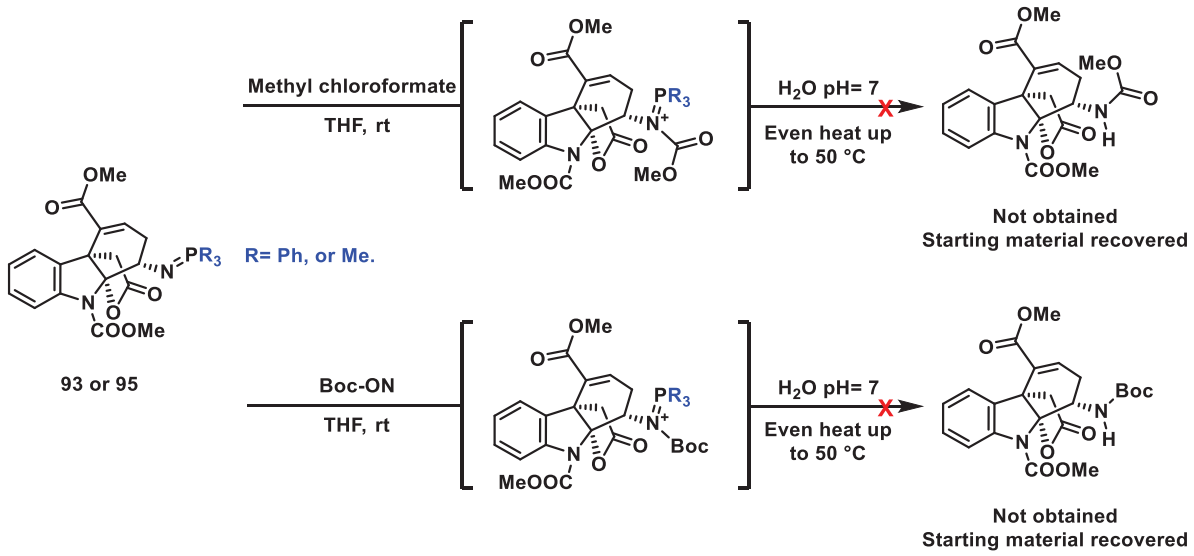
First attempts using phosphine chemistry[56] were envisaged. As shown in scheme 75, desired iminophosphorane **93** was obtained using triphenylphosphine in THF and reached full conversion within 4 hours. Based on crude NMR, the isolated yield was estimated to be around 90%, however, after purification on silica gel the desired product **93** was obtained in only 61% yield. Under similar conditions, using trimethylphosphine, iminophosphorane **95** was obtained. Unfortunately, this compound was not stable on silica gel and was thus used in the next step without further purification.



Scheme 75: Iminophosphorane formation.

[56]a)Afonso, C. A. M.; *Tetrahedron letters*, **1995**, *48*, 8857. b) Ariza, X.; Urpi, F.; Viladomat, C.; Vilarrasa, J.; *Tetrahedron letters*, **1998**, *39*, 9001. c) Ariza, X.; Urpi, F.; Vilarrasa, J.; *Tetrahedron letters*, **1999**, *40*, 7515.

Iminophosphoranes **93** and **95** were then submitted to different electrophiles. As shown in scheme 76, using compound **93** (R = phenyl) with two different electrophiles (Methyl chloroformate or Boc-ON), a precipitate appeared during the reaction. Full consumption of the starting material was also observed by TLC and NMR after a few hours. It was supposed that the observed precipitate could correspond to the proposed intermediates. However, when the reaction was quenched with water at neutral pH, starting material **93** was fully recovered.



Scheme 76: Attempts for trapping iminophosphorane and subsequent hydrolysis.

Unfortunately, changing the R substituent from phenyl to methyl did not lead to satisfactory results. The desired protected amines were never observed. These results were due to the surprising stability of the iminophosphoranes. Based on the preliminary results, it was concluded that generation of free amine **91** using phosphine was probably not appropriate. It was then decided to generate the N-carbamates moiety *via* a one-pot reduction by hydrogenation.

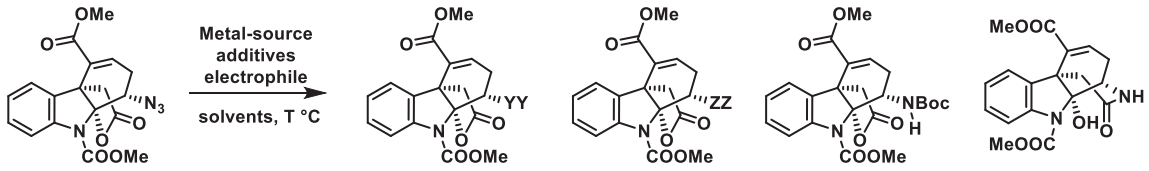
Because of the presence of the α,β-unsaturated ester, the first experiment was performed using Lindlar catalyst (Pd on $CaCO_3$, entry 1, table 14).[57] The reaction reached full conversion after 5 hours but afforded a very messy mixture with at least 6 or 7 compounds. Despite this messy reaction, a small amount of the desired Boc-protected amine was detected. The reaction was therefore repeated using 1.5 equivalents of Boc_2O, instead of 1.1 equiv., leading to larger amount of desired product **96** formed (entry 2). It was then decided to use a large excess of Boc_2O, however, no reaction was observed under this condition (entry 3). Different palladium catalysts were then screened. Palladium poisoned with barium sulfate (entry 4) led to

[57] Reddy, P. G.; Pratap, T. V.; Kumar, G. D. K.; Mohanty, S. K.; Baskaran, S.; *Eur. J. Chem.* **2002**, 3740.

same results as entry 2. Using Pearlman's Catalyst with triethylsilane as hydrogen source also afforded a messy reaction mixture.[58]

Changing the electrophile from Boc_2O to Boc-ON decreased the amount of desired product **96** formed (entry 6). In all cases, hydrogenation using palladium-based catalysts led to a messy mixture of desired product **96**, lactam **94** and other undetermined compounds. Among those unknown compounds, products **C2** and **D2** were constantly obtained in relatively large amount. It was supposed that one of them could be the amine **91** but attempts to purify the products failed.

Table 14:Attempts for the one-pot conversion of azide into t-butyl carbamate.



88 C2 D2 96 94

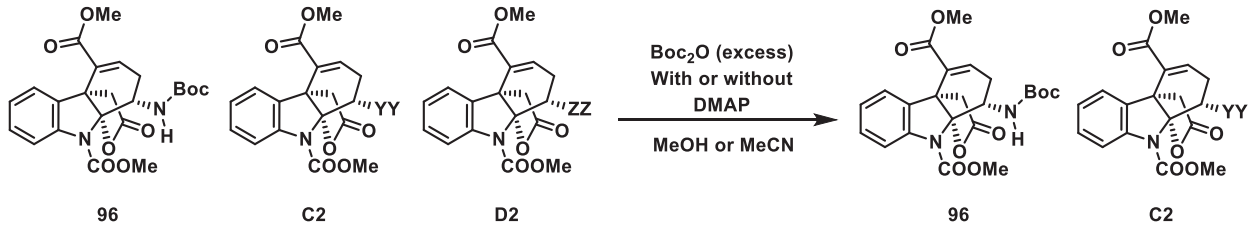
Entry	Metal-source	Additives	E^+	Equiv.	Solvent	T °C	Comment
1	Pd on $CaCO_3$ poisoned with lead	H_2	Boc_2O	1.1	MeOH	rt	~ 5 hours.Messy reaction, 96 observed
2	Pd on $CaCO_3$ poisoned with lead	H_2	Boc_2O	1.5	MeOH	rt	~5 hours. Messy reaction, more 96 observed
3	Pd on $CaCO_3$ poisoned with lead	H_2	Boc_2O	10	MeOH	rt	No reaction
4	Pd on $BaSO_4$	H_2	Boc_2O	1.5	MeOH	rt	Same than entry 2
5	$Pd(OH)_2$	Et_3SiH	Boc_2O	1.5	MeOH	rt	Same than entry 2
6	Pd on $CaCO_3$ poisoned with lead	H_2	Boc-ON	1.5	MeOH	rt	~ 5 hours. Messy, traces 96
7	Zn (100 equiv.)	1 M NH_4Cl	Boc_2O	10	MeOH	rt	~ 30 minutes full conversion. Clean NMR Only 2 compounds. C2, D2
8	Zn (100 equiv.)	$CaCl_2$	Boc_2O	10	MeOH	60 °c	~ 30 minutes. Only lactam 94
9	Pd/C 3 %	H_2	Boc_2O	10	MeOH	rt	~ 30 minutes. Only 2 compounds C2, D2 Cleaner than using zinc.

Some attempts using zinc-mediated reduction were then conducted. As shown in table 14, using zinc dust in combination with ammonium chloride and excess of Boc_2O led to full conversion within 30 min and allowed the formation of only 3 compounds (entry 7). In fact, the desired product **96** was formed as a mixture with undetermined compounds **C2** and **D2**. Interestingly, it was also noticed that compound **C2** slowly converted into **D2** in $CDCl_3$. The reaction was then performed using zinc dust and calcium chloride at 60 °C and afforded lactam **94** as the only product. According to previous experiments, it was noticed that a short

[58] Kotsuki, H.; Ohishi, T.; Araki, T.; *Tetrahendron Letters*, **1997**, *38*, 2129.

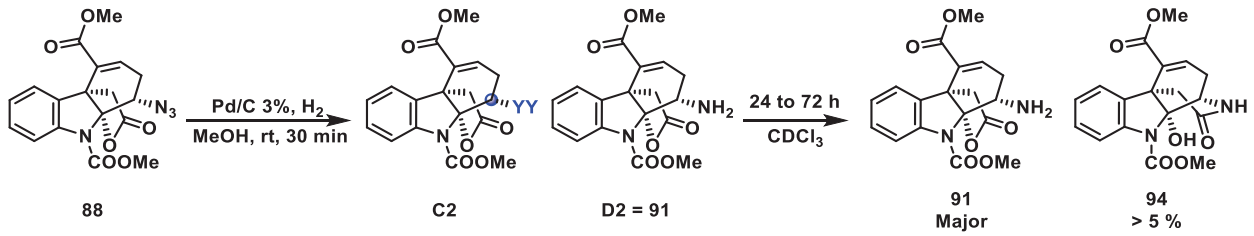
reaction time led to cleaner reaction and avoided the lactam formation. Moreover, longer reaction times or heating resulted in the lactam **94** as a major product. Despite the presence of the α,β-unsaturated ester, hydrogenation in the presence of Pd/C was examined (entry 9). The reaction was complete within 30 min and afforded a mixture of **C2**, **D2** and **96** cleaner than entry 7.

Under hydrogenation conditions (entry 9 table 14) it was decided to push the conversion toward the N-Boc desired product. The crude mixture of **C2**, **D2** and **96** was then submitted to excess of Boc_2O in MeOH or MeCN (scheme 77). Interestingly, the amount of desired NHBoc product **96** increased as well as the amount of compound **D2** decreased. This observation supported the hypothesis that compound **D2** could be the free amine specie. Unfortunately, prolonged reaction time (often 24 hours) generated side products, even in the presence of DMAP. Moreover, the amount of compound **C2** remained unchanged during the reaction.



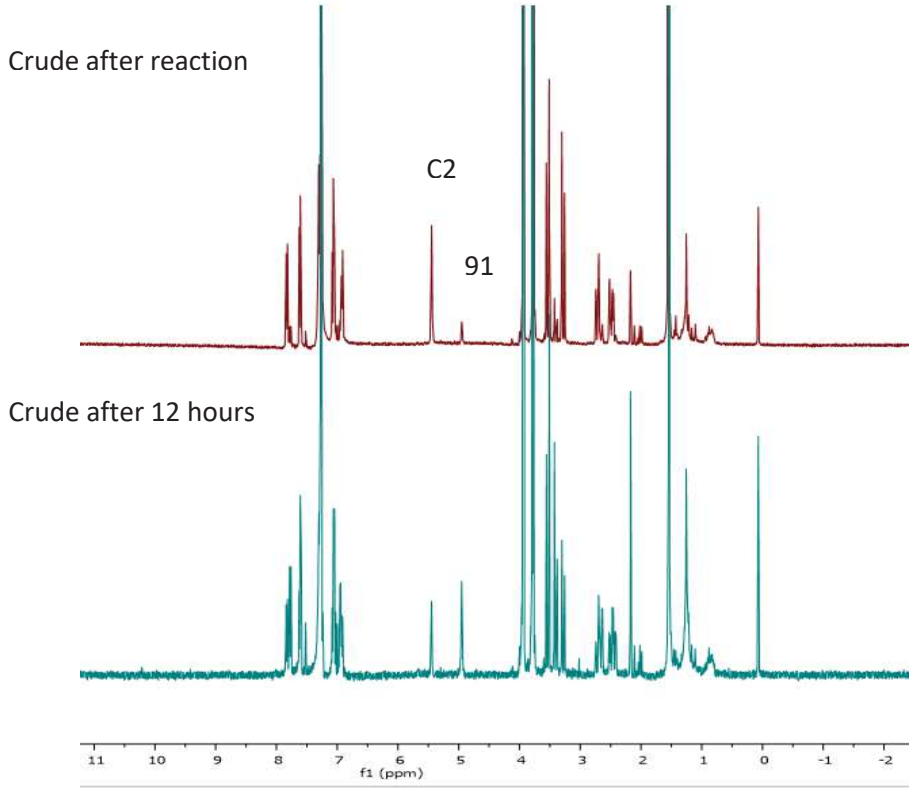
Scheme 77: Attempts to push the Boc protection.

Then, the reduction of the azide using palladium on charcoal as catalyst was repeated without Boc_2O. NMR analysis of the crude mixture of **C2** and **D2** were then performed (scheme 78). As expected, it was confirmed that compound **D2** was the free amine **91**. However, the structure of **C2** remained unclear. Indeed, according to NMR analysis, the general structure of compound **C2** was similar to azide **88** and amine **91**. The only difference was attributed to the function highlighted in blue. The carbon highlighted in blue (scheme 78) was present at 64 ppm in ^{13}C NMR whereas the corresponding carbon was present at 58 ppm for starting material **88**, at 45 ppm for the amine **91** and 53 ppm for lactam **94**.



Scheme 78: Chemo-selective azide reduction by hydrogenation and evolution of by-product C2 in $CDCl_3$.

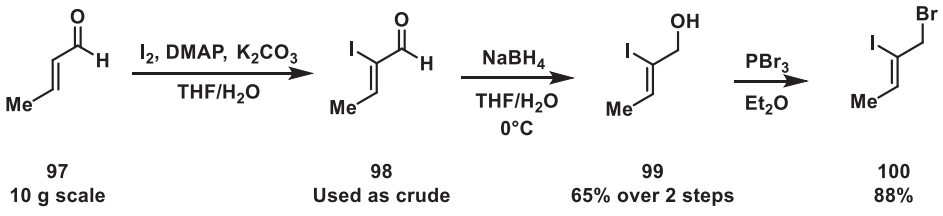
Moreover, as previously observed, compound **C2** was converted to the desired free amine **91** in deuterated chloroform (scheme 79). Unfortunately, attempts to purify the free amine on silica gel promoted the undesired lactamization reaction.



Scheme 79: Conversion of C2 to 91 in $CDCl_3$ after 12 hours

Since it was noticed that using Pd/C in MeOH allowed the formation of amine **91** without lactamization, it was decided to undertake the next step: allylation of the free amine moiety.

Desired allyl bromide **100** was prepared in 3 steps starting from *trans*-crotonaldehyde (scheme 80)[59]. The first step consisted in α-iodination using iodine, DMAP and potassium carbonate in a mixture of THF/water. Subsequent reduction of the unstable aldehyde using sodium borohydride generated the alcohol **99** in 65% yield over 2 steps. The last step was performed using phosphorus tribromide in diethyl ether to afford the desired product in 88% yield.

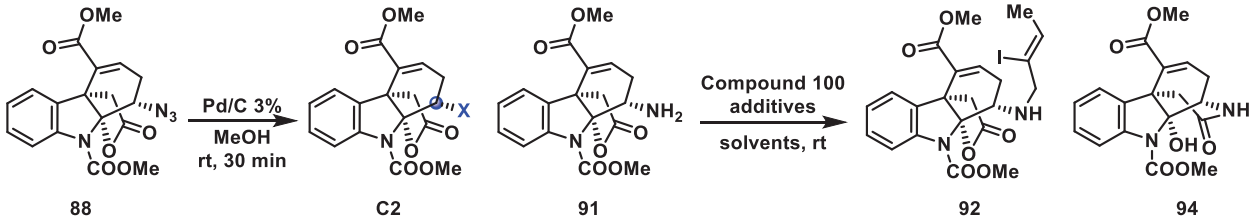


Scheme 80: Allyl bromide preparation through a 3 steps sequence.

[59] Yin,W.; Shahjahan Kabir, M.; Wang, Z.; Rallapalli, K. S.; Ma, J.; Cook, M. J. *J. Org. Chem*, **2010**, *75*, 3339.

With the desired allyl-bromide **100** in hand, allylation of free amine **91** was examined (table 15). The first reaction was performed in a THF/DMF mixture but a messy reaction was obtained (entry 1). To favor the S_N2, the reaction was performed in DMF with a catalytic amount of potassium iodide (entry 2). Under these conditions, the desired product was observed in small amount in a mixture of lactam and many side products. Using another iodide source (entry 3) or adding molecular sieves (entry 4) did not provide better results.

Table 15: Attempts for amine allylation.

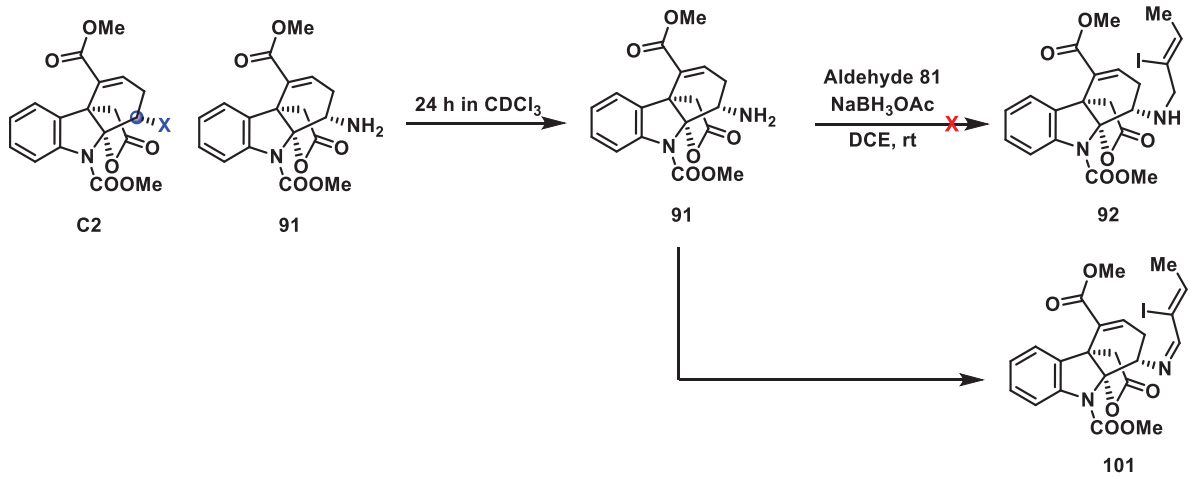


88 C2 91 92 94

Entry	Additives	Solvent	Comment
1	-	THF/DMF	Messy
2	KI	DMF	92 (small amount) + lactame. Messy
3	NBu_4I	DMF	92 (small amount) + lactame. Messy
4	KI + MS 3A	DMF	92 (small amount) + lactame. Messy

Performing the reaction *via* a nucleophilic substitution led to a slow reaction (around 24 hours). Consequently, the amine moiety lactamized before the substitution of allyl bromide. It was then decided to generate the allyl amine **92** via reductive amination. It was thought that the imine intermediate should be rapidly formed avoiding lactamization, and subsequent imine reduction would afford the desired allylated product.

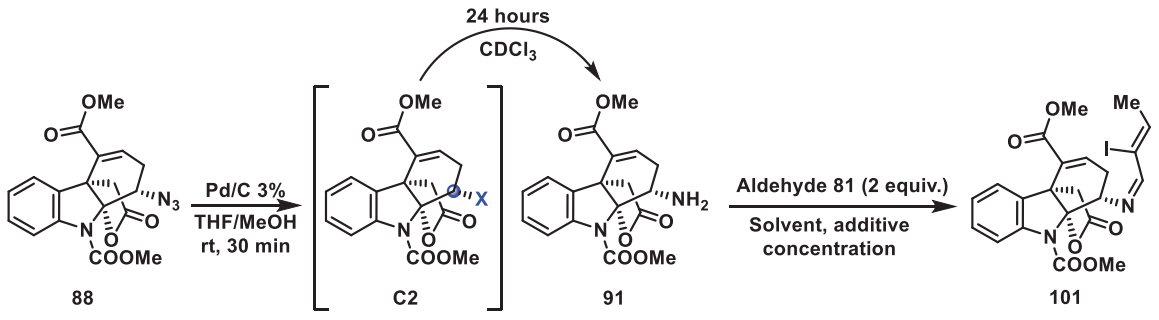
Based on this hypothesis, azide **88** was reduced under the previously described conditions (H_2, Pd/C in THF/MeOH) affording undetermined **C2** compound and free amine **91**. After 24 hours in chloroform, undetermined **C2** compound was totally converted into amine **91** (Scheme 81). This amine was then submitted to aldehyde **98** in the presence of sodium triacetoxyborohydride. As shown in scheme 81, under this condition, imine **101** was obtained as the only product even when the reaction time was prolonged to 24 hours. To our delight, lactam **94** was not obtained, indicating that imine formation was faster than lactamization.



Scheme 81: First attempt for reductive amination.

It was then decided to optimize each step of the reductive amination: the imine formation and its reduction. During the optimizations, it was noticed that the azide reduction was even cleaner using a mixture of THF/MeOH as solvent. The amine was then submitted to different conditions in order to generate imine **101** (table 16). Using DCE as solvent (c = 1 M) and on absence of additive, the desired imine was obtained in 10 hours (entry 1). Using MeOH and 3 Å MS, imine **101** was obtained in 6 hours. Purification on silica gel afforded only 32% yield of the imine (entry 2). Increasing the mixture concentration from 0.1 to 0.2 M shortened the reaction time to 5 hours (entry 3). This time, the purification was performed by adding 1% Et_3N to the eluent affording the desired product **101** in 61% yield over 2 steps. It was noteworthy that using the imine in a one-pot process avoided decomposition during the purification on silica gel.

Table 16: Optimizations for the imine formation.

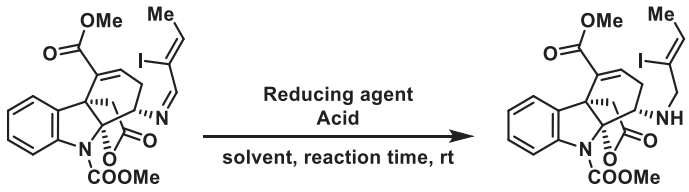


Entry	Solvent	Additives	[C]	Yield	Comments
1	DCE	-	0.1	-	Reaction time: 10 hours
2	MeOH	Ms 3 Å	0.1	32%	Reaction time: 6 hours. Classic column
3	MeOH	Ms 3 Å	0.2	61%	Reaction time: 5 hours. 0.1% Et_3N with eluent

Nevertheless, it was decided to examine the reduction of the imine **101**. As described in table 17, when $NaBH(OAc)_3$ was used in DCE, no reaction occurred (entry 1). However, addition of AcOH allowed a

slow reduction of the iminium species. Unfortunately, the reaction did not reach full conversion and needed further addition of reagent, leading to an unclean reaction (entry 2). Using $NaBH_4$ in MeOH did not afford better results (entry 3). Using 1.5 equivalents of $NaBH_3CN$ in MeOH and 1.5 equivalents of AcOH afforded a clean reaction even if full conversion was not reached (entry 4). Finally increasing the amount of $NaBH_3CN$ to 3 equivalents afforded desired product **92** in 79% yield (entry 5). The use of PTSA afford the same result (entry 6).

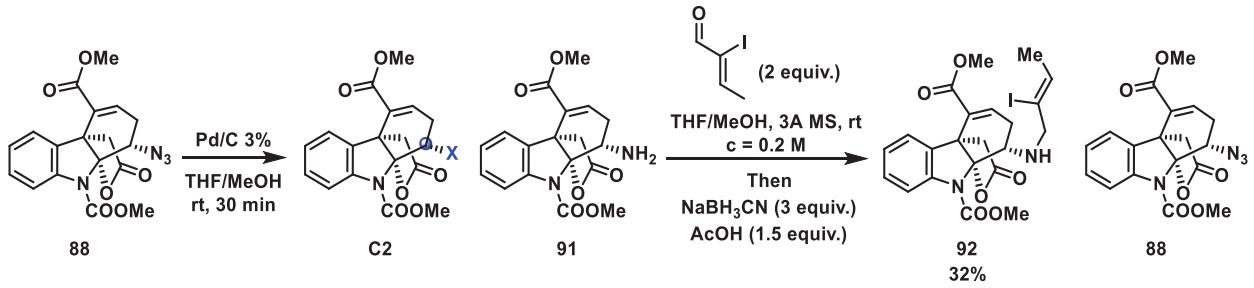
Table 17: Optimizations for the Imine reduction.



101 92

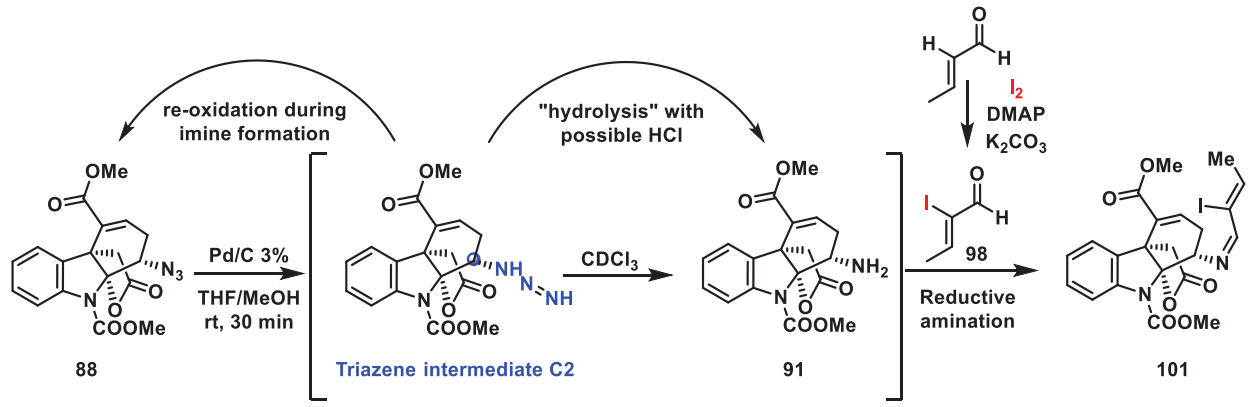
Entry	Solvent	Reducing agent	Equiv	Acid	Equiv.	Comment
1	DCE	$NaBH(OAc)_3$	1.5	-		No reaction
2	DCE	$NaBH(OAc)_3$	1.5	AcOH	1.3	Not complete
3	MeOH	$NaBH_4$	2	AcOH	1.3	Messy
4	MeOH	$NaBH_3CN$	1.5	AcOH	1.5	Not complete
5	MeOH	$NaBH_3CN$	3	AcOH	1.5	Clean. 79% isolated yield.
6	MeOH	$NaBH_3CN$	3	PTSA	1.5	same

With optimized conditions for the stepwise process in hand, the one-pot reductive amination was envisaged. Since it was noticed that unknown intermediate **C2** was converted into free amine **91**, the one-pot reductive amination using the mixture of **C2** and **91** (scheme 82) was undertaken. According to table 16 and 17, the best solvent for this reductive amination should be MeOH. However, when MeOH was added to the crude mixture of **C2** and amine **91** a precipitate appeared. The addition of THF in a 1:1 ratio with MeOH allowed the complete solubilization of both compounds **C2** and **91**. After mixing with aldehyde and after full conversion of both **C2** and **91** (followed by TLC) was reached, $NaBH_3CN$ and AcOH were added to the reaction mixture affording desired product **92** in 32% yield over 2 steps. Surprisingly, some azide **88** (~20% according to crude NMR) was recovered, even though TLC monitoring of the hydrogenation indicated full conversion of the starting material.



Scheme 82: Complete azide reduction/reductive amination sequence.

Since the amine was not oxidized into the azide under the conditions used for reductive amination, this intriguing result was most probably due to the re-oxidation of unknown compound **C2** during the imine formation. Therefore, it was concluded that compound **C2** could be an intermediate formed during the reduction of azide **88** into amine **91**. According to mass spectrometry and NMR analysis, a triazene intermediate was proposed as plausible structure (scheme 83).



Scheme 83: Triazene intermediate as proposed structure for the "unknown" product.

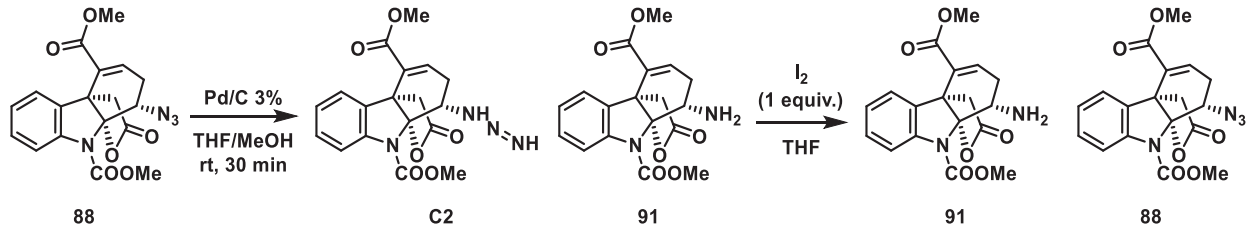
The monosubstituted triazenes are transiently produced during the reduction of azides, followed by elimination of nitrogen spontaneously to yield the amine products. While aromatic triazenes have been isolated as unstable compounds, aliphatic monosubstituted triazenes are rarely encountered in scientific literature. Indirect evidence of their formation was first provided by the isolation of triazoles resulting from intramolecular interaction of a triazene with geminal nitrile or carboxylic ester groups.[60,61] Later, in 1994, the group of Gaoni reported for the first time a series of isolable and stable triazenes obtained by catalytic hydrogenation of a number of tertiary azides.[62] Gaoni concluded that the stability of the triazene seemed to be directely related to the bulkiness of the environnement. He reported that triazenes were unstable under heating (reflux in EtOAc) and more interestingly, he noticed that the pH of the solution was a critical factor

[60] Hohenlohe-Oehringen, K. *Monatsh. Chem.* **1958**, *89*, 557.
[61] Hohenlohe-Oehringen, K. *Monatsh. Chem.* **1958**, *89*, 562.
[62] Gaoni, Y. *J. Org. Chem.* **1994**, *59*, 6853.

for the stability of triazenes. Indeed, silica gel caused some decomposition of the less stable triazenes, and their half-lifes were shortened in acidic media.

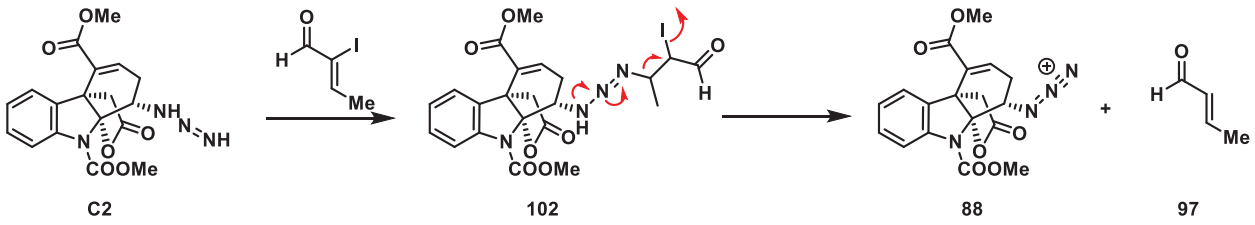
The characteristics of aliphatic monosubstituted triazenes described by Gaoni are consistant with the observation previously done about the **C2** intermediate. Indeed, in our case it was observed that the presence of HCl in deuterated chloroform allowed the hydrolysis of the triazene leading to the amine **91**.

Regarding the oxidation step, it was first supposed that the remaining trace of iodine in aldehyde **98** (scheme 83) could be responsible for the triazene oxidation, leading to the regeneration of the azide. Although α-iodination reaction was worked-up using sodium thiosulfate, it was thought that trace amount of iodine remained in the crude. Therefore, a control experiment was conducted in order to evaluate the influence of iodine on the oxidation of triazene (scheme 84). The azide was first reduced under the established conditions and the crude triazene/amine mixture was submitted to one equivalent of iodine in THF. As expected, the triazene intermediate was converted into azide **88** in only 30 min.



Scheme 84: control experiment using I_2.

It was also supposed that the aldehyde itself could regenerate the azide. Indeed, as shown in scheme 85, after 1,4 addition of the triazene **C2** on aldehyde, intermediate **102** could be formed. Subsequent iodide elimination could regenerate azide **88**.



Scheme 85: Second proposition for the reoxidation of triazene to azide.

According to previous results, it was clear that triazene **C2** had to be fully converted into amine **91** before conducting the reductive amination. Some reports described the conversion of triazene species to the corresponding amines under mild conditions using TFA in DCM . [63,64] Therefore, the mixture of triazene **C2**

[63] Bräse, S.; Köbberling, J.; Enders, D.; Lazny, R.; Wang, M.; *Tetrahedron letters*, **1999**, *40*, 2105.
[64] Bräse, S.; Köbberling, J.; Enders, D.; Lazny, R.; Poplawski, J.; *Synlett*, **1999**, *8*, 1304.

and amine **91** was treated with one equivalent of TFA in DCM. Unfortunately, a messy mixture was obtained after one hour. When 0.2 equivalent of TFA was used, full conversion of triazene **C2** into free amine **91** was reached in only 10 min. However, the conversion was not clean. Similar experiment using acidic conditions (NH_4Cl, AcOH, H_2SO_4, PTSA, HCl) in catalytic amount did not help to get a clean formation of the amine **91**. Attempts to get a thermal decomposition of the triazene **C2** under various solvent systems also led to decomposition or lactamization.

The relative stability of the triazene under various conditions turn out to be a problematic point to continue the sequence in an efficient way. As shown previously, metal-catalyzed (Pd/Zn/Fe) reduction led to lactamization or unclean reaction. Hydrogenation using Pd/C allowed the formation of the amine in mixture with the triazene which was impossible to convert cleanely to the amine in a reproducible maner. After additional attempts we turned our attention to the use of Raney Nickel. Although Raney nickel is mostly used for its unusual property of reducing C-S bonds to C-H bonds, it is also a powerful reducing agent to cleave N-N and N-O bonds. After optimizations, it turned out that a specific type of Raney-Nickel proved to be an optimal solution for a clean and reproducible reduction, without formation of either triazene or translactamization product.

Historically, Murray Raney joined the "Lookout Oil and Refining Company" in Tennessee with responsibility for installation of electrolytic cells for the production of hydrogen which was used in the hydrogenation of vegetable oils. At that time, the industry used a nickel catalyst that was prepared by hydrogen reduction of supported nickel oxide. Raney believed that better catalysts could be produced and, in 1921, he created his own research company. In 1924, he prepared a 50% nickel-silicon alloy which was treated with aqueous sodium hydroxide to provide a greyish metallic solid which was then tested by hydrogenation of cottonseed oil. He found at that the activity of this catalyst was five times greater than the best catalyst used in industry. Murray Raney applied for a patent which was issued on December 1, 1925. [65] Subsequently Raney produced a nickel catalyst by leaching a 50 wt% Ni-Al alloy in aqueous sodium hydroxide, the resulting catalyst was even more active and a patent application was filled in 1926. [66]

Since Murray's discovery, many types of Raney-Nickel have been reported. This catalyst is generally prepared by the selective removal of aluminum from the alloy particles using aqueous sodium hydroxide. The dissolution of aluminum in aqueous sodium hydroxide generates sodium aluminate ($NaAlO_2$). This process requires a high concentration of sodium hydroxide in order to avoid the formation of aluminum hydroxide which precipitates as bayerite. The bayerite deposition causes a blocking of pores and surface sites formed

[65] Raney, M. *Ind. Eng. Chem.* **1940**, *32*, 1199. Raney, M. *US Patent*, 1563587, **1925**.
[66] Raney, M. *US Patent*, 162810-, **1927**.

during the leaching, it therefore decreases the active surface area and reduces the catalyst activity. The temperature used to leach the alloy has a marked effect on the pore structure and surface area of the catalyst. As show in table 18, concentration, temperature, time of leaching and wash method can be combined in order to generate Raney/Nickel with different properties.

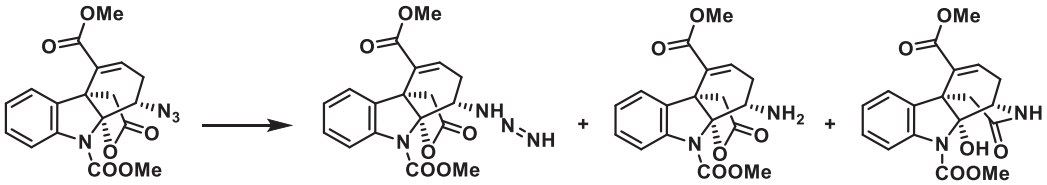
Table 18: Raney/Nickel from W-1 to W-7

Type	NaOH/Al (molar)	NaOH soln. conc. (wt%)	Temp. (°C) (time, h)	Water wash method
W-1	1.65	17	115-120 (4)	Decant to neutral
W-2	1.71	20	75-80 (8-12)	Decant to neutral
W-3	1.73	20	50 (0.83)	Continuous to neutral
W-4	1.73	20	50 (0.83)	Continuous to neutral
W-5	1.80	21	50 (0.83)	Continuous to neutral
W-6	1.80	21	50 (0.83)	Continous to neutral
W-7	1.80	21	50 (0.83)	Directly washed with EtOH

It is important to mention that those Raney/Nickel catalysts are extremely pyrophoric due to the small sizes of the metal crystallites that form during the leaching process. If the catalysts are allowed to dry in air the metal particles rapidly oxidize generating large amounts of heat. It is therefore important that after its preparation, the catalyst has to be properly stored in H_2O, MeOH or EtOH.

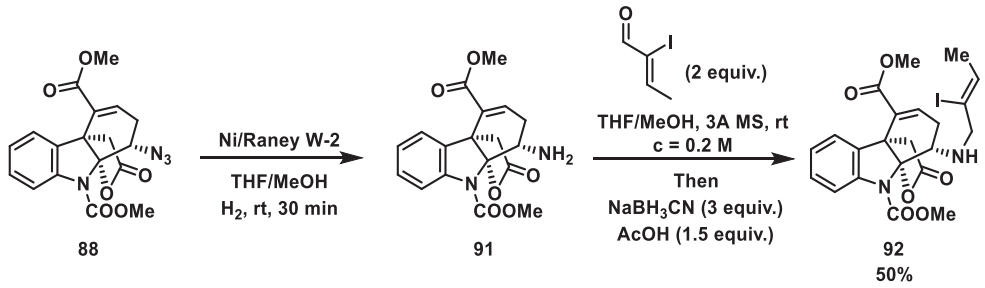
As shown in table 19 when azide **88** was submitted to commercial Ni/Raney (entry 1) in a mixture of THF/MeOH at room temperature lactam **94** was obtained as the only product. Changing temperature (entry 2) or solvent (entry 3 and 4) did not modify the outcome of the reaction. Changing the supplier of Ni/Raney from Acros (activated catalyst, 50% slurry in water) to Merck (entry 5) or VWR (Raney nickel catalyst activated for hydrogenation, with about 50% water, entry 6) provided similar results. However, using Ni/Raney from Aldrich (Raney 4200 nickel, active catalyst, slurry in water, entry 7) afforded an interesting result. For the first time, it was possible to observe amine **91** without triazene intermediate **C2.** Unfortunately, 30% of the lactam was formed during this experiment. Moreover, the reaction turned out to be unreproducible, as shown in entry 8. Changing solvent and temperature (entries 9, 10, 11) did not improve this result. Difficulties encountered led us to focus on uncommercial Raney-Nickel. We were delighted to see that the use of “home-made” Ni/Raney W-2 in a 1:1 mixture of THF/MeOH afforded desired amine **91** in a very short reaction time, without observation of triazene **C2** and almost without lactam **94** formation (entry 12). Entry 13 and 14 indicated that a mixture of solvent was necessary. The reaction turned out to be fast, and reproducible as long as the Ni/Raney W-2 was freshly prepared before conducting the reduction. Indeed, it was observed that the older batch of “home-made” Ni/Raney W-2 was more prone to cleave the azide.

Table 19: Screening of Ni/Raney for the reduction of azide 88



Entry	Reagent	Solvent	Temp (°C)	Results (NMR ratio: C2/91/94)
1	Ni/Raney (acros)	THF/MeOH 1:1	rt	After 5 min, only lactam.
2	Ni/Raney (acros)	THF/MeOH 1:1	0 °C	Only lactam
3	Ni/Raney (acros)	MeOH	rt	Only lactam
4	Ni/Raney (acros)	THF	rt	Only lactam
5	Ni/Raney (Merck)	THF/MeOH 1:1	rt	Only lactam
6	Ni/Raney (VWR)	THF/MeOH 1:1	rt	Only lactam
7	Ni/Raney (Aldrich)	THF/MeOH 1:1	rt	Good result: 0:70:30
8	Ni/Raney (Aldrich)	THF/MeOH 1:1	rt	Not reproducible: 0:50:50
9	Ni/Raney (Aldrich)	THF/MeOH 1:1	0 °C	Not better
10	Ni/Raney (Aldrich)	MeOH	rt	Lactam
11	Ni/Raney (Aldrich)	THF	rt	Same than 7
12	Ni/Raney W-2 (home-made)	THF/MeOH 1:1	rt	Really good 0:98:2
13	Ni/Raney W-2 (home-made)	THF	rt	Slow, less good
14	Ni/Raney W-2 (home-made)	MeOH	rt	Precipitation/not good

Finally, the two steps sequence was performed without further purification of amine **91**. Crude amine **91** was then mixed with aldehyde **98** until full conversion to the imine was observed by TLC. Then, the reducing agent $NaBH_3CN$ and AcOH were added in order to generate the desired product **92** in 50% yield over two steps (scheme 86).

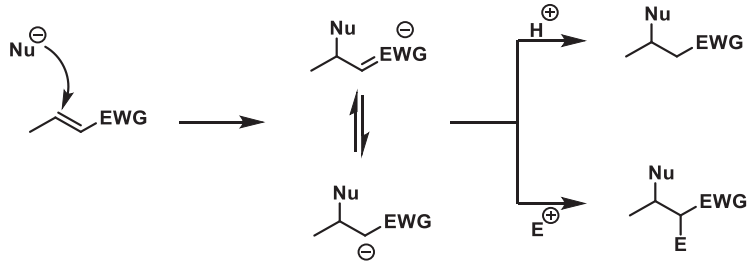


Scheme 86: Two steps sequence toward compound 92

This sequence was performed on a 100 mg scale without any troubles. Having intermediate **92** in hand, it was decided to move to the most challenging step of the strategy: the 1,4-addition of the vinyl iodide to the α,β-unsaturated ester.

V. Key steps

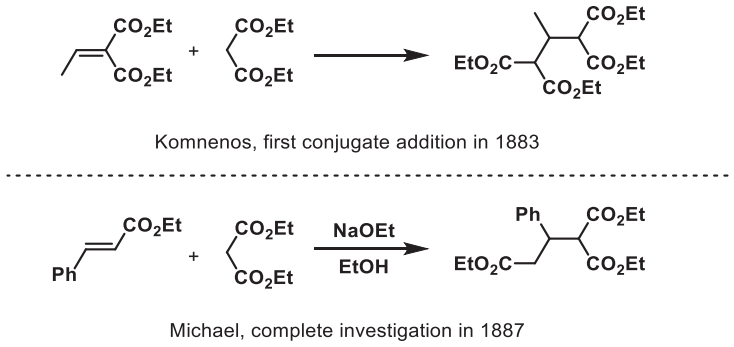
Conjugate additions are some of the most powerful carbon–carbon bond forming reactions in the synthetic chemist's toolbox. These reactions have been the key step in the syntheses of numerous natural products and pharmaceutically relevant compounds.[67] A conjugate addition reaction involves the addition of a nucleophile to an electron-deficient double or triple bond. The addition takes place at the carbon that is β to the electron-withdrawing group (EWG), resulting in the formation of a stabilized carbanion intermediate. At this point, the carbanion can be either protonated to form the β-substituted product or an electrophile can be added to form the α,β-disubstituted product.



Scheme 87: Conjugate addition, a powerful tool of the synthetic chemist

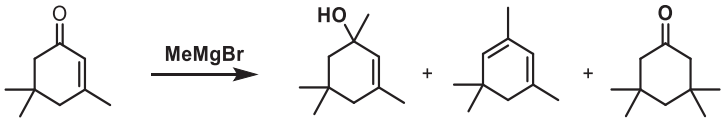
In 1883, Komnenos reported the first conjugate addition where he added the diethyl malonate anion to ethylidene malonate[68]. This reaction was not fully investigated until 1887, when Michael thoroughly studied this reaction using various stabilized nucleophiles and α,β-unsaturated systems[69]. Most of the early work, including Michael's, involved the use of stabilized or "soft" nucleophiles such as malonates and nitroalkanes[70].

[67] Suzuki, M.; Yanagisawa, A.; Noyori, R. *J.Am.Chem.Soc*. **1988**, *110*, 4718.
[68] Komnenos, T. *Liebigs Ann. Chem.* **1883,** *218,* 145.
[69] Michael, A. J. *Prakt. Chem./Chem.-Ztg.* **1887**, *35* ,349.
[70] Pearson, R. G. *J. Am. Chem. Soc.* **1963,** *85,* 3533.



Scheme 88: Initial reports of conjugate addition by Komnenos & Michael

The first real investigation of conjugate-addition to enones in the presence of a catalytic amount of metal was reported in 1941 by Kharasch.[71] Indeed, as described in scheme 89 isophorone successfully reacted with methyl magnesium bromide, in the presence of 1.0 mol% of copper chloride, to afford 3,3,5,5-tetramethylcyclohexanone in good yield.



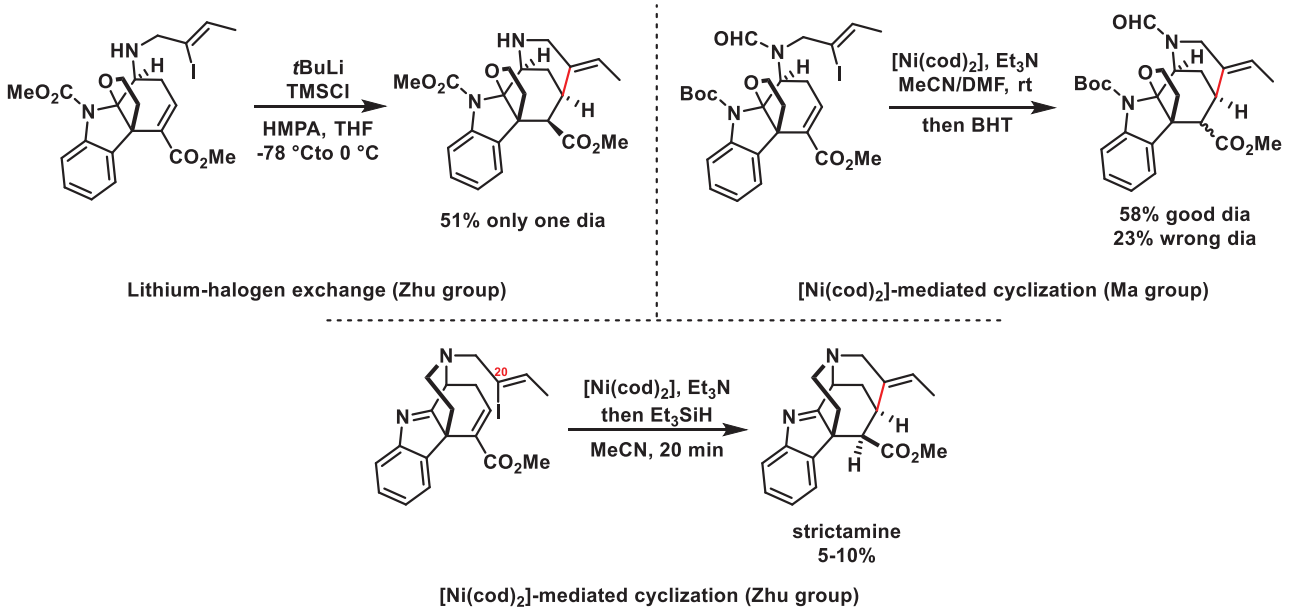
Entry	mol% metal halide			
1	None	67.2%	23.6%	-
2	1.0% CuCl	6.9%	-	82.5%

Scheme 89: First real investigation of metal-catalyzed conjugate-addition

Since then, a vast number of studies on metal-catalysed 1,4-addition were performed using Grignard/copper, organolithium, palladium, nickel and rhodium.

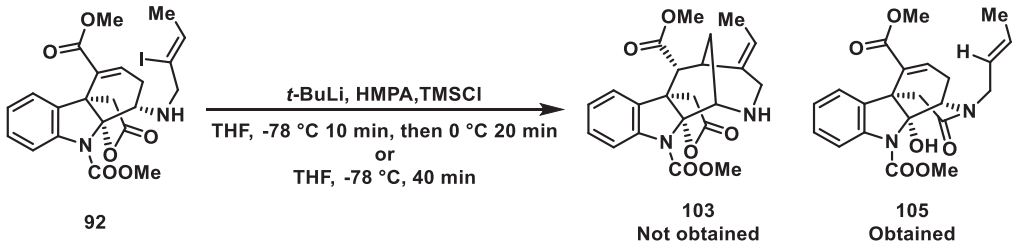
Intramolecular Michael addition has some precedent in the history of akuammiline synthesis. As shown in scheme 90, a representative example was reported by our group for the total synthesis of aspidophylline A. Indeed, the use of *t*BuLi was found to deliver the product with a pentacyclic scaffold in 51% yield with only 1 diastereoisomer.[23] The same year, the group of Dawei Ma reported an efficient nickel-mediated cyclization in good yield but with a mixture of two epimers at carbon 16.[25] Finally, the final part of the total synthesis of strictamine involved an intramolecular Michael addition. This last step turned out to be extremely difficult and despite extensive optimizations, the desired alkaloid was obtained in only 5-10% yield using $[Ni(COD)_2]$, Et_3N and triethylsilane in MeCN.[26]

[71] Kharasch, M. S, Tawney, P. O. *J. Am. Chem. Soc.* **1941**, *63*, 2308.



Scheme 90: Some precedent of intramolecular Michael addition for akuammiline synthesis

As shown in scheme 91, when the vinyl iodide was submitted to *t*-BuLi in THF at -78 °C for 10 min and then warmed to 0 °C for 20 min, lactam **105** was cleanly obtained as the only product. Performing the reaction at -78 °C for 40 minutes afforded a mixture of starting material **92** and lactam **105**. The order of reagent addition was also examined, but the desired product was not observed. It was concluded that the use of a strong base led first to the deprotonation of the secondary amine, affording directly the translactamized product. Lithium-halogen exchange was then undertaken in a second step, leading to deiodinated compound **105** after quenching the reaction.

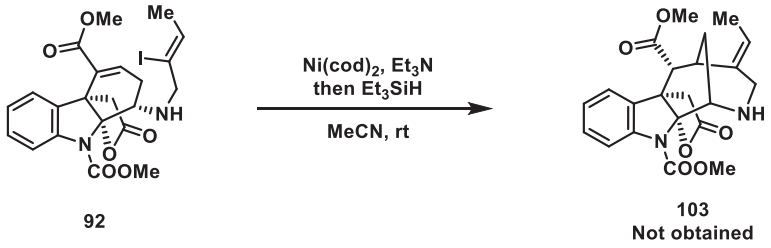


Scheme 91: Attempts for intramolecular Michael addition using t-BuLi.

Nickel was reported to promote 1,4 addition in combination with a soft base.[72] Therefore, the 1,4-addition reaction was performed by treating starting material **92** with 3 equivalents of $Ni(cod)_2$ and 6 equivalents of Et_3N. After 1 hour, Et_3SiH (3 equivalents), a hydride donor, was added into the reaction mixture

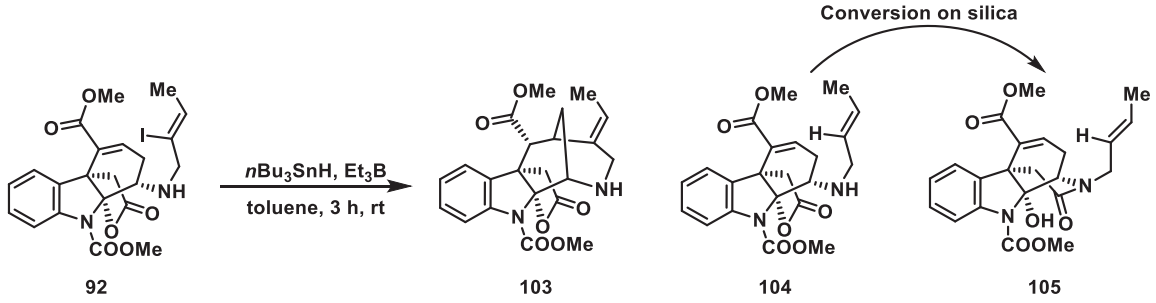
[72] a) F. Yu, B. Cheng, H. Zhai, *Org. Lett*. **2011**, *13*, 5782. b) J.Ma, W. Yin, H. Zhou, X. Liao, J. M. Cook, *J.Org.Chem.* **2009**,*74*, 264. c) S. Yu, O. Mathias, J. M. Cook, *J. Am. Chem. Soc*.**2000**, *122*, 7827. d) J. Bonjoch, D. Sol, S. Garca-Rubio, J.Bosch, *J. Am. Chem. Soc*. **1997**, *119*, 7230.

(scheme 92). Unfortunately, a very messy reaction mixture was obtained and the desired product was not detected.



Scheme 92: Attempts for intramolecular Michael addition using $Ni(cod)_2$

Radical cyclization was then performed using nBu$_3$SnH in the presence of a catalytic amount of Et_3B (scheme 93). After 3 hours, the reaction reached full conversion. Deiodinated product **104** was observed in majority in the crude mixture, nevertheless, it slowly underwent lactamization on silica gel leading to compound **105**. Unfortunately, the desired product was not observed.



Scheme 93: Attempts for intramolecular Michael addition using radical pathway.

According to previous results, the major issue was the undesired lactamization which seemed to be predominant under either basic or neutral conditions. It was concluded that secondary amine **92** had to be protected or alkylated in order to avoid lactamization issues.

Therefore, a reductive amination was performed in order to install a methyl at the N4 position of Alstolactine A. Surprisingly, standard conditions used for reductive amination failed to provide the desired methyl amine.[73] As shown in table 20, when the reaction was performed using formaldehyde (37% in water), $NaBH_3CN$ as reducing agent in either methanol or DCE, the desired product was not detected (entry 1 and 2). It was thought that the presence of water was not favorable to form the iminium intermediate. Thus, paraformaldehyde in DCE and 3A MS were employed (entry 3) affording a mixture of starting material/desired product (4/1) after 20 hours. When AcOH (entry 4) or PTSA (entry 5) were used as additive,

[73] a)Borch, R. F.; Bernstein, M. D.; Durst, H. D.; *J. Am. Chem. Soc.* **1971**, *12*, 2897.b)Magid, A. F. A.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849.

it was observed that the stronger the acid, the faster the reaction was. However, the reaction never reached full conversion. Changing the solvent to MeCN did not lead to full conversion of the starting material (entry 6). Varying the reducing agent from $NaBH_3CN$ to $NaBH(OAc)_3$ resulted in no reaction despite the addition of 1.3 equivalent of acetic acid (entry 7). When PTSA was employed as an additive in a 1:1 mixture of THF/MeOH the reaction reached 50% conversion, further addition of reagent and stirring at room temperature for 12 hours led to full conversion (entry 8). Unfortunately, almost 40% of the undesired lactam was formed under this condition. Another source of aldehyde was then envisaged (entries 9 and 10) but no reaction was observed despite addition of either AcOH or PTSA.

Table 20: Reductive amination of the secondary amine.

92 106 107

Entry	Aldehyde source	Solvent	Sydride source	Additives	Comments
1	Formaldehyde 37% in water 10 equiv.	MeOH	$NaBH_3CN$ 10 equiv.		Withe suspension. Add THF 1:1 with MeOH. After 3 days, full conf. Only Lactam 107
2	Formaldehyde 37% in water 10 equiv.	DCE	$NaBH_3CN$ 10 equiv.		No suspension, After 24 h only SM reaction stoped
3	Paraformaldehyde 10 equiv.	DCE MS	$NaBH_3CN$ 10 equiv.		After 12 h, new spot but SM remain After 20 h, 75/88 = 4:1
4	Paraformaldehyde 10 equiv.	DCE MS	$NaBH_3CN$ 10 equiv.	AcOH 1.3 equiv.	Same entry 3, but reaction faster 75/88 = 1.4:1
5	Paraformaldehyde 10 equiv.	DCE MS	$NaBH_3CN$ 10 equiv.	PTSA 1.3 equiv.	Same than entry 3 after 1 night 75/88 = 1:3
6	Paraformaldehyde 10 equiv.	MeCN	$NaBH_3CN$ 10 equiv.	AcOH 1.3 equiv.	After 8 h, big spot of 106 but 92 remain After all night no evolution, w-up. 75/88 = 2:1
7	Paraformaldehyde 10 equiv.	DCE	$NaBH(OAc)_3$ 10 equiv.	AcOH 1.3 equiv.	more than 24 h, almost no 106
8	Paraformaldehyde 10 equiv.	MeOH/THF	$NaBH_3CN$	PTSA	After 16 hours, 50% conf. Add reagents. Full conf after 12 h, 37% lactam 107, 63% 106
9	1,3,5-Trioxane	MeCN	$NaBH_3CN$	AcOH	Only SM after 12 hours
10	1,3,5-Trioxane	MeCN	$NaBH_3CN$	PTSA	Only SM after 12 hours

According to these results, conditions described in entry 6 seemed to be the most efficient. The reaction was repeated under this condition and full conversion was finally reached by adding another 1 equivalent of both $NaBH_3CN$ and AcOH to the reaction mixture after 6 hours. The reaction was performed up to 125 mg with an isolated yield of 93% (Scheme 94).

Scheme 94: Formation of tertiary amine 88

Having intermediate **106** in hand, more optimization was attempted in order to achieve the 1,4-addition.

As described in table 21, the first experiment was performed using *t*-BuLi, HMPA and TMSCl at -78 °C in THF. Under these conditions, no reaction occurred, even with a second addition of *t*-BuLi (entry 1). Raising the temperature from -78 °C to 0 °C mainly afforded the deiodinated compound (entry 2) meaning that lithium halogen exchange occurred but subsequent cyclization did not proceed. It was then decided to explore radical chemistry.[74]

Tributyltin hydride is the most commonly used reagent to conduct free-radical reactions. Simple reduction of an organic halide by tin hydride involves a controlled chain reaction. As described in table 21, two equivalents of Bu_3SnH and small amount of triethylborane as initiator were mixed in toluene at room temperature. Unfortunately, the deiodinated compound was mainly formed (entry 3). Using AIBN as initiator in benzene at 80°C was also not succesfull (entry 4).

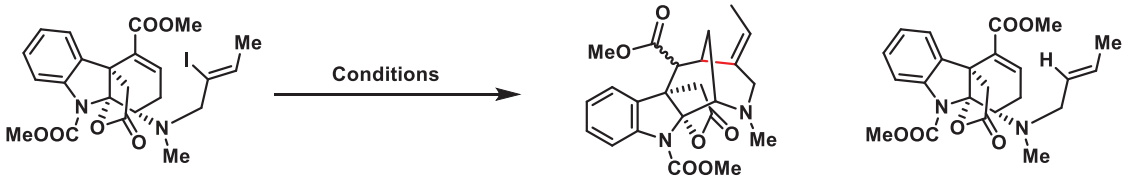
Looking at the target, this key C-C bond could also be formed under reductive Heck conditions. Indeed, the Pd-catalyzed reductive Heck reaction has been well-exploited in the synthesis of natural products.[75] Alkyl-palladium-halide complex, used for both Heck and reductive Heck reaction, is transformed into a hydrido-palladium-alkyl complex through reaction with formic acid or trialkylamines. Reductive elimination of this intermediate provides the reductive Heck product, whereas β-hydride elimination of the palladium-alkyl complex affords the Mizoroki-Heck product. Both conditions (entries 5 & 6) were examined using a catalytic amount of palladium (II) acetate with triphenylphosphine as ligand in DMF at 60 °C. Two hydride donors were used to perform this reaction: sodium formate (entry 5) and a tertiary amine (entry 6). In both cases, the starting material was recovered in more than 50%, deiodinated compound and decomposition were also observed.

Further attempts of 1,4-addition were conducted on compound **106** using nickel chemistry. As shown in entry 7, the first attempt using nickel was performed using bis(1,5-cyclooctadiene)nickel (0), trietylamine, in a 2:1

[74] Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem.Rev*. **1991**, *91*, 1237.
[75] Ghosh, T. *ChemistrySelect* **2019**, *4*, 4747.

mixture of DMF/MeCN at room temperature. After 1 hour, 2 equivalents of a proton source (here BHT: butylated hydroxytoluene) were added to the reaction mixture. Unfortunately, the starting material was fully recovered meaning that the nickel insertion did not occur at room temperature (entry 7). However, when the temperature was increased from rt to 40 °C, the reaction directely turned black. After 1 hour at 40°C, BHT was added and stirred for another 1 hour. After work-up, we were delighted to isolate the desired product in 60% yield, in mixture with 20% of deiodinated product (entry 8). Performing the reaction with a pre-heated oil bath at 40 °C and with a freshly distilled batch of triethylamine afforded the desired product in 85% yield (entry 9). During the nickel mediated cyclization, a mixture of diastereoisomers (~ 1:1) was observed. This observation is consistent with the results reported by Dawei Ma in the synthesis of aspidophiline A where a mixture of epimers was observed at carbon 16 (see scheme 90, p 74).

Table 21: Attempts for intramolecular Michael addition



106
2 mg scale

108

109

Entry	Conditions	Result
1	t-BuLi (4 equiv.), HMPA (4 equiv.), TMSCl (8equiv.) THF, -78 °C	No reaction, add of more t-BuLi (4 equiv.): SM major reaction stoped.
2	t-BuLi (4 equiv.), HMPA (4 equiv.), TMSCl (8equiv.) THF, -78 °C to 0 °C	Deionidated product
3	Bu_3SnH (2 equiv.), Et_3B (0.2 equiv.) Toluene, rt	After 5 hours stop. *Deiodinated major (1 dia)*
4	Bu_3SnH (2 equiv.), AIBN (0.2 equiv.) benzene, 80 °C	After 5 hours, no evolution, 1 small spot more polar. Add of Bu_3SnH & AIBN: after 1 hour decomposition.
5	$Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol %), HCOONa (2 equiv.) DMF, 60 °C	After 16 h ~ 50% SM recover, major deiodinated 2 very small spots more polar 2 others on baseline
6	$Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol %), DIPEA (2 equiv.) DMF, 60 °C	After 16 h, SM major, some product on baseline
7	Ni(COD) (5 equiv.), Et_3N (10 equiv.) then BHT (2 equiv.) DMF/MeCN = 2:1, rt	No reaction
8	Ni(COD) (5 equiv.), Et_3N (10 equiv.) then BHT (2 equiv.) DMF/MeCN = 2:1, rt then 40 °C	rt no reaction. rt to 40 °C turn black, 1 h full conv. DP 60%, deiodinated 20%
9	Ni(COD) (5 equiv.), Et_3N (10 equiv. Distilled) then BHT (2 equiv.) DMF/MeCN = 2:1, 40 °C	40 °C turn black, 1 h full conv. Only DP 85%, (d.r = ~1:1)

Fortunately, promising conditions (entry 9, table 21) for the key 1,4-addition were obtained. In order to get a robust and reproducible reaction, optimizations were conducted (table 22). The reaction temperature (entries 1 to 5), the solvent system (entries 6 to 8), the proton source (entries 9 to 13), the temperature during the protonation (entries 14 & 15), the reaction time (entries 16 to 19), as well as some other combinations (entries 20 to 22) were examined (table 22). According to entry 1, the oxidative addition did

not occur on this substrate at room temperature. Entries 2 and 3 showed that 40 °C was an appropriate temperature for this reaction. At 50 °C (entry 4), no improvement of yield or d.r was observed. However, decreasing the temperature to 30 °C (entry 5) resulted in an incomplete reaction with a diastereoselectivity in favor of the undesired epimer. It was decided to keep 40 °C for the rest of the optimizations.

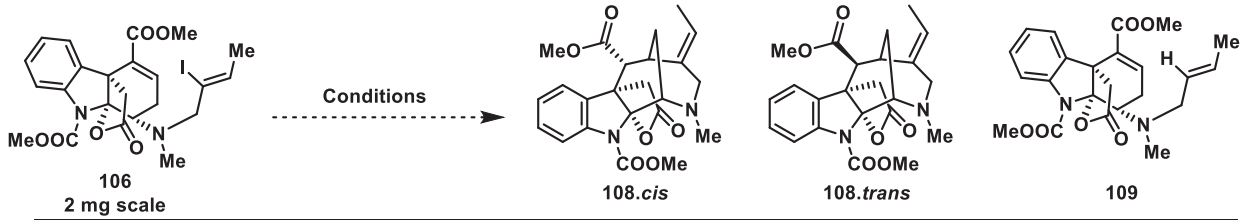
The previous reactions were performed using a 2:1 mixture of DMF/MeCN as solvent system. It is noteworthy that when the ratio of solvent was reversed, using a 1:2 mixture of DMF/MeCN, the reaction was not complete (entry 6). Performing the reaction only in DMF afforded a very small amount of the desired product (entry 7). Whereas using only MeCN (entry 8) as solvent resulted in no reaction. The solvent system has a really important role in this reaction, consequently, it was decided to continue the screening with a 2:1 mixture of DMF/MeCN.

Different proton sources & hydride donor were then examined. When 5 equivalents of BHT were added to the reaction mixture, a cleaner crude was obtained even if the diastereoselectivity did not change (entry 9). Using triethylsilane (entry 10) or $NaHCO_3$ (entry 11) afforded a very unclean reaction. According to entry 9, the use of phenol derivatives seemed to be the key for a mild and clean protonation. It was then supposed that playing on the PKa and the bulkyness of the phenol could have an influence on the diastereoselectivity of the reaction. Thus, para-nitrophenol (entry 12) was used as a proton source but is was less clean than using BHT for a similar diastereoselectivity. The use of phenol (entry 13) afforded similar results than entry 12. BHT was finally used for the rest of the experiments.

It was then decided to evaluate the influence of the temperature during the protonation step. As shown in entry 14, when BHT was added for 1h at 40 °C the same d.r as entry 9 was obtained. However, when BHT was added for 1h at 0 °C (entry 15), the diastereoselectivity increased in favor of the undesired epimer (**108.*trans***). The addition of BHT at room temperature was finally kept for the other attempts.

The influence of the reaction time was then investigated. As shown in entry 16, when the reaction time was reduced to 20 min at 40 °C, the d.r increased to 7:1 in favor of desired epimer **108.*cis***. These conditions were repeated (entry 17) on 6 mg and similar results were obtained. Reducing the reaction time to 10 minutes (entry 18) or extended to 40 minutes (entry 19) did not afford a better result than entries 16 & 17. Additionnal attempts (entries 20, 21 and 22) did not improve the d.r of the reaction.

Table 22: Optimizations for the [Ni(cod)2]-mediated cyclization



106
2 mg scale

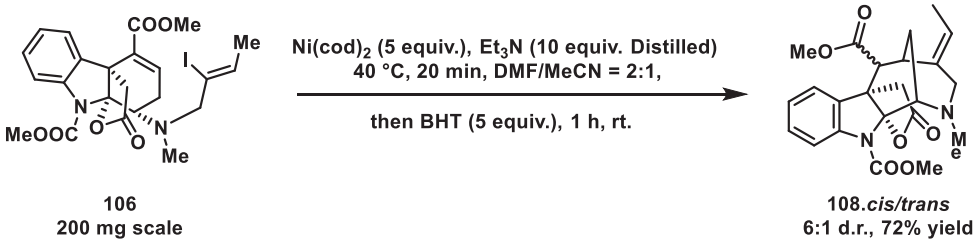
108.*cis*

108.*trans*

109

Entry	Conditions	Results
1	Ni(COD) (5 equiv.), Et_3N (10 equiv. Distilled), rt, 1 h in DMF/MeCN = 2:1, then BHT (2 equiv.), 1 h, rt.	No reaction at rt.
2	Ni(COD) (5 equiv.), Et_3N (10 equiv. Distilled), rt to 40 °C, 1h in DMF/MeCN = 2:1, then BHT (2 equiv.), 1 h, rt.	rt to 40 °C turn black, 1 h full conv. DP 60%, deiodinated 20%
3	Ni(COD) (5 equiv.), Et_3N (10 equiv. Distilled), 40 °C, 1 h in DMF/MeCN = 2:1, then BHT (2 equiv.), 1 h, rt.	40 °C turn black, 1 h full conv. Only DP 85%, (dr = ~1:1)
4	Ni(COD) (5 equiv.), Et_3N (10 equiv. Distilled), rt to 50 °C, 1 h in DMF/MeCN = 2:1, then BHT (2 equiv.), 1 h, rt.	d.r. = ~ 57:43, some deiodinated
5	Ni(COD) (5 equiv.), Et_3N (10 equiv. Distilled), rt to 30 °C, 1 h in DMF/MeCN = 2:1, then BHT (2 equiv.), 1 h, rt.	SM remain. d.r. = ~ 37:63, some deiodinated
6	$Ni(cod)_2$ (5 equiv.), Et_3N (10 equiv. Distilled), 40 °C, 1 h in DMF/MeCN = 1:2, then BHT (2 equiv.) 1 h, rt.	d.r. = 1:1.5, not full conversion
7	$Ni(cod)_2$ (5 equiv.), Et_3N (10 equiv. Distilled), 40 °C, 1 h in DMF, then BHT (2 equiv.), 1 h, rt.	Small amount of DP in mixture with another product
8	$Ni(cod)_2$ (5 equiv.), Et_3N (10 equiv. Distilled), 40 °C, 1 h in MeCN, then BHT (2 equiv.), 1 h, rt.	No reaction, SM recovered
9	$Ni(cod)_2$ (5 equiv.), Et_3N (10 equiv. Distilled), 40 °C, 1 h in DMF/MeCN = 2:1, then BHT (5 equiv.), 1 h, rt.	d.r. = ~1:1
10	$Ni(cod)_2$ (5 equiv.), Et_3N (10 equiv. Distilled), 40 °C, 1 h in DMF/MeCN = 2:1, then Et_3SiH (5 equiv.), 1 h, rt.	Not clean, d.r. impossible by NMR.
11	$Ni(cod)_2$ (5 equiv.), Et_3N (10 equiv. Distilled), 40 °C, 1 h in DMF/MeCN = 2:1, then $NaHCO_3$, 1 h, rt.	Not clean, d.r. impossible by NMR.
12	$Ni(cod)_2$ (5 equiv.), Et_3N (10 equiv. Distilled), 40 °C, 1 h in DMF/MeCN = 2:1, then para-nitrophenol (5 equiv.), 1 h, rt.	less clean than BHT
13	$Ni(cod)_2$ (5 equiv.), Et_3N (10 equiv. Distilled), 40 °C, 1 h in DMF/MeCN = 2:1, then phenol (5 equiv.), 1 h, rt.	Cleaner than 12 but not as good as BHT
14	$Ni(cod)_2$ (5 equiv.), Et_3N (10 equiv. Distilled), 40 °C, 1 h in DMF/MeCN = 2:1, then BHT (5 equiv.), 1 h, 40 °C	d.r. = ~1:1, some deiodinated
15	$Ni(cod)_2$ (5 equiv.), Et_3N (10 equiv. Distilled), 40 °C, 1 h in DMF/MeCN = 2:1, then BHT (5 equiv.), 1 h, 0 °C	d.r. = ~35:65, some deiodinated
16	$Ni(cod)_2$ (5 equiv.), Et_3N (10 equiv. Distilled), 40 °C, 20 min in DMF/MeCN = 2:1, then BHT (5 equiv.), 1 h, rt.	d.r. = ~7:1, best result
17	$Ni(cod)_2$ (5 equiv.), Et_3N (10 equiv. Distilled), 40 °C, 20 min in DMF/MeCN = 2:1, then BHT (5 equiv.), 1 h, rt.	d.r. = ~6:1, test of reproducibility on 6 mg
18	$Ni(cod)_2$ (5 equiv.), Et_3N (10 equiv. Distilled), 40 °C, 10 min in DMF/MeCN = 2:1, then BHT (5 equiv.), 1 h, rt.	Full conv, DP in mixture with another product.
19	$Ni(cod)_2$ (5 equiv.), Et_3N (10 equiv. Distilled), 40 °C, 40 min in DMF/MeCN = 2:1, then BHT (5 equiv.), 1 h, rt.	Not better than entry 15 & 16.
20	$Ni(cod)_2$ (5 equiv.), Et_3N (10 equiv. Distilled), 40 °C, 20 min in DMF/MeCN = 2:1, then BHT (2 equiv.), 1 h, rt.	d.r. = ~1:1
21	$Ni(cod)_2$ (5 equiv.), Et_3N (10 equiv. Distilled), 40 °C, 20 min in DMF/MeCN = 2:1, then BHT (5 equiv.), 3 h, rt.	Same than 16 & 17
22	$Ni(cod)_2$ (5 equiv.), Et_3N (10 equiv. Distilled) 40 °C, 20 min in DMF/MeCN = 2:1, then BHT (5 equiv.), 1 h, 40 °C.	d.r. = 1:1

Finally, under the optimized conditions it was possible to obtain up to 70% yield with a 6:1 diastereoselectivity in favour of desired product (**108.*cis***). The reaction turned out to be efficient, fast, and reproducible even on a 200 mg scale (Scheme 95).

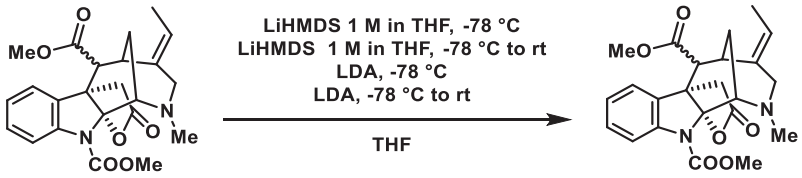


106
200 mg scale

108.*cis/trans*
6:1 d.r., 72% yield

Scheme 95: Optimized conditions for the [Ni(cod)2]-mediated cyclization

Additional experiments were then performed on the mixture of epimers. In order to study the possible increase of the d.r, the mixture of products was submitted to strong bases. As described in scheme 96, using LiHMDS at -78 °C did not have any influence on the diastereoselectivity, even when increasing the temperature to rt. Using LDA was also unsuccessful.

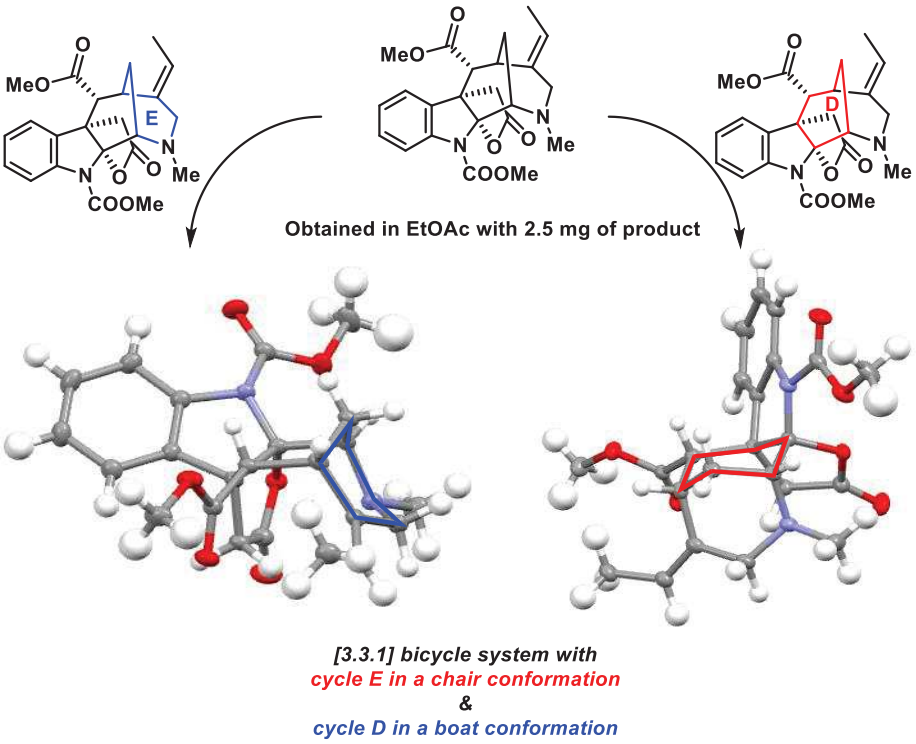


108.*cis/trans*

108.*cis/trans*
d.r. did not change

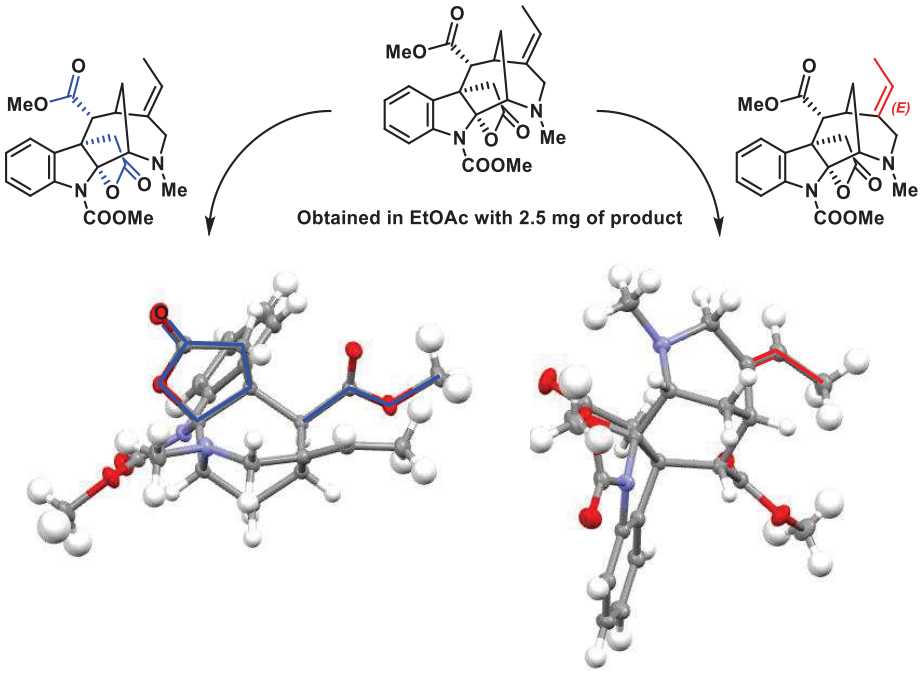
Scheme 96: No evolution of the diastereoselectivity under basic conditions

Fortunately, as described in scheme 97, the desired epimer **108.*cis*** afforded a monocrystal in EtOAc. It is noteworthy that the bicyclic bridge system possesses one ring in a chair conformation and another one in a boat conformation.



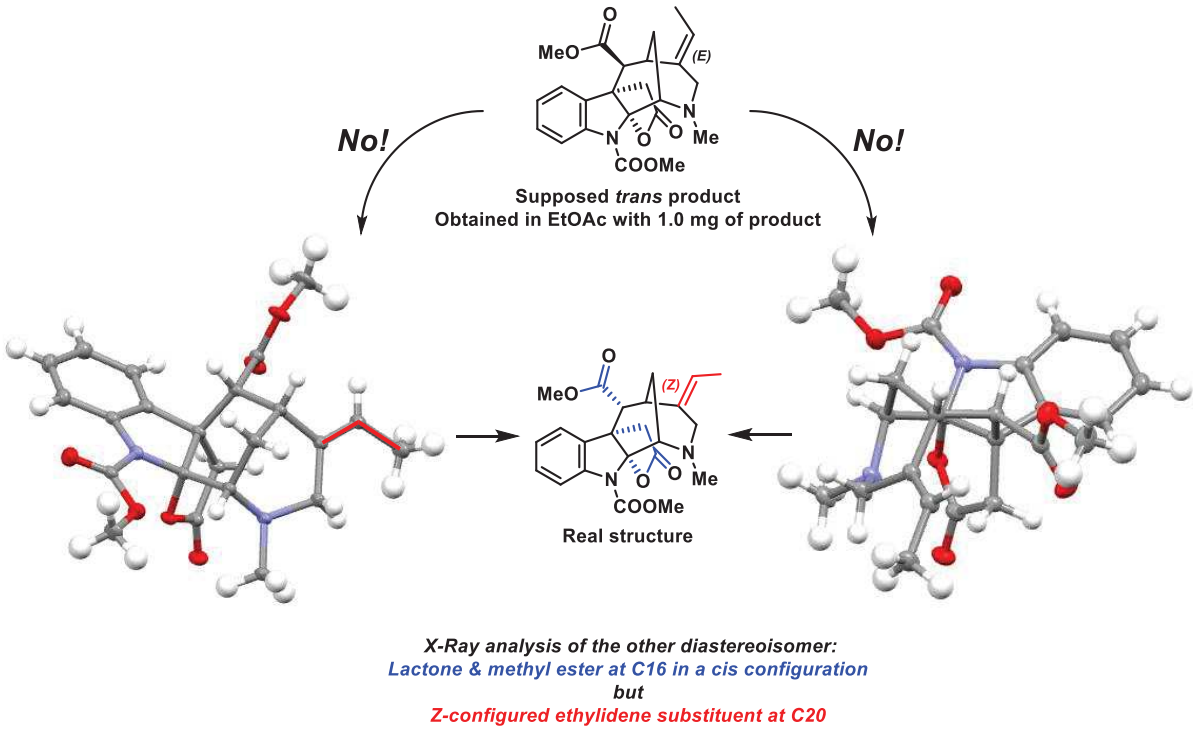
Scheme 97: X-ray of desired product 108.cis, conformation of the bicyclic bridge system.

Moreover, the X-Ray confirmed the *cis*-relationship between the γ-lactone and the ester at C16. Furthermore, the ethylidene substituent at C20 exhibits (*E)*-configuration with the methyl pointing in the direction of the ester moiety (scheme 98).



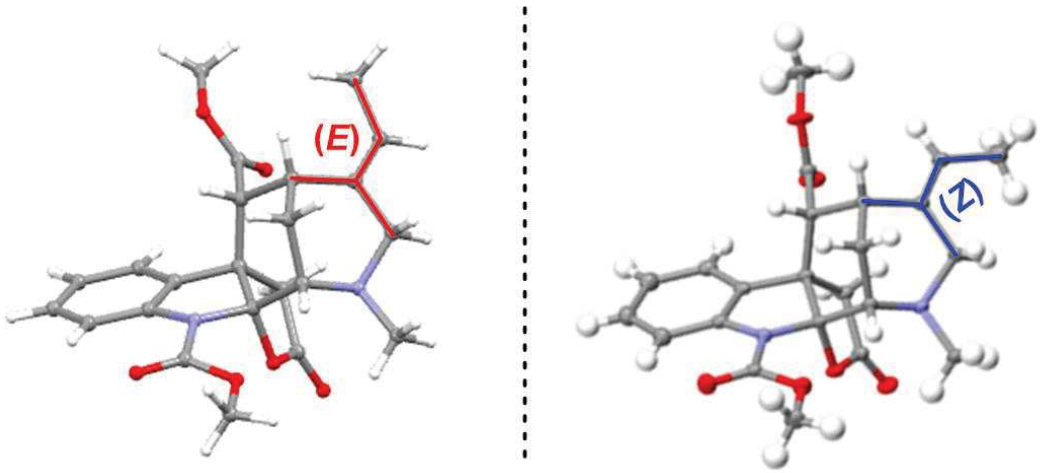
Scheme 98: X-ray of desired product 108.cis, confirmation of the cis-relationship

After several attempts, we were delighted to observe that the second diastereoisomer was also crystalline in EtOAc. To our surprise, the 3D-sequeleton of this product also showed a *cis*-relationship between the lactone and the ester at C16. It finally turned out that the difference between the two diastereoisomers came from the configuration of the double bond. Indeed, the *Z*-configured ethylidene was formed during the reaction (scheme 99).



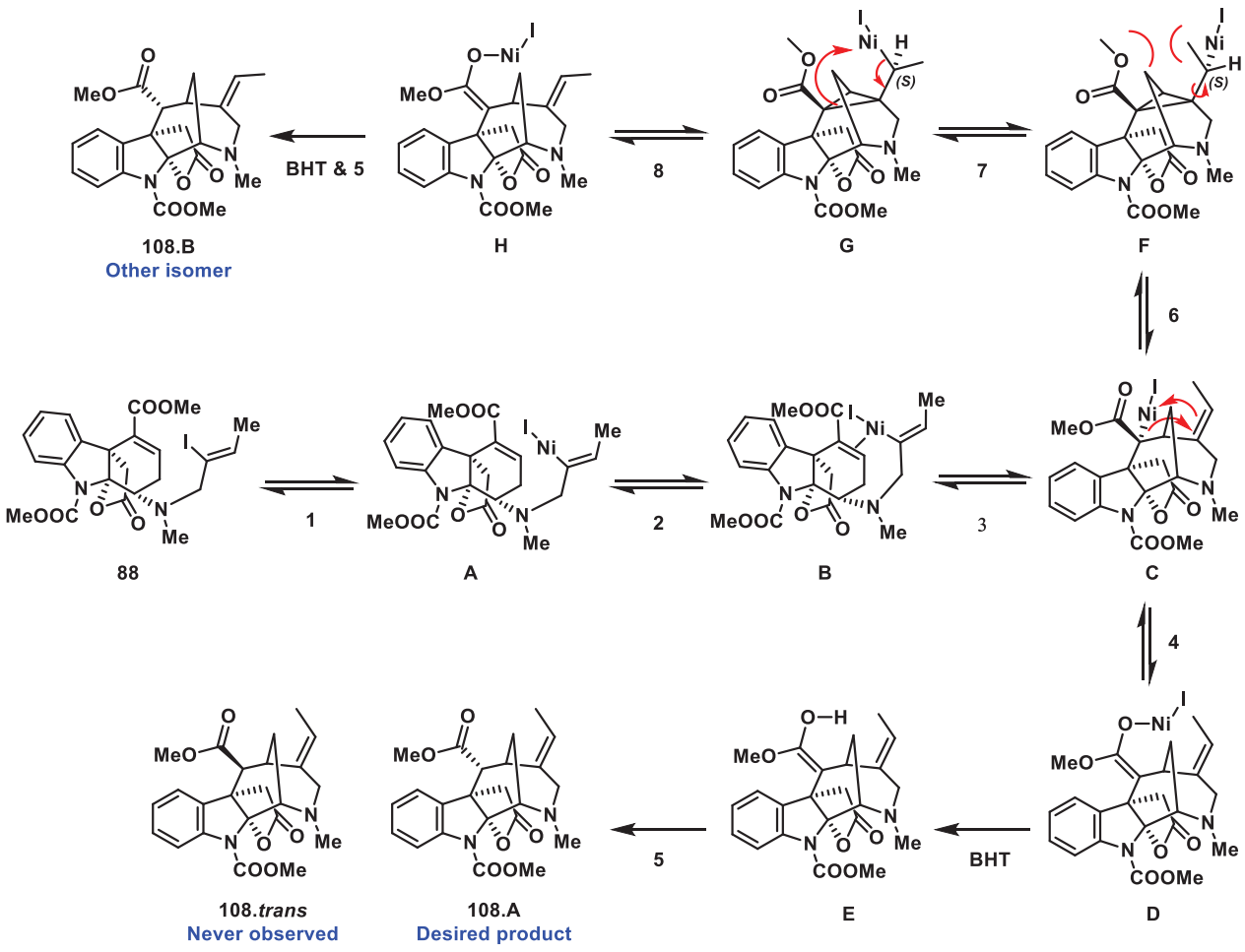
Scheme 99: X-ray of second diastereoisomer, Z-configured ethylidene at C20.

The X-ray comparison of the two isomers is presented in scheme 100. It clearly appears that isomerization of the double bond occurred during the reaction. It also explained why attempts to perform epimerization under strong bases in scheme 96 were all unsuccessful.



Scheme 100: Comparison of the two isomers of compound 90.

This interesting result could be explained by the proposed mechanism described scheme 101. The first elementary step is the oxidative addition of Ni^0 to the vinyl iodide to generate the Ni^{II} intermediate **A**. After coordination to the double bond, this compound underwent a β-migratory insertion leading to a equilibrium between **C** and the nickel enolate **D**. The introduction of BHT in the reaction mixture produced the enol **E**, which finally tautomerized to generates the first isomer **108.A**. The other diastereoisomer **108.B** could be generated starting from **C** *via* intramolecular formation of cyclopropane, producing the sigma alkyl nickel species **F.** The rotation of the C-C bond in intermediate **F** allowed a reduction of the steric clash between the methyl ester and the methyl of the ethylidene. After this process, the species **G** underwent a retro-β-migratory insertion, reducing the strain of the cyclopropane to generates the nickel enolate **H**. Subsequent protonation with BHT and tautomerization led to the other isomer **108.B** of the double bond. A similar isomerization of double bond *via* cyclopropane formation was reported by Rawal using palladium catalyst on the synthesis of strychnine.[76]

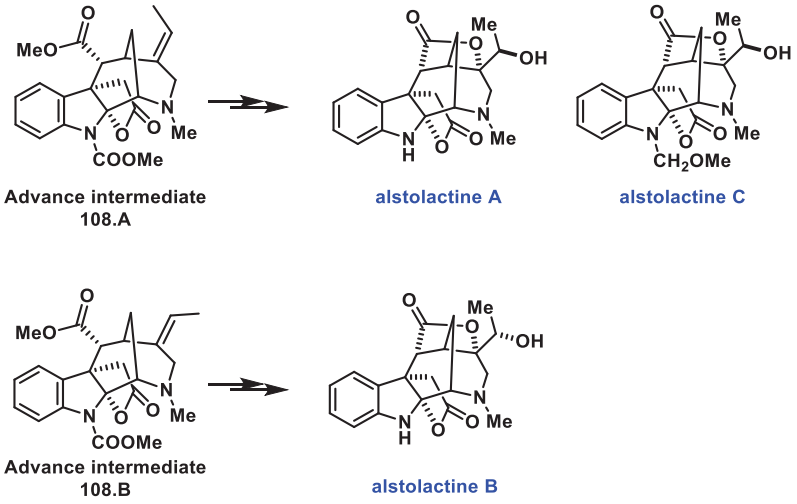


Steps: 1. Oxidative addition; 2. Coordination; 3. b- Migratory insertion; 4.Nickel enolate; 5.Tautomerization; 6.Cyclopropane formation; 7.Rotation to reduce the steric hindrance; 8. Retro- b- migratory insertion & nickel enolate formation.

Scheme 101: Proposed mechanism for the isomerization of the double bond

[76] Michoud, C.; Rawal, V. R. *J. Org. Chem.*, **1993**, *58*, 5583.

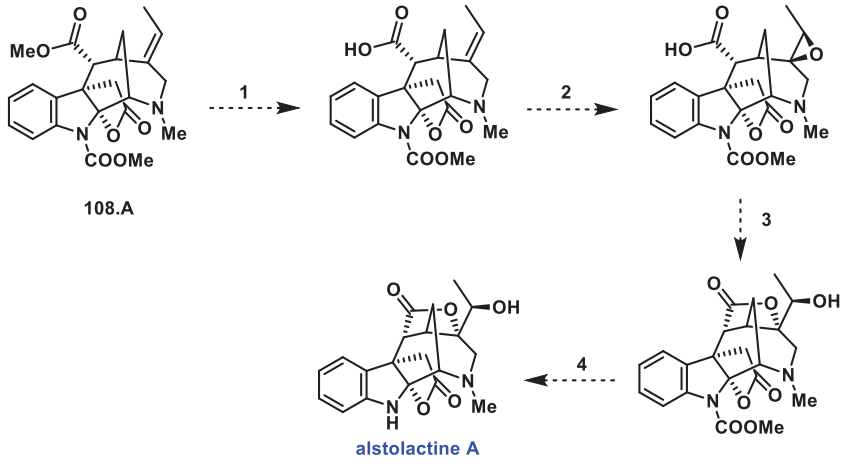
This result has a crutial importance for the outcome of our strategy. Indeed, as described in scheme 102, having both isomers of the double bond in hand would allow the synthesis of alstolactine A, B & C.



Scheme 102: From isomerization of the double bond to the synthesis of alstolactine A, B, C.

VI. End game

The end-game strategy towards alstolactine A is described in scheme 103. The sequence begins with the saponification of the methyl ester followed by the epoxidation of the double bond. Subsequent epoxide opening to generate the second γ-lactone followed by cleavage of the carbamate would afford the desired natural product.



Steps: 1. Saponification; 2. Epoxidation; 3. Epoxide opening; 4. Deprotection.

Scheme 103: Plan toward alstolactine A

With this strategy in mind, we first investigated the methyl ester saponification.

VI.1. Saponification of the methyl ester.

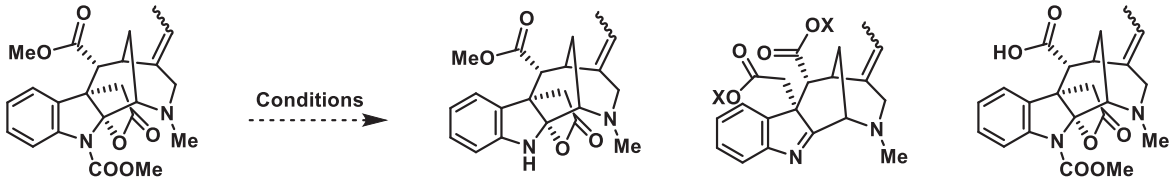
Although saponification is a very common and an apparently simple reaction, we encontered major difficulties to achieve this transformation. Indeed, since our substrate incorporates a methyl carbamate, a γ-lactone, and a methyl ester, highly chemoselective conditions were required.

As shown in table 23, attempts at using sodium hydroxide in a mixture of THF/MeOH/H_2O did not afford any product (entries 1 & 2). Performing the reaction in MeOH/H_2O resulted in poor solubility of the starting material even at elevated temperature (entry 3). Increasing the amount of NaOH to 10 equivalents at 50 °C resulted in the formation of 2 products in low yield but with low conversion of the starting materiel. Employing LiOH instead of NaOH in a 1:1 mixture of MeOH/H_2O or THF/H_2O was not successful. This was mainly due to bad solubility of the SM in the solvent system even when heating to 70 °C (entries 5 to 8). The THF/H_2O ratio was then increased to 10:1 in order to improve the solubilization of the starting material. Moreover, performing the reaction with 2.5 equivalents of LiOH at rt (entry 9), 50 °C (entry 10) or 70 °C (entry 11) provided two diastereoisomers of hydrolyzed carbamate **110** after 24 hours. Increasing the temperature to 90 °C (entry 13) or 110 °C (entry 14) led to full conversion of **110** but resulted in an unclean reaction mixture. The amount of LiOH was then increased from 2.5 to 10 equivalents, unfortunately, at 70 °C (entry 12) desired product **112** was not observed.

Using trimethylthin hydroxide (entries 15 to 18) from 1 to 5 equivalents resulted in an unclean reaction mixture or in the recovery of the starting material. Employing thiophenol in presence of a base at 50 °C in DMF (entry 19), or using potassium terbutoxide in DMSO or THF (entries 20 & 21) resulted in a messy reaction mixture. The use of Ph_3SiSH under basic conditions in DMF, at rt or 50 °C did not afford the desired product either. Using potassium cyanide at 80 °C led to carbamate cleavage and afforded compound **110** (entry 24) with no effect on the methyl ester moiety. Using acidic conditions (entry 25) in a 2:1 mixture of dioxane/ 6N HCl did not afford better results. Starting materials **108.A&B** were recovered even when high temperature was employed (up to 110 °C). Harsher acidic conditions using 37% HCl in acetic acid (entry 26) did not allow the formation of the desired product.

Finally, when silanolate was employed (entry 27) full conversion toward the unprotected indole **110** was observed after 3 hours. Running the reaction overnight, at room temperature, allowed the formation of a highly polar unknown product and other apolar compounds. After quenching the reaction, with 1 M HCl for 5 minutes, followed by extraction with EtOAc, the unknown product disappeared. However, a new compound was obtained with a very low mass balance. Careful analysis of proton NMR and HRMS allowed us to determine that the unknown compound was actually the desired product.

Table 23: Saponification of compounds 108.A&B



108.A&B
1 mg scale

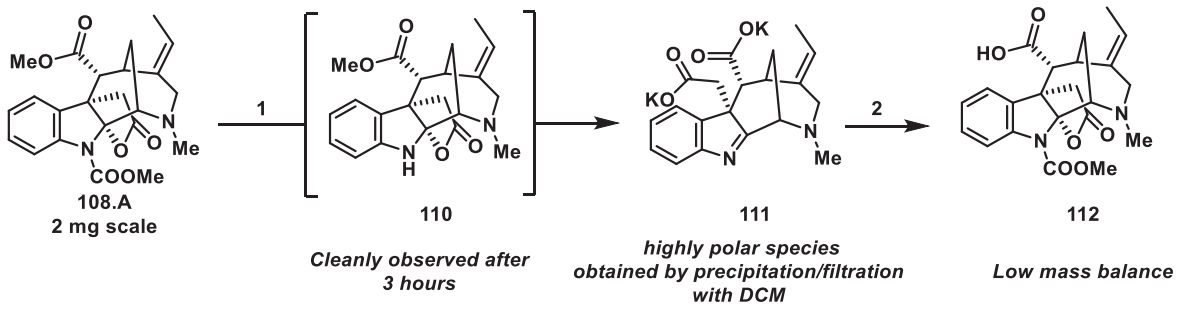
110

111

112
Desired product

Entry	Conditions	Results
1	NaOH (1 equiv.), THF/MeOH/H_2O, rt, 10 h	No reaction
2	NaOH (10 equiv.), THF/MeOH/H_2O, rt, 10 h	No reaction
3	NaOH (2.5 equiv.), MeOH/H_2O = 1/1, rt to 40 °C	Not soluble at rt without THF, same after heating
4	NaOH (10 equiv.), THF/MeOH/H_2O, rt to 50 °C, 10 h	SM remained major, 2 small new spots
5	LiOH (10 equiv.), MeOH/H_2O = 1:1, rt, 18 h	Not really soluble, SM remained major
6	LiOH (10 equiv.), THF/H_2O = 1:1, rt, 18 h	Not completely soluble, SM remained major
7	LiOH (2.5 equiv.), THF/H_2O = 1:1, rt to 40 °C	Same even after heating
8	LiOH (2.5 equiv.), THF/H_2O = 1:1, rt to 70 °C	Same solubility but small new spots
9	LiOH (2.5 equiv.), THF/H_2O = 10:1, rt, 24 h	SM remaining, 2 new spots
10	LiOH (2.5 equiv.), THF/H_2O = 10:1, 50 °C, 24 h	SM remaining, same 2 spots more UV active
11	LiOH (2.5 equiv.), THF/H_2O = 10:1, 70 °C, 24 h	SM remaining, two spots from entry 9/10/11 are the two dia of product 110
12	LiOH (10 equiv.), THF/H_2O = 10:1, 70 °C, 24 h	Almost full conversion of SM, 110 major product, small spot more polar.
13	LiOH (2.5 equiv.), THF/H_2O = 10:1, 90 °C, 24 h	Full conversion of SM, lower amount of 110, less clean
14	LiOH (2.5 equiv.), THF/H_2O = 10:1, 110 °C, 24 h	Full conversion of SM, full conversion of 110, really not clean.
15	Me_3SnOH (1.1 equiv.), DCE, 60 °C, 10 h	No reaction
16	Me_3SnOH (1.1 equiv.), DCE, 80 °C, 10 h	No reaction
17	Me_3SnOH (3 equiv.), DCE, 80 °C, 10 h	SM remaining, not clean.
18	Me_3SnOH (5 equiv.), DCE, 60 °C, 24 h	SM major, not clean.
19	PhSH, Cs_2CO_3, DMF, rt to 50 °C	No reaction at rt, not clean after 3 h at 50 °C
20	KO^{t}Bu, DMSO, 50 °C	Full conversion but not clean
21	KO^{t}Bu, THF, 50 °C	Same
22	BHT (0.2 equiv.), Ph_3SiSH (3 equiv.), Cs_2CO_3 (3 equiv.), DMF, rt	SM remain, not clean
23	BHT (0.2 equiv.), Ph_3SiSH (3 equiv.), Cs_2CO_3 (3 equiv.), DMF, 50 °C	Not clean
24	KCN (1 equiv.), Et_3N (3 equiv.), DMF/H_2O = 10:1, 80 °C	Slow reaction, after 3 days SM remained a bit 110 mainly observed
25	Dioxane / 6 N HCl = 2:1, rt to 50 °C, 50 to 90 °C, 90 to 110 °C	No reaction, SM remaining.
26	HCl 37%, AcOH, rt	Full conversion, DP not obtained
27	TMSOK (10 equiv.), THF, rt	Full conv after 3h. A major. After 1 night at rt & special work-up, DP 112 observed.

To simplify the reaction mixture analysis, experiments were then performed using a single diastereoisomer **108.A** instead of a 6:1 mixture. When starting material **108.A** was mixed with 10 equivalents of TMSOK at room temperature, the first reaction to occur was the carbamate cleavage. This step occurred cleanly in only 3 hours and afforded compound **110**. Extending the reaction time led to the formation of compound **111** along with nonpolar side-products. Indeed, it had already been observed that intermediate **111** could generate desired product **112** under acidic conditions. In order to characterize compound **111**, it was decided to evaporate the crude reaction mixture to dryness after an overnight reaction. Undetermined intermediate **111** was not stable on silica. However, it was noticed that most of the nonpolar side-products were soluble in DCM whereas compound **111** precipitated as a white solid. After several DCM washings, a small amount of **111** was isolated, which permitted full characterization (in D_2O). As shown in scheme 104, compound **111** corresponds to imine intermediate (190 ppm on ^{13}C NMR) which had probably been generated by lactone opening producing the hemiketal, followed by OH^- release. The low mass balance of desired product **112**, obtained after quenching the reaction with 1 M HCl, could be explained by an incomplete cyclization (only 5 min in HCl) of intermediate **111**. This might have resulted in a loss of material in the aqueous layer during the work-up.



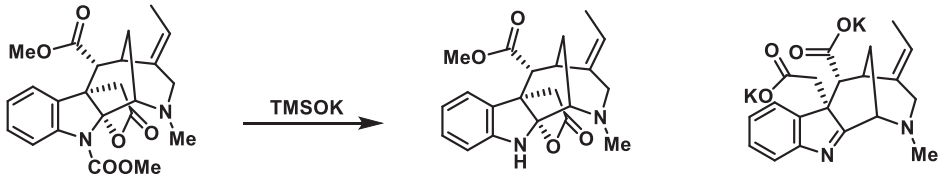
Scheme 104: Elucidation of intermediates during saponification of 108.A

With this information in hand, we decided to optimize the sequence for the saponification of the methyl ester. We first focused on having a cleaner formation of intermediate **111**.

As described in table 24, performing the reaction with 10 equivalents of TMSOK in THF afforded a messy reaction mixture (entries 1 to 3). Performing the reaction in Et_2O (entry 4) or toluene (entry 5) did not afford better results. Interestingly, a mixture of THF/ether provided similar results to entry 2. Increasing the temperature to 50 °C provided a messier reaction mixture than at room temperature (entry 7). Lowering the temperature to 0 °C afforded a cleaner mixture. Even after 48 hours compound **110** was not converted to the desired product **111** (entry 8). Lowering the amount of TMSOK to 3 equivalents at 0 °C allowed a chemoselective cleavage of the carbamate moiety. Finally, the best results were observed when the reaction was performed at room temperature in the presence of 10 equivalents of TMSOK for 10 hours. Unfortunately, under these conditions product **111** was obtained in a mixture with 3 other undetermined compounds.

Having the optimal conditions established we turned our attention to the cyclization step.

Table 24: Optimizations toward formation of compound 111



108.A
2 mg scale

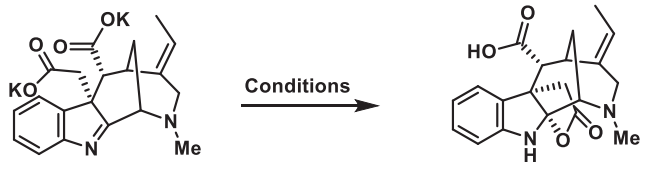
110

111

Entry	Solvent	Temp. (°C)	Equiv.	Work-up	Comments
1	THF	rt	10	Quench HCl 1M 5 min, extract EtOAc	Very low mass balance.
2	THF	rt	10	Evap to dryness	Not clean
3	THF	rt	10	same + wash with DCM to remove non polar products	111 relatively clean but low mass balance
4	Et_2O	rt	10	Evap to dryness	Less clean than THF
5	Toluene	rt	10	same	Less clean than THF and Et_2O
6	THF/Et_2O	rt	10	same	Not bad but THF better
7	THF	50 °C	10	same	Not clean
8	THF	0 °C	10	same	Cleaner but very slow. 110 remain even after 48 hours
9	THF	0 °C	3	same	Selective way to get a really clean formation of 110. Useful for the last step!
10	THF	rt	10	same	10 hours, full conv of SM & 110. 111 major even if not perfect (mixed with 3 other products)

The lactonization step was then performed under conditions described in table 25. Starting material **111** was obtained by the wash/filtration sequence previously described. Although substantial losses of product **111** were observed during the washing process, it was decided to move to the next step as it was so far the best way to get a “relatively clean” starting material. When THF was used as solvent (entry 1), starting material **111** precipitated and did not react even after an extended reaction time. Addition of water improved the mixture’s homogeneity, however, 3 equivalents of HCl was not enough to favor the cyclization of the lactone (entry 2). Employing a 2:1 ratio of HCl 1 M/THF was necessary to complete cyclization at room temperature in 4 hours (entry 3). Higher temperatures (entries 4 & 5) did not afford successful results.

Table 25: Cyclization of 111 under acidic conditions affording 112

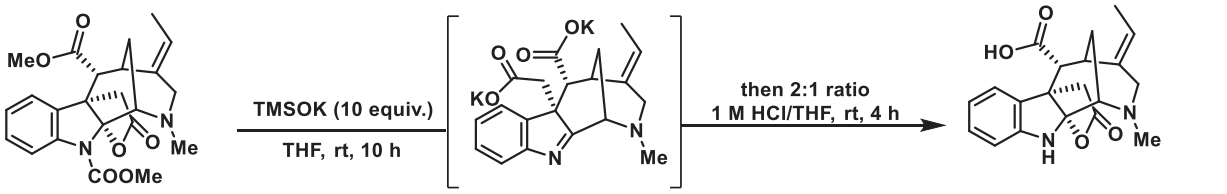


111

112
Desired product

Entry	Conditions	Comments
1	HCl 4 N (3 equiv.), THF, rt	111 not really soluble in THF, no reaction
2	HCl 4 N (3 equiv.), THF/H_2O = 1:1	Low amount of product, 111 remain.
3	HCl 1 M/THF = 2:1, rt, 4 h	Desired product 112 major
4	HCl 1 M/THF = 2:1, 50 °C	DP obtained in mixture with 3 other products
5	HCl 1 M/THF = 2:1, 40 °C	Same

It was then decided to perform the reaction in one-pot as attempts to purify compound **111** failed. As shown in scheme 105, when compound **108.A** was mixed with 10 equivalents of TMSOK for 10 hours and then directly quenched with HCl 1 M for 4 hours, desired product **112** was obtained in the crude reaction mixture. However, product **112** was observed in a mixture with impurities and was not stable enough to be purified.



108.A
2 mg scale

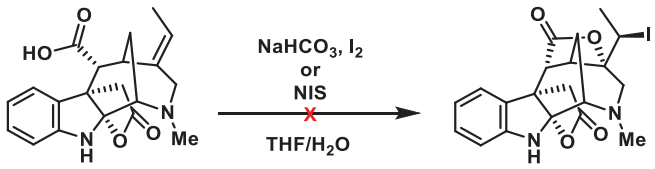
111

Desired product 112

Observed in the crude mixture
Not clean
Not stable for purification

Scheme 105: One-pot sequence for the saponification & γ-lactone cyclization

It was supposed that the instability of product **112** was due to the carboxylic acid and therefore iodolactonization was thus envisaged. As described in scheme 106, standard conditions using I_2 in presence of $NaHCO_3$ or simple NIS led to starting material decomposition.



112
use as crude

Only decomposition

Scheme 106: Attempts for iodolactonization

The difficulties encountered during saponification of the methyl ester were mainly due to a lack of chemoselectivity toward nucleophilic conditions. It was observed that the hindered cagelike structure of **108.A** is more prone to be first deprotected at the indole nitrogen position. Extending the reaction time led to the isolation of **111**, meaning the hydrolysis chemoselectivity was not satisfactory. Unfortunately, none of the conditions examined allowed a clean saponification and all intermediate were unstables and highly water-soluble.

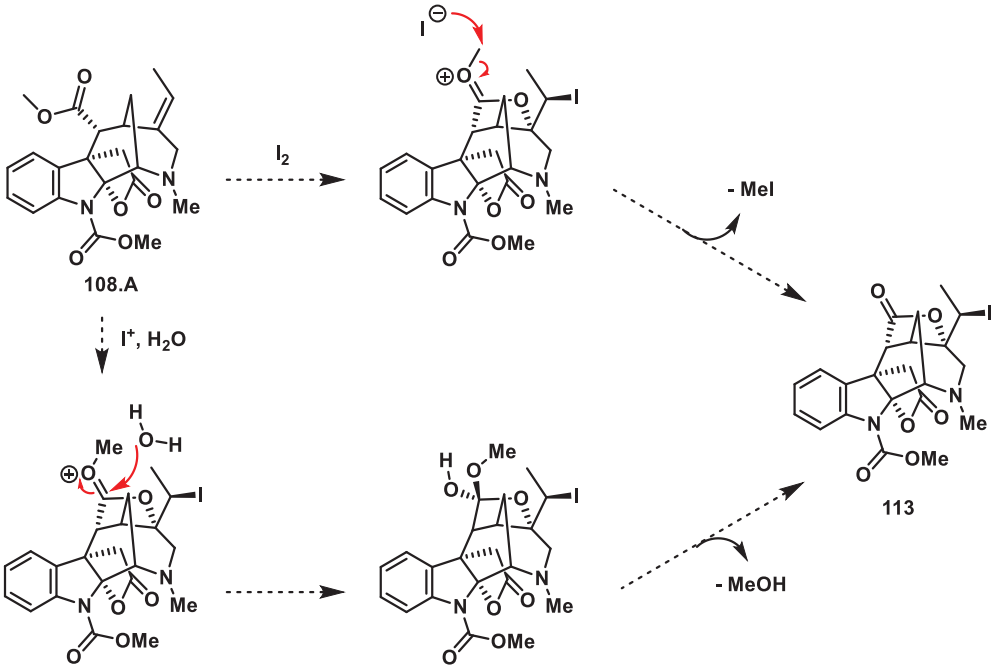
It was then envisaged to achieve the total synthesis of alstolactine A, B & C *via* iodolactonization using the methyl ester.

VI.2. Iodolactonization attemped

The straightforward iodolactonization *via* electrophilic mediated intramolecular cyclization using esters are reported in literature. Iodine has been widely used to realize such cyclizations[77] as well as NIS[78] or ICl[79].

As shown in scheme 107, depending on the conditions employed, two mechanisms could be envisaged. Using I_2 under anhydrous conditions could form the γ-lactone, followed by the attack of the iodide onto the methyl. Finally, loss of MeI could afford desired product **113**. Performing the iodolactonization in presence of water could generate the mixed acetal intermediate. Desired product **113** could then be generated with the release of MeOH.

[77] A) Willis, C. L. *Tetrahedron Lett.*, **1998**, *39*, 7415. B) Morimoto, A. *J. Org. Chem.*, **1985**, *50*, 5179. C) Hirama, M. *Tetrahedron*, **2002**, *58*, 6493. D) Burton, J. W. *Tetrahedron*, **2009**, *65*, 10882. E) Yeung, Y. Y. *Org. Biomol. Chem.*, **2016**, *14*, 3202.
[78] Frbault, F.; Maulide, N. *Angew. Chem. Int. Ed.*, **2010**, *49*, 5672.
[79] Senanayake, C. H. *Org. Lett.*, **2014**, *16*, 4142.

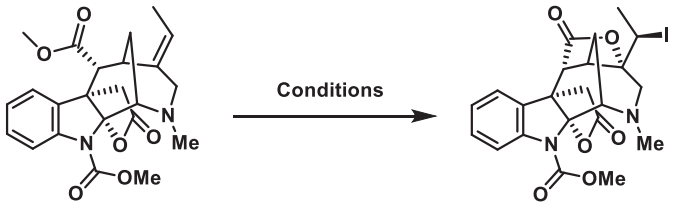


Scheme 107: Straightforward iodolactonization with methyl ester

As described in table 26, using I_2 in DCM at 0°C led to an incomplete and messy reaction (entry 1). Employing MeCN (entry 2) afforded a similar result. It was thought that the addition of water could favor the release of MeOH. However, adding 10% water in MeCN led to decomposition (entry 3). Under common conditions for iodolactonization (I_2 in THF) a messy reaction was obtained (entry 4).

It was then thought that stronger electrophiles could allow a faster generation of desired product **113** and lower the formation of by-products. Iodine chloride seemed to be a good candidate. Due to the difference of electronegativity between iodine and chlorine, ICl is highly polar and behaves as a source of I^+. Unfortunately, in MeCN at room temperature or at 0°C decomposition was observed (entries 5 & 6 respectively). Employing THF as solvent at room temperature or -78°C did not provide successful results either (entries 7 & 8).

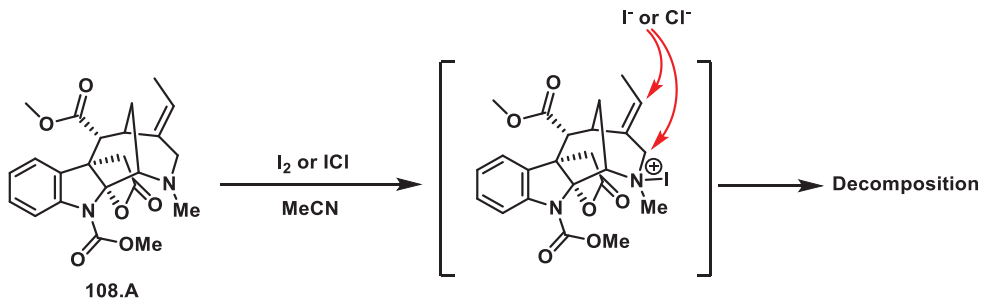
Table 26: Attempts for iodolactonization in the presence of the methyl ester



108.A 113

Entry	Conditions	Comments
1	I_2 (3 equiv.), CH_2Cl_2, 0 °C, 14 h	SM remained, messy reaction
2	I_2 (3 equiv.), MeCN, 0 °C, 14 h	SM remained, at least 3/4 other products
3	I_2 (3 equiv.), MeCN/H_2O = 10:1, 0 °C	Decomposition
4	I_2 (3 equiv.), THF, 0 °C, 14 h	SM remained, messy reaction
5	ICl (1.3 equiv.), MeCN, rt	Decomposition
6	ICl (1.3 equiv.), MeCN, 0 °C, 14 h	Some SM remained, mainly decomposition
7	ICl (1.3 equiv.), THF, rt	Decomposition
8	ICl (1.3 equiv.), THF, -78 °C	Not clean

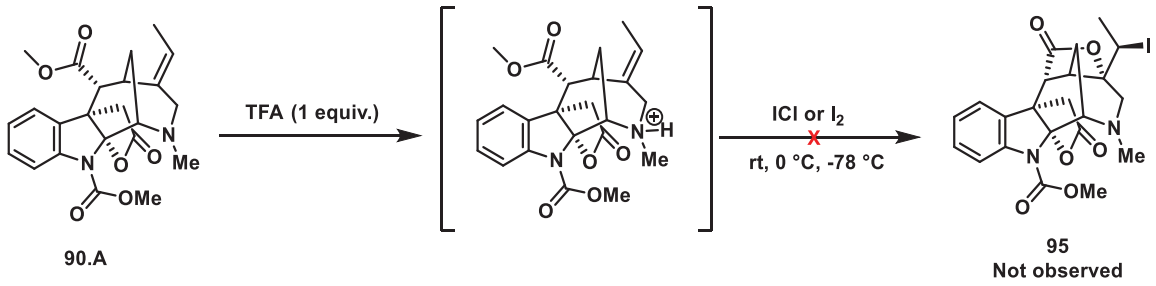
It was supposed that the tertiary amine could be responsible for the instability of substrate **108.A**. As described in scheme 108 the lone pair of electrons of the tertiary amine could react with the electrophilic iodine to generate a quaternary ammonium salt. The counter anion (I^- or Cl^- depending on the reagent used) could then react with the double bond *via* either S_N2' reaction, or directely with the carbon in α to the nitrogen leading to decomposition.



108.A

Scheme 108: Lone pair of electrons from tertiary amine could be responsible for decomposition

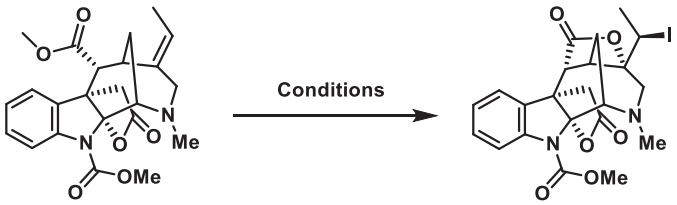
In order to prevent these side reactions, two alternatives were envisaged. The first option was to use a pre-formed iminium salt in order to provide a selective iodination toward the double bond. Unfortunately, performing the reaction using either I_2 or ICl at 0 °C or -78 °C did not lead to successful results (scheme 109).



Scheme 109: Iminium salt improving the selectivity toward the double bond

The second alternative, described in table 27, consisted in using reagents having a counter anion with limited nucleophilicity. NIS was therefore employed in a 7:3 mixture of THF/H_2O. Surprisingly, no reaction was observed at room temperature or even at 50 °C (entries 1 & 2). Increasing the temperature to 70 °C led to slow decomposition (entry 3). Extending the reaction time did not provide the desired product (entry 3). The use of hypervalent iodine was also unsuccessful and led to decomposition (entries 4 & 5).[80]

Table 27: Iodolactonization with methyl ester.



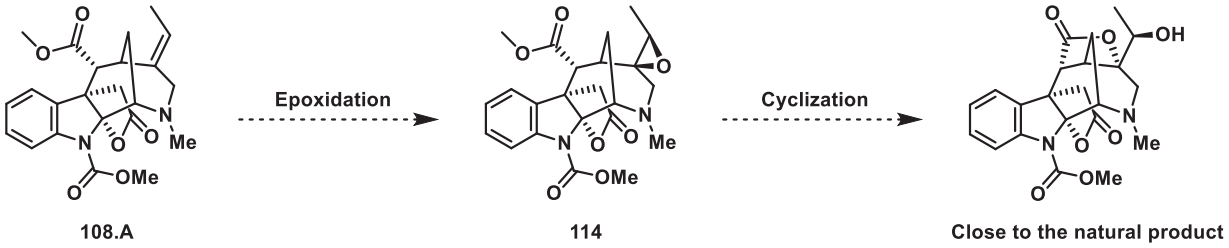
Entry	Conditions	Comments
1	NIS (2 equiv.), THF/H_2O = 7:3, rt	No reaction
2	NIS (2 equiv.), THF/H_2O = 7:3, 50 °C	No reaction
3	NIS (2 equiv.), THF/H_2O = 7:3, 70 °C	Decomposition
4	PIFA/KI, EtOH, 3Å MS	Decomposition after 30 min
5	PIDA/I_2, MeCN	Decomposition

All attempts for direct iodolactonization (in the presence of the methyl ester) failed, mainly due to the instability of the SM. Moreover, the desired product **113** was never observed. It was then decided to investigate oxidative conditions.

[80] A) Mal, P.; Achar, T. *Org. Biomol. Chem.*, **2016**, *14,* 4654. B) Beltran, R; Cariou, K. *Org. Biomol. Chem.*, **2016**, *14*, 8448.

VI.3. Oxidative conditions.

As shown in scheme 110, our strategy was based on the generation of the epoxide followed by cyclization of the methyl ester in order to provide the γ-lactone and the secondary alcohol.



Scheme 110: Strategy via epoxidation/ epoxide opening

The epoxidation of alkenes using a stoichiometric amount of non-metal organic oxidant is a fundamental reaction for organic synthesis. 3-Chloroperbenzoic acid (*m*-CPBA) is a widely used reagent for this transformation as it is a convenient and relatively stable oxidant which is commercially available in approximately 80% purity.[81] Dimethyldioxirane (DMDO) is an alternative milder oxidant for alkene epoxidation under neutral conditions and results in acetone as the coproduct.[82] DMDO was easily prepared according to the literature.[83] Both *m*-CPBA & DMDO as well as other peroxides were examined in order to achieve the chemoselective epoxidation of our substrate. Since the tertiary amine was prone to oxidation to the *N*-oxide, most of the conditions were performed in the presence of an acid in order to pre-form the ammonium species. Although the epoxidation of double bonds has been widely reported in the literature, epoxidation of compounds with unprotected nitrogens are still challenging. Different conditions reported to be successful for the total synthesis of alkaloids having an unprotected nitrogen were examined (table 28). Other well-known epoxidations such as Jacobsen[84], Sharpless[85], Mukaiyama[86] were not explored since they do not tolerate unprotected amines.

As described in table 28, the use of TFA (to generate the ammonium salt) followed by the addition of *m*-CPBA in EtOAc at room temperature led only to decomposition (entry 1). Employing DCM as solvent at 0 °C or room temperature (entries 2 & 3 respectively) did not allow any reaction. Raising the temperature to 50 °C resulted in an unclean reaction mixture (entry 4). A more reactive oxidant such as DMDO was then examined. As shown in entry 5, when 1.1 equivalent of DMDO was used in acetone at 0 °C, a messy reaction was observed.

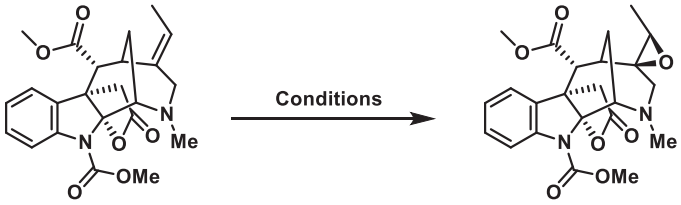
[81] Schwartz, N.N.; Blumbergs, J. H. *J. Org. Chem.* **1964**, *29*, 1976.
[82] Murray, R.W. *Chem.Rev*. **1989**, *89*, 1187.
[83] *Org. Synth.* **2013**, *90*, 350.
[84] 1) E. N. Jacobsen, W. Zhang, A. R. Muci, J. R. Ecker, L. Deng, *J. Am. Chem. Soc.*, **1991**, *113*, 7063. 2) B. D. Brandes, E. N. Jacobsen, *J. Org. Chem*., **1994**, *59*, 4378.
[85] Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc*. **1980**, *102*, 5974.
[86] Feiters, M. C.; Nolte, R. J. M. *J. Org. Chem.* **2004**, *69*, 3453.

In 1993 Gregorio Asensio reported a method that allows the regioselective oxidation of inactivated tertiary and secondary C-H bonds of alkylamines by DMDO using a tetrafluoroborate salt in order to avoid the *N*-oxidation.[87] Based on this antecedent, our starting material **108.A** was premixed with HBF_4 before the addition of DMDO, unfortunately it resulted in a messy reaction (entry 7). Performing the reaction with TFA led to similar results (entry 6). In 2002, a chemoselective epoxidation of an advanced intermediate in the synthesis of Vinca alkaloids was performed in the presence of an unprotected tertiary amine using $HClO_4$, *m*-CPBA in MeOH.[88] Unfortunately, under these conditions no reaction occurred even when heating the reaction to 50°C (entries 8 & 9). Employing MeOH and DCM as solvent system did not promote the reaction (entry 10). Using HBF_4 in DCM (entry 11) did not provide the desired product either. Mioskowski reported the epoxidation in the presence of unprotected amine using TFA, *t*-BuOOH in THF. [89] Unfortunately, no reaction occurred (entries 12 & 13). Oxidation using trifluoroperoxyacetic acid (TFPAA) *via* its *in-situ* generation from trifluoroacetic anhydride and H_2O_2 was then examined. TFPAA is considered as the most reactive organic peroxy-acid. This reagent allows the oxidation of relatively unreactive alkenes to epoxides while other peroxy-acids fail. Unfortunately, when TFPAA was employed on substrate **108.A** no reaction was observed at 0 °C (entry 14). When the temperature was increased to rt, the starting material was fully consumed but the desired epoxide was not observed (entry 15). In 2011, the Steinbach group reported the use of urea-hydrogen peroxide (UHP) in combination with trifluoroacetic anhydride in DCM at 0 °C to achieve the synthesis of *N*-substituted 3,4-epoxypiperidines without formation of the amine *N*-oxide by-product.[90] As presented in entries 16 and 17, no reaction occurred under these conditions.

Conditions described in entries 4 to 7, 10, 11 & 15 resulted in messy mixtures and the desired epoxide was never observed. It was concluded that either the epoxide was not formed or it was too sensitive under the acidic conditions, which resulted in decomposition.

[87] Asensio, G. *J. Am. Chem. Soc.* **1993**, *115*, 7250.
[88] Szabó, L.; Szántay. C. *J. Org. Chem*. **2002**, *67*, 7255.
[89]Hardouin, C.; Doris, E.; Rousseau, B. ; Mioskowski, C. *J. Org. Chem*. **2002**, *67*, 6571.
[90] Scheunemann, M.; Steinbach, J. *Tetrahedron*. **2011**, *67*, 3448.

Table 28: Attempts for the epoxidation of compound 108.A

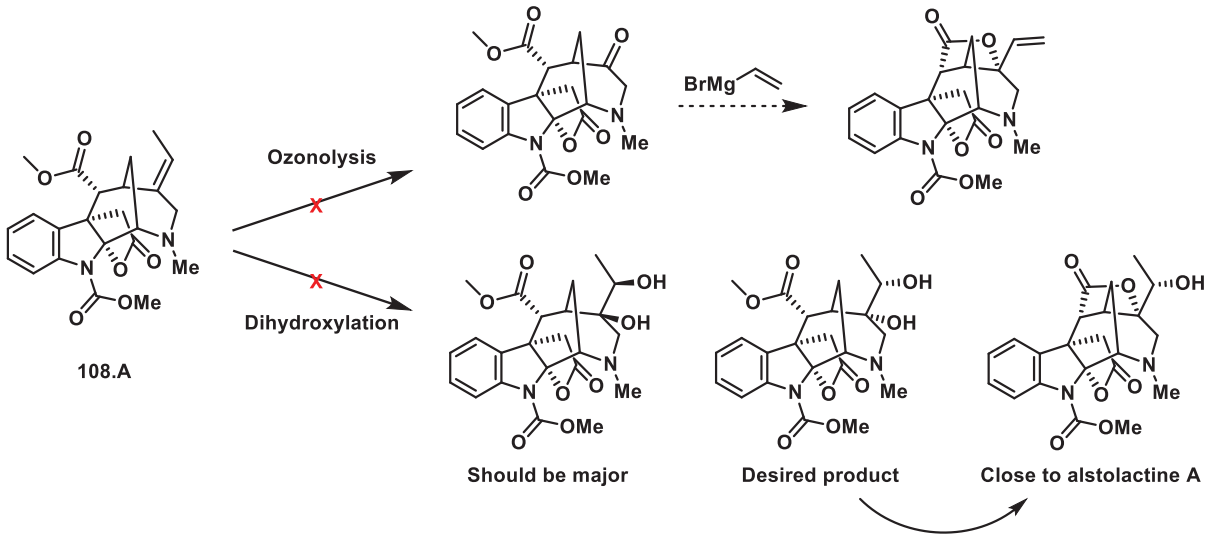


108.A 114

Entry	Conditions	Comments
1	TFA, *m*-CPBA, EtOAc, rt, 1 h	Decomposition
2	TFA, *m*-CPBA, DCM, 0 °C, 12 h	No reaction
3	TFA, *m*-CPBA, DCM, rt, 12 h	No reaction
4	TFA, *m*-CPBA, DCM, 50 °C, 12 h	Not clean
5	DMDO (1.1 equiv.), acetone, 0 °C	Not clean
6	TFA, DMDO (1.1 equiv.), 0 °C	Not clean
7	HBF_4, DMDO (1.1 equiv.), 0 °C	Not clean
8	$HClO_4$, *m*-CPBA, MeOH, 0 °C	No reaction
9	$HClO_4$, *m*-CPBA, MeOH, 50 °C	No reaction
10	$HClO_4$, *m*-CPBA, MeOH/DCM, 50 °C	Not clean
11	HBF_4, *m*-CPBA, DCM, 0 °C	New spot, no epoxide
12	TFA, *t*-BuO_2H 5 M in decane, THF, 0 °C, 12 h	No reaction
13	TFA, *t*-BuO_2H 5 M in decane, THF, rt, 12 h	No reaction
14	TFA, TFAA, H_2O_2 (30% in water), DCM, 0 °C, 12 h	No reaction
15	TFA, TFAA, H_2O_2 (30% in water), DCM, rt, 12 h	Almost full conversion, no epoxide
16	TFA, TFAA, UHP (urea hydrogen peroxide), DCM, 0 °C, 12 h	No reaction
17	TFA, TFAA, UHP, DCM, rt, 12 h	No reaction

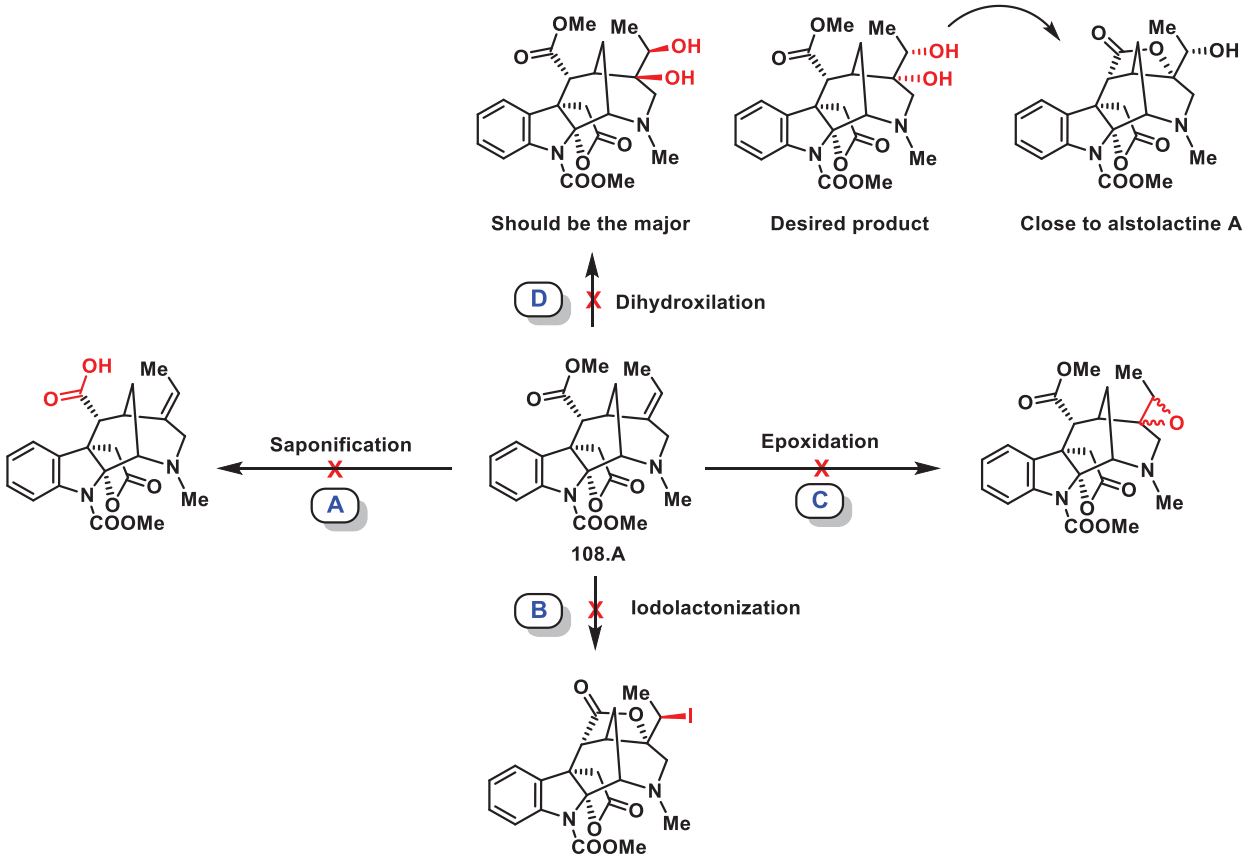
We then envisaged 2 new strategies: either dihydroxylation or ozonolysis of substrate **108.A**. As described in scheme 111, an ozonolysis of the double bond could provide the ketone. Due to its cagelike structure, addition of vinyl magnesium bromide might react chemo & diastereoselectively onto the ketone to afford the alcoholate. Concomitant cyclization would afford the desired γ-lactone. Ozonolysis was performed in a mixture of MeOH/EtOAc at -78 °C and quenched using Me_2S or PPh_3, unfortunately, in both cases the desired product was not observed. Performing the reaction in only MeOH resulted in a messy reaction.

Dihydroxylation was next examined (scheme 111). Although the undesired diastereoisomer may be generated predominantly, it was suspected that the small amount of the desired diastereoisomer could cyclize to the desired lactone. Unfortunately, dihydroxylation using OsO_4 was not successful even upon heating. Changing the solvent did not afford the desired product and the starting material was always recovered.



Scheme 111: Double bond functionalization via ozonolysis or dihydroxylation

As described in scheme 112, this strategy proved to be unsuccessful. Indeed, the saponification failed due to a lack of chemoselectivity (path A) while issues with the unprotected nitrogen account for the difficulties encountered (path B, C and D). The route was then considered as a dead-end.

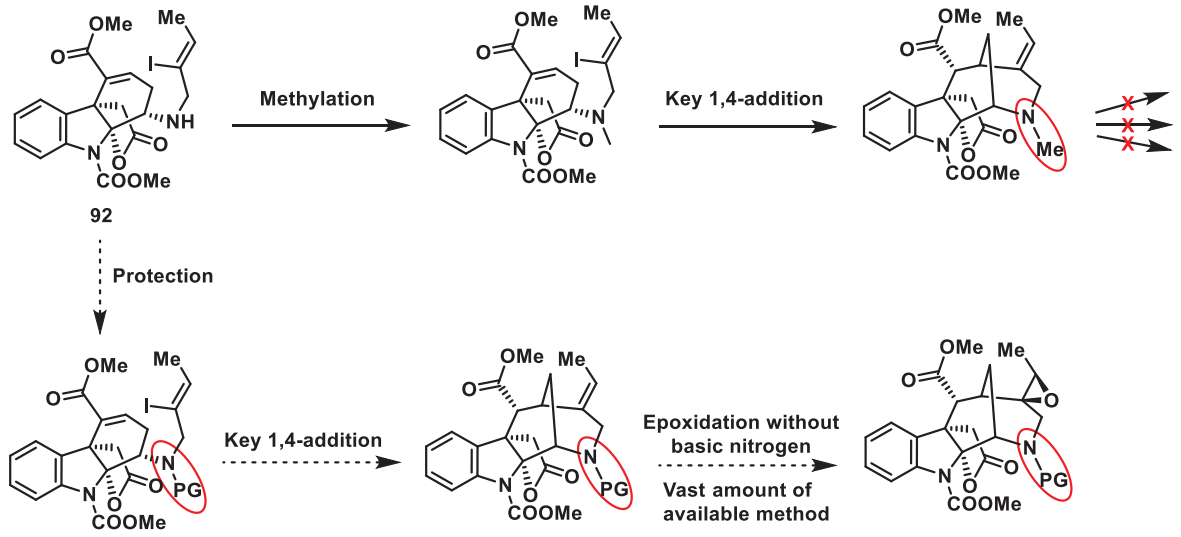


Scheme 112: Summary of the attempts for the functionalization of compound 108.A

In order to prevent troubles caused by the tertiary amine, it was decided to move back to compound **92** and to protect the secondary amine.

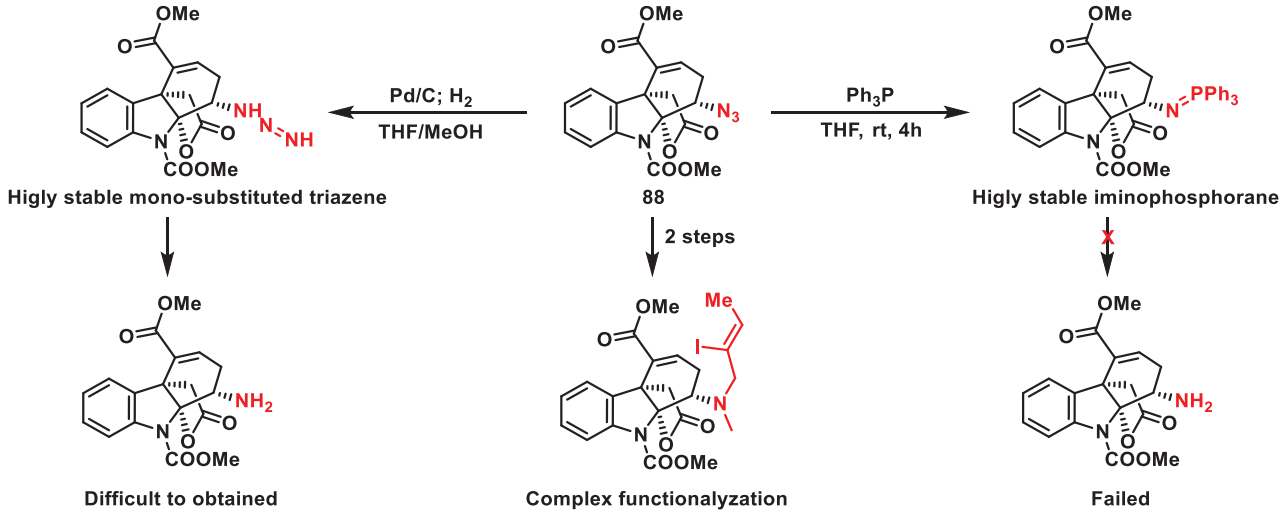
VI.4. Protection of the free secondary amine.

As described in scheme 113, having a protected and non-nucleophilic nitrogen would allow to broadening of the scope of the conditions that could be used for the epoxidation and iodolactonization steps.



Scheme 113: Strategy with N-protecting group.

According to experiments performed along the synthesis, we were already aware of the hindered environment around the azide. As shown in scheme 114, hydrolysis of the iminophosphorane to get the primary amine never succeeded, the mono-substituted triazene was highly stable and difficult to reduce under classic conditions. Finally, the final reductive amination to generate the tertiary amine required several screenings to be effective.

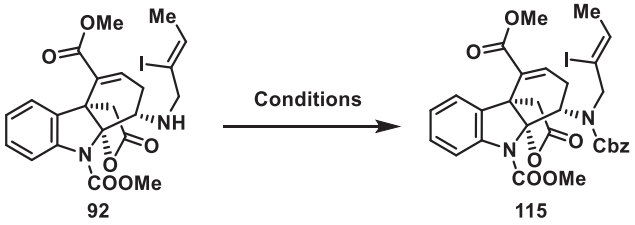


Scheme 114: Hindered environment around the nitrogen.

With this information in hand, the protection of the secondary amine was investigated. As described in table 29, when 2 equivalents of CbzCl was mixed with compound **92** in DCM, at room temperature, the starting

material was recovered (entry 1). Increasing the temperature to 50 °C did not provide better result (entry 2). When the temperature was increased to 70 °C, a small amount of the amine cyclized intramolecularly to form the lactam by-product (entry 3). Employing MeCN instead of DCM did not afford better results even when increasing the temperature (entry 4). An excess of CbzCl was not successful either (entry 5). Using Na_2CO_3 as base in a 1:1 mixture of MeCN/H_2O did not provide the desired product (entries 6 to 8).

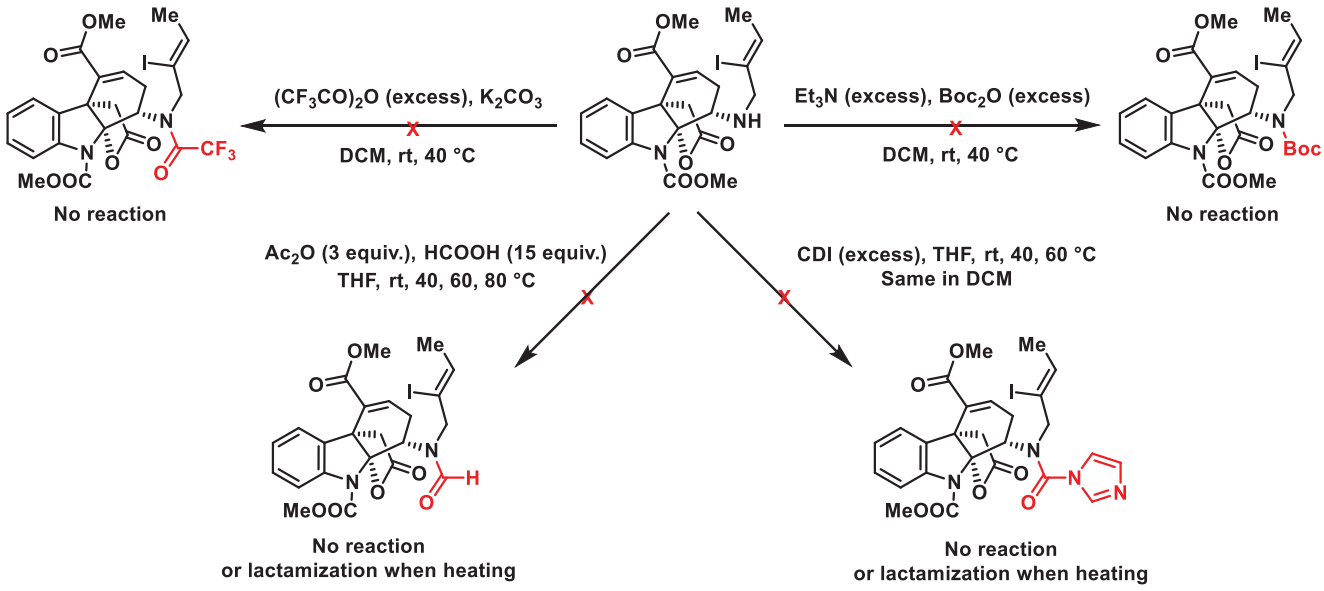
Table 29:Attempts for a Cbz protection of compound 92



92 115

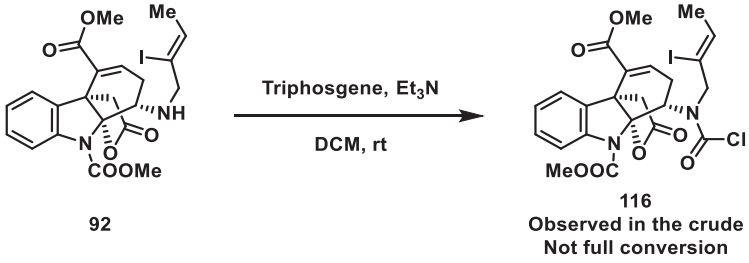
Entry	Conditions	Comments
1	Et_3N (3 equiv.), CbzCl (2 equiv.), DCM, 0 °C to rt	No reaction
2	Et_3N (3 equiv.), CbzCl (2 equiv.), DCM, rt to 50 °C	No reaction
3	Et_3N (3 equiv.), CbzCl (2 equiv.), DCM, rt to 70 °C	No DP, bit of lactamization
4	Et_3N (3 equiv.), CbzCl (2 equiv.), MeCN, 0 °C to 70 °C	Same
5	Et_3N (3 equiv.), CbzCl (excess), MeCN, 0 °C to 70 °C	Same
6	Na_2CO_3 (3 equiv.), CbzCl (2 equiv.), MeCN/H_2O = 1:1, 0 °C to rt	No reaction
7	Na_2CO_3 (3 equiv.), CbzCl (2 equiv.), MeCN/H_2O = 1:1, 50 °C	No reaction
8	Na_2CO_3 (3 equiv.), CbzCl (excess), MeCN/H_2O = 1:1, rt	No reaction

Different protecting groups were then screened. As shown in scheme 115, attempts to install either a Boc, a trifluoroacetyl or formyl group were not successful and the starting material was recovered.



Scheme 115: Attempts for amine protection

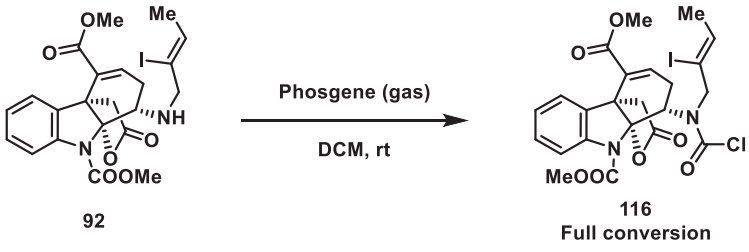
Attempts to introduce the Cbz group in a two steps sequence using CDI (scheme 115) were not successful. However, carbamoyl chloride could be generated using triphosgene which could then react with benzyl alcohol to afford the desired Cbz group. Unfortunately, as shown in scheme 116, using triphosgene in combination with Et_3N in DCM afforded only traces of desired carbamoyl chloride **116**. The addition of reagents or extended reaction time, up to 3 days, did not lead to full conversion.



Scheme 116: First attempts for carbamoyl chloride synthesis

Full conversion of starting material **92** was reached when phosgene gas was employed. Phosgene was synthesized by the British chemist John Davy in 1812 by exposing a mixture of carbon monoxide and chlorine to sunlight. He named it "phosgene" in reference of the use of light to promote the reaction; from Greek, phos (light) and gene (born).[91] Phosgene is an insidious poison as the odor may not be noticed and symptoms may be slow to appear. The odor detection threshold for phosgene is 0.4 ppm, four times the threshold limit value. Its high toxicity is due to its action on the proteins in the pulmonary alveoli, the site of gas exchange. Indeed, when these proteins are damaged, it disrupts the blood-air barrier, causing suffocation. Phosgene gas could be formed *via* thermic decomposition or using the addition of a nucleophile like pyridine on neet triphosgene.

As show in scheme 117, the use of phosgene gas allowed the formation of carbamoyl chloride **116** at room temperature and within a short reaction time.

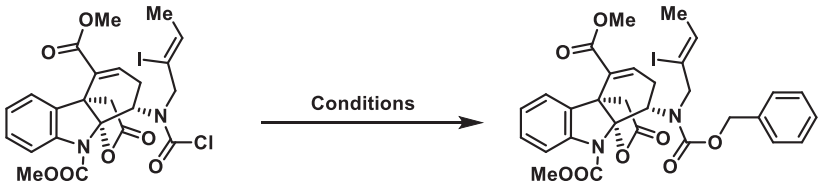


Scheme 117: Formation of carbamoyl chloride using phosgene gas.

[91] John Davy (1812). "On a Gaseous Compound of Carbonic Oxide and Chlorine". Philosophical Transactions of the Royal Society of London **102**: 144–151. doi:10.1098/rstl.1812.0008.

In order to afford the desired Cbz protected compound **115**, intermediate **116** was directly used for the next step without purification. When benzyl alcohol was employed in DCM at room temperature or 60 °C, no reaction occurred (table 30, entries 1 & 2). Changing the solvent to THF did not have any influence (entry 3). Addition of catalytic amount of DMAP (entry 4) or performing the reaction neat (entries 5 & 6) were not successful. When NaH was used in order to deprotonate the benzyl alcohol before reacting with the carbamoyl chloride, the desired product was detected (entry 8). Unfortunately, the reaction mixture was messy.

Table 30: Attemps to generate the Cbz protected compound 115

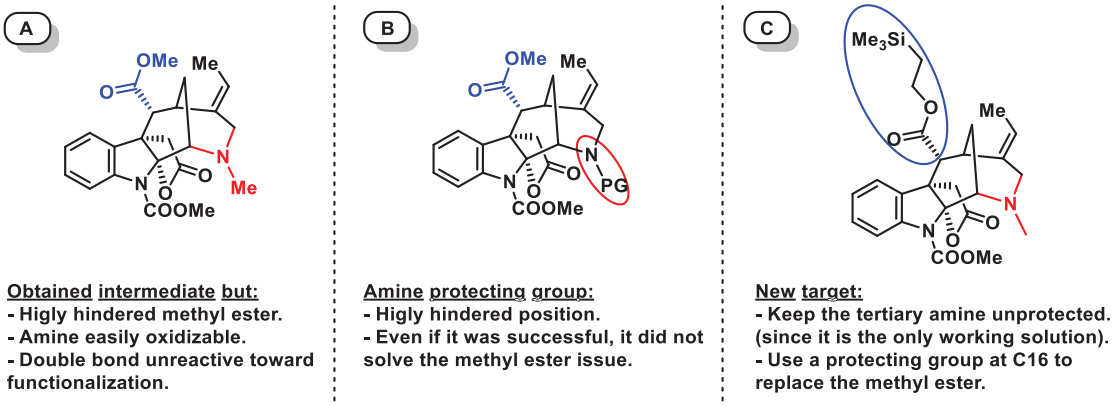


Crude 116 — 115

Entry	Conditions	Comments
1	Et_3N. BnOH, DCM, 0 °C or rt	No reaction
2	Et_3N. BnOH, DCM, 60 °C	No reaction
3	Et_3N. BnOH, THF, 60 °C	No reaction
4	DMAP, Et_3N. BnOH, THF, rt	No reaction
5	Et_3N, BnOH, neet, rt	No reaction
6	Et_3N, BnOH, neet, 60 °C	No reaction
7	DMAP, Et_3N, BnOH, neet, 60 °C	Decomposition
8	NaH, BnOH, THF, 0 °C to rt	DP observed but messy

The numerous issues we encountered while attempting to functionalize product **108.A** and the difficulty to introduce a protecting group on the nitrogen of compound **92**, led us to re-evaluate our strategy.

Desired product **108.A** from the 1,4-addition was obtained in 18 steps. However, the “end game” of the synthesis turned out to be highly challenging (section A scheme 118). As shown in section B of scheme 118, attempts to protect the amine were also unsuccessful due to the steric hindrance around the nitrogen. Finally, the last strategy we envisaged consisted of using a protecting group instead of the methyl ester. It was thought that a silyl derivative (section C) could be an appropriate candidate for a mild and selective deprotection.



Scheme 118: New strategy toward the total synthesis of alstolactine A, B & C.

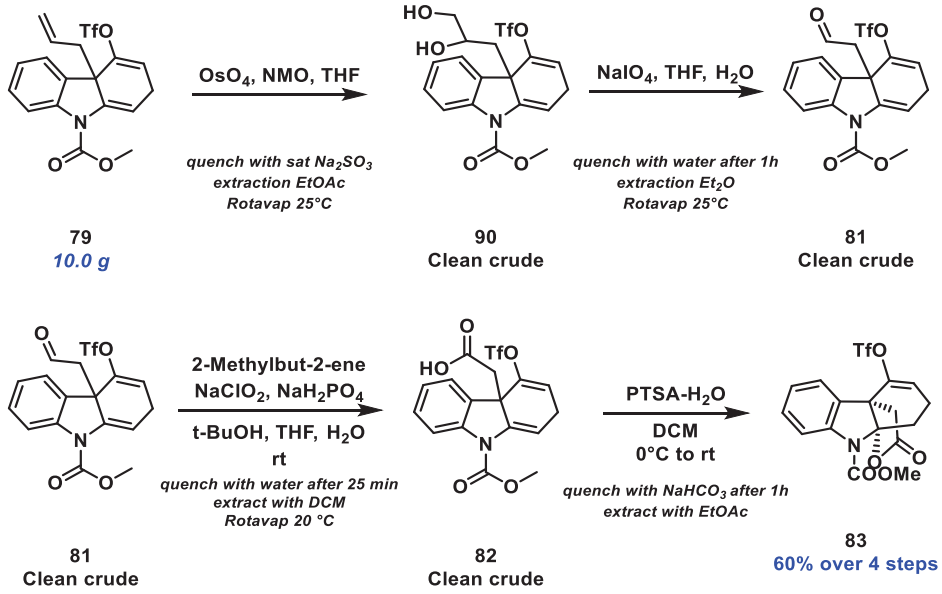
The strategy we developed to reach the new target will be discussed in Chapter IV.

CHAPTER 4 - Synthetic studies of alstolactine A, B & C: 2nd strategy

I. Based on previous experiments

I.1. Palladium-Catalyzed carboxylation

As presented in chapter 3, the four-step sequence provided desired lactone **83** with an overall yield of 60% (scheme 119).



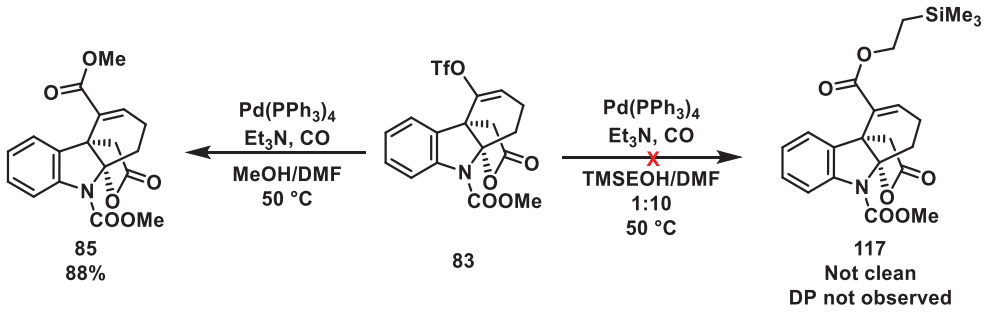
Scheme 119: Optimized 4 steps sequence for lactone formation.

Once having synthesized lactone **83**, the introduction of a new substituent was investigated. It was thought that introducing a teoc-protecting group could be a judicious choice. Indeed, 2-(Trimethylsilyl)ethoxycarbonyl (Teoc) is stable towards hydrolysis and other nucleophilic attacks. Moreover, it tolerates the most acidic and reductive conditions including heterogeneous hydrogenation. Its removal is most commonly performed by treatment with fluoride reagents such as TBAF.[92] Fluoride attack on the silicon atom results in the release of the free carboxylic acid along with ethylene and Me_3SiF. This protecting group

[92] Shute, R. E.; Rich, D. H. *Synthesis* **1987**, 346.

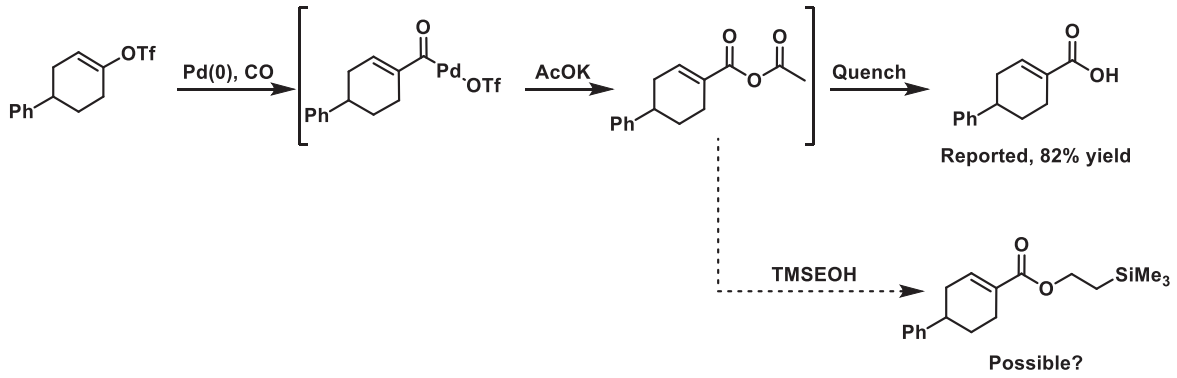
was used by Ang Li *et al.* for the synthesis of xiamycin A and was stable towards radical cyclization, oxidations, Grignard addition and high temperature (up to 120 °C) under air. [93]

The previously described palladium catalyzed methoxycarbonylation was performed in the presence of catalytic amount of tetrakis(triphenylphosphine)palladium(0), triethylamine and carbon monoxide. The reaction was conducted in MeOH/DMF at 50 °C for 1 h affording the desired α,β-unsaturated ester in 88% yield. It was supposed that replacing MeOH by TMSEOH could generate the desired product in one step. Unfortunately, the desired product was not observed (scheme 120).



Scheme 120: Palladium catalyzed methoxycarbonylation using TMSEOH.

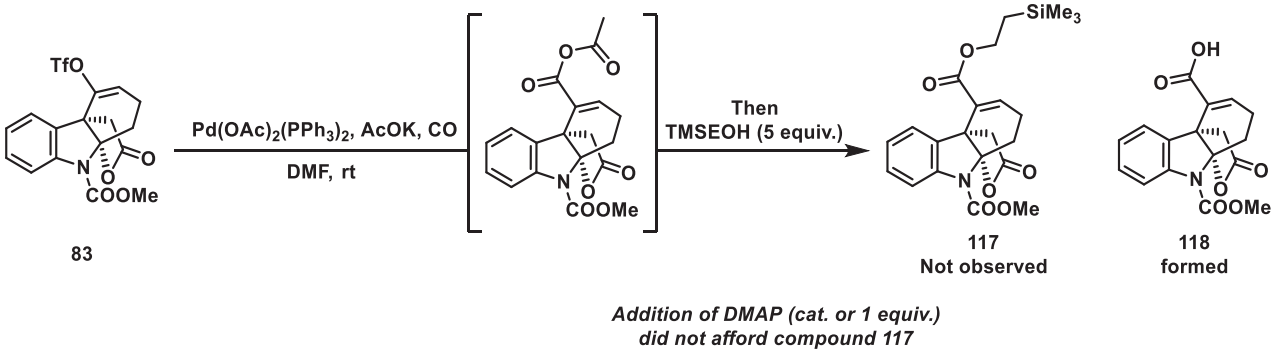
In 1992, the Cacchi group reported a palladium-catalysed hydrocarbonylation of vinyl triflates for the synthesis of α,β-unsaturated carboxylic acid (scheme 121).[94] The reaction was conducted at room temperature in the presence of $Pd(OAc)_2(PPh_3)_2$, AcOK and CO in DMF. The reported results appeared to support the hypothesis of mixed acetic anhydrides intermediate. Based on this postulate, it was supposed that the carboxylation and the protection could be achieved, in a one-pot process, via the introduction of TMSEOH at the end of the reaction.



Scheme 121: Palladium-catalysed hydrocarbonylation of vinyl triflates

[93] Meng, Z.; Yu, H.; Li, A. *Nature Comm.* **2015**, *6*, 6096.
[94] Cacchi, S. ; Lupi, A. *Tetrahedron Lett.* **1992**, *33*, 3939.

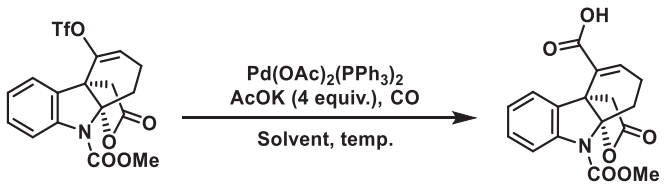
Unfortunately, as shown in scheme 122, the addition of TMSEOH after a full conversion of compound **83** did not provide desired product **117**. Similar result was obtained when employing DMSO as solvent or adding DMAP. However, acid **118** was always isolated in mixture with the starting material.



Scheme 122: Initial attempt via mixed acetic anhydrides intermediate

The formation of acid **188** was then optimized. As shown in table 31, when the reaction was conducted at room temperature in DMF with 0.05 equivalent of palladium, the desired product was obtained in 50% yield (entry 1). Increasing the temperature to 40 °C led to an unclean reaction mixture (entry 2). Performing the reaction with sequential addition of 0.05 equivalent of palladium increased the yield up to 73% (entry 3). When the reaction was performed using DMSO similar result was obtained (entry 4). It is worthy to note that increasing the scale of the reaction provided higher yield (entries 5 to 10). When the carboxylation reaction was conducted on a gram scale, up to 80% yield was obtained.

Table 31: Optimization of the palladium-catalysed hydrocarbonylation



83 118

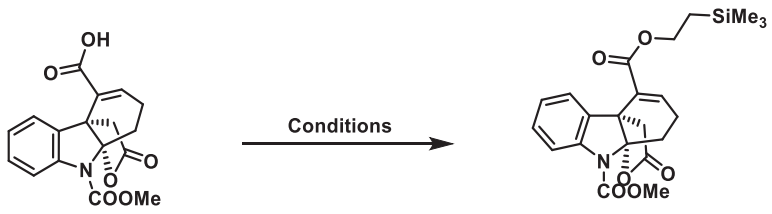
Entry	Scale	Pd equiv.	Solvent	Temp.	Comments
1	2 mg	0.05	DMF	rt	~ 50% yield
2	2 mg	0.05	DMF	40 °C	Less clean
3	2 mg	2*0.05	DMF	rt	73% yield
4	2 mg	2*0.05	DMSO	rt	Same than entry 3
5	10 mg	2*0.05	DMF	rt	73% yield
6	50 mg	2*0.05	DMF	rt	74% yield
7	150 mg	2*0.05	DMF	rt	75%
8	500 mg	2*0.05	DMF	rt	75%
9	1.3 g	2*0.05	DMF	rt	82%
10	2.0 g	2*0.05	DMF	rt	80%

With an efficient route for the preparation of intermediate **100** in hand, we turned out our attention to the protection of the carboxylic acid.

I.2. First attempts for the protection of the carboxylic acid.

The teoc-protection of the carboxylic acid moiety was performed using common peptide coupling reagents. Carbodiimides have been used as activators for decades in peptide synthesis. DCC is a popular condensation reagent that has been commonly used in solution, mostly in combination with additives such as HOBt. Another common coupling reagent often used is EDC·HCl. It is a water-soluble carbodiimide that was especially designed for coupling in aqueous solution even though its stability under these conditions is limited. Usually, EDC-mediated coupling is performed in polar solvents such as DMF or NMP or even in methylene chloride. Contrary to DCC, the urea formed from EDC is readily soluble. As described in table 32, using DCC and HOBt in either DCM or DMF did not afford the desired product (entries 1 & 2). Employing EDC in combination with HOBt, in either DCM or DMF, was also unsuccessful and the starting material was completely recovered (entries 3 & 4). Adding a catalytic amount of DMAP to the reaction mixture allowed the formation of compound **119** in 20% yield (entry 5). Increasing the amount of DMAP to 1 equivalent afforded a spot to spot reaction, however, the desired product was isolated in only 35% yield (entry 6). It was then suspected that compound **119** was unstable under acidic conditions and decomposed either during work-up or during purification on silica-gel. Indeed, when the work-up was performed using a 5% aqueous solution of $KHSO_4$ instead of a 1 M HCl solution, the yield increased from 35% to 55% (entry 7). Avoiding acidic work-up afforded similar result (entry 8). Compound **119** was surprisingly unstable, even on silica, explaining the low yield obtained. Attempts to purify this compound on alumina also afforded poor yield.

Table 32: Protection of the acid 118 using carbodiimide reagents.



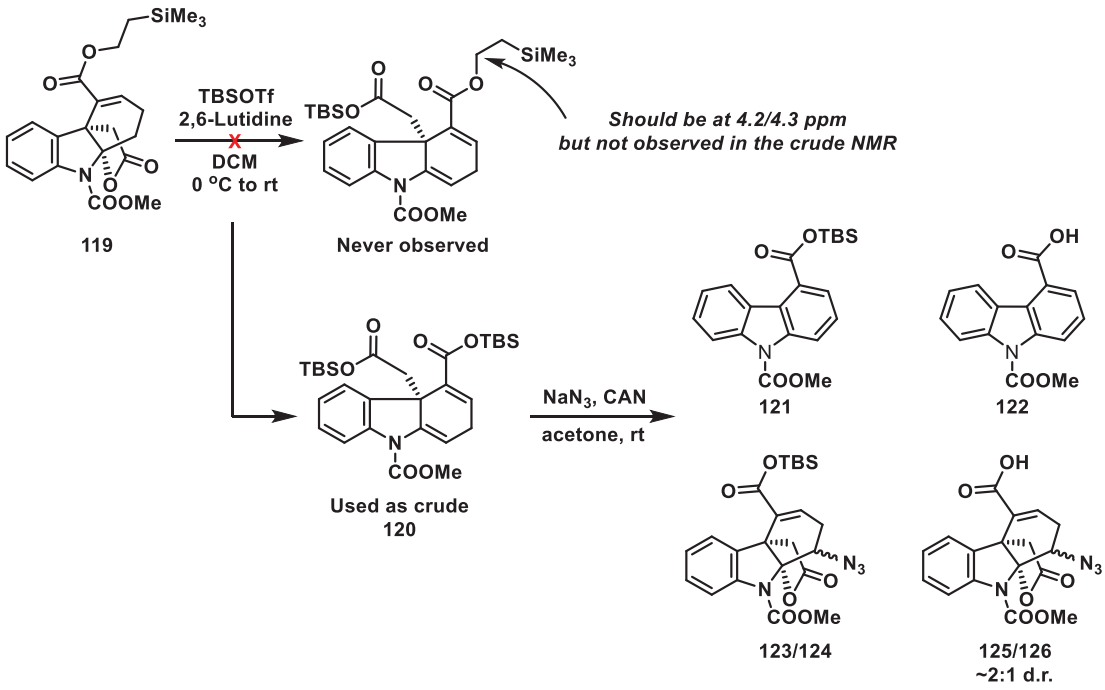
118 119

Entry	Conditions	Work-up	Comments
1	TMSEOH, DCC, HOBt, DCM, rt	1 M HCl, $NaHCO_3$, brine	Traces of DP, SM remained
2	TMSEOH, DCC, HOBt, DMF, rt	Same	Same
3	TMSEOH, EDC.HCl, HOBt, DCM, rt	Same	Same
4	TMSEOH, EDC.HCl, HOBt, DMF, rt	Same	Same
5	TMSEOH, EDC.HCl, DMAP (cat), DCM, rt	Same	SM remained, 20% yield
6	TMSEOH, EDC.HCl, DMAP (1 equiv.), DCM, rt	Same	Spot to spot reaction, 35% yield
7	Same	5% aq. $KHSO_4$, $NaHCO_3$, brine	Spot to spot reaction, 55% yield
8	Same	No acidic work-up	Spot to spot reaction, 57% yield

Once the acid moiety protected by the teoc group, the azidolactonization sequence was undertaken.

I.3. Azidolactonization

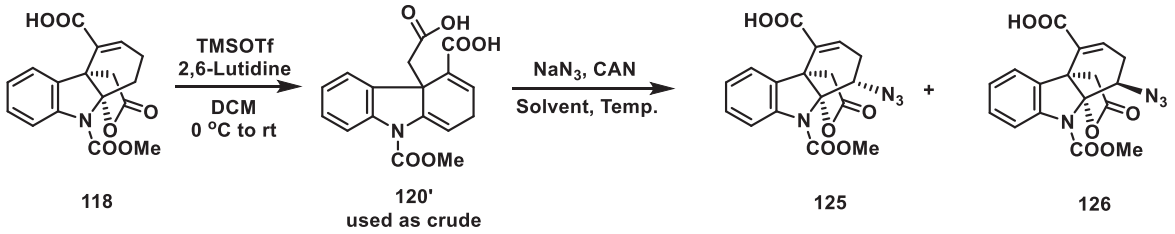
First attempts focused on the lactone opening using TBSOTf and 2,6-lutidine as a weak and non-nucleophilic base. Unfortunately, under these conditions, the teoc-protecting group turned out to be unstable and was cleaved leading to compound **120** (scheme 123). The azidolactonization was finally performed under previously optimized conditions described in chapter 3. However, a mixture of 6 compounds was generated after work-up. Among them, the two diastereoisomers **125** and **126** were observed in a 2:1 ratio. This mixture of products was mainly due to the partial cleavage of the TBS-ester moiety during the reaction.



Scheme 123: Azidolactonization sequence using TBSOTf

Due to the instability of the teoc-group towards the azidolactonization step, it was decided to optimize the sequence starting from acid **118**. First attempts focused on the lactone opening using TMSOTf and 2,6-lutidine. As suspected, the desired silyl ester was not obtained (see chapter 3 with methyl ester). The silyl-ester moiety was cleaved during work-up leading to free carboxylic acid **120'**. The azidolactonization was then conducted as shown in scheme 124. When a solution of CAN in acetone was added dropwise, at room temperature, into a solution of intermediate **120'** and sodium azide, the desired diastereoisomer **125** was obtained with a d.r. of 2:1 (entry 1). Unfortunately, the reaction mixture was not clean. When the reaction was performed in acetone at -20 °C, the d.r. decreased to 1:2.5 in favor of the *trans* undesired isomer (entry 2). It is worthy to note that, as previously observed with the methyl ester, increasing the temperature from

-20 °C to 20 °C completely reversed the diastereoselectivity of the reaction. Finally, the use of MeCN as solvent led to a poor d.r. of 1:1 (entry 3).

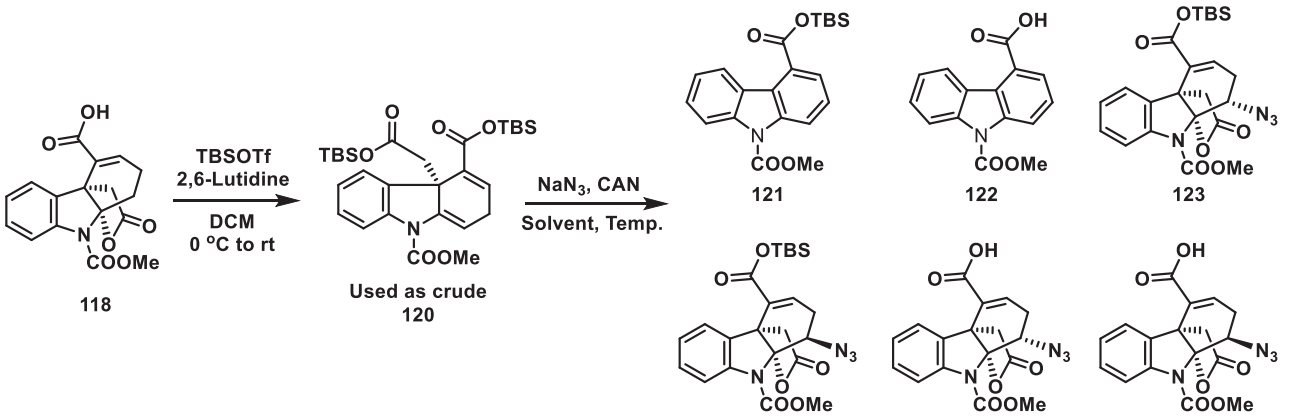


118 | 120' used as crude | 125 | 126

Entry	Conditions	Ratio 107/108	Comments
1	Acetone, rt	2:1	Not clean
2	Acetone, -20 °C	1:2.5	Not clean & bad d.r.
3	MeCN. rt	1:1	Durtier than 1 & 2

Scheme 124: Azidolactonization sequence using TMSOTf

As unclean reaction mixtures were observed, it was supposed that TBS-ester intermediate **120** would afford cleaner reaction. As shown in scheme 125, the second attempt was performed using TBSOTf, instead of TMSOTf. Desired silyl ester **120** was generated with concomitant formation of the ene-carbamate moiety. Then, intermediate **120** underwent azidolactonization under the conditions described in scheme 125. As previously observed, performing the reaction in acetone, at room temperature, afforded compounds **125** and **126** in a 3:1 ratio (entry 1). When the reaction was performed at 0 °C, the d.r. decreased to 1:1 (entry 2). Performing the reaction at -20 °C afforded a diastereoisomeric ratio of 1:2 in favor of compound **126** (entry 3). Finally, using MeCN instead of acetone as solvent led to a messy reaction with a poor d.r. of 1:1 (entry 4).



118 | Used as crude 120 | 121 | 122 | 123 | 124 | 125 | 126

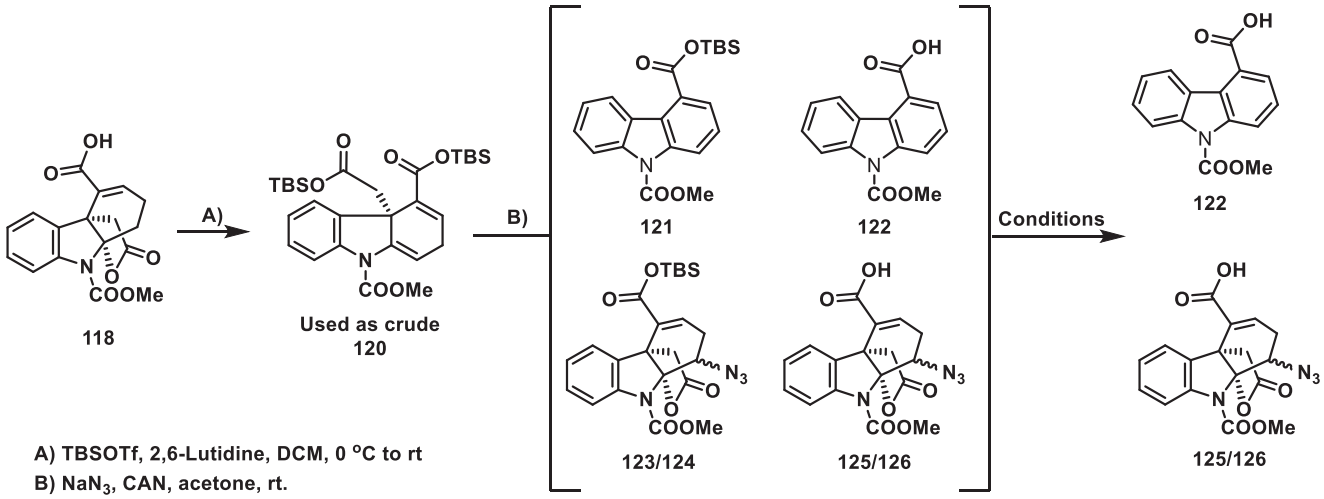
Entry	Conditions	Ratio 107/108	Comments
1	Acetone, rt	3:1	Clean, good d.r.
2	Acetone, 0 °C	1:1	-
3	Acetone, -20 °C	1:2	Bad d.r.
4	MeCN, rt	1:1	Messy

Scheme 125: Diastereoselectivity of the azidolactonization

The conversion of remaining silyl derivatives **121**, **123** and **124** into corresponding carboxylic acid **122**, **125** and **126** was then undertaken. As described in table 33, the use of 2 equivalents of TBAF (1 M in THF) did not allow full conversion of the silyl intermediate (entry 1). Increasing the amount of TBAF to 4 equivalents provided a clean and full conversion into the desired products (entry 2). Interestingly, dilution of the reaction mixture with water, before the addition of 2 equivalents of TBAF, allowed a full and clean conversion in only 1 hour (entry 3). The dilution of the reaction mixture with 1 M HCl afforded a clean but slow reaction (entry 4). Employing 4 M HCl did not provide a clean reaction mixture (entry 5).

Finally, entry 3 was established as the best conditions to cleave the silyl intermediates in a clean and efficient way.

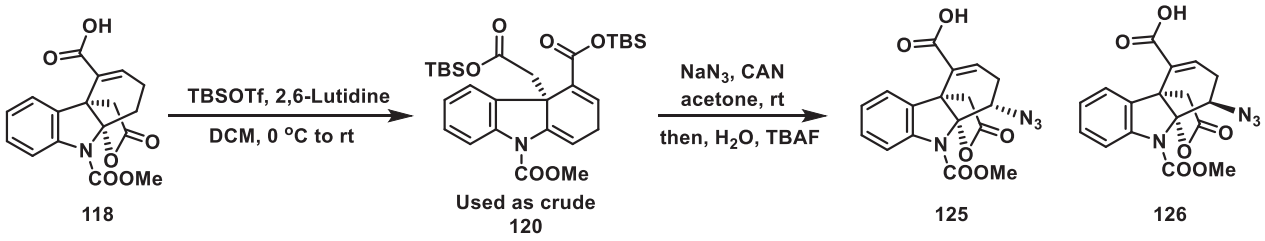
Table 33: Optimizations toward a clean cleavage of the silyl intermediates.



Entry	Conditions	Comments
1	TBAF (2 equiv.) 1 M in THF	Incomplete conversion
2	TBAF (4 equiv.) 1 M in THF	Full conversion & clean
3	Dilute reaction mixture with water 1:1 v/v then TBAF (2 equiv.) 1 M in THF	Full conversion & clean
4	Dilute reaction mixture with HCl 1 M 1:1 v/v	Slow
5	Dilute reaction mixture with HCl 4 M 1:1 v/v	Faster than entry 4, less clean

The sequence was finally performed at various scales from 10 mg to 565 mg, to our delight, the yield remained around 73% over two steps with a diastereoselectivity of ~2.5:1 (table 34).

Table 34: Scale of the azidolactonization sequence.

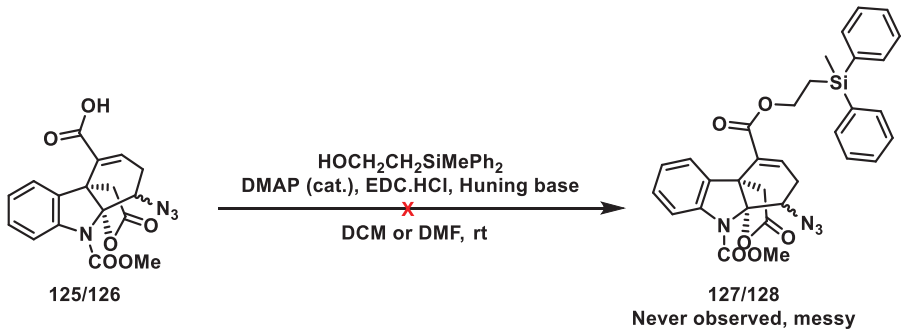


Entry	Scale	Yield over 2 steps	Ratio 125/126
1	10 mg	70%	3:1
2	50 mg	74%	2.2:1
3	100 mg	70%	2:1
4	200 mg	75%	3:1
5	340 mg	70%	2:1
6	565 mg	72%	2.5:1

Unfortunately, despite several attempts, the two diastereoisomers remained inseparable and were used for the next step without further purification. The carboxylic acid protection step was then undertaken using a mixture of compounds **125** and **126.**

I.4. Second attempt for the protection of the carboxylic acid

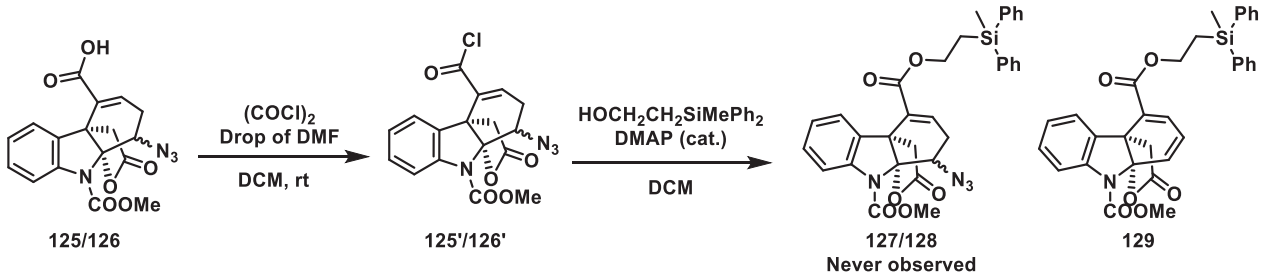
As previously observed, the protection of the carboxylic acid using a teoc group turned out to be unsuccessful due to its surprising instability under slightly acidic conditions. It was thus decided to use a more stable protecting group having two phenyl substituents attached to the silicon atom. As shown in scheme 126, the use of coupling reagents in either DCM or DMF did not afford the desired products and led to a messy reaction mixture.



Scheme 126: Initial attempt using $SiMePh_2$ as protecting group.

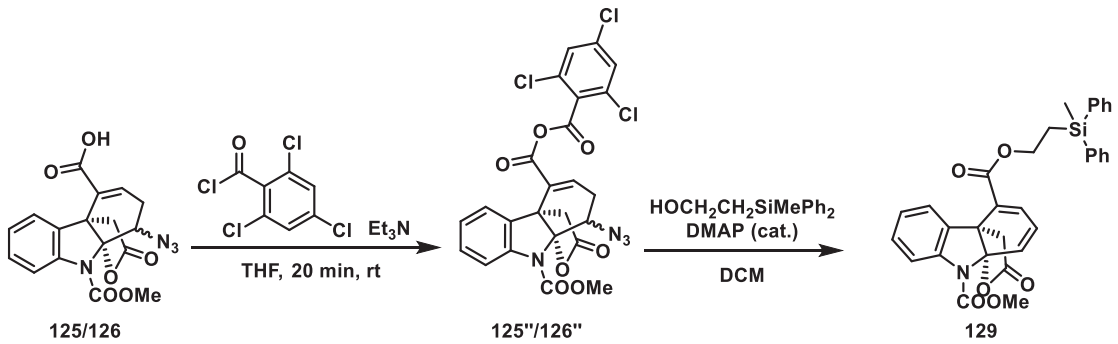
The formation of the ester moiety was then attempted *via* the generation of an acyl-chloride intermediate. As shown in scheme 127, the use of oxalyl chloride in presence of catalytic amount of DMF, at room temperature, afforded the desired acyl-chlorides **125'/126'**. The formation of these intermediates was

confirmed by IR. After evaporation to dryness, the crude intermediates were mixed with the alcohol and catalytic amount of DMAP. Surprisingly, the desired products **127** and **128** were not observed and diene **129** was formed as a major product, probably through elimination of the azide group. Performing the reaction without DMAP did not provide better results.



Scheme 127: Attempt via acyl-chloride intermediate

The Yamaguchi esterification was then examined (scheme 128). This reaction allows the mild synthesis of highly functionalized esters.[95] After formation of a mixed anhydride **125''/126''** between the Yamaguchi Reagent (2,4,6-trichlorobenzoyl chloride) and carboxylic acids **125/126** the volatiles were removed under reduced pressure. The solubilization of the mixed anhydrides in DCM followed by addition of the alcohol, in presence of catalytic amount of DMAP, afforded a full and clean conversion into diene **129**.

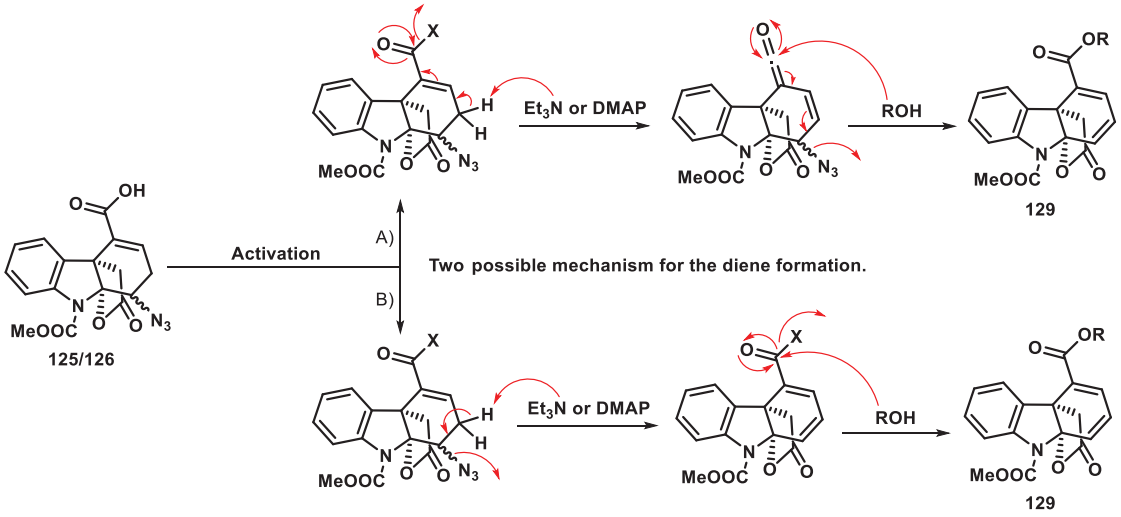


Scheme 128: Attempt via Yamaguchi esterification.

According to previous experiments, it was supposed that the activation of the carboxylic acid led to the formation of diene **129** through azide elimination. Two mechanisms could be envisaged to explain this result. As shown in scheme 129, after activation of acids **125** and **126**, a proton in α-position to the azide could be deprotonated. Subsequent electron shift promoted by the α,β-unsaturated system could generate the ketene intermediate (Path A). The alcohol could then react with the reactive ketene to generate the ester moiety followed by the formation of diene **129** *via* elimination of the azide. The second pathway (Path B)

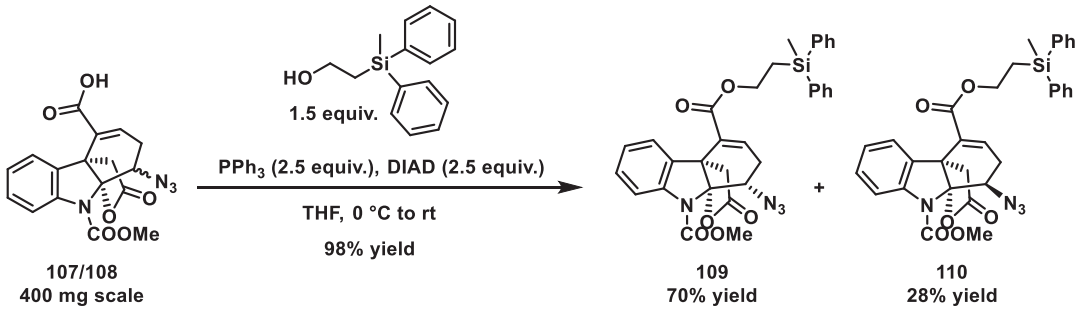
[95] Junji, I.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

involves E_2 elimination of the azide moiety resulting in the formation of a diene followed by the addition of the alcohol on the activated ester.



Scheme 129: Proposed mechanisms toward the formation of 129.

These unsuccessful results confirmed that performing the esterification by activating the carboxylic acid moiety was not appropriate. Thus, it was decided to examine Mitsunobu conditions as it proceeds *via* activation of the alcohol instead of the acid.[96] Under optimized conditions, the desired products were obtained in up to 98% yield on 400 mg scale (scheme 130). It is noteworthy that the order of reagents addition plays a crucial role on the reaction yield. Indeed, when the alcohol, PPh_3 and the SM were diluted in THF, cooled at 0 °C for 5 min, followed by the dropwise addition of DIAD, the major product obtained was diene **129**. At this stage of the synthesis, the two diastereoisomers were easily separable on silica gel.

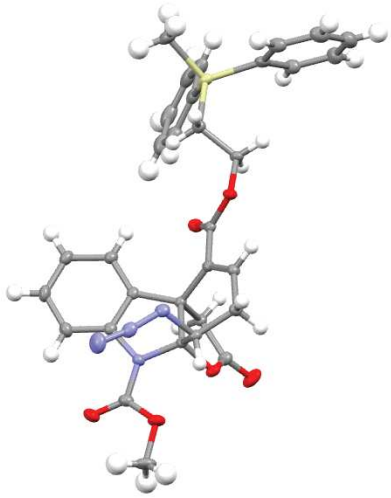


NB: The alcohol and PPh_3 were diluted in THF and cooled at 0 °C, DIAD was then added dropwise. After 20 min at 0 °C, the SM was added in 1 portion and the reaction was warmed to rt.

Scheme 130: Mitsunobu, appropriate method for a clean esterification of the carboxylic acid.

[96] But, T. Y. S.; Toy, P. H. *Chem. Asian. J.* **2007**, *2*, 1340.

As shown in scheme 131, the *trans*-relationship between the lactone and the azide was confirmed by X-Ray analysis.



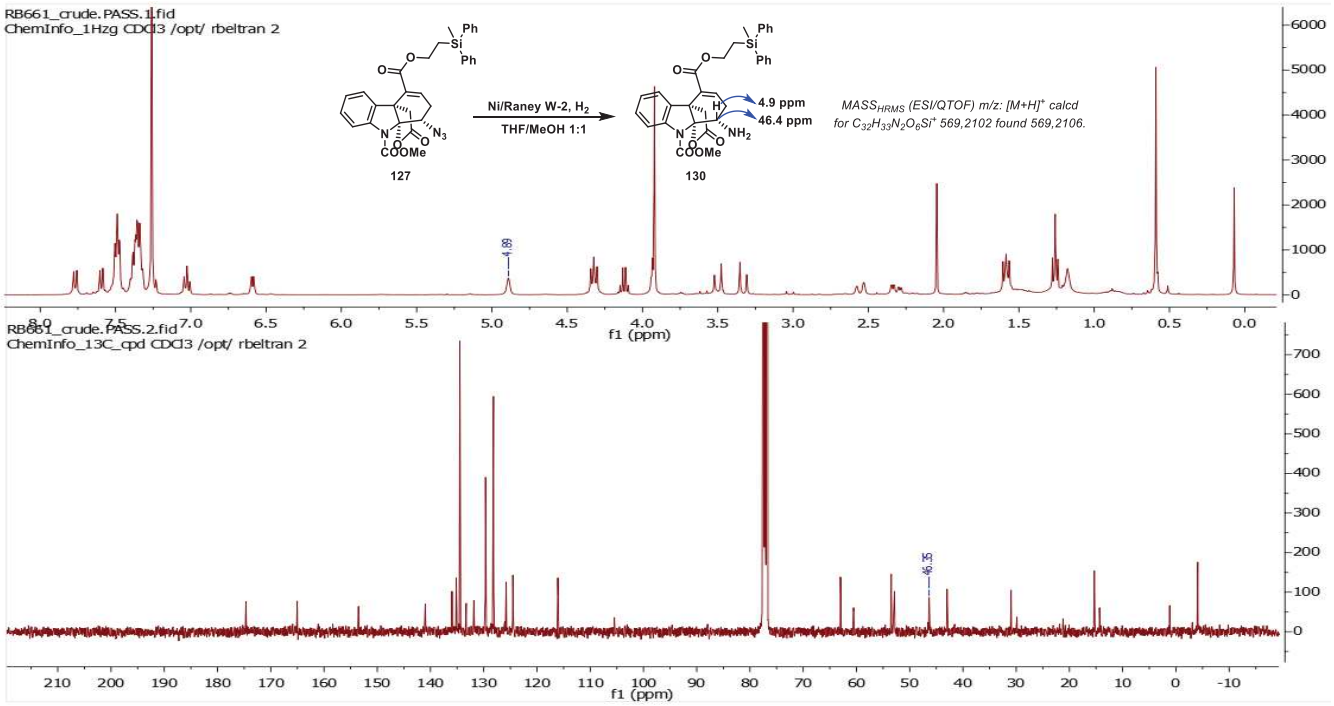
Scheme 131: X-ray of the trans-diastereoisomer 128

Once the silyl-protecting group installed on desired diastereoisomer **127**, we turned our attention to the next sequence of the synthesis.

I.5. Azide reduction and *N*-allylation

The reduction of azide **127** will not be discussed here as the conditions used have previously been described for the methyl ester (chapter 3). Among them, Staudinger, aza-Wittig, reduction and hydrogenation using several metals (Zn, Fe, Pd/c, Pd($CaCO_3$), Pd($BaSO_4$) etc.) were all unsuccessful mainly due to the formation of a triazene intermediate and translactamization.

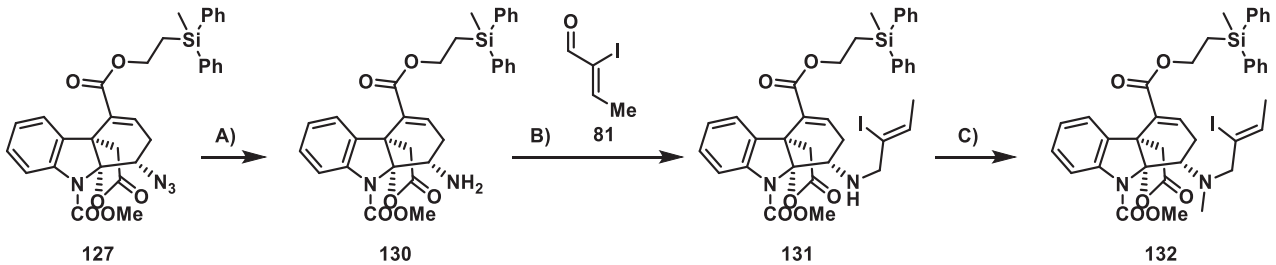
The use of freshly prepared W-2 Ni/Ramey was crucial for having clean and reproducible reduction. The resulting amine turned out to be unstable towards purification and was used as a crude mixture for the next step. Nevertheless, as described in scheme 132, crude amine **130** has been fully characterized.



Scheme 132: Crude analysis of amine 130

Optimization of the complete sequence (reduction & *N*-allylation) was then undertaken. Solvent, reducing agent, temperature and additive were examined. The optimized conditions are described in table 35. After reduction of azide **127**, the resulting crude amine **130** was mixed with aldehyde **98** in MeOH/DCE 10:1. Once the amine fully converted into the corresponding imine intermediate, $NaBH_3CN$ and AcOH were added to the reaction mixture affording secondary amine **131**. Finally, reductive amination of amine **131,** in the presence of paraformaldehyde and $NaBH_3CN$, provided tertiary amine **132** in 44% yield over three steps. The yield of this three-step sequence was reproducible on different scales up to 200 mg.

Table 35: Complete sequence toward the generation of tertiary amine 132.



Entry	Scale	Yield over 3 steps
1	20 mg	45%
2	50 mg	46%
3	100 mg	42%
4	200 mg	43%

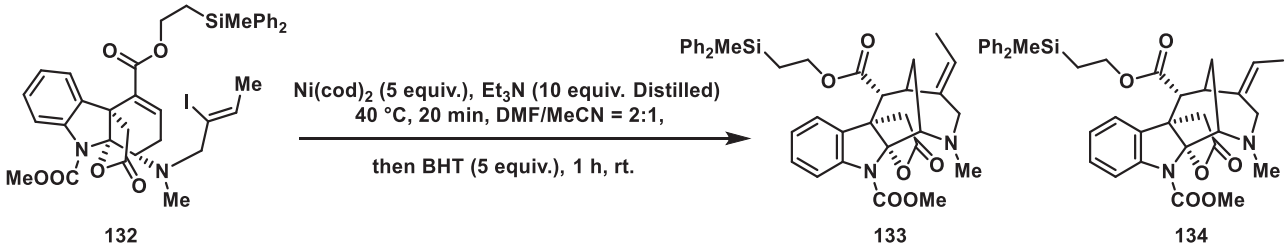
Conditions:
A) Ni/Raney W-2, H_2, THF/MeOH 1:1; B) Aldehyde 81 in MeOH/DCE 10:1, 3Å MS, then $NaBH_3CN$, AcOH; C) Paraformaldehyde AcOH, $NaBH_3CN$, MeCN/MeOH 4:1

Having the silyl protected intermediate **132** in hand, it was decided to move to the challenging 1,4-addition.

I.6. Key step

To our delight, the key step of our strategy proceeded properly in the presence of the silyl-protecting group. However, under previously optimized conditions, a mixture of isomers was obtained in 62% yield (10% less than with methyl ester **106**). Moreover, the ratio of isomers **133** and **134** decreased from 6:1, for the methyl ester, to 2.5: 1 for the silyl ester (table 36).

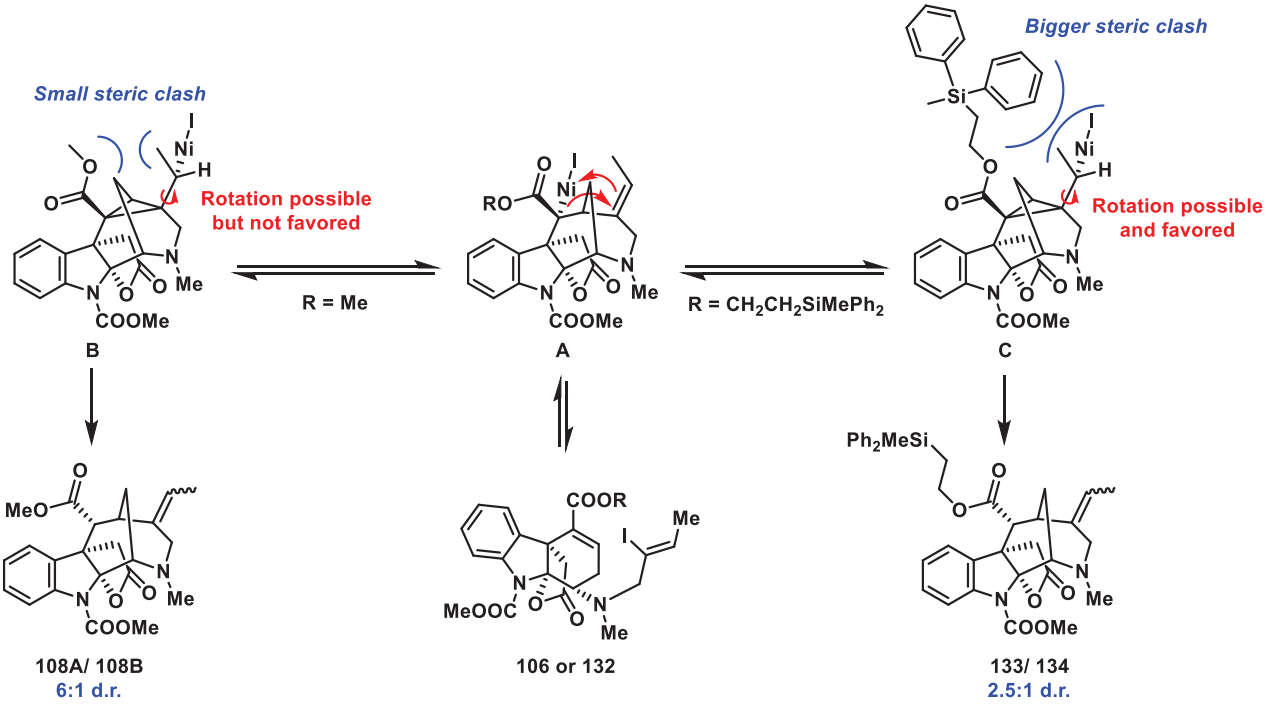
Table 36: Reaction scale for the [Ni(cod)2]-mediated cyclization



132 133 134

Entry	Scale	Yield	Ratio 133/134
1	2 mg	-	2.2:1
2	10 mg	60%	2:1
3	25 mg	62%	2.5:1
4	40 mg	63%	3:1
5	50 mg	62%	3:1

The difference of diastereoselectivity observed could be explained by the proposed mechanism described in scheme 133. Oxidative addition of Ni^0 of either compound **106** or 1**32**, coordination to the double bond and β-migratory insertion affords intermediate **A**. The intramolecular formation of cyclopropane produces the sigma alkyl nickel species **B** or **C** allowing the simultaneous free rotation of the C-C bond. The rotation around the carbon-carbon bond is determined by the steric hindrance between the ester (methyl or silyl ester) and the ethylidene moiety. As the steric clash is bigger with the silyl protecting group than with the methyl ester, the rotation of the C-C bond of compound **C** is favored, resulting in the decrease of diastereoselectivity. Then, species **B** and **C** undergo a retro-β-migratory insertion, reducing the strain of the cyclopropane to generate the desired products.

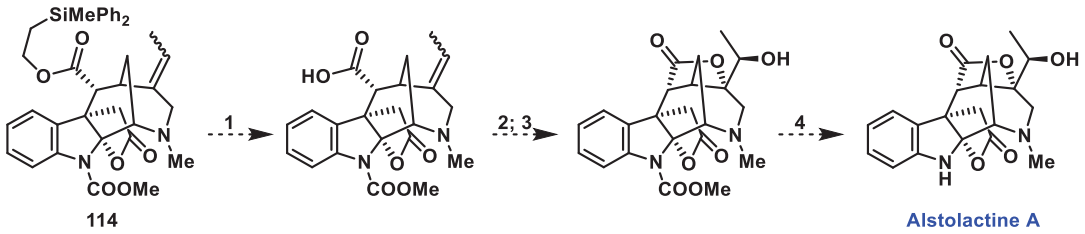


Scheme 133: Variation of diastereoselectivity, proposed mechanism

Further optimization to improve both the diastereoselectivity and the yield were not successful. It was finally concluded that 62% yield for such complex reaction was enough to continue the synthesis toward alstolactine A. It is important to note that diastereoisomers **133** and **134** were difficult to separate, the mixture was thus used without further purification for the next step.

II. End game

The end-game strategy towards alstolactine A is described in scheme 134. The sequence begins with the deprotection of the silyl-protecting group followed by the epoxidation of the double bond. Subsequent epoxide opening and separation of the two diastereoisomers followed by cleavage of the carbamate would afford the desired natural product.

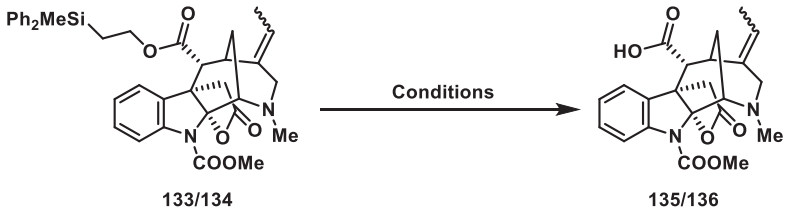


Steps: 1. Deprotection; 2. Epoxidation; 3. Epoxide opening; 4. Deprotection.

Scheme 134: Strategy towards alstolactine A

Based on this strategy, the deprotection of the carboxylic acid was investigated. As shown in table 37, the use of TBAF in THF allowed the clean formation of desired carboxylic acids **135** and **136**. Unfortunately, these compounds turned out to be unstable and decomposed quickly during concentration under reduced pressure (entry 1). Performing the reaction in DCM did not provide better results (entry 2). The use of CsF in various solvents did not allow any reaction even when increasing the equivalents of CsF (entries 3 to 7).

Table 37: Deprotection of the carboxylic acid.

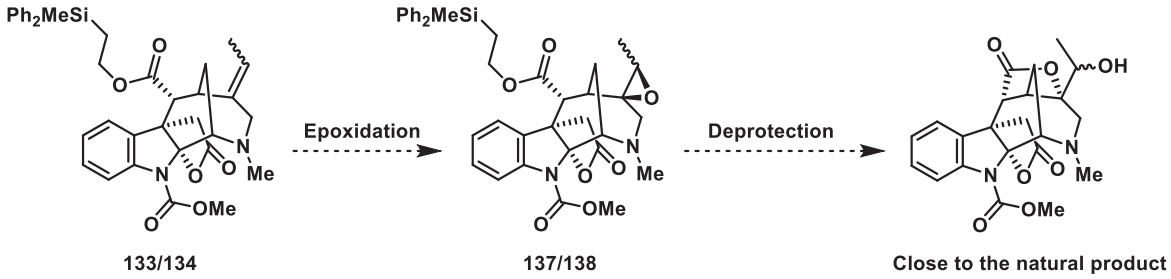


Entry	Solvent	Reagent (equiv.)	Temp.	Comments
1	THF	TBAF 1 M in THF (2 equiv.)	rt	DP obtained but decomposed
2	DCM	TBAF 1 M in THF (2 equiv.)	rt	DP obtained but decomposed
3	THF	CsF (2 equiv.)	0 °C to rt	No reaction after all night
4	DCM	CsF (2 equiv.)	0 °C to rt	No reaction after all night
5	MeCN	CsF (2 equiv.)	0 °C to rt	No reaction after all night
6	MeCN	CsF (8 equiv.)	0 °C to rt	No reaction after all night
7	MeCN/H_2O	CsF (8 equiv.)	0 °C to rt	No reaction after all night

It was finally decided to perform the epoxidation first. However, it is noteworthy that deprotection of silyl ester **133/134** under mild conditions was a huge improvement toward the synthesis of alstolactine A.

II.1. Chemoselective epoxidation of the double bond.

As shown in scheme 135, our strategy consisted in the generation of epoxides **137/138** followed by deprotection and *in-situ* cyclization in order to generate the δ-lactone and the secondary alcohol.

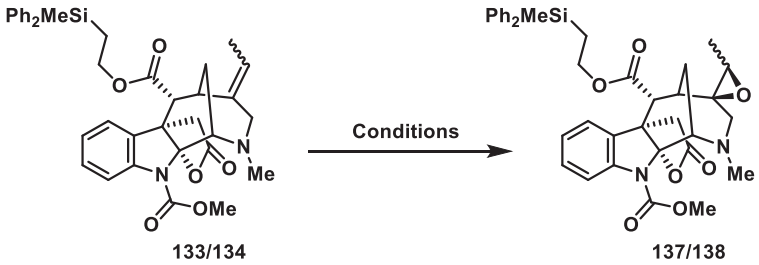


Scheme 135: Strategy via epoxidation/epoxide opening

The chemoselective epoxidation of compounds **133/134** was investigated. Indeed, similarly to the epoxidation of the methyl ester **108.A**, different peroxides were examined including *m*-CPBA and DMDO. As the tertiary amine was prone to be oxidized into *N*-oxide, most of the conditions used were performed in the presence of acid in order to pre-form the ammonium species. As described in table 38, the use of TFA (to generate the ammonium salt) followed by the addition of *m*-CPBA in DCM at -78 °C did not allow any reaction (entry 1). Performing the reaction at 0 °C led to similar results (entry 2). Employing 3 equivalents of *m*-CPBA at room temperature did not afford any reaction either (entry 3). The use of $HClO_4$ or $BF_3.OEt_2$ afforded the same result even with excess of oxidant (entries 4, 5 and 6). A more reactive oxidant such as DMDO was then examined. As shown in entry 7, when 1.1 equivalent of DMDO was used in acetone at 0 °C, a messy reaction was observed. The formation of the salt using TFA afforded the same result (entry 8). In 1995, Mario Rubiralta group reported a method for the chemoselective oxidation of tertiary amines bearing alkene moieties.[97] They reported that the use of protic acid medium, to pre-form the ammonium salt, had a limited chance of success due to the sensitivity of epoxides toward acid conditions. Thus, they envisaged the quaternarization of the amino moiety via the formation of an adduct using a non-protic Lewis acid: $BF_3.OEt_2$. The salt formation in presence of DMDO allowed an interesting scope of chemoselective epoxidations. Based on this precedent, starting materials **133** and **134** were premixed with $BF_3.OEt_2$ in Et_2O at -78 °C for 15 minutes. After removal of Et_2O under vacuum the white salt obtained was solubilized in acetone, cooled at -78 °C and DMDO was added dropwise. Unfortunately, no reaction was observed neither at -78 °C nor -30 °C (entries 9 & 10). However, when the temperature was increased to rt, the starting material was fully consumed and two new spots were observed on TLC (entry 11). Despite several attempts, the isolation and characterization of these compounds were unsuccessful due to their instability. As for the methyl-ester, the condition described by Mioskowski using TFA, *t*-BuOOH in THF did not allow any reaction (entry 12). [98] Finally, the Mukaiyama epoxidation was attempted, under air[99], using a catalytic amount of nickel, 2 equivalents of isobutyraldehyde and TFA to generate the salt. However, no reaction occurred even after 16 hours (entry 13).

[97] Ferrer, M. Rubiralta, M. *J. Chem. Soc., Chem. Commun.* **1995**, 293.
[98]Hardouin, C.; Doris, E.; Rousseau, B. ; Mioskowski, C. *J. Org. Chem*. **2002**, *67*, 6571.
[99] 1) Yamada, T.; Mukaiyama, T. *Chemistry Letters*, **1991**, *20*, 1. 2) Lassila, K. R. *Tetrahedron Lett.*, **1994**, *35*, 8077. 3) Wentzel, B.; Nolte, J. M. *J. Org. Chem.* **2004**, *69*, 3453.

Table 38: Attempts for the epoxidation of compound 133/134.



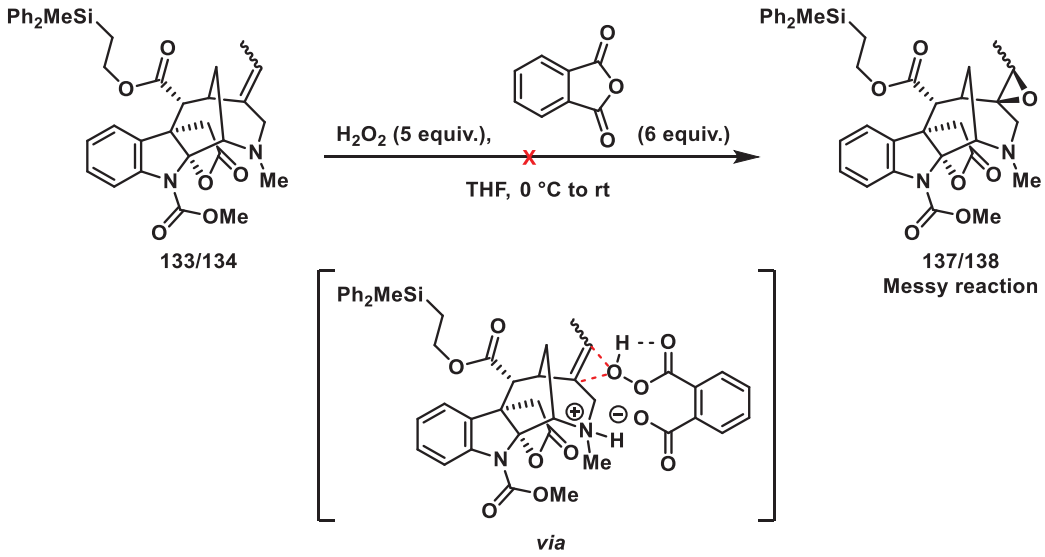
133/134 137/138

Entry	Conditions	Comments
1	TFA (15 equiv.), *m*-CPBA (1 equiv.), DCM, -78 °C, 12 h	No reaction
2	TFA (15 equiv.), *m*-CPBA, DCM (1 equiv.), 0 °C, 12 h	No reaction
3	TFA (15 equiv.), *m*-CPBA (3 equiv.), DCM, 0 °C to rt, 12 h	No reaction
4	$HClO_4$ (15 equiv.), *m*-CPBA (1 equiv.), DCM, -78 °C to rt	No reaction
5	$BF_3.OEt_2$ (15 equiv.), *m*-CPBA (1 equiv.), DCM, -78 °C to rt	No reaction
6	$BF_3.OEt_2$ (15 equiv.), *m*-CPBA (15 equiv.), DCM, -78 °C to rt	No reaction
7	DMDO (1.1 equiv.), acetone, 0 °C	Not clean
8	TFA, DMDO (1.1 equiv.), 0 °C	Not clean
9	1) $BF_3.OEt_2$, Et_2O, 20 min then dryness 2) Acetone, DMDO (1.1 equiv.), -78 °C	No reaction
10	1) $BF_3.OEt_2$, Et_2O, 20 min then dryness 2) Acetone, DMDO (1.1 equiv.), -30 °C	No reaction
11	1) $BF_3.OEt_2$, Et_2O, 20 min then dryness 2) Acetone, DMDO (1.1 equiv.), 0 °C	2 new spots, not the epoxide decomposed on silica gel
12	TFA, *t*-BuO_2H 5 M in decane, THF, rt, 12 h	No reaction
13	$Ni(acac)_2$ (cat.), isobutyraldehyde (2 equiv.), TFA, DCM, O_2, 0 °C to rt, 16 h	No reaction

In 2015, Ellman *et al.* reported a bifunctional reagent for the chemoselective epoxidation of tetrahydropyridine.[100] This reagent was designed to incorporate highly reactive percarboxy acid and pendant carboxylic acid group.

The formation of hydrogen bonding with the amino group would avoid the *N*-oxide and direct the epoxidation toward the double bond. Unfortunately, under the conditions described in scheme 136, a messy reaction was observed.

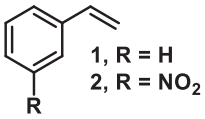
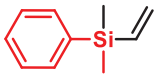
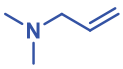
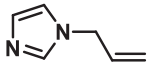
[100] Chen, S.; Ellman, J. A. *J. Org. Chem.* **2015**, *80*, 6660.



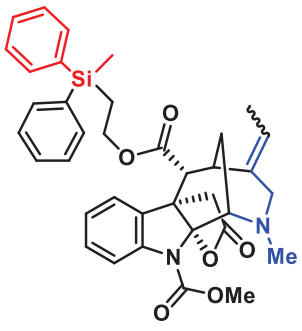
Scheme 136: Failed attempt using a bifunctional reagent.

In 2016, Du Bois and Stack groups reported an *in-situ* generated catalyst system based on manganese (II), picolinic acid, and peracetic acid to converts a wide scope of olefins into the corresponding epoxides.[101] Our great interest for this report was triggered by the possibility to extent this methodology to basic *N*-containing substrates with only minor modifications of the standard conditions. The scope containing unprotected nitrogen is depicted in table 39.

Table 39: Scope of the reaction VS starting material 133 and 134.

Entry	Substrate	Conversion (%)	Yield (%)
1	 1, R = H	77	61
2	2, R = NO_2	91	85
3	 3, 2-vinyl	87	80
4	4, 4-vinyl	85	77
5		71	50
6		100	68
7		52 62	49 59

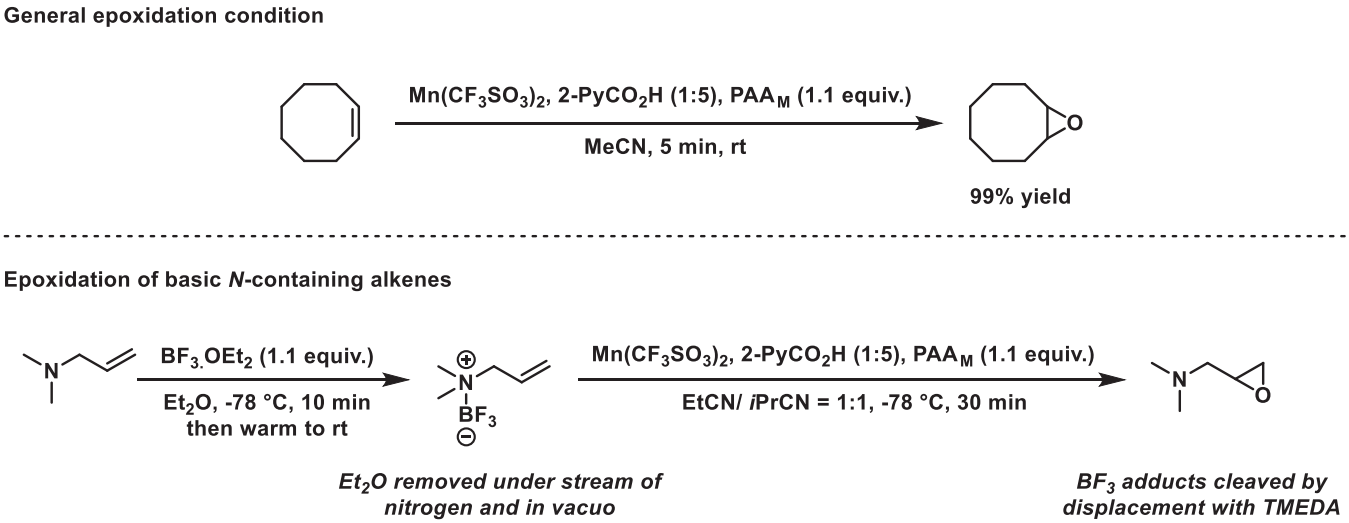
Vs



133/134

[101] Moretti, R. A.; Du Bois, J.; Stack, T. D. P. *Org. Lett*. **2016**, *18*, 2528.

It is noteworthy that even if the transformation tolerates sensitive substrates such as phenyldimethylvinylsilane, pyridines, imidazole, or tertiary amine, the isolated yield remains moderate. As shown in scheme 137, the general epoxidations consisted in the addition of 0.4 mol % of $Mn(CF_3SO_3)_2$ and 2 mol % of 2-$PyCO_2H$, in MeCN at 0 °C, over 5 minutes followed by slow addition of 1.1 equivalent of a base-modified commercial peracetic aic (PAA_M). However, for *N*-containing alkenes, the upstream amine quaternarization using $BF_3.OEt_2$ in ether was necessary, followed by the oxidative conditions at -78 °C in a 1:1 mixture of EtCN/*i*PrCN for 30 minutes.



Scheme 137: General condition VS condition for N-containing alkenes

In our case, preliminary results showed that pre-formation of the ammonium salt in Et_2O did not have any influence on the outcome of the reaction. It was also observed that using 5 equivalents of $BF_3.OEt_2$ provided a cleaner crude mixture. Furthermore, the use of commercial PAA instead of a modified PAA (PAA_M) afforded similar results.

The reaction was set-up as follow: starting materials **133/134** were mixed with $Mn(CF_3SO_3)_2$ and 2-$PyCO_2H$ in a 1:5 ratio. A mixture of EtCN/*i*PrCN 1:1 (or MeCN, table 40) was then added and the reaction was stirred for 5 min at room temperature until complete solubilization of the catalyst and ligands. The solution was then cooled to -78 °C and $BF_3.OEt_2$ (5 equiv.) was added dropwise. The reaction mixture was warmed to rt for 2 min and cooled down to -78 °C (or -30 °C, table 40). Finally, PAA was added. Under this standard condition, the equivalent of manganese, the solvent system, the temperature, the reaction time, the speed of PAA addition and the quenching/work-up procedure were examined. A summary of some experiments is presented in table 40.

As shown in entry 1, the use of 0.4 mol % of manganese and 1.1 equivalent of PAA at -78 °C did not provide any reaction. Increasing the amount of catalyst to 0.4 equivalent led to the same result (entry 2). Interestingly, the use of 10 equivalents of PAA allowed the formation of desired epoxides **137/138** (entry 3).

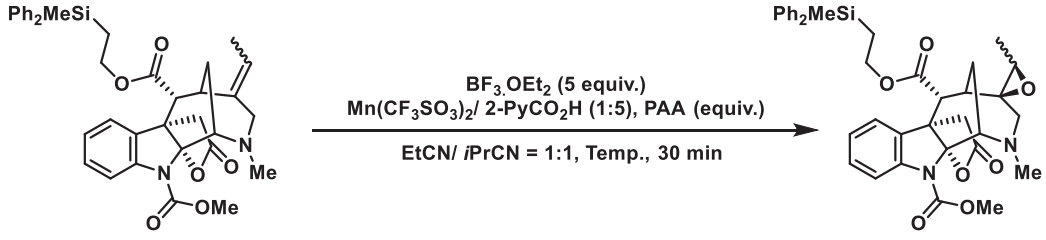
For the first time, the epoxide intermediate was generated without complete decomposition. Unfortunately, the conversion was low and the stability of the epoxides on silica gel was limited. Performing the reaction with 20 equivalents of PAA and increasing the temperature from -78 to -30 °C provided improved the conversion (entry 4). Employing MeCN as solvent at -30 °C resulted in only decomposition (entry 5). Playing on the addition of PAA (2 equivalents per 15 minutes) or reducing the amount of catalyst to 0.2 equivalent were unsuccessful (entries 6 & 7). It was thus concluded that on our substrates, the use of acetonitrile as solvent was probably not appropriate. When 0.05 equivalent of manganese and 20 equivalents of PAA at -78 °C were employed, no reaction occurred (entry 8). Increasing the temperature from -78 to -30 °C provided similar result (entry 9). Based on entries 1, 8 and 9, it was concluded that low amount of catalyst resulted in a very low conversion.

According to previous experiments, the use of 0.4 equivalent of manganese, 20 equivalents of PAA at -78 to -30 °C was established as the optimized condition to generate epoxides. In order to reach full conversion, the amount of catalyst was increased to 0.5 equivalent (entries 10 & 11). Unfortunately, in both cases, only decomposition was observed. It was supposed that either the excess of PAA or the active manganese oxide species could be responsible for the decomposition of the desired products during work-up.

Two quenching procedure were then examined. The first one (entry 12) was performed *via* a) a dilution of the reaction mixture with acetone at -30 °C, followed by b) a dropwise addition of an aqueous solution of sodium sulphite at the same temperature. The mixture was then diluted with EtOAc at -30 °C and warmed to room temperature. This quenching procedure afforded a cleaner crude. The second quenching procedure (entry 13) was performed *via* a) dilution of the reaction mixture with acetone at -30 °C; b) dropwise addition of an aqueous solution of sodium sulphite followed by the c) dropwise addition of $NaHCO_3$. The mixture was then diluted with EtOAc at -30 °C and warmed to room temperature. This quenching procedure provided an even cleaner crude mixture than previous method (entry 12). Entries 12 and 13 showed that the work-up was crucial on the outcome of the reaction.

Having an appropriate work-up procedure in hand, we then focused on reaching a full conversion of starting materials **133/134**. As shown in entries 14 and 15, increasing the reaction time to 1h30 or employing 1 equivalent of manganese did not provide a better conversion. The addition speed of PAA into the reaction mixture was then examined. According to entries 16 to 19, a dropwise addition of PAA (1 drop/10 s) into the reaction mixture was the best compromise between a clean reaction and a satisfactory conversion. All other attempts to reach full conversion led to decomposition. Additional experiments to improve the quenching method using amylene, Et_3N, Me_2S or isobutene to trap the excess of PAA were ineffective (entries 20 to 23). Finally, the dilution of the reaction mixture using EtOAc at -78 °C followed by a rapid transfer into a solution of $NaHCO_3$, under stirring at room temperature, turned out to be the most efficient and convenient method to quench this reaction (entry 25).

Table 40: Epoxidation using manganese (II), picolinic acid, and peracetic acid.



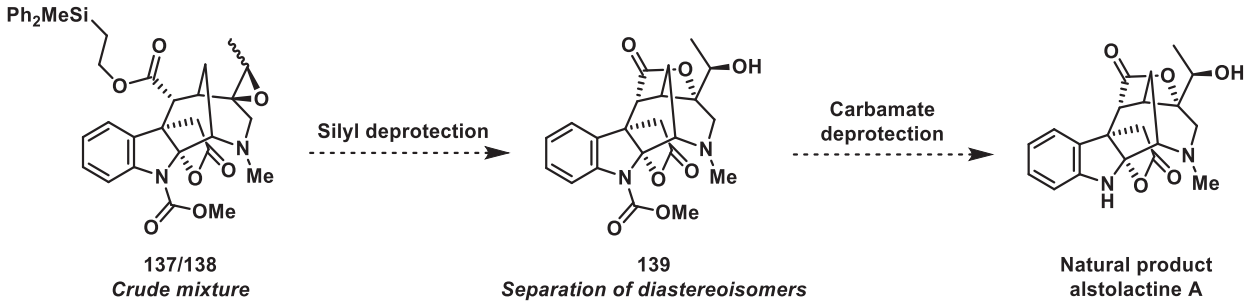
133/134 137/138

Entry	Equiv. Mn	Equiv. PAA	Temp. (°C)	Work-up	Comment
1	0.4 mol%	1.1	-78	$NaHCO_3$	No reaction
2	0.4	1.1	-78	$NaHCO_3$	No reaction
3	0.4	10	-78	$NaHCO_3$	DP observed, SM remained
4	0.4	20	-78 to -30	$NaHCO_3$	Clean, good conversion but not completed
5 a	0.4	20	-30	$NaHCO_3$	Decomposition
6 a	0.4	2 equiv./15 min	-30	$NaHCO_3$	Slow conversion then decomposition
7 a	0.2	2 equiv./15 min	-30	$NaHCO_3$	Slow conversion then decomposition
8	0.05	20	-78	$NaHCO_3$	No DP, SM recovered
9	0.05	20	-78 to -30	$NaHCO_3$	No DP, less clean than entry 8
10	0.5	20	-78 to -30	$NaHCO_3$	Decomposition
11	0.5	20	-78	$NaHCO_3$	Decomposition
12	0.4	20	-78 to -30	See A	Cleaner reaction but not completed
13	0.4	20	-78 to -30	See B	Cleaner reaction but not completed
14 b	0.4	20	-78 to -30	B	Same than entry 13
15	1	20	-78 to -30	B	Did not improve the conversion
16	0.4	4 equiv./ 3 min until 20 equiv.	-78 to -30	B	Better conversion, not clean
17	0.4	2*20 equiv.	-78 to -30	B	Full conversion but decomposed
18	0.4	30 equiv.	-78 to -30	B	Almost full conversion, less clean
19	0.4	20 (1 drop/10 s)	-78 to -30	B	Not full conversion, but clean
20	0.4	20 (1 drop/10 s)	-78 to -30	50 equiv. amylene then C	Low mass balance
21	0.4	20 (1 drop/10 s)	-78 to -30	50 equiv. Et_3N then C	Decomposition
22	0.4	20 (1 drop/10 s)	-78 to -30	50 equiv. Me_2S then C	Decomposition
23	0.4	20 (1 drop/10 s)	-78 to -30	50 equiv. isobutene then C	Messy
24	0.4	20 (1 drop/10 s)	-78 to -30	D	Not full conv. but clear spots of both dia on TLC, no decomp during work-up.
25	0.4	20 (1 drop/10 s)	-78 to -30	E	Same than entry 24, work-up more convenient.

a) MeCN was used as solvent instead of EtCN/ *i*PrCN
b) Reaction time 1H30 instead of 30 min.
A) Dilute with acetone at -30 °C, add of sodium sulfite (aq.)
B) Dilute with acetone at -30 °C, add of sodium sulfite (aq.), then $NaHCO_3$, dilute with EtOAc and warm to rt.
C) Dilute with EtOAc at -30 °C, then add brine and warm to rt.
D) Colled to -78 °C then add of sodium sulfite (aq.), then $NaHCO_3$, dilute with EtOAc and warm to rt.
E) Colled to -78 °C, then dropwise addition of EtOAC at -78 °C (until dilution by 10), followed by a rapid transfer into a solution of $NaHCO_3$ at room temperature under stirring.

II.2. Silyl deprotection and cyclization.

Due to the limited stability of epoxides **137/138** on silica gel, it was decided to use the crude mixture for the next step. As described in scheme 138, the one-pot silyl deprotection/cyclization would provide two diastereoisomers **139** and **140**. Separation of the major diastereoisomer and deprotection of the indole protecting group would provide natural product alstolactine A.

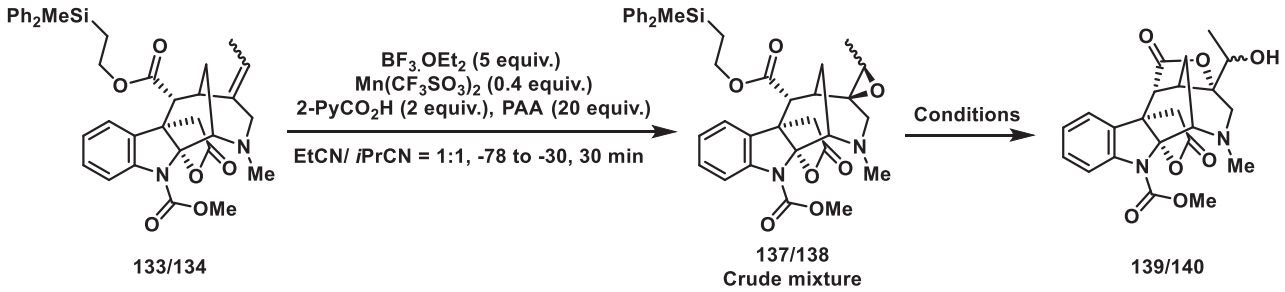


Scheme 138: Strategy toward alstolactine A.

Once our strategy established, the silyl deprotection was investigated. As shown in table 41, when the crude mixture of epoxides **137/138** was submitted to 5 equivalents of TBAF, in DCM at room temperature, a slow deprotection was observed but the δ-lactone was not generated (entry 1). However, the addition of 5 equivalents of $BF_3.OEt_2$ into the reaction mixture allowed a clean cyclization (entry 2). When the amount of TBAF was reduced to 2 equivalents similar results were obtained (entry 3). Repeating the conditions described in entries 1, 2 and 3 in THF instead of DCM afforded comparable results (entries 4, 5 and 6). As shown in entry 7, the use of 2 equivalents of TASF in THF allowed a very slow deprotection without cyclization. However, repeating the reaction in DMF afforded a clean one-pot deprotection/cyclization (entry 8). The use of TFA also provided the desired products **139/140,** however, the reaction was not clean (entry 9).

Conditions described in entries 3 & 8 were established as the optimized conditions and the one-pot two steps process was repeated in slightly bigger scale.

Table 41: Conditions for a clean deprotection/ cyclization.

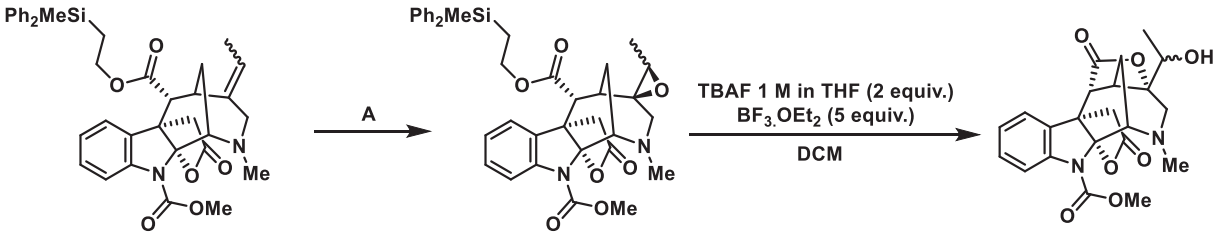


133/134 — 137/138 Crude mixture — 139/140

Entry	Solvent	Conditions	Comments
1	DCM	TBAF 1 M in THF (5 equiv.)	Slow reaction, no cyclization
2	DCM	TBAF 1 M in THF (5 equiv.), $BF_3.OEt_2$ (5 equiv.)	Clean deprotection/ cyclization
3	DCM	TBAF 1 M in THF (2 equiv.), $BF_3.OEt_2$ (5 equiv.)	Clean deprotection/ cyclization
4	THF	TBAF 1 M in THF (5 equiv.)	Deprotection, no cyclization
5	THF	TBAF 1 M in THF (5 equiv.), $BF_3.OEt_2$ (5 equiv.)	Clean deprotection/ cyclization
6	THF	TBAF 1 M in THF (2 equiv.), $BF_3.OEt_2$ (5 equiv.)	Clean deprotection/ cyclization
7	THF	TASF (2 equiv.)	Really slow deprotection, no cyclization
8	DMF	TASF (2 equiv.)	Slow and clean deprotection/ cyclization
9	DCM	TFA	Slow, deprotection/cyclization, not clean

As shown in table 42, the mixture of compounds **133/134** in the presence of 5 equivalents of $BF_3.OEt_2$, 0.4 equivalents of $Mn(CF_3SO_3)_2$, 2 equivalents of picolinic acid, and 20 equivalents of PAA, in a 1:1 mixture of EtCN/*i*PrCN from -78 to -30 °C, allowed the formation of epoxides **137/138**. Finally, the solubilization of the crude mixture in dry DCM followed by the addition of 2 equivalents of TBAF and $BF_3.OEt_2$ provided desired alcohols **139/140.** It is noteworthy that the 3:1 ratio of compounds **133/134** remained almost unchanged during the all sequence. The epoxidation/deprotection/cyclization sequence was reproducible with a constant 40% yield over 2 steps.

Table 42: Two-steps sequence epoxidation/deprotection/ cyclization using TBAF & $BF_3.OEt_2$



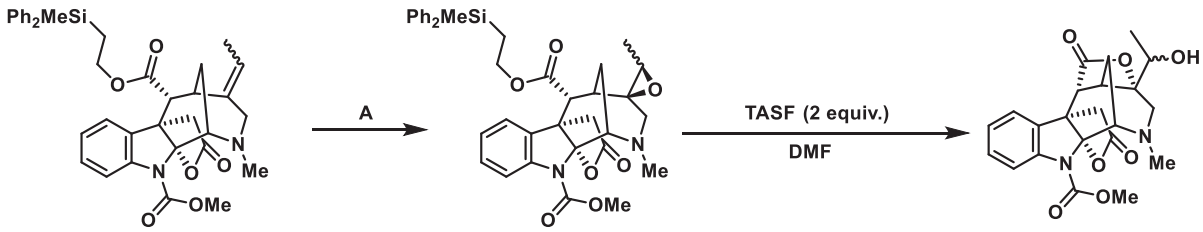
133/134 3:1 | 137/138 Crude mixture | 139/140 ~3:1

A) $BF_3.OEt_2$ (5 equiv.), $Mn(CF_3SO_3)_2$ (0.4 equiv.), 2-$PyCO_2H$ (2 equiv.), PAA (20 equiv.), EtCN/ *i*PrCN = 1:1, -78 to -30, 30 min

Entry	Scale	Yield
1	2 mg	42% over 2 steps
2	4 mg	40% over 2 steps
3	6 mg	40% over 2 steps

However, repeating the sequence using TASF in DMF provided a lower yield over two steps than using TBAF/$BF_3.OEt_2$. As shown in table 43, alcohols **139/140** were obtained in only 32% yield over these two-steps sequence.

Table 43: Two-steps sequence epoxidation/deprotection/ cyclization using TASF.

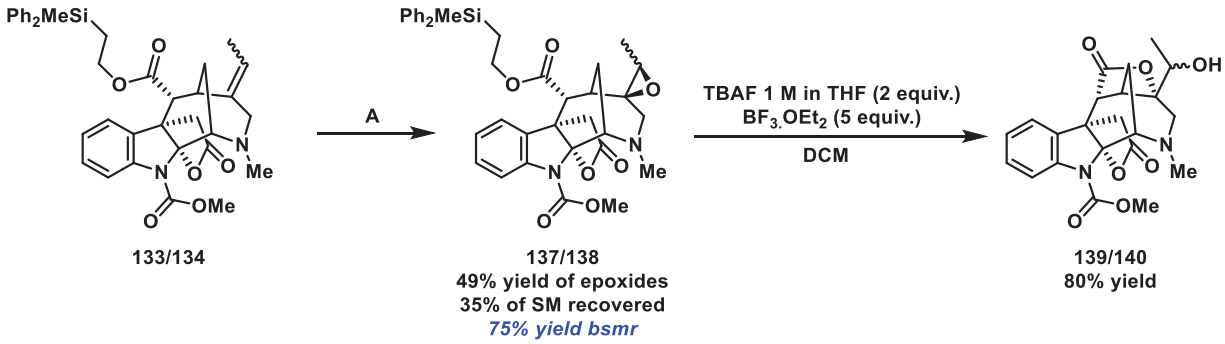


114/115 3:1 | 118/119 Crude mixture | 120/121 ~3:1

A) $BF_3.OEt_2$ (5 equiv.), $Mn(CF_3SO_3)_2$ (0.4 equiv.), 2-$PyCO_2H$ (2 equiv.), PAA (20 equiv.), EtCN/ *i*PrCN = 1:1, -78 to -30, 30 min

Entry	Scale	Yield
1	2 mg	34% over 2 steps
2	5 mg	30% over 2 steps

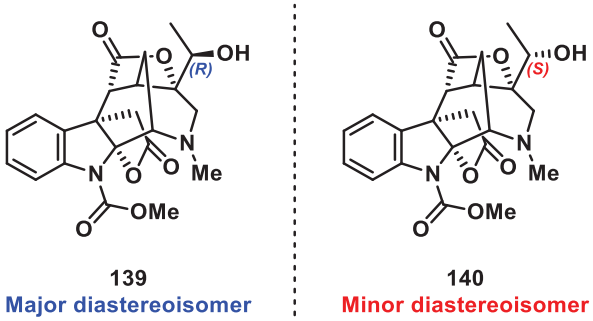
Very recently, we noticed that the partial decomposition of epoxides **137/138** during purification could be avoided by using THF to do the deposit on silica. Moreover, the two epoxides **137** and **138** were easily separable and isolated in 49% yield along with 35% of starting material corresponding to a 75% yield based on starting material recovered (scheme 139). Finally, having a purified batch of epoxides in hand, compounds **139/140** were prepared in 80% yield. It is noteworthy that the yield obtained over these two-steps was similar to the yield obtained when crude mixture of epoxides was used.



A) $BF_3.OEt_2$ (5 equiv.), $Mn(CF_3SO_3)_2$ (0.4 equiv.), 2-$PyCO_2H$ (2 equiv.), PAA (20 equiv.), EtCN/ *i*PrCN = 1:1, -78 to -30, 30 min

Scheme 139: Successful purification using THF for the deposit on silica

Fortunately, at this stage of the synthesis, the two diastereoisomers **139** and **140** were stable on silica gel and easily separable (scheme 140).



Scheme 140: Separation of the two epimers before the natural product synthesis.

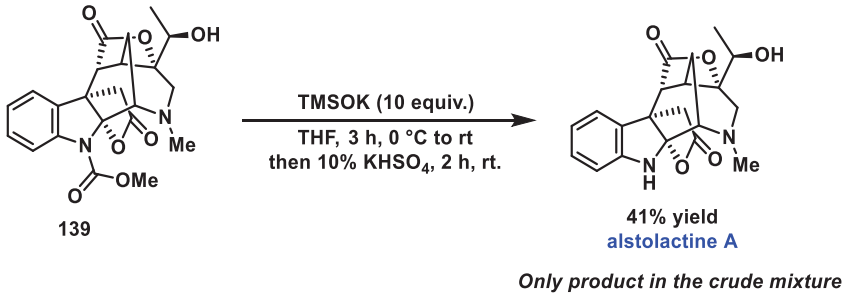
Major diastereoisomer **139** was used for the last step of the total synthesis of alstolactine A.

II.3. Final step toward alstolactine A.

The last step of the total synthesis of Alstolactine A consisted in the cleavage of the carbamate moiety. It has already been observed (see chapter 3) that TMSOK in THF allowed the cleavage of the methyl carbamate on a similar substrate (**108.A**).

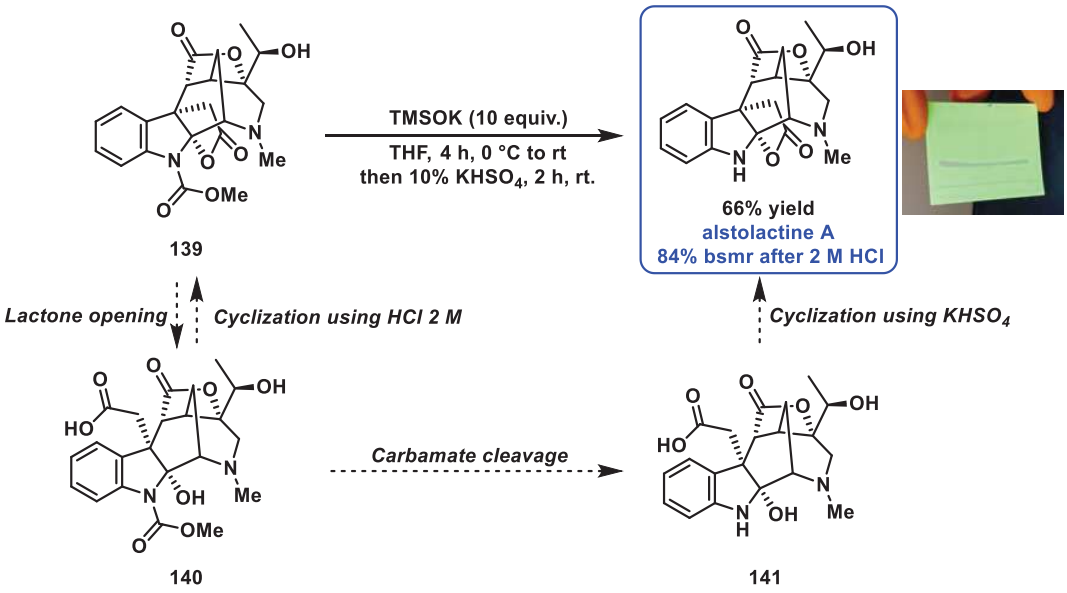
Based on this observation, compound **139** was mixed with 10 equivalents of TMSOK, for 3 hours at room temperature, until full conversion of the starting material was reached. Monitoring of the reaction by TLC showed the formation of two highly polar intermediates. After 3 hours, a 10% solution of $KHSO_4$ was added to the reaction mixture and stirred for 2 hours at rt (scheme 141). Under these conditions, we were delighted to obtain 41% yield of alstolactine A. Surprisingly, the natural product was the only compound observed in

the crude mixture. It was thus supposed that the previously observed highly polar intermediates were lost in the aqueous layer during work-up.



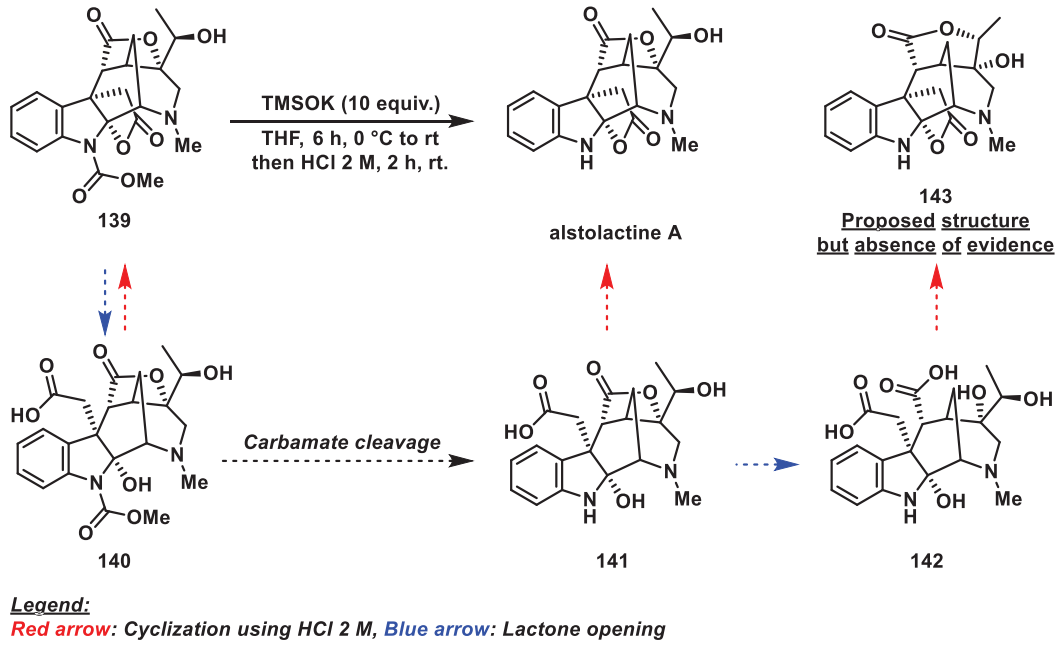
Scheme 141: Initial attempt for carbamate cleavage

According to the previous experiment, a full conversion of starting material **139** was observed within 3 hours. However, it was decided to extend the reaction time up to 4 hours and then to quench it using a 10% $KHSO_4$ solution. As shown in scheme 142, under these conditions alstolactine A was isolated in 66% yield. Once again, the natural product was the only compound detected in the crude mixture (see TLC). The remaining aqueous layer was then mixed in a 1:1 ratio of THF/2 M HCl at room temperature. After 2 hours, some starting material **139** was recovered. Finally, the calculated yield of this final step was 84% based on starting material recovered. Mechanistically, it was supposed that one of the γ -lactones reacted first to generate compound **140**. Subsequent cleavage of the carbamate moiety would afford compound **141**. Quenching the reaction with 10% $KHSO_4$ for 2 hours would allow the exclusive cyclization of compound **141** affording the natural product. However, the use of HCl 2 M would be needed to achieve the cyclization of compound **140**.



Scheme 142: Achievement of the total synthesis of alstolactine A.

In order to improve the conversion toward alstolactine A, it was decided to extend the reaction time up to 6 hours and then to quench it using a 2 M HCl solution. As shown in scheme 143, a slightly more polar compound (proposed structure **143**) was isolated in low amount. Despite the absence of structural analysis (due to the small scale of the reaction), it was thought that increasing the reaction time to 6 hours was enough to open the second γ-lactone affording 1,2-diol **142**. Under acidic conditions, the secondary alcohol, less hindered and more reactive than the tertiary alcohol, could react with the carboxylic acid to generate the proposed structure **143**.

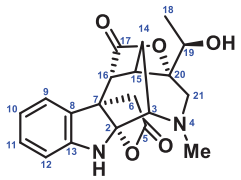


Scheme 143: Further optimizations of the last step.

Finally, conditions described in scheme 142 were established as the optimized conditions affording 84% yield of alstolactine A based on starting material recovered.

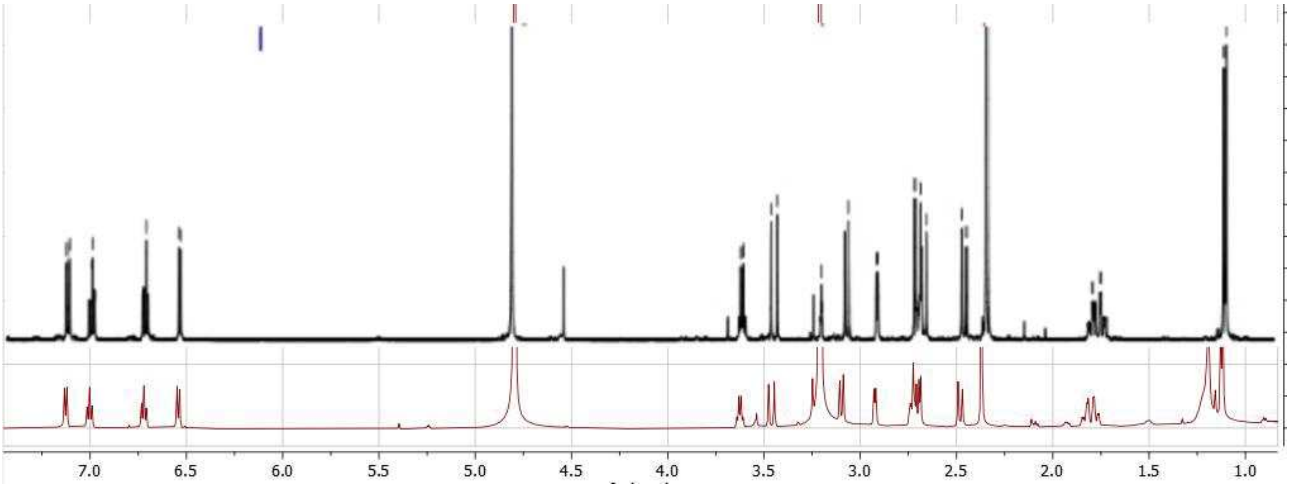
As shown in tables 44 to 45 & schemes 144 to 145, the spectral properties of the synthetic natural product were identical to the values reported in the isolation paper.

Table 44: Comparison of ^{1}H NMR spectroscopic data of natural and synthetic alstolactine A



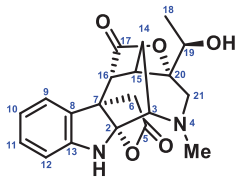
alstolactine A

Position	Natural δ ^{1}H [ppm, mult, *J* (Hz)] 600 MHz	Synthetic δ ^{1}H [ppm, mult, *J* (Hz)] 600 MHz	Deviation (natural-synthetic) Δδ (ppm)
3	3.00 (d, 5.4)	2.99 (d, 5.4)	0.01
6	3.55 (d, 18.1)	3.53 (d, 17.8)	0.02
-	2.80 (d, 18.1)	2.78 (d, 17.8)	0.02
9	7.21 (d, 7.9)	7.20 (dd, 7.5, 1.2)	0.01
10	6.80 (t, 7.9)	6.79 (td, 7.5, 1.0)	0.01
11	7.08 (t, 7.9)	7.07 (td, 7.7, 1.2)	0.01
12	6.63 (d, 7.9)	6.61 (d, 7.8)	0.02
14	1.89 (dd, 14.7, 5.4)	1.90 (ddd, 14.7, 5.6, 2.3)	-0.01
-	1.85 (dd, 14.7, 4.5)	1.85 (ddd, 14.7, 4.3, 1.5)	-
15	2.79 (m)	2.79 (m)	-
16	3.17 (d, 11.3)	3.17 (d, 11.2)	-
18	1.21 (d, 6.4)	1.19 (d, 6.5)	0.02
19	3.71 (q, 6.4)	3.69 (q, 6.5)	0.02
21β	2.77 (d, 13.6)	2.77 (d, 13.3)	-
21α	2.56 (d, 13.6)	2.55 (d, 13.3)	0.01
NMe	2.44 (s)	2.44 (s)	-



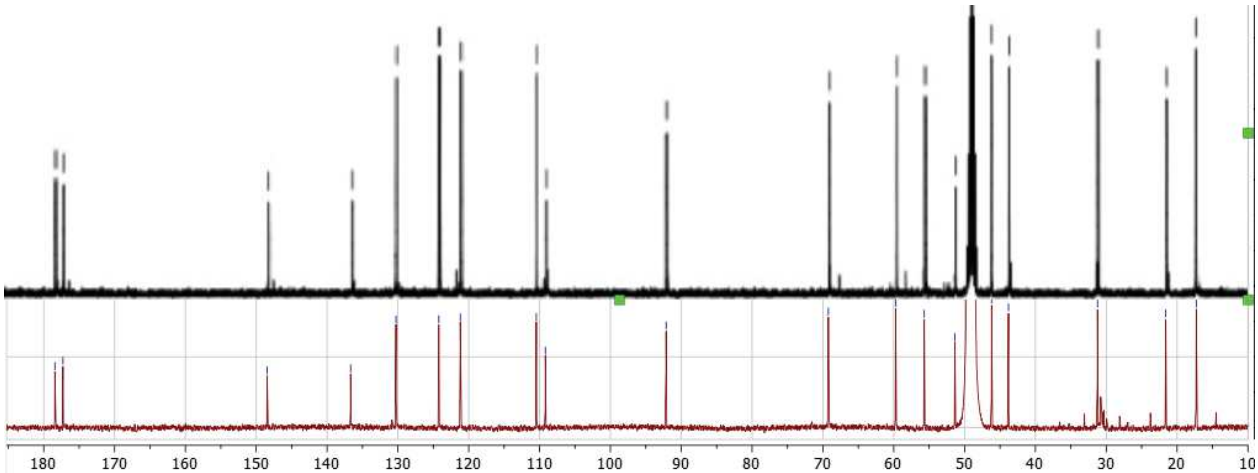
Scheme 144: Alstolactine A comparison spectra ^{1}H NMR. Top (black): natural, Bottom (red): synthetic

Table 45: Comparison of ^{13}C NMR spectroscopic data of natural and synthetic alstolactine A



alstolactine A

Position	Natural δ ^{13}C [ppm] 100 MHz	Synthetic δ ^{13}C [ppm] 151 MHz	Deviation (natural-synthetic) Δδ (ppm)
2	109.1	109.2	-0.1
3	59.6	59.7	-0.1
5	177.2	177.3	-0.1
6	43.8	43.8	-
7	51.3	51.4	-0.1
8	136.6	136.7	-0.1
9	124.2	124.2	-
10	121.2	121.2	-
11	130.2	130.3	-0.1
12	110.5	110.5	-
13	148.4	148.5	-0.1
14	21.6	21.6	-
15	31.2	31.2	-
16	49.1	49.1	-
17	178.4	178.4	-
18	17.3	17.3	-
19	69.2	69.2	-
20	92.1	92.1	-
21	55.6	55.7	-0.1
N-Me	46.2	46.2	-

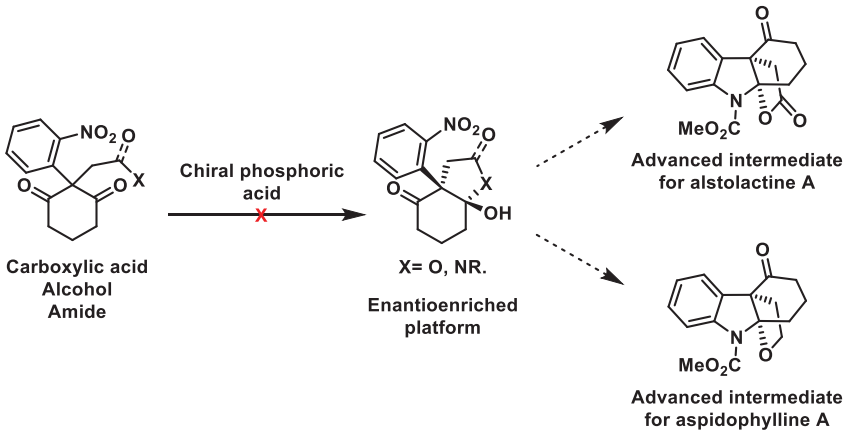


Scheme 145: Alstolactine A comparison spectra ^{13}C NMR. Top (black): natural, Bottom (red): synthetic

CHAPTER 5 - Conclusion

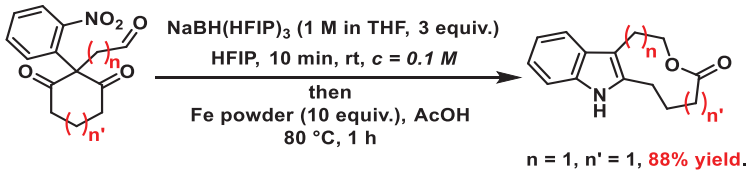
Our interest in monoterpene indole alkaloids led us to study the *Akuammiline* family and to attempt the synthesis of alstolactine A.

The development of a general methodology allowing the preparation of an enantioenriched platform for the synthesis of *akuammiline* alkaloids turned out to be unsuccessful. Despite a series of attempts using chiral phosphoric acid, starting from carboxylic acid, alcohol or amides, no promising results were obtained (scheme 146).



Scheme 146: Attempts for a general methodology providing an enantioenriched platform.

However, starting from an aldehyde intermediate, an efficient one-pot reaction was developed allowing the synthesis of indole-fused macrolactones in good yields (scheme 147). In connection with our laboratory's interests in indole alkaloids, it could be interesting to explore the scope of the transformation and to apply it in a more valuable project.

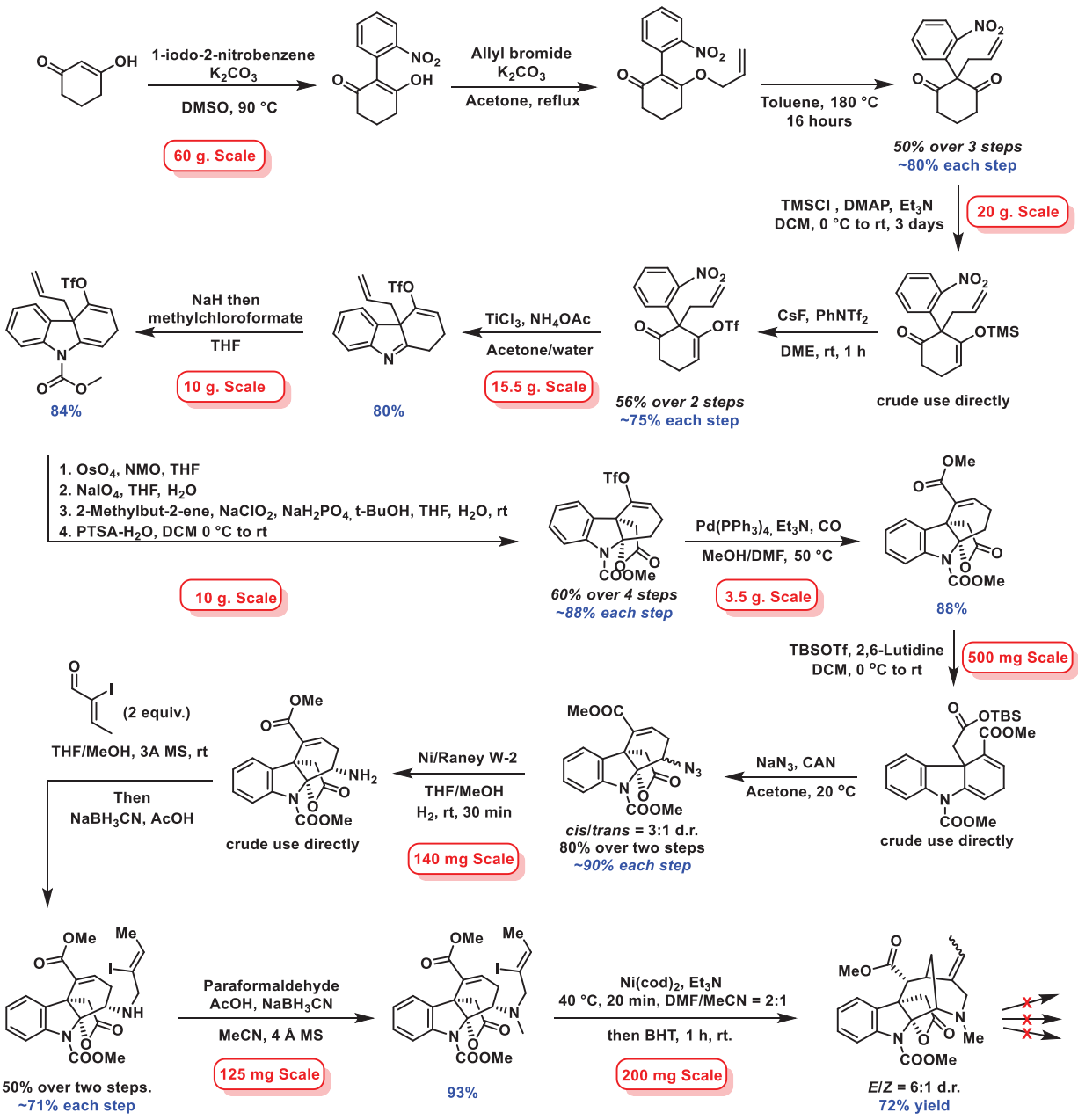


Scheme 147: One-pot formation of indole-fused macrolactones.

The initial strategy to reach alstolactine A has been discussed in chapter 3 and is summarized in scheme 148.

Our approach involves the creation of a quaternary stereocenter *via* a Claisen rearrangement followed by a rapid build–up of the first γ-lactone. The initial 12 steps of the synthesis were performed on multi gram-scale. The introduction of the azide was achieved in excellent yield *via* a diastereoselective azidolactonization

sequence and afforded the *cis*-product as the major diastereoisomer. The reduction of the azide without formation of side-products (triazene & translactamization) and the functionalization to the tertiary amine were some of the most exciting and challenging parts of this PhD. Unfortunately, despite extensive optimization, this sequence remains the weakest point of this first strategy. Finally, the key 1,4-addition reaction was achieved in good yield and good diastereoselectivity using a [Ni(cod)$_2$]-mediated intramolecular cyclization to construct the [3.3.1] bicycle system. The numerous issues we encountered while attempting to functionalize the resulting intermediate in combination with the difficulty to introduce a protecting group on the nitrogen led us to re-evaluate our strategy.



Scheme 148: Summary of the initial strategy.

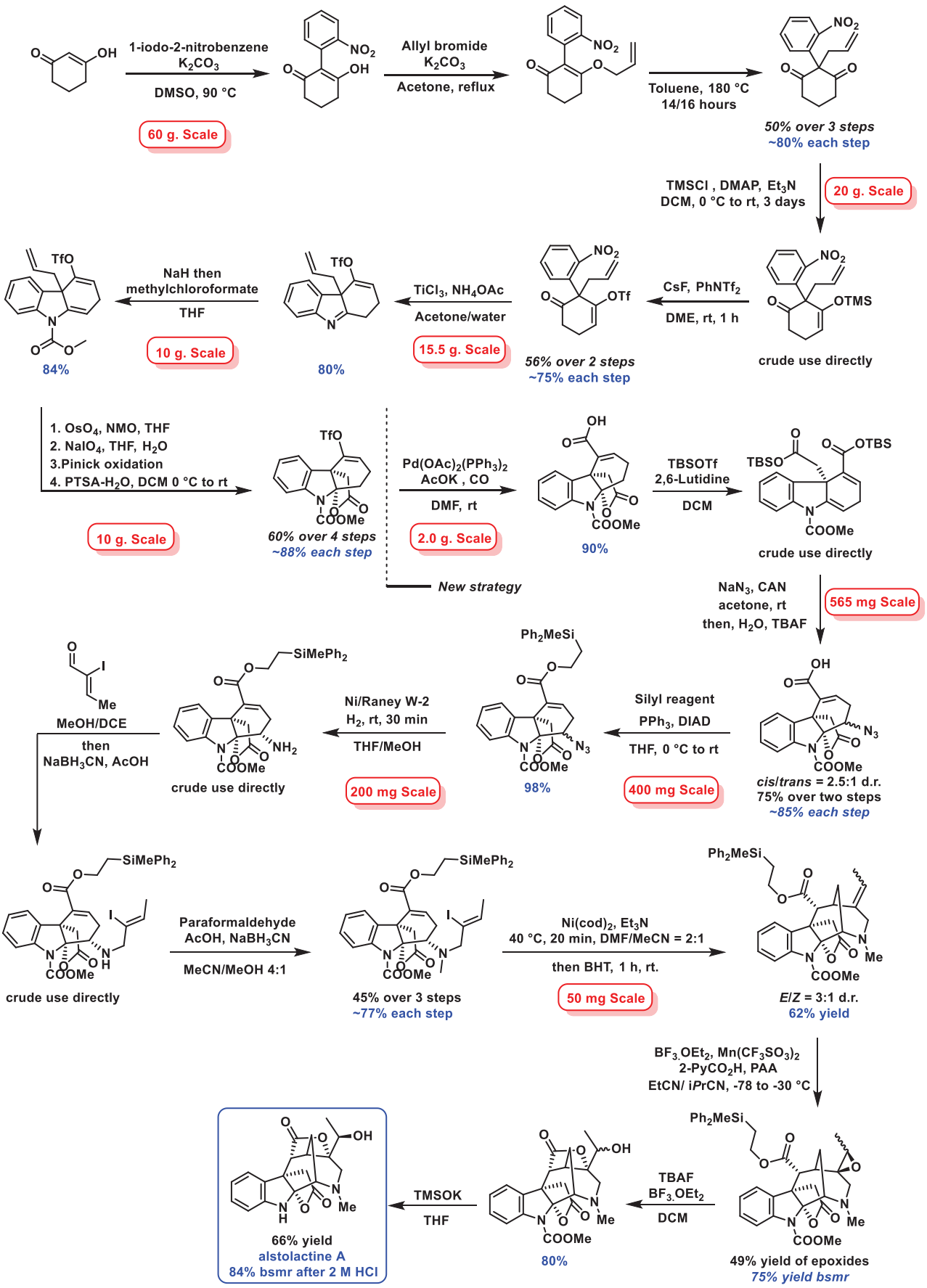
Based on our previous observations, we decided to introduce another group instead of the methyl ester. This new strategy has been discussed in chapter 4 and is summarized in scheme 149. After the formation of the carboxylic acid in good yield, we were delighted to observe that the azidolactonization sequence afforded similar results than the previous strategy. Esterification of the carboxylic acid with silyl-alcohol derivative under Mitsunobu conditions afforded the corresponding ester in 98% yield.

The functionalization and the reduction of the azide into the corresponding tertiary amine was adapted with minor modifications compared to the previously optimized sequence. The 1,4-addition reaction resulted in a lower yield and a reduction of the diastereoselectivity. However, we were delighted to achieve this transformation with the introduction of the new silyl group.

The epoxidation step was another stimulating and complex challenge of this PhD. Despite numerous attempts on both strategies using various oxidants and conditions, the epoxide synthesis was unsuccessful. It was finally required to use very special conditions such as manganese(II)/picolinic acid catalyst in order to obtain a mixture of epoxides in 49% isolated yield and 75% yield when based on recovered starting material. The epoxidation step was followed by the saponification of the silyl group providing the secondary alcohol after epoxide opening. The desired alcohols were isolated in 80% yield and were easily separable on silica-gel.

Finally, the last step toward the total synthesis of alstolactine A was achieved *via* the cleavage of the methyl carbamate in 66% isolated yield and in 84% yield based on recovered starting material.

To conclude, the total synthesis of alstolactine A starting from commercially available starting materials was successfully achieved in 22 steps. Our approach consisted of: a) The creation of a quaternary stereocenter C7 at an early stage; b) The rapid build–up of the first γ-lactone; c) A diastereoselective azidolactonization; d) A [Ni(cod)$_2$]-mediated intramolecular cyclization to construct the [3.3.1] bicycle and e) formation of the last γ-lactone via epoxide opening.



Scheme 149: Summary of the final strategy.

CHAPTER 6 - Outlook

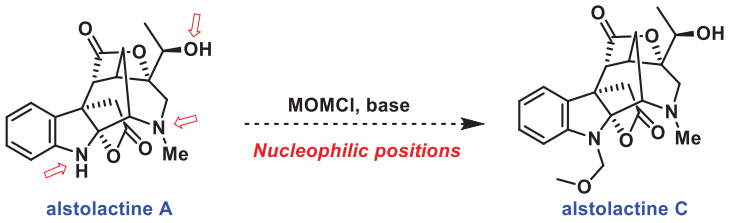
I. Final steps toward alstolactine B & C.

I.1. Final step toward alstolactine C.

The final step to achieve the total synthesis of alstolactine C consisted in the functionalization of the indole nitrogen with a methoxymethyl group (scheme 150).

Scheme 150: Toward the total synthesis of alstolactine C.

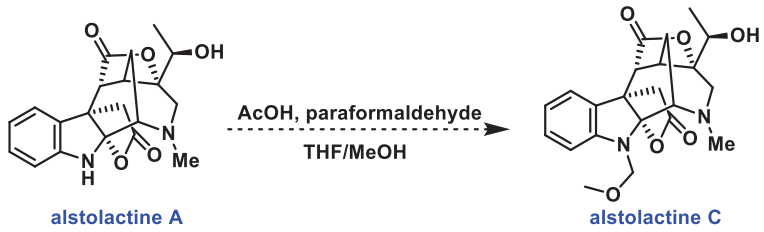
The use of common conditions like methoxymethyl chloride could lead to the functionalization of various positions (scheme 151). Indeed, the tertiary amine would probably react first to generate the ammonium salt. The secondary alcohol is less reactive than the tertiary amine, however, its nucleophilicity will be in competition with the aniline moiety even in the presence of a base.



Scheme 151: Competitive reactions using MOMCl

The most convenient and safest conditions to install the *N*-MOM group is probably the use of AcOH/TMSCl in combination with paraformaldehyde and MeOH (scheme 152). Such conditions were used with excellent yield in the synthesis of diazonamide A macrocyclic core.[102]

[102] A) Zajac, M. A.; Vedejs, E. *Org. Lett.* **2004**, *6*, 237. B) Vedejs, E.; Suna, E. *J. Org. Chem.* **2015**, *80*, 3058.

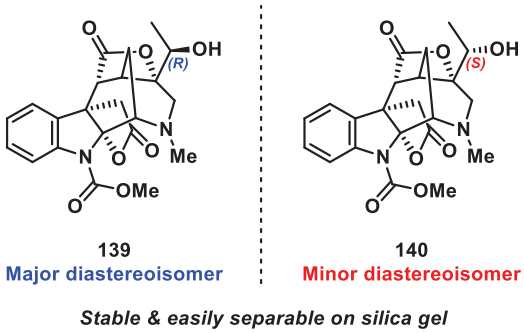


Scheme 152: Acid-mediated reaction using paraformaldehyde and MeOH

Conditions described in scheme 152 should be the most efficient in order to reach alstolactine C.

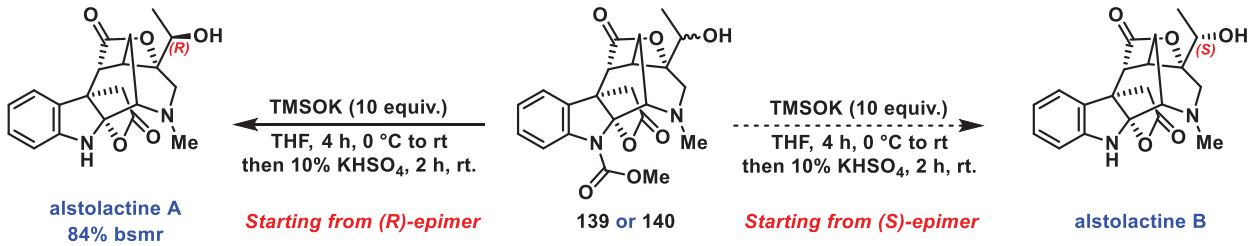
I.2. Final step toward alstolactine B.

As previously described in chapter 4, both compounds **139** and **140** were separated on silica gel. As shown in scheme 153, these two compounds differ by the configuration of the secondary alcohol.



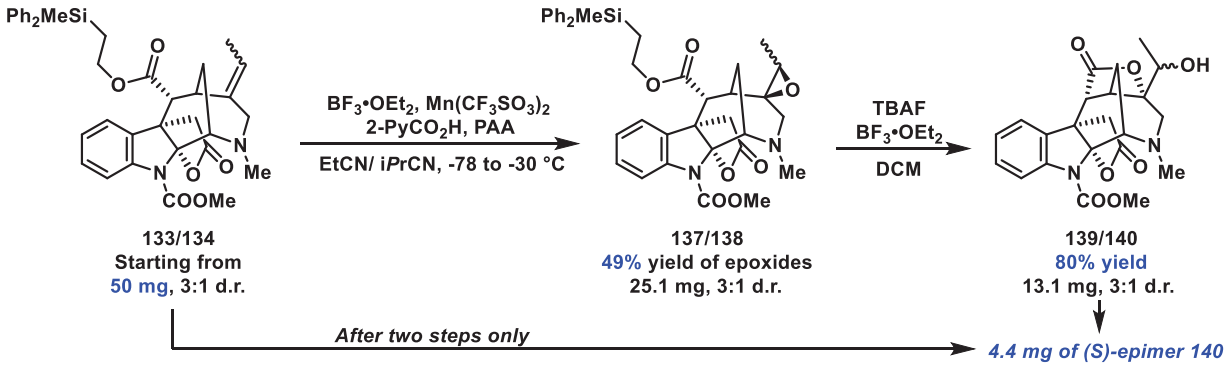
Scheme 153: Two epimers of an advanced intermediate toward alstolactine A & B.

It was already shown that the *(R)*-epimer led to alstolactine A in good yield. We could assume that, under identical conditions, the *(S)*-epimer would lead to desired alstolactine B in good yield.



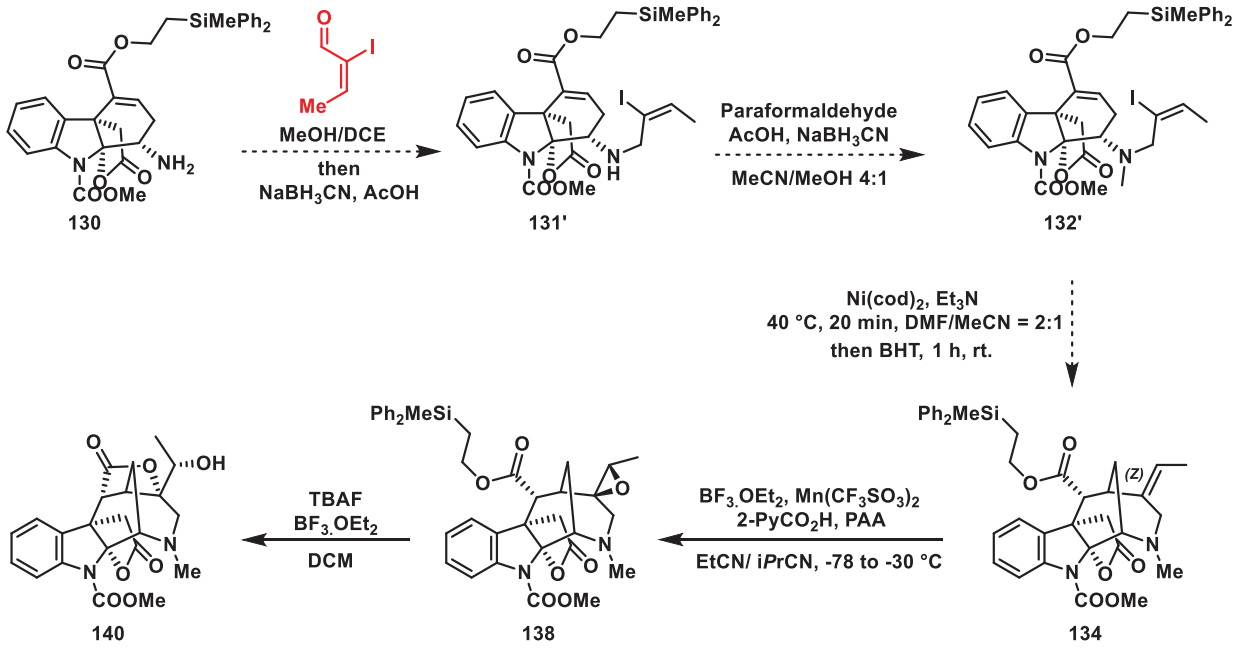
Scheme 154: Synthesis of alstolactine B.

This reaction was limited by the availability of precursor **140**. Indeed, as shown scheme 155, 50 mg of compound **133/134** would afford only 4.4 mg of epimer **140** after 2 steps.



Scheme 155: Availability of precursor 140.

An alternative to get a larger amount of compound **140** could be to perform the condensation of amine **130** with the other isomer of the olefine (scheme 156). The 1,4-addition would be undoubtedly highly diastereoselective and would afford compound **134** as the major (maybe single) isomer. Subsequent epoxidation, deprotection of the silyl group and epoxide opening would afford epimer **140** in large amount.

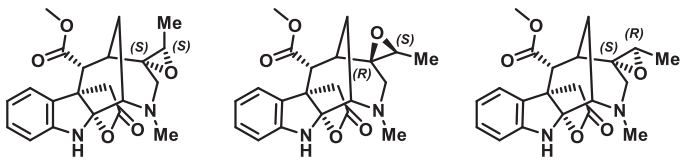


Scheme 156: Alternative pathway to get epimer 121 as major product.

Finally, starting from isomer **140**, the natural product alstolactine B could be obtained under identical conditions as for alstolactine A (scheme 154).

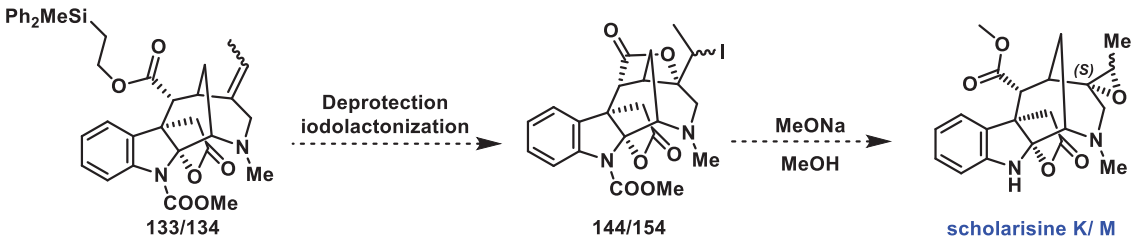
II. Towards the total synthesis of scholarisine K, scholarisine L, scholarisine M.

In 2015, Liu group reported eight new monoterpenoid indole and quinoline alkaloids isolated from a seven-year stored leaves of *Alstonia scholaris*.[103] Among them, scholarisine K, scholarisine L and scholarisine M exhibit a similar scaffold to alstolactine A, B & C (scheme 157).



Scheme 157: Structure of scholarisine K, L and M.

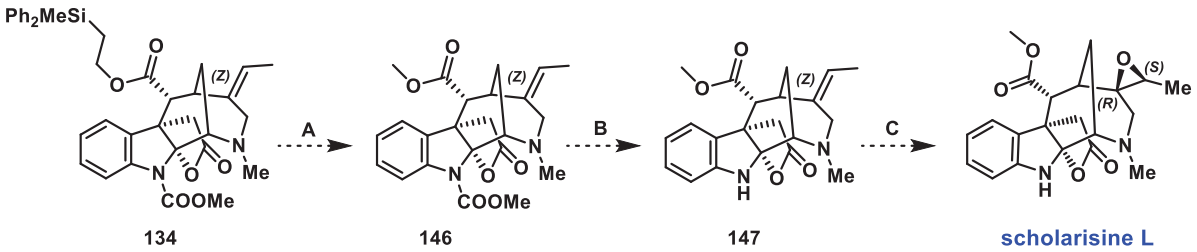
Based on our strategy, these three natural products could be synthesized starting from advanced intermediates **133** and **134**. As shown in scheme 158, starting from compounds **133** and **134**, a saponification followed by iodolactonization would provide intermediates **144** and **145**. The use of sodium methoxide in methanol would then afford scholarisine K and M *via* carbamate deprotection and concomitant transesterification/ S_N2-type epoxide formation.



Scheme 158: Strategy toward the synthesis of scholarisine K and M.

Finally, the synthesis of scholarisine L could be performed *via* deprotection & methylation of the carboxylic acid to afford intermediate **146** (scheme 159). Carbamate cleavage and subsequent epoxidation would provide the last natural product, scholarisine L.

[103] Liu, Y. P. *tetrahedron*, **2015**, *71*, 3694.



Reactions:
A) Deprotection/methylation. B) Carbamate cleavage. C) Epoxidation.

Scheme 159: Strategy toward the synthesis of scholarisine L.

CHAPTER 7 - Supporting Information

I. General Information

Reagents and solvents were purchased from commercial sources (Aldrich, Acros, Merck, Fluka and VWR international) and preserved under argon. More sensitive compounds were stored in a desiccator or in a glovebox if required. Reagents were used without further purification unless otherwise noted.

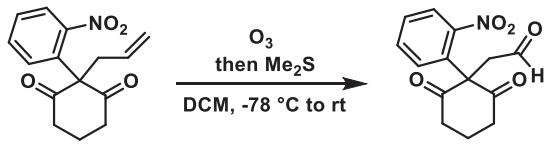
All reactions were performed under argon and stirring unless otherwise noted. When needed, glassware was dried overnight in an oven (T > 100 °C) or under vacuum with a heat gun (T > 200 °C).
Flash column chromatography was performed using Fluka 60 Å silica: 230-400 mesh (40-63 µm) silica.
Reactions were monitored using Merck Kieselgel 60F254 aluminium plates. TLC were visualized by UV fluorescence (254 nm) then one of the following: $KMnO_4$, phosphomolybdic acid, ninhydrin, p-anisaldehyde, vanillin.

NMR spectra were recorded on a Brüker AvanceIII-400, Brüker Avance-400 or Brüker DPX-400 spectrometer at room temperature, ^{1}H frequency is at 400.13 MHz, ^{13}C frequency is at 100.62 MHz. Chemical shifts (δ) were reported in parts per million (ppm) relative to residual solvent peaks rounded to the nearest 0.01 for proton and 0.1 for carbon (ref: $CHCl_3$ [^{1}H: 7.26, ^{13}C: 77.16]). Coupling constants (J) were reported in Hz to the nearest 0.1 Hz. Peak multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Attribution of peaks was done using the multiplicities and integrals of the peaks. When needed, a COSY and/or HSQC experiments were carried out to confirm the attribution.

IR spectra were recorded in a Jasco FT/IR-4100 spectrometer outfitted with a PIKE technology MIRacleTM ATR accessory as neat films compressed onto a Zinc Selenide window. The spectra were reported in cm^{-1}.

Mass spectra were determined with a Waters ACQUITY H-class UPLC/MS ACQ-SQD by electron ionisation (EI positive and negative) or a Finnigan TSQ7000 by electrospray ionization (ESI^{+}). The accurate masses were measured by the mass spectrometry service of the EPFL by ESI-TOF using a QTOF Ultima from Waters or APPI-FT-ICR using a linear ion trap Fourier transform ion cyclotron resonance mass spectrometer from Thermo Scientific.

II. Desymmetrization of achiral 1,3-cyclohexanediones

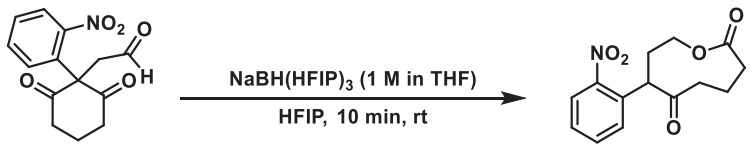


57 65

2-(1-(2-nitrophenyl)-2,6-dioxocyclohexyl)acetaldehyde (65): A stream of ozone (O_3) was bubbled into a solution of **57** (150 mg, 0.548 mmol) in DCM (4.5 mL) at -78 °C until a persistent blue color was observed (about 10 min). The solution was then treated with a stream of argon until the blue color was discharged. Dimethyl sulfide (0.8 mL, 10.89 mmol) was added at -78 °C and the reaction mixture was warmed to room temperature and stirred overnight. Water was added and the organic phase extracted with DCM. The combined organic layers were washed with brine and dried over Na_2SO_4. The solvents were removed *in vacuo* to yield a clear yellow powder (143 mg, 95%) which was used directly without any further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.52 (t, *J* = 2.1 Hz, 1H), 8.08 (d, *J* = 8.1 Hz, 1H), 7.70 (t, *J* = 7.7 Hz, 1H), 7.56 (t, *J* = 7.7 Hz, 1H), 7.38 (d, *J* = 7.9 Hz, 1H), 3.21 (d, *J* = 2.1 Hz, 2H), 2.87 (t, *J* = 6.9 Hz, 4H), 2.36 (dp, *J* = 15.2, 7.6 Hz, 1H), 2.25 – 2.10 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 204.2, 197.6, 147.9, 134.0, 130.9, 129.5, 126.4, 70.3, 45.5, 37.2, 17.3.



65 67

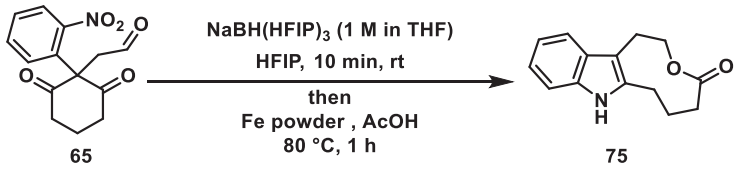
7-(2-nitrophenyl)oxonane-2,6-dione (67): To a solution of aldehyde (80 mg, 0.29 mmol) in HFIP (2.1 mL) was added dropwise $NaBH(HFIP)_3$ (1 M in THF, 0.9 mL, 0.87 mmol) at room temperature. After 10 min the reaction mixture was cooled to 0 °C and quenched with water. The mixture was extracted with DCM and the combined organic layers were washed with brine and were dried over Na_2SO_4. The solvents were removed in *vacuo* and the residue was then purified by flash column chromatography (petroleum ether/EtOAc, 7:3) to yield a light yellow solid (70 mg, 88%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, *J* = 7.5 Hz, 1H), 7.71 (d, *J* = 7.7 Hz, 1H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.38 (t, *J* = 7.7 Hz, 1H), 4.48 (ddd, *J* = 11.3, 6.5, 1.6 Hz, 1H), 4.37 (dd, *J* = 11..2, 2.0 Hz, 1H), 4.19 (td, *J* = 11.3, 5.0 Hz, 1H), 3.03 – 2.81 (m, 2H), 2.56 (ddd, *J* = 14.7, 8.0, 1.7 Hz, 1H), 2.49 – 2.19 (m, 3H), 2.06 – 1.90 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 211.1, 172.2, 149.2, 133.4, 133.2, 130.3, 127.9, 124.0, 61.8, 50.5, 42.5, 36.1, 33.7, 22.4.

IR: 2956 (w), 2360 (w), 1738 (s), 1704 (m), 1607 (w), 1577 (w), 1524 (s), 1446 (w), 1350 (s), 1317 (m), 1244 (m), 1208 (m), 1145 (m), 1073 (w), 1048 (w), 1004 (m), 856 (w), 787 (w), 770 (w), 753 (w), 732 (w), 712 (w), 668 (w).

HRMS (ESI): calcd for $C_{14}H_{15}NNaO_5^+$ $[M+Na]^+$ 300.0842; found 300.0850.



The reaction was performed in a sealed tube.

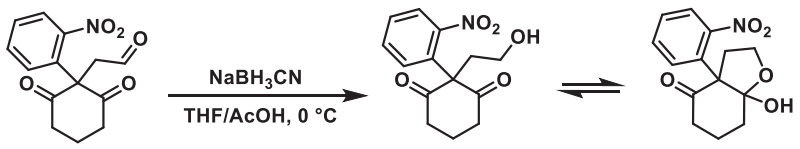
1,2,5,6,7,8-hexahydro-4H-oxonino[5,4-b]indol-4-one (75): To a solution of aldehyde (30 mg, 0.108 mmol) in HFIP (0.33 mL) was added dropwise $NaBH(HFIP)_3$ (1M in THF/ 0.33 ml, 0.33 mmol) at room temperature. After 10 min, the reaction mixture was cooled to 0 °C and Fe powder (60.3 mg, 1.08 mmol) was added followed by AcOH (0.6 mL, 10.4 mmol). The tube was sealed and heated at 80 °C for 1 hour. After full conversion was observed by TLC, the reaction mixture was cooled to rt and then filtered through a pad of Celite. The solvents were removed *in vacuo* and the residue was purified by flash column chromatography (petroleum ether/EtOAc, 7:3) to yield the desired product (22 mg, 88%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (s, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.31 – 7.23 (m, 1H), 7.19 – 7.05 (m, 2H), 4.33 (t, *J* = 5.2 Hz, 2H), 3.01 (t, *J* = 5.2 Hz, 2H), 2.99 – 2.91 (m, 2H), 2.38 (t, *J* = 6.8 Hz, 2H), 2.27 – 2.16 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.7, 136.4, 135.9, 127.9, 121.8, 119.4, 117.9, 110.4, 108.7, 62.9, 34.2, 28.1, 25.4, 24.4.

IR: 3392 (w), 3054 (w), 2954 (w), 2926 (w), 2847 (w), 1718 (s), 1621 (w), 1490 (w), 1464 (m), 1438 (m), 1364 (w), 1351 (w), 1332 (m), 1304 (w), 1272 (m), 1246 (w), 1200 (s), 1159 (w), 1146 (w), 1118 (m), 1106 (w), 1035 (w), 1002 (w), 996 (w), 908 (w), 855 (w), 765 (w), 745 (m), 695 (w).

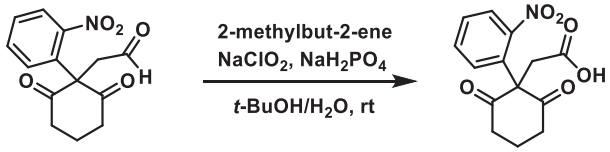
HRMS (ESI): calcd for $C_{14}H_{16}NO_2^+$ $[M+H]^+$ 230.1176; found 230.1185.



65 60 61

To a solution of aldehyde (60 mg, 0.22 mmol) in THF/AcOH, 10:1 (2.2 mL) was added $NaBH_3CN$ (34.3 mg, 0.55 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 40 min until full conversion of starting material. The mixture was quenched with water and extracted with EtOAc. The combined organic layers were washed with brine and then dried over Na_2SO_4. The solvents were removed *in vacuo* to yield a colorless oil which was used directly without any further purification.

NB: Purification on silica gel lead to cyclization to give the macrolactone product.



65 58

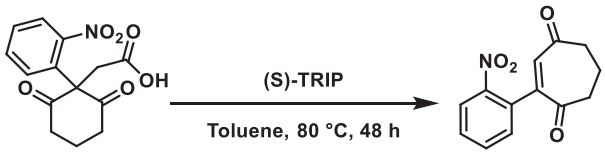
2-(1-(2-nitrophenyl)-2,6-dioxocyclohexyl)acetic acid (58): To a solution of aldehyde (437 mg, 1.58 mmol) in *t*BuOH (8 mL) at room temperature was added 2-methylbut-2-ene (1.67 mL, 15.8 mmol) followed by an aqueous solution (8 mL) of $NaClO_2$ (431.7 mg, 4.76 mmol) and NaH_2PO_4 (947.7 mg, 7.9 mmol). The solution was stirred for 35 min and was quenched with 1 M HCl. The aqueous phase was extracted with EtOAc and the combined organic layers were washed with brine and dried over Na_2SO_4. After filtration the solvents were removed *in vacuo* and the residue was then purified by flash column chromatography (DCM: 100% then DCM/MeOH 98:2, then DCM/MeOH 95:5) to yield a white solid (450.8 mg, 98%).

^{1}H NMR (400 MHz, MeOD): δ 8.10 (d, *J* = 8.1 Hz, 1H), 7.80 – 7.72 (m, 2H), 7.63 – 7.54 (m, 1H), 3.41 (s, 2H), 3.12 (m, 2H), 2.67 (dt, *J* = 16.6, 4.7 Hz, 2H), 2.24 – 2.11 (m, 2H).

^{13}C NMR (101 MHz, MeOD): δ 206.3, 172.2, 149.6, 134.8, 133.0, 132.0, 130.1, 126.7, 75.1, 40.3, 37.7, 18.5.

IR: 2973 (w), 1731 (s), 1674 (s), 1580 (w), 1524 (s), 1454 (w), 1406 (w), 1349 (s), 1322 (m), 1223 (m), 1171 (s), 1154 (w), 1080 (w), 1045 (w), 899 (w), 858 (w), 788 (m), 733 (m), 703 (w), 677 (w).

HRMS (ESI): calcd for $C_{14}H_{13}NNaO_6^+$ $[M+Na]^+$ 314.0635; found 314.0633.



58 66

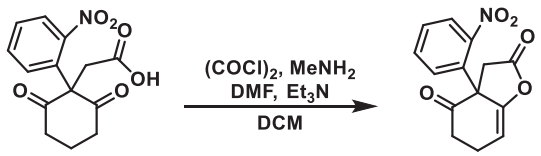
2-(2-nitrophenyl)cyclohept-2-ene-1,4-dione (66): In a sealed tube was added acid **58** (15 mg, 0.052 mmol) and (*S*)-TRIP (1.96 mg, 0.0026 mmol) in toluene (0.5 mL). The tube was sealed and the mixture was heated at 80 °C for 24 h. The solvents were removed *in vacuo* and the residue was purified by flash column chromatography (DCM: 100% then DCM/MeOH 98:2, them DCM/MeOH 95:5) to yield a colorless oil (1.9 mg, 15%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.73 (td, *J* = 7.5, 1.3 Hz, 1H), 7.60 (ddd, *J* = 8.2, 7.5, 1.5 Hz, 1H), 7.41 (dd, *J* = 7.5, 1.5 Hz, 1H), 6.50 (s, 1H), 3.00 – 2.92 (m, 2H), 2.87 – 2.79 (m, 2H), 2.36 – 2.29 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 201.9, 200.7, 148.6, 146.4, 134.7, 134.4, 133.5, 132.6, 130.4, 125.2, 44.0, 43.1, 17.9.

IR: 3660 (m), 2987 (s), 2901 (s), 1734 (w), 1678 (w), 1598 (w), 1576 (w), 1527 (w), 1407 (m), 1394 (m), 1345 (w), 1251 (m), 1228 (m), 1076 (s), 1067 (s), 893 (m), 869 (m), 831 (m), 775 (m).

HRMS (ESI): calcd for $C_{13}H_{12}NO_4^+$ $[M+H]^+$ 246.0760; found 246.0756.



58 68

3a-(2-nitrophenyl)-3,3a,5,6-tetrahydrobenzofuran-2,4-dione (68): To a suspension of acid **58** (100 mg, 0.34 mnol) in DCM (3.5 mL) and a few drops of DMF at 0 °C was added oxalyl chloride (59 µL, 0.69 mmol). The reaction mixture was stirred at 0 °C for 20 min then warmed to room temperature until full conversion of the acid was observed. The reaction mixture was concentrated *in vacuo* and the residue was placed under high vacuum to remove any excess of oxalyl chloride.

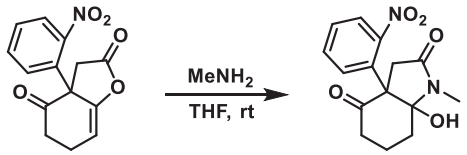
The residue was dissolved in DCM (3.5 mL). At 0 °C, Et3N (93 µL, 0.69 mmol) and MeNH2 (189 µL, 0.38 mmol) was consecutively added dropwise and stirred during 10 min. The reaction mixture was then warm to room temperature for 1 hour and was quenched using NaHCO3. The aqueous phase was extracted with DCM. The combined organic layers were washed with brine and t dried over Na2SO4. The solvents were removed in

vacuo and the residue was then purified by flash column chromatography (petroleum ether/EtOAc, 1:1) to yield a withe solid (75 mg, 94%).

NB: The desired amide was not obtained following this procedure.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 – 7.81 (m, 1H), 7.70 – 7.67 (m, 2H), 7.57 (ddd, *J* = 7.9, 5.9, 2.9 Hz, 1H), 5.76 (dd, *J* = 5.7, 2.9 Hz, 1H), 3.84 (d, *J* = 18.6 Hz, 1H), 2.77 (d, *J* = 18.6 Hz, 1H), 2.53 – 2.27 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 200.0, 171.0, 148.9, 148.8, 133.8, 130.7, 130.3, 129.8, 125.9, 105.5, 60.3, 35.9, 32.9, 21.2.



68 69

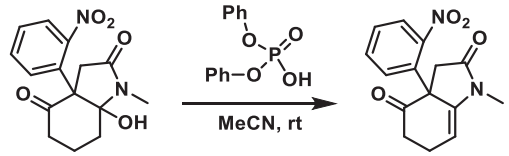
7a-hydroxy-1-methyl-3a-(2-nitrophenyl)hexahydro-1H-indole-2,4-dione (69): To a solution of **68** (50 mg, 0.18 mmol) in THF (1.5 mL) was added methylamine (2 M in THF, 0.28 mL, 0.54 mmol). The reaction mixture was stirred at room temperature for 12 hours and was quenched using 1 M HCl. The aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. The solvents were removed *in vacuo* and the residue was purified by flash column chromatography (DCM/MeOH, 95:5) to yield a withe solid (47 mg, 85%).

^{1}H NMR (400 MHz, MeOD) δ 8.12 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.73 (td, *J* = 7.7, 1.5 Hz, 1H), 7.56 (td, *J* = 7.8, 1.3 Hz, 1H), 7.45 (dd, *J* = 8.0, 1.3 Hz, 1H), 3.01 (d, *J* = 18.3 Hz, 1H), 2.95 (d, *J* = 18.3 Hz, 1H), 2.84 – 2.70 (m, 1H), 2.71 (s, 3H), 2.65 – 2.53 (m, 1H), 2.42 – 2.29 (m, 1H), 2.25 – 2.08 (m, 2H), 1.92 – 1.76 (m, 1H).

^{13}C NMR (101 MHz, MeOD) δ 206.9, 171.47, 150.46, 134.76, 134.72, 131.00, 129.77, 126.80, 95.05, 63.61, 41.86, 38.23, 34.02, 24.66, 18.42.

IR: 3315 (w), 2927 (w), 2853 (w), 1671 (s), 1607 (w), 1575 (w), 1524 (s), 1484 (w), 1430 (m), 1391 (m), 1345 (s), 1264 (w), 1230 (w), 1199 (m), 1176 (m), 1134 (w), 1092 (w), 1077 (w), 1019 (w), 998 (m), 968 (m), 908 (w), 861 (w), 855 (w), 855 (w), 829 (w), 794 (m), 744 (m), 720 (m), 688 (m), 674 (w).

HRMS (ESI): calcd for $C_{15}H_{17}N_2O_5^+$ $[M+H]^+$ 305.1132; found 305.1131.



69 70

1-methyl-3a-(2-nitrophenyl)-3,3a,5,6-tetrahydro-1H-indole-2,4-dione (70): To a solution of **69** (10 mg, 0.03 mmol) in MeCN (0.3 mL) was added the phosphoric acid (0.8 mg, 0.003 mmol). The reaction mixture was heat to 50 °C and stirred for 16 hours. The solution was cooled to room temperature. The solvents were removed *in vacuo* and the residue was purified by flash column chromatography (DCM/MeOH, 98:2) to yield a withe solid (8.4 mg, 98%).

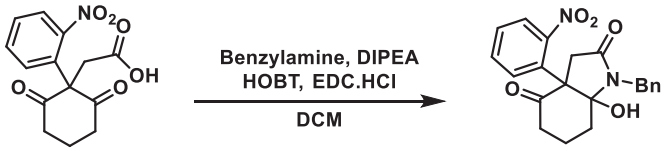
NB: Performing the reaction in toluene or dioxane afforded the same product with similar yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.60 (td, *J* = 7.7, 1.5 Hz, 1H), 7.50 (td, *J* = 7.7, 1.4 Hz, 1H), 7.46 (dd, *J* = 7.8, 1.4 Hz, 1H), 5.26 (dd, *J* = 6.2, 2.7 Hz, 1H), 3.76 (d, *J* = 18.1 Hz, 1H), 3.02 (s, 3H), 2.52 (d, *J* = 18.1 Hz, 1H), 2.46 – 2.36 (m, 3H), 2.24 – 2.09 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 202.3, 172.1, 149.4, 142.9, 133.1, 131.1, 129.6, 129.4, 125.5, 101.4, 57.5, 37.8, 34.7, 26.7, 21.4.

IR: 2925 (w), 2853 (w), 2359 (w), 1724 (s), 1668 (s), 1531 (s), 1473 (w), 1426 (w), 1390 (w), 1358 (w), 1325 (w), 1299 (w), 1123 (w), 994 (w), 949 (w), 853 (w), 786 (w), 722 (w).

HRMS (ESI): calcd for $C_{15}H_{15}N_2O_4^+$ $[M+H]^+$ 287.1026; found 287.1030.



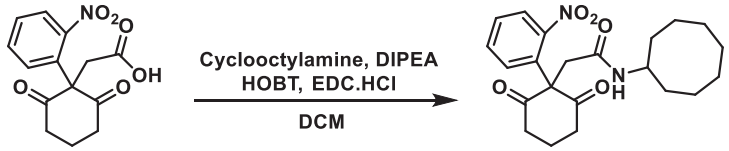
58 71

1-benzyl-7a-hydroxy-3a-(2-nitrophenyl)hexahydro-1H-indole-2,4-dione (71): To a solution of acid **58** (15 mg, 0.05 mmol) in DCM (0.5 mL) was added benzylamine (5 µL, 0.047 mmol), DIPEA (13.4 µL, 0.078 mmol), HOBt (7.7 mg, 0.057 mmol) and then EDC.HCl (10.9 mg, 0.057 mmol). The reaction mixture was stirred at room temperature for 1 h 30 and was quenched using NH_4Cl (aq). The aqueous phase was extracted with DCM. The combined organic layers were washed with brine and dried over Na_2SO_4. The solvents were removed *in vacuo* at 30 °C to give crude **71**.

^{1}H NMR (400 MHz, MeOD) δ 8.13 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.69 (td, *J* = 7.7, 1.5 Hz, 1H), 7.56 (td, *J* = 7.9, 1.3 Hz, 1H), 7.45 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.17 (m, 5H), 4.50 (d, *J* = 15.3 Hz, 1H), 4.20 (d, *J* = 15.3 Hz, 1H), 3.11 (d,

J = 17.7 Hz, 1H), 2.97 (d, *J* = 17.7 Hz, 1H), 2.80 – 2.66 (m, 1H), 2.64 – 2.51 (m, 1H), 2.21 – 2.11 (m, 1H), 2.09 – 1.94 (m, 2H), 1.84 – 1.71 (m, 1H).

^{13}C NMR (101 MHz, MeOD) δ 207.1, 171.8, 150.6, 139.5, 134.6, 134.5, 131.2, 129.8, 129.3, 128.9, 128.2, 126.8, 95.5, 63.8, 43.4, 41.6, 38.1, 35.9, 18.6.



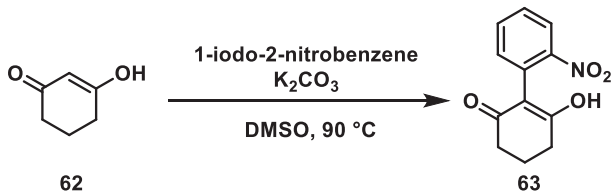
58 72

N-cyclooctyl-2-(1-(2-nitrophenyl)-2,6-dioxocyclohexyl)acetamide (72): To a solution of acid **58** (15 mg, 0.05 mmol) in DCM (0.5 mL) was added cyclooctylamine (6.4 µL, 0.047 mmol), DIPEA (13.4 µL, 0.078 mmol), HOBt (7.7 mg, 0.057 mmol) and then EDC.HCl (10.9 mg, 0.057 mmol). The reaction mixture was stirred at room temperature for 3 hours and was quenched using $NaHCO_3$ (aq). The aqueous phase was extracted with DCM. The combined organic layers were washed with brine and dried over Na_2SO_4. The solvents were removed *in vacuo* and the residue was purified by flash column chromatography (PE/EtOAc, 1:1) to yield a withe solid (11.4 mg, 57%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.65 (td, *J* = 7.7, 1.5 Hz, 1H), 7.52 (td, *J* = 7.7, 1.3 Hz, 1H), 7.48 (dd, *J* = 7.9, 1.3 Hz, 1H), 5.88 (d, *J* = 7.9 Hz, 1H), 3.86 (m, 1H), 3.17 (s, 2H), 2.96 – 2.78 (m, 4H), 2.36 – 2.24 (m, 1H), 2.16 (m, 1H), 1.67 – 1.58 (m, 3H), 1.54 – 1.40 (m, 11H).

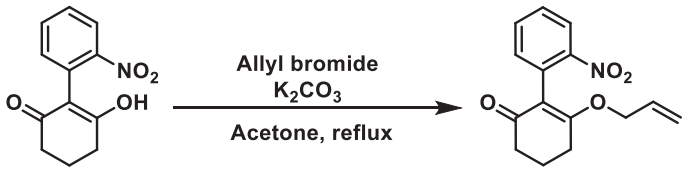
^{13}C NMR (101 MHz, $CDCl_3$): δ 205.7, 165.8, 147.9, 133.5, 131.3, 131.2, 129.2, 125.9, 70.7, 49.9, 41.5, 37.3, 31.6, 27.3, 25.3, 23.4, 17.3.

III. Synthetic studies of alstolactine A



62 63

6-(allyloxy)-2'-nitro-4,5-dihydro-[1,1'-biphenyl]-2(3H)-one (63): A mixture of 1,3-cyclohexanedione (81.04 g, 723 mmol), *o*-iodonitrobenzene (90 g, 361.4 mmol) and anhydrous potassium carbonate (150 g, 1084 mmol) in DMSO (1.2 L) was heated at 90 °C for 4 hours. After cooling to room temperature, the solution was acidified using HCl 6 N at -20 °C. The reaction mixture was then filtered over a plug of celite. The filtrate was extracted with EtOAc and the combined organic layers were washed with a solution of $Na_2S_2O_3$, brine, and dried over Na_2SO_4. The solvents were removed *in vacuo* to give a brown foam. The residue was used directly without any further purification.

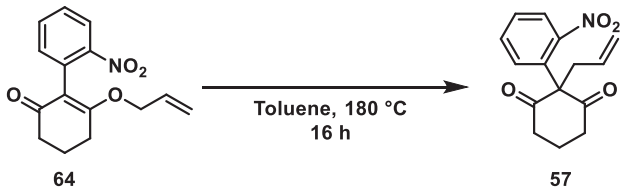


63 64

6-(allyloxy)-2'-nitro-4,5-dihydro-[1,1'-biphenyl]-2(3H)-one (64): To a mixture of the previously obtained crude was added anhydrous potassium carbonate (99.8 g, 722.86 mmol) and allyl bromide (34.4 mL, 397.6 mmol) in acetone (1 L). The reaction mixture was stirred at reflux temperature for 4 hours. After cooling to room temperature, water was added to the reaction mixture, and acetone was removed under reduced pressure. The aqueous layers was extracted with EtOAc and the combined organic layers were washed with brine and dried over Na_2SO_4. The solvents were removed *in vacuo* and the residue was purified by flash column chromatography (petroleum ether/EtOAc, 6:5 to 5:5) to yield a yellow-brownish oil (59.3 g, 60%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, *J* = 8.2 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.38 (t, *J* = 7.8 Hz, 1H), 7.25 (m, 1H), 5.76 (ddt, *J* = 16.1, 10.3, 4.9 Hz, 1H), 5.17 – 5.11 (m, 2H), 4.45 (d, *J* = 4.45 Hz, 2H), 2.68 (m, 2H), 2.49 – 2.45 (m, 2H), 2.18 – 1.99 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 196.3, 171.6, 149.6, 133.5, 132.5, 132.3, 129.0, 128.0, 124.3, 118.0, 117.9, 69.0, 36.7, 26.0, 20.7.

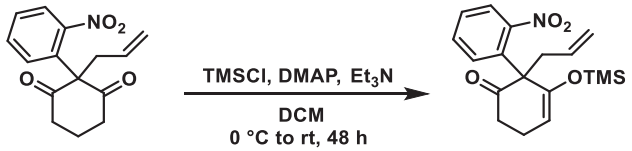


64 57

2-allyl-2-(2-nitrophenyl)cyclohexane-1,3-dione (57): A solution of **64** (9.39 g, 34.36 mmol) in toluene (95 mL) was stirred at 180 °C in a sealed tube for 16 h. After cooling to room temperature, the solvent was removed *in vacuo* and the residue was purified by recrystallization from EtOAc. After filtration, the desired product was washed using cold petroleum ether and then dried on the oil pump to afford the product X as a white powder (7.46 g, 79%).

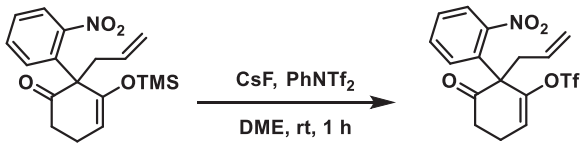
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.71 – 7.67 (m, 1H), 7.58 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.50 (ddd, *J* = 8.5, 7.3, 1.4 Hz, 1H), 5.59 (ddt, *J* = 16.8, 10.2, 6.6 Hz, 1H), 5.25 (dq, *J* = 17.0, 1.5 Hz, 1H), 5.16 (dq, *J* = 10.2, 1.4 Hz, 1H), 3.07 (dt, *J* = 6.6, 1.5 Hz, 2H), 2.88 – 2.74 (m, 4H), 2.43 – 2.31 (m, 1H), 2.22 – 2.13 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 205.3, 147.8, 133.8, 132.4, 131.4, 130.9, 128.8, 126.1, 120.1, 72.8, 38.0, 36.9, 17.0.



57 76

1-allyl-2'-nitro-6-((trimethylsilyl)oxy)-3,4-dihydro-[1,1'-biphenyl]-2(1H)-one (76): To a solution of **57** (20 g, 73.17 mmol) in DCM (185 mL) were added Et_3N (61.46 mL, 439 mmol), DMAP (8.796 g, 73.17 mmol) and TMSCl (27.95 mL, 219.5 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 48 hours. The reaction was quenched with NH_4Cl at -78 °C and the solvent was removed in vacuo. The aqueous phase was extracted with hexane. The combined organic layers were dried over Na_2SO_4 and the solvents were removed in vacuo. The residue was used directly without any further purification.



76 77

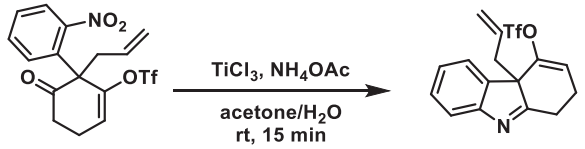
1-allyl-2'-nitro-6-oxo-1,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl trifluoromethanesulfonate (77): To a flame-dried flask was added a solution of crude **76** in distilled DME (185 mL), followed by addition of N-phenyltrifluoromethanesulfonimide (52.2 g, 146.34 mmol) and vacuum dried (300 °C) cesium fluoride (33.17 g, 219.5 mmol) under a stream of argon. The reaction mixture was vigorously stirred at room temperature for 1 hour. The pressure inside the flask was released carefully and the mixture was partitioned between ether and a pH 7 buffer solution. The aqueous phase was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and the solvents were removed in vacuo. The residue was then purified by flash column chromatography (petroleum ether/EtOAc, 25:1 then 1:1) to yield a brown oil (16.87 g, 57% over two steps).

^{1}H NMR (400 MHz, CDCl3): δ = 8.00 (d, *J* = 8.0 Hz, 1H), 7.69-7.68 (m, 2H), 7.54-7.50 (m, 1H), 6.18-6.16 (m, 1H), 5.76-5.66 (m, 1H), 5.22-5.18 (m, 2H), 3.12 (dd, *J* = 14.0, 8.0 Hz, 1H), 3.02 (dd, *J* = 14.0, 6.2 Hz, 1H), 2.92-2.85 (m, 1H), 2.78-2.70 (m, 1H), 2.65-2.55 (m, 2H).

^{13}C NMR (101 MHz, CDCl3): δ = 203.1, 149.0, 146.0, 133.5, 131.7, 131.5, 131.3, 129.5, 126.2, 120.9, 118.2 (q, JC-F = 317.8 Hz), 118.1, 58.5, 41.5, 36.1, 20.9.

IR (neat): 1718, 1534, 1413, 1353, 1208, 1138 cm–1

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{16}H_{15}F_3NO_6S$: 406.0572; found: 406.0584.



77 78

4a-Allyl-2,4a-dihydro-1H-carbazol-4-yl trifluoromethanesulfonate (78): To a vigorously stirred aqueous solution of NH_4OAc (229.4 mL, 2.5 M, 573.5 mmol) was added dropwise an aqueous solution of $TiCl_3$ (127.5 mL, 1.5 M, 191.2 mmol) at room temperature and then was diluted with acetone (130 mL). To the resulting purple solution was added a solution of **77** (15.5 g, 38.2 mmol) in acetone (130 mL). The reaction mixture was stirred at room temperature for 10 minutes. After completion of the reaction, the solution was extracted with EtOAc. The combined organic layers were washed with $NaHCO_3$ (aq.), brine and then were dried over

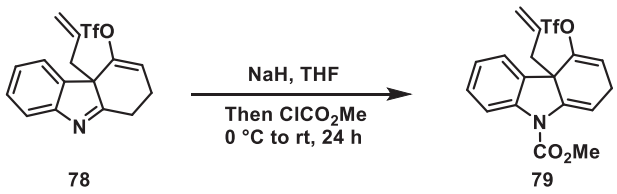
Na_2SO_4. The solvents were removed *in vacuo* and the residue was then purified by flash column chromatography (petroleum ether/EtOAc, 15:1 then 2:1) to yield a yellow oil (10.9 g, 80%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 (d, *J* = 7.7 Hz, 1H), 7.54 (d, *J* = 7.4 Hz, 1H), 7.42 (t, 7.6 Hz, 1H), 7.32-7.28 (m, 1H), 5.85 (dd, *J* = 5.1, 2.6 Hz, 1H), 5.13-5.03 (m, 1H), 5.0-4.96 (m, 1H), 4.91-4.89 (m, 1H), 3.02-2.96 (m, 2H), 2.90-2.72 (m, 3H), 2.54-2.45 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 182.4, 155.1, 147.2, 137.0, 130.0, 129.3, 126.2, 124.2, 120.8, 118.5 (q, JC-F = 319.8 Hz), 119.7, 117.3, 61.1, 41.5, 26.6, 25.6.

IR (neat): 1414, 1205, 1138 cm–1

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{16}H_{15}F_3NO_3S$: 358.0725; found: 358.0720.



78 79

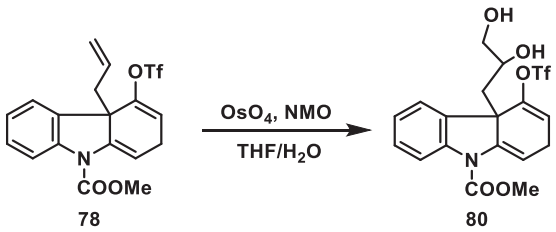
Methyl 4a-allyl-4-(((trifluoromethyl)sulfonyl)oxy)-2,4a-dihydro-9H-carbazole-9-carboxylate (79): To a suspension of NaH (2.24 g, 56 mmol) in THF (120 mL) was added a solution of **78** (10 g, 28 mmol) at 0 °C . The resulting mixture was stirred at 0 °C for 10 minutes, followed by addition of methyl chloroformate (4.33 mL, 55.9 mmol). The resulting light brown solution was warmed to room temperature and stirred for 24 h and then was quenched with NH_4Cl (aq.). The aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine and then dried over Na_2SO_4. The solvents were removed in vacuo and the residue was then purified by flash column chromatography (petroleum ether/EtOAc, 15:1) to yield a yellow oil (9.76 g, 84%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 8.2 Hz, 1H), 7.53 (d, *J* = 7.7 Hz, 1H), 7.31 (t, *J* = 7.9 Hz, 1H), 7.13 (t, *J* = 7.6 Hz, 1H), 6.26 (d, *J* = 5.2 Hz, 1H), 6.06 (dd, *J* = 5.4, 1.7 Hz, 1H), 5.66-5.55 (m, 1H), 5.04-4.99 (m, 2H), 3.96 (s, 3H), 3.14 (dt, *J*= 22.1, 2.5 Hz, 1H), 2.96 (dt, *J* = 22.1, 5.9 Hz, 1H), 2.50 (dd, *J* = 13.5, 7.6 Hz, 1H), 2.39 (dd, *J* = 13.5, 7.2 Hz, 1H).

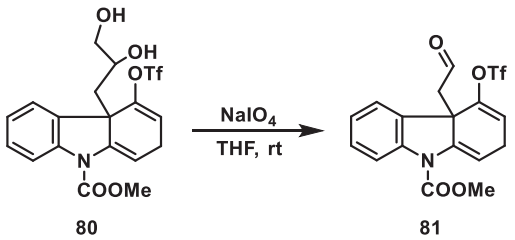
^{13}C NMR (101 MHz, $CDCl_3$): δ = 152.9, 149.1, 141.3, 140.6, 131.1, 130.7, 128.8, 124.3, 124.0, 120.2, 118.5 (q, JC-F = 318.0 Hz), 115.6, 115.3, 107.1, 53.2, 50.5, 46.4, 26.3

IR (neat): 1721, 1417, 1371, 1203, 1138 cm–1

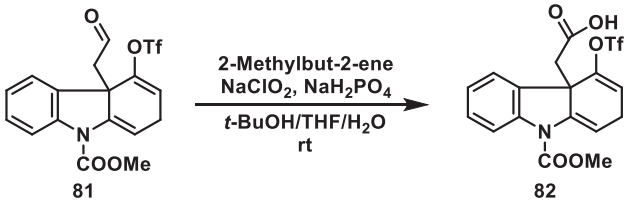
HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{18}H_{17}F_3NO_5S$: 416.0779; found: 416.0787.



Methyl 4a-(2,3-dihydroxypropyl)-4-(((trifluoromethyl)sulfonyl)oxy)-2,4a-dihydro-9H-carbazole-9-carboxylate (80): To a solution of **78** (10.0 g, 22.9 mmol) in THF (220 mL) and H_2O (9 mL) were added an aqueous solution of OsO_4 (5.55 mL, 4 wt%, 0.912 mmol) followed by NMO (3.23 g, 27.48 mmol) at 0 °C. The resulting solution was gradually warmed to room temperature and was stirred overnight. The reaction mixture was quenched with an aqueous solution of Na_2SO_3 and stirred for 5 min. The mixture was extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. The solvents were removed *in vacuo* at 25 °C and the residue was used directly without any further purification.

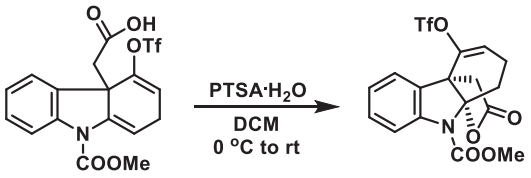


Methyl 4a-(2-oxoethyl)-4-(((trifluoromethyl)sulfonyl)oxy)-2,4a-dihydro-9H-carbazole-9-carboxylate (81): To a solution of crude **80** in THF (220 mL) and H_2O (64 mL) at room temperature was added $NaIO_4$ (14.7 g, 68.7 mmol). The resulting suspension was stirred at room temperature for 1 h and was then partitioned between ether and H_2O. The aqueous phase was extracted with Et_2O and the combined organic layers were washed with brine and then dried over Na_2SO_4. The solvents were removed *in vacuo* at 25 °C and the residue was used directly without any further purification.



2-(9-(methoxycarbonyl)-4-(((trifluoromethyl)sulfonyl)oxy)-2,9-dihydro-4aH-carbazol-4a-yl)acetic acid (82): To a solution of crude **81** in *t*BuOH/THF (175 mL/88 mL) at 0 °C was added 2-methylbut-2-ene (48 mL, 457.5 mmol), followed by an aqueous solution (44 mL) of $NaClO_2$ (7.8 g, 68.8 mmol) and NaH_2PO_4 (8.25 g, 68.9 mmol). The solution was then warmed to rt, and was quenched with water after 25 min. The aqueous

phase was extracted with DCM and the combined organic layers were washed with brine and dried over Na_2SO_4. The solvents were removed *in vacuo* at 20 °C and the residue was used directly without any further purification.



82 83

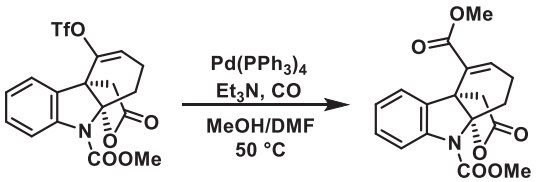
Methyl(4bS,8aS)-11-oxo-5-(((trifluoromethyl)sulfonyl)oxy)-7,8-dihydro-9H-8a,4b(epoxyethano)carbazole-9-carboxylate (83): To a solution of the crude acid **82** in DCM (440 mL) at 0 °C was added PTSA·H_2O (6.57 g, 34.3 mmol), and the reaction mixture was stirred at room temperature for 1 hour. $NaHCO_3$ (aq.) was added and the aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. The solvents were removed *in vacuo* and the residue was purified by flash column chromatography (petroleum ether/EtOAc, 8:2) to yield a yellow oil (5.97 g, 60% over 4 steps).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, *J* = 8.4 Hz, 1H), 7.37 (m, 2H), 7.15 (td, *J* = 7.6, 1.0 Hz, 1H), 5.96 (dd, *J* = 6.3, 2.4 Hz, 1H), 3.95 (s, 3H), 3.61 (dt, *J* = 14.3, 3.7 Hz, 1H), 3.25 (d, *J* = 17.6 Hz, 1H), 3.18 (d, *J* = 17.6 Hz, 1H), 2.45-2.24 (m, 2H), 2.00 (ddd, *J* = 14.2, 11.9, 5.0 Hz, 1H).

^{13}C NMR (400 MHz, $CDCl_3$): δ 170.9, 153.0, 146.3, 141.0, 130.8, 127.2, 125.2, 124.7, 118.9, 118.8 (q, JC-F = 317.8 Hz), 116.8, 103.8, 54.2, 53.6, 39.1, 28.2, 21.1.

IR (neat): 2959 (w), 2357 (w), 1792 (m), 1726 (m), 1602 (w), 1481 (m), 1441 (m), 1417 (m), 1366 (m), 1282 (m), 1209 (s), 1139 (s), 1108 (m), 1084 (s), 1054 (m), 1021 (m), 936 (s), 904 (s), 819 (m), 758 (m), 734 (m).

HRMS (ESI) calcd for $C_{17}H_{15}F_3NO_7S^+$ $[M+H]^+$ 434.0516; found 434.0516.



83 85

Dimethyl (4bS,8aS)-11-oxo-7,8-dihydro-9H-8a,4b-(epoxyethano)carbazole-5,9-dicarboxylate (85): To a solution of **83** (3.5 g, 8.08 mmol) in MeOH (92 mL) and DMF (47 mL) were added Et_3N (3.27 mL, 24.2 mmol) and $Pd(PPh_3)_4$ (466.8 mg, 0.404 mmol) at room temperature. The resulting mixture was heated to 50 °C under

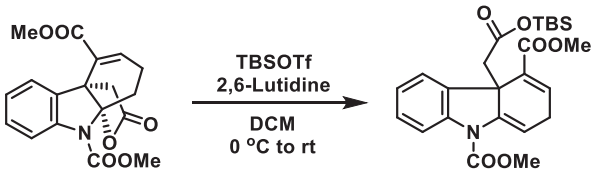
CO atmosphere (1 atm). After 1 h, the mixture was cooled to room temperature and then quenched with NH_4Cl (aq.). The mixture was extracted with Et_2O and the combined organic layers were washed with brine, dried over Na_2SO_4. After filtration the solvents were removed in *vacuo* and the residue was then purified by flash column chromatography (petroleum ether/EtOAc, 8:2) to yield a withe solid (2.44 g, 88%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.2 Hz, 1H), 7.52 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.20 (m, 1H), 7.05 (dd, *J* = 6.1,1.8 Hz, 1H), 6.97 (t, *J* = 7.6 Hz, 1H), 3.87 (s, 3H), 3.70 (s, 3H), 3.57 (d, *J* = 18.5 Hz, 1H), 3.53 (m, 1H), 3.04 (d, *J* = 18.5 Hz, 1H), 2.34 (m, 1H), 2.22 (m, 1H), 1.79 (td, *J* = 13.4, 4.8 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.1, 165.8, 153.3, 140.9, 140.5, 132.7, 130.5, 129.9, 125.9, 124.4, 116.1, 104.0, 53.4, 53.1, 52.1, 41.5, 28.1, 23.1.

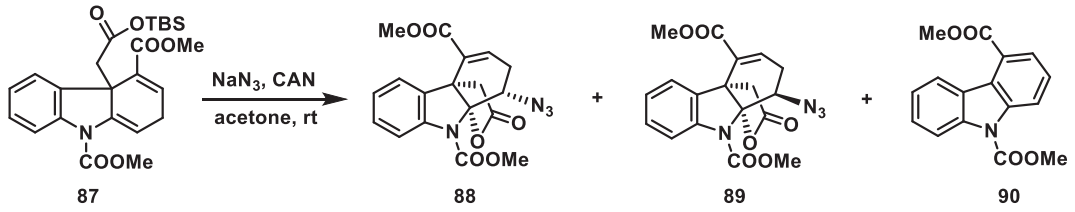
IR: 2955 (w), 2357 (w), 1785 (s), 1714 (s), 1641 (w), 1598 (w), 1479 (m), 1439 (m), 1366 (s), 1283 (s), 1257 (m), 1194 (m), 1111 (m), 1087 (m), 1024 (m), 978 (m), 916 (m), 758 (m), 737 (m).

HRMS (ESI): calcd for $C_{18}H_{18}NO_6^+$ $[M+H]^+$ 344.1129; found 344.1134.



85 87

Dimethyl 4a-(2-((tert-butyldimethylsilyl)oxy)-2-oxoethyl)-2,4a-dihydro-9H-carbazole-4,9-dicarboxylate (87): To a solution of **85** (200 mg, 0.583 mmol) in DCM (6 mL) was added 2,6-lutidine (0.68 mL, 5.825 mmol) followed by addition of TBSOTf (0.67 mL, 2.913 mmol) at 0 °C. The resulting solution was gradually warmed to room temperature and stirred for 48 hours. After the reaction was completed the solution was cooled to 0 °C and quenched with Na_2CO_3 (aq.). The aqueous phase was extracted with Et_2O. The combined organic layers were washed with brine and dried over Na_2SO_4. The solvents were removed *in vacuo* and the oily residue was dried under vacuum to remove the 2,6-lutidine. The resulting oil was used directly without any further purification.



Dimethyl (4bS,8S,8aR)-8-azido-11-oxo-7,8-dihydro-9H-8a,4b-(epoxyethano)carbazole-5,9-dicarboxylate (88): To a solution of the crude **87** in acetone (5.4 mL) was added NaN_3 (56.8 mg, 0.874 mmol) under argon. At rt, a solution of CAN (958.1 g, 1.748 mmol) in acetone (21.5 mL) was added dropwise using syringe pump (1 ml/min). The resulting yellow solution was stirred at rt and then was quenched with H_2O. After removal of most of the acetone *in vacuo*, the aqueous phase was extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4. The solvents were removed *in vacuo* and the residue was then purified by flash column chromatography (petroleum ether:EtOAc, 8:2) to yield a withe foam (176.7 mg, 80% over 2 steps. *d.r* 2.5:1 in favor of the desired isomer). The two isomers were separated by flash column chromatography (DCM/Acetone/Toluene, 300:1:1).

Desired *cis*-isomer 88:

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.3 Hz, 1H), 7.60 (d, *J* = 7.7 Hz, 1H), 7.29 (m, 1H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.90 (t, *J* = 4.4 Hz, 1H), 5.66 (s, 1H), 3.97 (s, 3H), 3.79 (s, 3H), 3.56 (d, *J* = 18.2 Hz, 1H), 3.35 (d, *J* = 18.2 Hz, 1H), 2.67 (t, *J* = 3.8 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.1, 165.0, 153.3, 140.1, 134.5, 132.9, 130.9, 129.9, 125.7, 124.8, 116.2, 102.9, 58.2, 53.7, 53.1, 52.2, 41.7, 28.5.

IR: 2955 (w), 2916 (w), 2849 (w), 2116 (m), 1797 (m), 1720 (s), 1480 (m), 1463 (w), 1440 (m), 1368 (m), 1296 (m), 1271 (m), 1257 (m), 1251 (m), 1112 (w), 1088 (m), 1027 (w), 911 (w), 734 (m).

HRMS (ESI): calcd for $C_{18}H_{16}N_4NaO_6^+$ $[M+Na]^+$ 407.0962; found 407.0960.

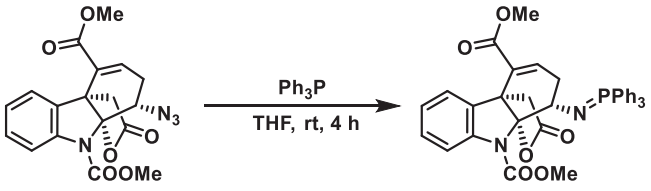
Aromatized product 90:

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.68 (ddd, *J* = 8.2, 1.4, 0.7 Hz, 1H), 8.63 (dd, *J* = 8.5, 1.1 Hz, 1H), 8.34 (dt, *J* = 8.5, 0.9 Hz, 1H), 7.88 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.58 – 7.46 (m, 2H), 7.38 (ddd, *J* = 8.2, 7.2, 1.1 Hz, 1H), 4.16 (s, 3H), 4.06 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.3, 152.9, 139.3, 138.9, 128.2, 126.4, 125.9, 125.7, 124.8 (2C), 124.4, 123.6, 120.1, 115.9, 53.9, 52.6.

IR: 2954 (w), 1726 (s), 1454 (m), 1439 (s), 1425 (m), 1358 (m), 1320 (s), 1286 (m), 1250 (s), 1195 (m), 1179 (m), 1147 (s), 1126 (m), 752 (m), 721 (w).

HRMS (ESI): calcd for $C_{16}H_{14}NO_4^+$ [M+H]$^+$ 284.0917; found 284.0921.



88 93

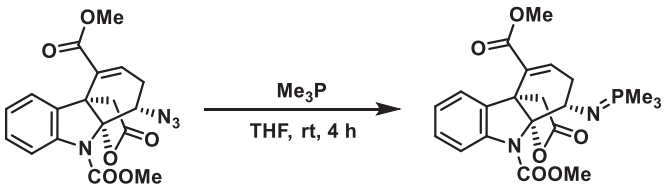
Dimethyl (4bS,8S,8aR)-11-oxo-8-((triphenyl-l5-phosphanylidene)amino)-7,8-dihydro-9H-8a,4b-(epoxyethano)carbazole-5,9-dicarboxylate (93): To a solution of **88** (5.0 mg, 0.013 mmol) in THF (100 µL) was added PPh_3 (5.1 mg, 0.019 mmol) at room temperature. The resulting mixture was stirred for 4 hours and the solvents were removed in *vacuo.* The residue was then purified by flash column chromatography (DCM/MeOH, 95:5) to yield a withe solid (4.9 mg, 61%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, *J* = 8.2 Hz, 1H), 7.68 – 7.58 (m, 7H), 7.56 – 7.40 (m, 9H), 7.21 (t, *J* = 7.8 Hz, 1H), 7.01 (t, *J* = 7.5 Hz, 1H), 6.84 (d, *J* = 6.7 Hz, 1H), 5.07 (dd, *J* = 21.0, 3.1 Hz, 1H), 3.78 (s, 3H), 3.74 (d, *J* = 17.6 Hz, 1H), 3.64 (s, 3H), 3.51 (d, *J* = 17.5 Hz, 1H), 2.43 (m, 1H), 2.12 – 2.06 (m, 1H).

^{31}P NMR (162 MHz, $CDCl_3$): δ 11.42.

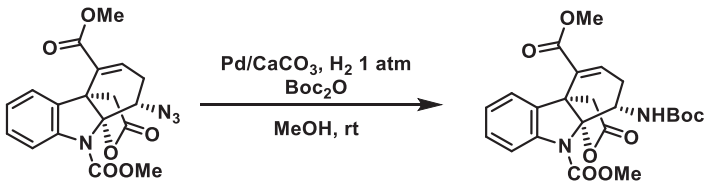
^{13}C NMR (101 MHz, $CDCl_3$): δ 175.3, 166.3, 153.7, 141.7, 138.0, 132.9, 132.8, 132.7, 131.5, 131.5, 131.6, 129.2, 128.6, 128.5, 125.7, 124.1, 115.9, 106.4, 53.7, 52.9, 51.8, 50.8, 43.3, 33.2.

HRMS (ESI): calcd for $C_{36}H_{32}N_2O_6P^+$ [M+H]$^+$ 619.1993; found 619.1990.



88 95

Dimethyl (4bS,8S,8aR)-11-oxo-8-((trimethyl-l5-phosphanylidene)amino)-7,8-dihydro-9H-8a,4b-(epoxyethano)carbazole-5,9-dicarboxylate (95): To a solution of **88** (2.0 mg, 0.0052 mmol) in THF (50 µL) was added PMe_3 (1 M in THF, 5.5 µL, 0.0055 mmol) at room temperature. The resulting mixture was stirred for 30 min and the solvents were removed in vacuo. The residue was used without further purification.



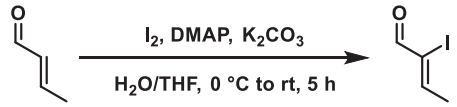
88 96

Dimethyl(4bS,8S,8aR)-8-((tert-butoxycarbonyl)amino)-11-oxo-7,8-dihydro-9H-8a,4b-(epoxyethano)carbazole-5,9-dicarboxylate (96): A suspension of **88** (4 mg, 0.010 mmol) and $Pd/CaCO_3$ (0.8 mg, 20% wt) in MeOH (0.1 mL) was stirred under an atmosphere of H_2 (1 atm, H_2 ballon) at room temperature for 5 hours. The mixture was filtered through Celite using EtOAc. The solvents were removed in *vacuo* at 25 °C and the residue was then purified by preparative TLC (petroleum ether/acetone, 8:2) to yield a colorless oil (9 mg, 15%)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, *J* = 8.3 Hz, 1H), 7.54 (d, *J* = 7.3 Hz, 1H), 7.32 – 7.25 (m, 1H), 7.04 (td, *J* = 7.6, 1.0 Hz, 1H), 7.04 – 6.97 (m, 1H), 5.79 (s, 1H), 4.60 (d, *J* = 9.5 Hz, 1H), 3.98 (s, 3H), 3.81 (s, 3H), 3.56 (d, *J* = 18.6 Hz, 1H), 3.17 (d, *J* = 18.6 Hz, 1H), 2.71 (m, 1H), 2.52 (m, 1H), 1.46 (s, 9H).

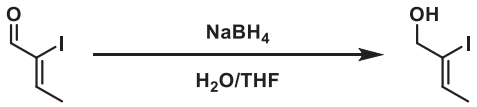
^{13}C NMR (101 MHz, $CDCl_3$): δ 172.7, 165.1, 155.1, 153.3, 140.9, 136.5, 133.8, 131.1, 130.1, 125.4, 124.7, 116.5, 103.8, 81.0, 53.8, 52.9, 52.4, 46.9, 42.1, 29.3, 28.4 (3C).

HRMS (ESI): calcd for $C_{23}H_{26}N_2NaO_8^+$ $[M+Na]^+$ 481.1581; found 481.1582.



97 98

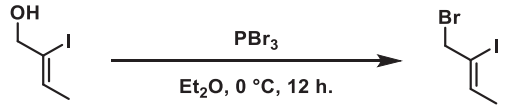
(Z)-2-iodobut-2-enal (98): Potassium carbonate (24 g, 172 mmol), I_2 (72.42 g, 286mmol), and DMAP (3.48 g, 28.6 mmol) were successively added to a solution of (*E*)-crotonaldehyde **97** (10 g, 143 mmol) in a mixture of THF (350 mL) and water (350 mL). After being stirred for 5 h, the reaction mixture was diluted with EtOAc and washed with a solution of saturated $Na_2S_2O_3$ (aq). The organic layer was dried over Na_2SO_4, and the crude product obtained after evaporation in *vacuo* was used in the next step without purification.



98 99

(Z)-2-iodobut-2-en-1-ol (99): The crude **98** product (143 mmol) was taken up in THF/H_2O, 9:1 and cooled to 0 °C. The $NaBH_4$ (2.69 g, 71.5 mmol) was added slowly, and the reaction was stirred for 1 h. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was concentrated and the residue purified by flash chromatography with silica gel in ethyl acetate/hexane 1:9 to obtain alcohol **99** (27.40 g, 92% yield). The spectral properties of this iodide were identical to the published values.

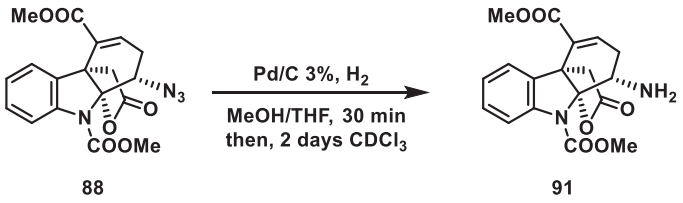
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.98 (q, *J* = 6.3 Hz, 1H), 4.23 (s, 2H), 1.79 (d, *J* = 6.3 Hz, 3H).



99 100

(Z)-1-bromo-2-iodobut-2-ene (100): Compound **99** (2 g, 10 mmol) was dissolved in anhydrous ethyl ether (20 mL). Phosphorus tribromide (0.380mL, 4 mmol) was added dropwise to this solution at 0 °C. This reaction mixture which resulted was stirred for 12 h at rt. The reaction was quenched with a cold solution of K_2CO_3 (aq.) and extracted with ethyl ether and was washed with brine. The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to give **100** (2.45 g, 89% yield). The spectral properties of this bromide were identical to the published values.

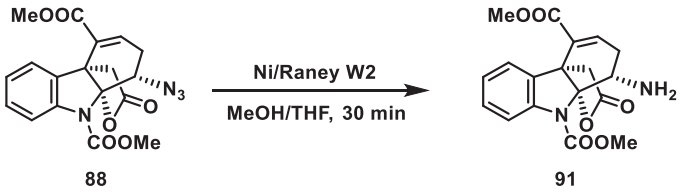
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.08 (q, *J* = 6.4 Hz, 1H), 4.36 (s, 2H), 1.81 (d, *J* = 6.4 Hz, 3H).



88 91

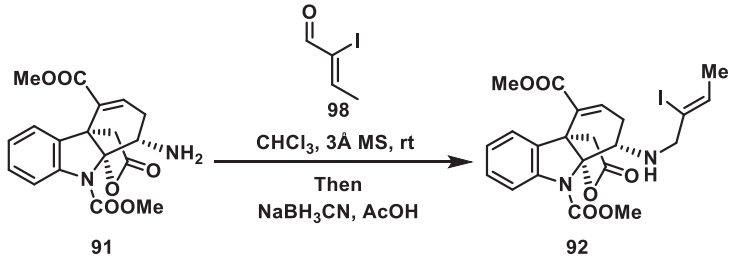
Dimethyl (4bS,8S,8aR)-8-amino-11-oxo-7,8-dihydro-9H-8a,4b-(epoxyethano)carbazole-5,9-dicarboxylate (91): A suspension of **88** (20 mg, 0.052 mmol) and Pd/C 3% mol (37 mg, 0.0104 mmol) in MeOH (0.5 mL) and THF (0.5 mL) was stirred under an atmosphere of H_2 (1 atm, H_2 ballon) at room temperature for 30 min. The mixture was filtered through Celite using EtOAc. The solvents were removed *in vacuo* at 25 °C and the residue was then solubilized in $CHCl_3$ until full conversion of triazene intermediate to the desired amine. The solvents were removed *in vacuo* at 25 °C and the residue was used directly without any further purification.

NB: The method using Ni/Raney W2 was more efficient. See page 173 for the preparation of Ni/Raney W2.



88 91

Dimethyl (4bS,8S,8aR)-8-amino-11-oxo-7,8-dihydro-9H-8a,4b-(epoxyethano)carbazole-5,9-dicarboxylate (91): A portion of the freshly prepared Raney-Ni (W2) in EtOH was introduce in a vial. After sedimentation of the nickel, supernatant EtOH was carefully removed and the residue nickel was washed with MeOH three time. Finally, the obtained Raney-Ni in MeOH (1.8 mL) was then transferred to a solution of the azide **88** (140 mg, 0.36 mmol) in THF (1.8 mL). After stirring at rt under an atmosphere of H_2 (1 atm, H_2 ballon) for 30 min, the reaction mixture was filtered through Celite using EtOAc. The solvents were removed *in vacuo* and the residue was used directly without any further purification.



91 92

Dimethyl (4bS,8S,8aR)-8-(((Z)-2-iodobut-2-en-1-yl)amino)-11-oxo-7,8-dihydro-9H-8a,4b-(epoxyethano)carbazole-5,9-dicarboxylate (92): To a solution of the crude primary amine **91** in $CHCl_3$ (3.6 mL) was added at rt the aldehyde (142.7 mg, 0.728 mmol). The reaction mixture was stirred at room

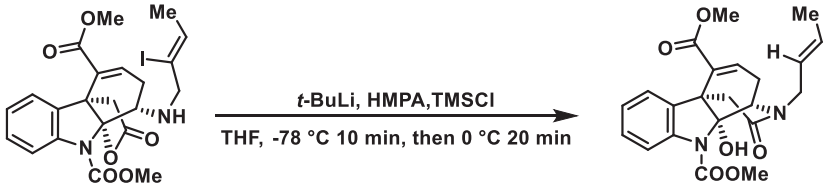
temperature for 2 hours under 3Å MS. After completion of the reaction monitored by TLC, the reaction mixture was cooled to 0 °C and a solution of $NaBH_3CN$ (68.6 mg, 1.1 mmol) in MeOH (0.92 mL) was added followed by the dropwise addition of AcOH (53 µL, 0.91 mmol). The orange/yellow solution was warmed to room temperature, stirred for 2 hours and then was quenched with $NaHCO_3$ (aq.). The aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. The solvents were removed *in vacuo* and the residue was purified by flash column chromatography (petroleum ether/EtOAc, 8:2) to yield a colorless oil (101.9 mg, 52% over 2 steps).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, *J* = 8.3 Hz, 1H), 7.52 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.21 – 7.16 (m, 1H), 6.97 (td, *J* = 7.7, 1.1 Hz, 1H), 6.88 (dd, *J* = 6.6, 2.5 Hz, 1H), 5.85 (q, *J* = 6.3 Hz, 1H), 4.46 (t, *J* = 3.5 Hz, 1H), 3.83 (s, 3H), 3.72 (s, 3H), 3.46 – 3.43 (m, 2H), 3.40 (d, *J* = 6.0 Hz, 2H), 2.61 – 2.44 (m, 2H), 1.76 (d, *J* = 6.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.3, 165.4, 153.4, 140.9, 135.4, 134.1, 133.4, 131.7, 129.7, 125.7, 124.5, 116.1, 112.2, 105.7, 61.3, 53.4, 53.3, 52.1, 49.9, 42.9, 30.5, 22.0.

IR: 2953 (w), 2360 (w), 1786 (m), 1716 (s), 1645 (w), 1597 (w), 1480 (m), 1463 (w), 1439 (m), 1364 (m), 1291 (m), 1260 (m), 1227 (m), 1111 (m), 1088 (m), 1026 (m), 912 (m), 756 (m), 733 (m).

HRMS (ESI): calcd for $C_{22}H_{24}IN_2O_6^+$ $[M+H]^+$ 539.0674; found 539.0667.



92 105

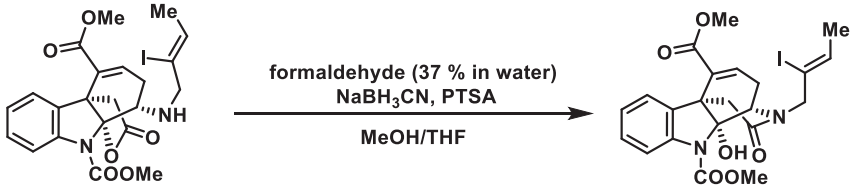
Dimethyl (1S,4aS,9aR)-12-((E)-but-2-en-1-yl)-9a-hydroxy-11-oxo-1,9a-dihydro-1,4a-(epiminoethano)carbazole-4,9(2H)-dicarboxylate (105): To a solution of **92** (1.5 mg, 0.0027 mmol) in THF (0.3 mL) were added distilled HMPA (2.16 µL, 0.012 mmol) and TMSCl (2.82 µL, 0.022 mmol) under argon. The resulting solution was stirred at room temperature for 10 min and then cooled down to -78 °C. At -78 °C, *t*-BuLi (10.4 µL, 1.2 M in pentane, 0.012 mmol) was added dropwise and the mixture was stirred at -78 °C for 10 min. The cooling bath was then removed, and the reaction was gradually warmed to 0 °C for 20 min. The mixture was cooled down to -78 °C again and quenched carefully with H_2O. The aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine and then were dried over Na_2SO_4. The solvents were removed in vacuo and the residue was then purified by flash column chromatography (petroleum ether/acetone, 8:2) to yield a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (s, 1H), 7.55 – 7.48 (m, 1H), 7.26 – 7.19 (m, 1H), 7.07 (td, *J* = 7.5, 1.0 Hz, 1H), 6.81 – 6.74 (m, 1H), 5.70 (m, 1H), 5.54 – 5.43 (m, 1H), 4.64 (s, 1H), 4.45 (dd, *J* = 15.0, 4.9 Hz, 1H), 3.94 (s, 3H), 3.65 (d, *J* = 17.2 Hz, 1H), 3.61 (s, 3H), 3.48 (dd, *J* = 15.0, 7.3 Hz, 1H), 3.07 (d, *J* = 17.2 Hz, 1H), 2.99 (s, 1H, OH), 2.67 – 2.64 (m, 2H), 1.72 (d, *J* = 6.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.9, 165.1, 154.3, 140.7, 134.9, 129.4, 129.0, 127.1, 125.8, 123.9, 115.6, 92.3, 57.1, 53.4, 51.7, 49.8, 48.3, 36.6, 29.3, 17.9. Two quaternary carbons missing due to low amount of product.

IR: 3902 (w), 3853 (w), 3839 (w), 3747 (w), 3649 (w), 3565 (w), 2952 (w), 2928 (w), 2852 (w), 2364 (w), 1717 (s), 1617 (m), 1542 (m), 1474 (m), 1458 (m), 1362 (w), 1248 (w), 752 (w).

HRMS (ESI): calcd for $C_{22}H_{25}N_2O_6^+$ $[M+H]^+$ 413.1707; found 413.1710.



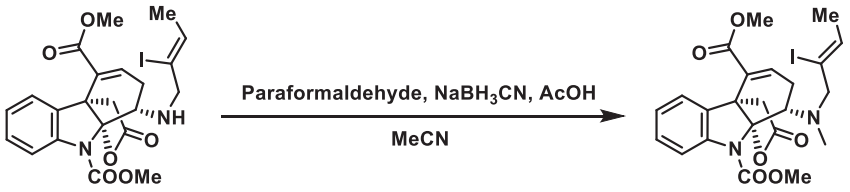
Dimethyl(1S,4aS,9aR)-9a-hydroxy-12-((Z)-2-iodobut-2-en-1-yl)-11-oxo-1,9a-dihydro-1,4a-(epiminoethano)carbazole-4,9(2H)-dicarboxylate (107): To a solution of **92** (2 mg, 0.0037 mmol) in MeOH (50 µL) were added formaldehyde (3 µL, 0.037 mmol) and $NaBH_3CN$ (2.3 mg, 0.037 mmol) under argon. The resulting solution was stirred at room temperature for 24 hours and was quenched with $NaHCO_3$ (aq.). The aqueous phase was extracted with EtOAc, washed with brine and dried over Na_2SO_4. The solvents were removed *in vacuo* and the residue was purified by preparative TLC (DCM/MeOH, 95:5) to yield a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (s, 1H), 7.51 (dd, *J* = 7.4, 1.4 Hz, 1H), 7.27 – 7.19 (m, 1H), 7.07 (td, *J* = 7.5, 1.0 Hz, 1H), 6.82 – 6.74 (m, 1H), 5.98 (q, *J* = 6.4 Hz, 1H), 4.97 (dt, *J* = 15.7, 1.7 Hz, 1H), 4.74 (s, 1H), 3.94 (s, 3H), 3.76 (d, *J* = 15.7 Hz, 1H), 3.68 (d, *J* = 17.2 Hz, 1H), 3.61 (s, 3H), 3.22 (s, 1H), 3.16 (d, *J* = 17.2 Hz, 1H), 2.76 – 2.64 (m, 1H), 2.66 – 2.54 (m, 1H), 1.81 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 169.3, 165.1, 154.3, 140.8, 134.7, 133.1, 132.9, 129.0, 127.1, 123.9, 115.6, 103.3, 92.2, 56.9, 55.8, 53.6, 53.5, 51.8, 49.8, 36.8, 29.0, 21.9.

IR: 3685 (w), 3662 (w), 2987 (s), 2972 (s), 2901 (s), 1408 (w), 1394 (m), 1251 (w), 1228 (w), 1076 (s), 1066 (s), 1057 (s), 890 (w), 868 (w).

HRMS (ESI): calcd for $C_{22}H_{24}IN_2O_6^+$ $[M+H]^+$ 539.0674; found 539.0681.



92 106

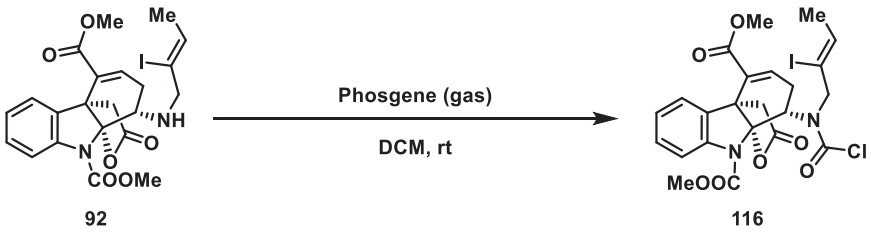
Dimethyl (4bS,8S,8aR)-8-(((Z)-2-iodobut-2-en-1-yl)(methyl)amino)-11-oxo-7,8-dihydro-9H-8a,4b-(epoxyethano)carbazole-5,9-dicarboxylate (106): To a solution of **92** (125 mg, 0.232 mmol) in MeCN (3 mL) were added paraformaldehyde (69.6 mg, 2.32 mmol), $NaBH_3CN$ (29.2 mg, 0.464 mmol) and AcOH (17.3 µL, 0.302 mmol) under argon. The resulting solution was stirred at room temperature for 24 hours and was quenched with $NaHCO_3$ (aq.). The aqueous phase was extracted with EtOAc, washed with brine and dried over Na_2SO_4. The solvents were removed *in vacuo* and the residue was purified by preparative TLC (petroleum ether/EtOAc, 8:2) to yield a colorless oil (119.2 mg, 93% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, *J* = 8.3 Hz, 1H), 7.57 (d, *J* = 7.7 Hz, 1H), 7.26 (m, 1H), 7.05 – 6.99 (m, 2H), 5.81 (q, *J* = 6.3 Hz, 1H), 4.61 (s, 1H), 3.93 (s, 3H), 3.79 (s, 3H), 3.74 (d, *J* = 18.0 Hz, 1H), 3.53 – 3.36 (m, 3H), 2.64 – 2.55 (m, 2H), 2.35 (s, 3H), 1.77 (d, *J* = 6.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.9, 165.5, 153.7, 140.7, 136.7, 133.8, 133.0, 132.1, 129.7, 125.6, 124.4, 116.3, 107.9, 106.2, 68.0, 57.5, 53.4, 52.2, 42.0, 40.5, 25.4, 21.8. One quaternary carbon on the indol is missing due to low amount of product.

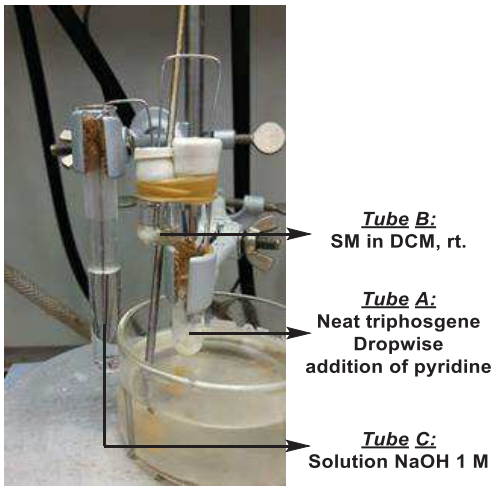
IR: 3683 (w), 3660 (w), 2987 (m), 2901 (w), 1790 (m), 1718 (s), 1480 (w), 1439 (w), 1395 (w), 1366 (w), 1292 (w), 1255 (w), 1226 (w), 1110 (w), 1066 (m), 893 (w), 759 (w).

HRMS (ESI): calcd for $C_{23}H_{26}IN_2O_6^+$ $[M+H]^+$ 553.0830; found 553.0832

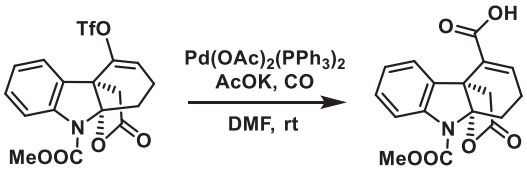


92 116

Dimethyl (4bS,8S,8aR)-8-((chlorocarbonyl)((Z)-2-iodobut-2-en-1-yl)amino)-11-oxo-7,8-dihydro-9H-8a,4b-(epoxyethano)carbazole-5,9-dicarboxylate (116): As depicted in the picture, tube A, containing neat triphosgene was connected *via* cannula to vial B containing a well-stirred solution of **92** (2 mg, 0.0037 mmol) in DCM (300 µL). Vial B was it-self connected to tube C containing an aqueous solution of NaOH 1 M in order to quench hydrogen chloride and excess of phosgene. Phosgene generation was initiated by the dropwise addition of pyridine into the tube A until full conversion of starting material 75 was observed. *It is noteworthy that generation of phosgene can be stopped immediately, at any time, by stopping the addition of pyridine to the tube A.* The solvent of tube B was removed *in vacuo* at 25 °C and the residue was used directly without further purification.



*After full conversion of SM, **tube A** was connected to **tube C** via cannula and a solution of NaOH was added dropwise to **tube A** in order to quench the excess of triphosgene.*



83 118

(4bS,8aS)-9-(methoxycarbonyl)-11-oxo-7,8-dihydro-9H-8a,4b-(epoxyethano)carbazole-5-carboxylic acid (118): To a solution of **83** (1.3 g, 2.99 mmol) in DMF (19.5 mL) was added potassium acetate (1.18 g, 11.99 mmol) and bis(triphenylphosphine)palladium(II) diacetate (156.6 mg, 0.209 mmol). The mixture was purged with carbon monoxide for 5 min and stirred under a CO balloon (1 atm) at 25 °C for 6 h. The reaction was diluted with water and acidified with 1 M HCl and extracted with EtOAc. The aqueous phase was extracted with EtOAc and the combined organic layers were washed with brine and dried over Na_2SO_4.The solvents were removed *in vacuo* and the residue was purified by flash column chromatography (petroleum ether/EtOAc, 6:4; 1% AcOH) to yield a white solid (888.7 mg, 90%).

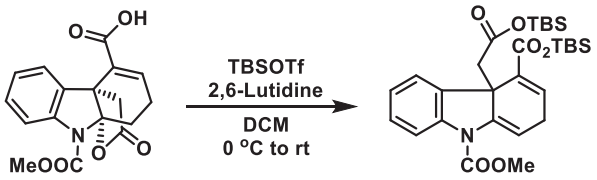
^{1}H NMR (400 MHz, THF-d_8): δ 9.57 (s, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.09 (t, *J* = 8.1 Hz, 1H), 6.97 (d, *J* = 6.2 Hz, 1H), 6.86 (t, *J* = 7.8 Hz, 1H), 3.75 (s, 3H), 3.38 (m, 2H), 3.04 (d, *J* = 18.0 Hz, 1H), 2.15 (m, 2H), 1.78 (t, *J* = 10.6 Hz, 1H).

^{13}C NMR (400 MHz, THF-d_8): δ 172.9, 167.4, 154.0, 142.3, 141.0, 134.2, 132.5, 130.2, 127.1, 124.7, 116.8, 104.7, 54.1, 53.4, 42.1, 28.7, 23.8.

IR (neat): 2979 (m), 1778 (m), 1715 (S), 1677 (m), 1639 (m), 1594 (w), 1481 (m), 1443 (m), 1367 (S), 1201 (S), 1089 (m), 917 (S), 1012 (m), 1113 (m), 1286 (m), 2160 (m) cm^{-1}.

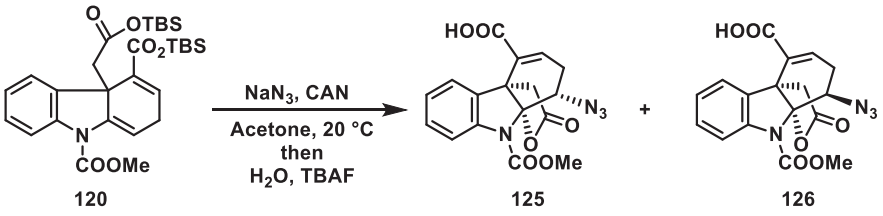
HRMS (ESI/QTOF): Calcd for $C_{17}H_{14}NO_6^-$ m/z: $[M + H-1]^-$ 328.0827; Found 328.0828.

MP: 218 °C



118 120

4-(tert-butyldimethylsilyl) 9-methyl 4a-(2-((tert-butyldimethylsilyl)oxy)-2-oxoethyl)-2,4a-dihydro-9H-carbazole-4,9-dicarboxylate (120): To a suspension of **118** (565 mg, 1.72 mmol) in DCM (16.6 mL) was added 2,6-lutidine (4.0 mL, 34.3 mmol) followed by addition of TBSOTf (3.9 mL, 17.2 mmol) at 0 °C. The resulting solution was gradually warmed to room temperature and stirred for 48 hours. After the reaction was completed the solution was cooled to 0 °C and quenched with Na_2CO_3 (aq.). The aqueous phase was extracted with Et_2O. The combined organic layers were washed with brine and dried over Na_2SO_4. The solvents were removed *in vacuo* and the oily residue was dried under vacuum to remove the 2,6-lutidine. The resulting oil was used directly without any further purification.



120 125 126

75% over 2 steps
125/126, ~2.5:1 d.r.

(4bS,8aR)-8-azido-9-(methoxycarbonyl)-11-oxo-7,8-dihydro-9H-8a,4b-(epoxyethano)carbazole-5-carboxylic acid (125): To a solution of the crude **120** in acetone (16.6 mL) was added NaN_3 (167.5 mg, 2.57 mmol) under argon. At rt, a solution of CAN (2.82 g, 5.15 mmol) in acetone (61.5 mL) was added dropwise using syringe pump (3.0 mL/min). The resulting yellow solution was stirred at rt and then was quenched with 80 mL of H_2O followed by the addition of TBAF (3.5 mL, 3.43 mmol). The obtained mixture was vigorously stirred during 1 hour at rt. After removal of most of the acetone *in vacuo*, the aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4. The solvents were removed *in vacuo* and the residue was then purified by flash column chromatography (petroleum ether/EtOAc, 6:4 + 2% AcOH) to yield a withe foam (477.7 mg, 75% over 2 steps, 2.5:1 d.r in favor of the *cis*-isomer).

***Cis*-isomer 125 (A) mixed with *trans*-isomer 126 (B):**

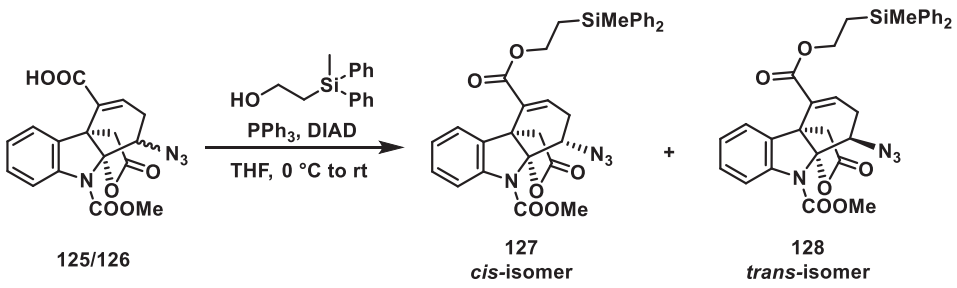
^{1}H NMR (400 MHz, THF-d8): δ 7.84 (d, *J* = 8.2 Hz, 1H, **B**), 7.79 (d, *J* = 8.3 Hz, 1H, **A**), 7.71 (d, *J* = 7.6 Hz, 1H, **A**), 7.55 (d, *J* = 7.6 Hz, 1H, **B**), 7.23 (t, *J* = 8.1 Hz, 1H, **A**), 7.18 (m, 1H, **B**), 7.01 (t, *J* = 7.5 Hz, 1H, **A**), 6.95 – 6.87 (m, 3H, **2B+1A**), 5.68 (t, *J* = 3.1 Hz, 1H, **A**), 5.03 (t, *J* = 3.0 Hz. 1H, **B**), 3.91 (s, 3H, **A**), 3.89 (s, 3H, **B**), 3.46 (d, *J* = 18.2 Hz, 1H, **A**), 3.44 (d, *J* = 18.6 Hz, 1H, **B**), 3.26 (d, *J* = 18.2 Hz, 1H, **A**), 2.95 (d, *J* = 18.6 Hz, 1H, **B**), 2.69-2.56 (m, 4H, **2A+2B**).

^{13}C NMR (101 MHz, THF): δ 173.6 (**B**), 172.9 (**A**), 168.0 (**B**), 166.8 (**A**), 154.0 (**A**), 153.4 (**B**), 142.3 (**B**), 141.7 (**A**), 138.5 (**B**), 135.5 (**A**), 134.4 (**B**), 133.1 (**B**), 132.9 (**A**), 130.8 (**B**), 130.4 (**A**), 129.4 (**A**), 126.9 (**A**), 125.2 (**A**), 125.2 (**B**), 124.1 (**B**), **117**.0 (**A**), 115.2 (**B**), 103.9 (**B**), 103.8 (**A**), 59.7 (**A**), 56.8 (**B**), 54.2 (**A**), 53.8 (**A**), 53.4 (**B**), 52.2 (**B**), 43.5 (**B**), 42.6 (**A**), 28.9 (**A**), 27.5 (**B**).

IR (neat): 3186 (w), 2110 (S), 1788 (S), 1723 (m), 1709 (S), 1691 (S), 1532 (m), 1481 (S), 1445 (S), 1356 (S), 1290 (m), 1230 (S), 1199 (m), 1091 (m), 1115 (m), 1004 (m), 1026 (m), 762 (S), 752 (S) cm^{-1}.

HRMS (ESI/QTOF): Calcd for $C_{17}H_{14}N_4NaO_6^+$ m/z: [M + Na]+ 393.0806; Found 393.0817.

MP: 212 °C with a 2.5:1 d.r.



125/126

127
cis-isomer

128
trans-isomer

9-methyl 5-(2-(methyldiphenylsilyl)ethyl) (4bS,8S,8aR)-8-azido-11-oxo-7,8-dihydro-9H-8a,4b-(epoxyethano)carbazole-5,9-dicarboxylate (127): To a solution of alcohol (1.02 g, 4.21 mmol) and PPh_3 (552.4 mg, 2.11 mmol) in dry THF (10.5 mL) was added dropwise DIAD (518 µL, 2.63 mmol) at 0 °C and under vigorous stirring. After being stirred 20 minutes, the acid **125/126** (390 mg, 1.05 mmol) was added in one portion. The cooling bath was removed, and the reaction was warmed to room temperature and stirred for 2 hours. The reaction was then dilute with water, acidified using a 10% $KHSO_4$ solution and extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. The solvents were removed *in vacuo* and the residue was purified by flash column chromatography (DCM/EtOAc, 100:0 to 97:3) to yield a white solid (607.4 mg, 97%).

The two isomers were then separated by flash column chromatography (PE/EtOAc, 8:2) allowing the isolation of *trans*-isomer **128** first, followed by the *cis*-isomer **127**.

***Cis*-isomer 127:**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.3 Hz, 1H), 7.60 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.51-7.47 (m, 4H), 7.42-7.28 (m, 7H), 7.05 (td, *J* = 7.6, 1.1 Hz, 1H), 6.51 (t, *J* = 4.4 Hz, 1H), 5.62 (t, *J* = 3.1 Hz, 1H), 4.37 – 4.28 (m, 2H), 3.96 (s, 3H), 3.53 (d, *J* = 18.3 Hz, 1H), 3.29 (d, *J* = 18.3 Hz, 1H), 2.55 (dd, *J* = 4.5, 3.0 Hz, 2H), 1.61 – 1.56 (m, 2H), 0.59 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.3, 163.7, 152.4, 139.2, 134.9 (**2C**), 133.5 (**4C**), 133.1, 132.1, 130.1, 128.9, 128.7(**2C**), 127.2 (**4C**), 124.9, 123.9, 115.3, 102.0, 62.2, 57.2, 52.8, 52.2, 40.8, 27.5, 14.3, -5.1.

IR (neat): 3066 (*w)*, 2162 (*m)*, 2117 (*S)*, 1797 (*S)*, 1725 (*S)*, 1480 (*S)*, 1367 (*S)*, 1249 (*S)*, 1112 (*S)*, 1443 (*m)*, 723 (*S)* cm^{-1}.

HRMS (ESI/QTOF): m/z: $[M + Na]^+$ Calcd for $C_{32}H_{30}N_4NaO_6Si^+$ 617.1827; Found 617.1834.

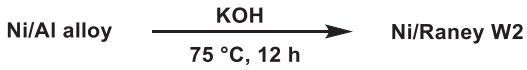
***Trans*-isomer 128:**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.2 Hz, 1H), 7.47-7.44 (m, 4H), 7.34 – 7.25 (m, 7H), 7.16 (td, *J* = 8.2, 1.1 Hz, 1H), 6.89 (td, *J* = 7.7, 1.1 Hz, 1H), 6.63 (dd, *J* = 6.4, 2.2 Hz, 1H), 4.9 (s, 1H), 4.46 – 4.26 (m, 2H), 3.87 (s, 3H), 3.42 (d, *J* = 18.9 Hz, 1H), 2.84 (d, *J* = 18.9 Hz, 1H), 2.50 (ddd, *J* = 19.5, 4.2, 2.3 Hz, 1H), 2.37 (ddd, *J* = 19.5, 6.3, 2.3 Hz,1H), 1.61-1.56 (m, 2H), 0.56 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.6, 165.6, 152.7, 140.5, 137.2, 135.9, 135.8, 134.5 (4C), 131.1, 129.7 (2C), 129.3, 129.1, 128.2 (4C), 124.1, 123.9, 114.5, 103.0, 63.5, 55.2, 53.5, 51.2, 42.9, 26.8, 15.3, -4.1.

IR (neat): 2110 (w), 1804 (m), 1711 (m), 1480 (w), 1441 (w), 1373 (w), 1300 (w), 1250 (m), 1111 (w), 1066 (m), 909 (m), 724 (S), 700 (m), 2961 (w) cm^{-1}.

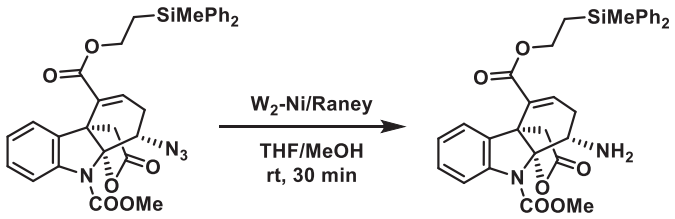
HRMS (ESI/QTOF): m/z: $[M + Na]^+$ Calcd for $C_{32}H_{30}N_4NaO_6Si^+$ 617.1827; Found 617.1824.



Preparation of Raney-Ni (W2):

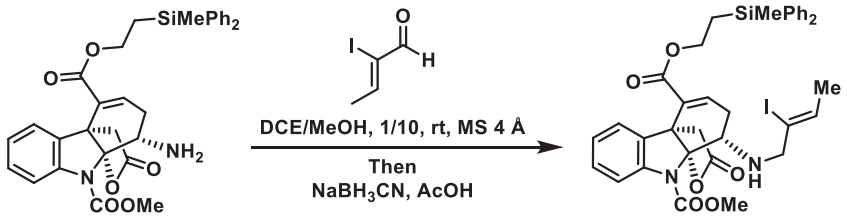
Nickel-aluminum alloy (3.75 g) was added in small portions to a solution of sodium hydroxide (4.75 g) in water (18 mL) during a period of 30 min. The temperature was maintained at 0 °C by controlling the rate of addition of the alloy. When all the alloy has been added, the suspension was warmed to RT with gentle stirring. After a period of digestion (75 °C for 12 h), the nickel was washed with distilled water by decantation. The catalyst was transferred to 625 mg of sodium hydroxide in 6 mL of water after its third washing. The catalyst was washed again with distilled water by decantation until the washings were neutral. The water washing was then repeated 10 times. The catalyst was then washed three times with 2.5 mL of 95% ethanol, and three times with absolute ethanol. The catalyst as to be stored in absolute ethanol at -30°C in a dark container.

NB: On this specific substrate, it appeared that a C-N cleavage was observed if the Ni/Raney was not freshly prepared. The Raney-Ni(W2) was thus freshly prepared before every reduction of the azide.



127 130

9-methyl 5-(2-(methyldiphenylsilyl)ethyl) (4bS,8S,8aR)-8-amino-11-oxo-7,8-dihydro-9H-8a,4b-(epoxyethano)carbazole-5,9-dicarboxylate (130): A portion of the freshly prepared Raney-Ni (W2) in EtOH was introduce in a *vial*. After sedimentation of the nickel, supernatant EtOH was carefully removed and the residue nickel was washed with MeOH three time. Finally, the obtained Raney-Ni in MeOH (1.6 mL) was then transferred to a solution of the azide **127** (200 mg, 0.336 mmol) in THF (1.6 mL). After stirring at rt under an atmosphere of H_2 (1 atm, H_2 ballon) for 30 min, the reaction mixture was filtered through Celite using EtOAc. The solvents were removed *in vacuo* and the residue was used directly without any further purification.



9-methyl 5-(2-(methyldiphenylsilyl)ethyl) (4bS,8S,8aR)-8-(((Z)-2-iodobut-2-en-1-yl)amino)-11-oxo-7,8-dihydro-9H-8a,4b-(epoxyethano)carbazole-5,9-dicarboxylate (131): To a solution of the crude primary amine **130** in freshly distilled DCE (0.3 mL) was added at rt a solution of the aldehyde (263.6 mg, 1.35 mmol) in freshly distilled MeOH (3 mL). The reaction mixture was stirred at room temperature for 2 hours under 3Å MS. After completion of the reaction monitored by TLC, the reaction mixture was cooled to 0 °C and a solution of $NaBH_3CN$ (126.8 mg, 2.02 mmol) in MeOH (1 mL) was added followed by the dropwise addition of AcOH (87 µL, 1.51 mmol). The orange/yellow solution was warmed to room temperature, stirred for 2 hours and then was quenched with $NaHCO_3$ (aq.). The aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine and were dried over Na_2SO_4. The solvents were removed *in vacuo* and the residue was used directly without any further purification.

9-methyl 5-(2-(methyldiphenylsilyl)ethyl) (4bS,8S,8aR)-8-(((Z)-2-iodobut-2-en-1-yl)(methyl)amino)-11-oxo-7,8-dihydro-9H-8a,4b-(epoxyethano)carbazole-5,9-dicarboxylate (132): To a solution of crude secondary amine **131** in MeCN (2.8 mL) was added paraformaldehyde (101 mg, 3.36 mmol). After cooling the mixture at 0 °C, AcOH (29 µL, 0.50 mmol) was added followed by the addition of $NaBH_3CN$ (42.3 mg, 0.67 mmol mmol) in MeOH (0.7 mL). The mixture was stirring during 6 hours after what another amount of AcOH was added to hold the pH ~ 5. After full conversion of the starting material, the reaction was quenched with $NaHCO_3$ (aq.). The aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine and were dried over Na_2SO_4. The solvents were removed *in vacuo* and the residue was purified by flash column chromatography (PE/EtOAc, 9:1) to yield a yellow oil (115.3 mg, 45%).

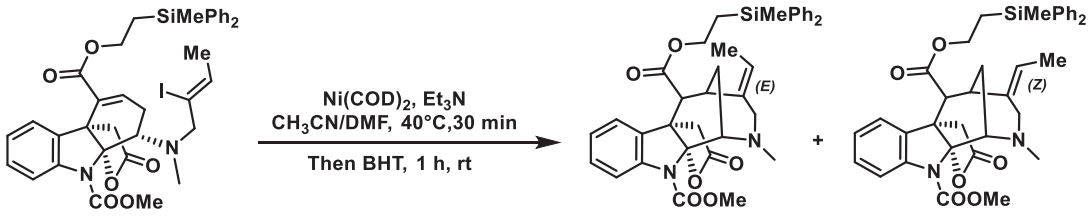
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, *J* = 8.3 Hz, 1H), 7.50 (d, *J* = 8.3 Hz, 1H), 7.44 – 7.39 (m, 4H), 7.33 – 7.23 (m, 6H), 7.16 (td, *J* = 7.6, 1.1 Hz, 1H), 6.93 (td, *J* = 7.6, 1.1 Hz, 1H), 6.47 (t, *J* = 4.5 Hz, 1H), 5.73 (q, *J* = 6.3 Hz,

1H), 4.47 (s, 1H), 4.26 (t, *J* = 8.1 Hz, 2H), 3.84 (s, 3H), 3.63 (d, *J* = 17.9 Hz, 1H), 3.41 – 3.23 (m, 3H), 2.37 (t, *J* = 4.4 Hz, 2H), 2.24 (s, 3H), 1.69 (d, *J* = 6.3 Hz, 3H), 1.54 – 1.48 (m, 2H), 0.51 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.9, 165.0, 153.7, 140.7, 136.2, 136.1, 136.0, 134.5 (2C), 134.5 (2C), 133.7, 132.9, 132.2, 129.6 (2C), 129.6, 128.2 (2C), 128.1 (2C), 125.7, 124.3, 116.2, 108.0, 106.2, 68.0, 62.9, 57.5, 53.5, 53.4, 42.0, 40.5, 25.0, 21.8, 15.3, -4.2.

IR (neat): 2954 (w), 2156 (m), 1792 (s), 1711 (s), 1479 (m), 1441 (m), 1363 (m), 1294 (m), 1252 (s), 1109 (s), 754 (s) cm^{-1}.

HRMS (ESI/QTOF): m/z: $[M + H]^+$ Calcd for $C_{37}H_{40}IN_2O_6Si^+$ 763.1695; Found 763.1699.



132 133 134

$Ni(COD)_2$ was weighed in the glovebox.

11-methyl 6-(2-(methyldiphenylsilyl)ethyl) (1S,6S,6aR,11aR,E)-4-ethylidene-2-methyl-13-oxo-1,2,3,4,5,6-hexahydro-11H-11a,6a-(epoxyethano)-1,5-methanoazocino[3,4-b]indole-6,11-dicarboxylate (133): To a solution of tertiary amine **132** (50 mg, 0.066 mmol) and $Ni(COD)_2$ (95.2 mg, 0.33 mmol) in a mixture of dry and degassed MeCN (2.25 mL) and dry and degassed DMF (4.37 mL) was added freshly distilled Et_3N (90 µL, 0.66 mmol). After being stirred during 30 min at 40 °C, BHT (72.2 mg, 0.33 mmol) was added in one portion at room temperature and the resulting mixture was stirred at the same temperature for 1 hour. The reaction was then dilute with water and basified using $NaHCO_3$ (aq). The aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine several time and dried over Na_2SO_4. The solvents were removed *in vacuo* and the residue was purified by flash column chromatography (PE/EtOAc, 8:2) to yield a clear foam of the two isomers (27 mg, 62%), d.r = 3:1 in favor of the (*E*)-isomer.

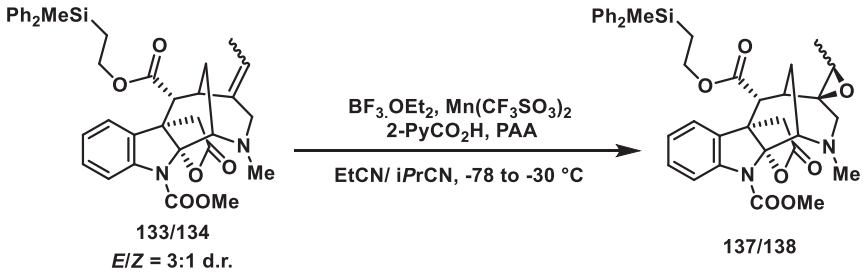
<u>Isomer (*E*)-133:</u>

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, *J* = 8.3 Hz, 1H), 7.49 – 7.28 (m, 11H), 7.10 (dd, *J* = 7.5, 1.4 Hz, 1H), 7.04 (td, *J* = 7.5, 1.0 Hz, 1H), 5.49 (q, *J* = 7.3 Hz, 1H), 4.39 (s, 1H), 4.32 (td, *J* = 10.7, 6.5 Hz, 1H), 4.07 (td, *J* = 10.7, 5.2 Hz, 1H), 3.97 (s, 3H), 3.66 (d, *J* = 18.1 Hz, 1H), 3.32 (d, *J* = 14.4 Hz, 1H), 3.15 (d, *J* = 14.4 Hz, 1H), 3.14 (d, *J* = 18.1 Hz, 1H), 3.06 (s, 1H), 2.45 (s, 3H), 2.23 (d, *J* = 4.2 Hz, 1H), 2.20 (m, 1H), 1.64 (d, *J* = 14.2 Hz, 1H), 1.59 – 1.52 (m, 1H), 1.48 – 1.41 (m, 1H), 1.40 (dd, *J* = 7.3, 2.5 Hz, 3H), 0.54 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 173.9, 171.2, 154.1, 140.4, 135.9, 135.9, 135.7, 134.4 (2C), 134.4 (2C), 133.5, 129.7, 129.6, 129.3, 128.2 (2C), 128.1 (2C), 124.5, 123.3, 122.7, 116.7, 103.8, 62.8, 55.8, 55.4, 53.7, 53.4, 52.4, 45.8, 39.1, 29.4, 26.3, 15.1, 13.4, -4.3.

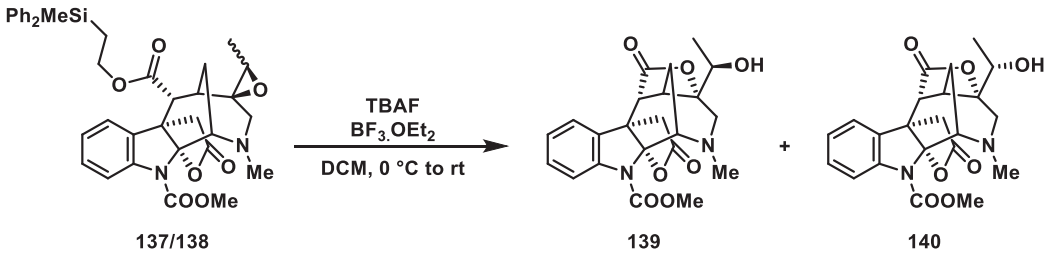
IR (neat): 2958 (m), 2360 (w), 1788 (s), 1726 (s), 1709 (s), 1479 (s), 1441 (m), 1369 (s), 1298 (m), 1248 (s), 1228 (s), 1111 (s), 756 (s) cm^{-1}

HRMS (ESI/QTOF): m/z: $[M + H]^+$ Calcd for $C_{37}H_{41}N_2O_6Si^+$ 637.2728; Found 637.2728.



$Mn(CF_3SO_3)_2$ was weighed in the glovebox.

11'-methyl 6'-(2-(methyldiphenylsilyl)ethyl) (1'S,2R,6'S,6a'R,11a'R)-2',3-dimethyl-13'-oxo-2',3',5',6'-tetrahydro-1'H,11'H-spiro[oxirane-2,4'-[11a,6a](epoxyethano)[1,5]methanoazocino[3,4-b]indole]-6',11'-dicarboxylate (137/138): A solution of alkene **133/134** (6 mg, 9.4 µmol), $Mn(CF_3SO_3)_2$ (1.32 mg, 3.7 µmol) and 2-$PyCO_2H$ (2.27 mg ,18.5 µmol) in EtCN (150 µL) and *i*PrCN (150 µL) was stirred for 3 minutes at room temperature until disappearance of the suspension. The solution was then cooled to -78 °C for 2 minutes and $BF_3.OEt_2$ (5.8 µL ,47 µmol) was added dropwise. After 1 minute, the solution was warmed to room temperature for another 2 minutes and then cooled back to -78 °C. Peracetic acid (39% in acetic acid/ need titration) (32.5 µL, 0.188 mmol) was then added dropwise (1 drop/10 seconds) and the reaction mixture was warmed to -30 °C. After 30 minutes, the reaction mixture was cooled down to -78 °C and 1 mL of EtOAc was added dropwise. The mixture was then quickly poured into a stirring aqueous solution of saturated $NaHCO_3$ at room temperature. The aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine several time and dried over Na_2SO_4. The solvents were removed in vacuo and the residue was used directly without further purification.



137/138 139 140

Methyl (3S,5S,5aR,10bR)-3-((R)-1-hydroxyethyl)-14-methyl-1,12-dioxo-1,3,3a,4,5,10c-hexahydro-6H-5,3-(epiminomethano)-5a,10b-(epoxyethano)furo[3,4-c]carbazole-6-carboxylate (139): To a solution of crude epoxides **137/138** in DCM (90 µL) at 0 °C was added dropwise a solution of TBAF 1 M in THF (18.4 µL, 18.4 µmol). The reaction was warmed to room temperature and stirred for 30 minutes. After this time, the reaction mixture was cooled back to 0 °C and $BF_3.OEt_2$ (5.8 µL,47 µmol) was added dropwise. The reaction was then warmed to room temperature and stirring for 1 hour. After full conversion of the starting material, the reaction was quenched with $NaHCO_3$ (aq.). The aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine and were dried over Na_2SO_4. The solvents were removed *in vacuo* and the residue was purified by TLC preparative (PE/EtOAc, 3:7) to yield a clear foam (1.62 mg, 40% over 2 steps). The two diastereoisomers were separated during the purification, allowing the isolation of compound **139** first followed by the epimer **140**.

Epimer (*R*)-139, major product:

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (br, 1H), 7.3-7.25 (m, 2H), 7.13 (td, *J* = 7.4, 1.0 Hz, 1H),3.96-3.92 (m, 1H), 3.92 (s, 3H), 3.69 (q, *J* = 6.5 Hz, 1H), 3.27 (d, *J* = 11.7 Hz, 1H), 2.84 (m, 1H), 2.78 (d, *J* = 18.3 Hz, 1H), 2.68 (d, *J* = 13.3 Hz, 1H), 2.59 (d, *J* = 13.3 Hz, 1H), 2.56 (s, 3H), 1.76 (m,1H), 1.69 (d, *J* = 8.5 Hz, 1H), 1.53 (dd, *J* = 15.0, 4.3 Hz, 1H), 1.27 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 175.4, 173.7, 153.1, 140.4, 135.8, 129.7, 125.1, 123.0, 115.8, 104.3, 90.0, 68.7, 56.7, 54.6, 53.4, 50.6, 45.9, 41.1, 30.2, 29.9, 20.1, 17.5.

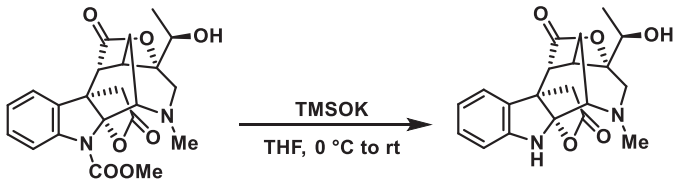
IR (neat): 2920 (s), 2852 (s), 2362 (s), 2187 (m), 1768 (s), 1720 (s), 1529 (m), 756 (s) cm^{-1}.

HRMS (ESI/QTOF): m/z: $[M + H]^+$ Calcd for $C_{22}H_{25}N_2O_7^+$ 429.1656; Found 429.1655.

Epimer (*S*)-140, minor product:

^{1}H NMR (600 MHz, Chloroform-*d*): δ 7.78 (d, *J* = 8.3 Hz, 1H), 7.68 (d, *J* = 7.7 Hz, 1H), 7.28 (m, 1H), 7.14 (td, *J* = 7.5, 1.1 Hz, 1H), 4.44 (q, *J* = 6.5 Hz, 1H), 4.22 (s, 1H), 3.94 (s, 3H), 3.52 (d, *J* = 9.2 Hz, 1H), 3.33 (d, *J* = 19.0 Hz, 1H), 2.88 (d, *J* = 19.0 Hz, 1H), 2.82 (d, *J* = 13.1 Hz, 1H), 2.71 (s, 3H), 2.63 (d, *J* = 13.1 Hz, 1H), 2.60 (s, 1H), 2.19 (dt, *J* = 14.5, 4.2 Hz, 1H), 2.13 (m, 1H), 1.40 (d, *J* = 6.5 Hz, 3H), 1.37 (m, 1H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 173.1, 169.9, 153.1, 139.2, 137.6, 129.5, 125.3, 123.8, 115.6, 105.4, 80.2, 67.8, 55.2, 53.4, 52.5, 50.8, 48.3, 44.7, 42.9, 35.6, 29.9, 22.6, 14.1.



139 **alstolactine A**

TMSOK was weighed in the glovebox.

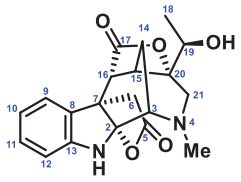
Alstolactine A: A solution of alcohol **139** (3 mg, 7.0 µmol) and TMSOK (9.0 mg, 70 µmol) was stirred in THF (70 µL) for 4 hours at room temperature. After this time, a 2 M HCl solution was added dropwise and the resulting mixture was stirred for 2 hours at room temperature. The reaction mixture was then cooled to 0 °C and quenched with a dropwise addition of $NaHCO_3$ (aq.). The aqueous phase was extracted with EtOAc and the combined organic layers were washed with brine and dried over Na_2SO_4. The solvents were removed *in vacuo* and the residue was purified by TLC preparative (DCM/MeOH, 97:3) to yield **alstolactine A** as a clear oil (1.7 mg, 66%) as well as starting material recovered (0.65 mg, 1.52 µmol).

Yield based on starting material recovered: 84%.

^{1}H NMR (600 MHz, Methanol-d_4): δ 7.20 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.07 (td, *J* = 7.7, 1.2 Hz, 1H), 6.79 (td, *J* = 7.5, 1.0 Hz, 1H), 6.61 (d, *J* = 7.8 Hz, 1H), 3.69 (q, *J* = 6.5 Hz, 1H), 3.53 (d, *J* = 17.8 Hz, 1H), 3.17 (d, *J* = 11.2 Hz, 1H), 2.99 (d, *J* = 5.4 Hz, 1H), 2.79 (m, 1H), 2.78 (d, *J* = 17.8 Hz, 1H), 2.77 (d, *J* = 13.3 Hz, 1H), 2.55 (d, *J* = 13.3 Hz, 1H), 2.44 (s, 3H), 1.90 (ddd, *J* = 14.7, 5.6, 2.3 Hz, 1H), 1.85 (ddd, *J* = 14.7, 4.3, 1.5 Hz, 1H), 1.19 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (151 MHz, MeOD): δ 178.4, 177.3, 148.5, 136.7, 130.3, 124.2, 121.2, 110.5, 109.2, 92.1, 69.2, 59.7, 55.7, 51.4, 49.1, 46.2, 43.8, 31.2, 21.6, 17.3.

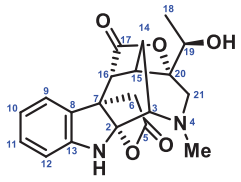
Table 46: Comparison of 1H NMR spectroscopic data of natural and synthetic alstolactine A



alstolactine A

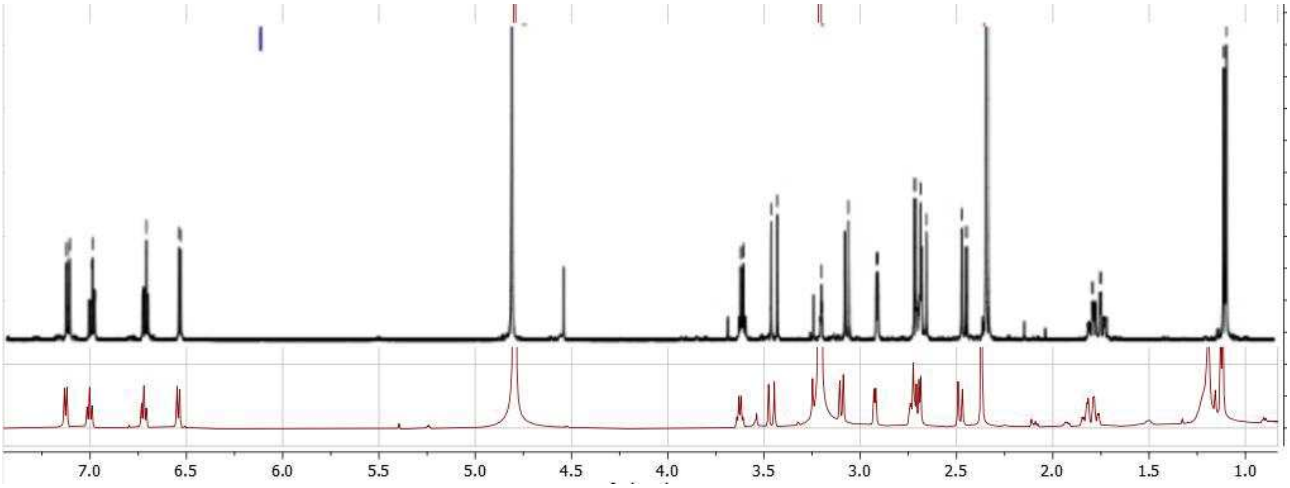
Position	Natural δ ^{1}H [ppm, mult, *J* (Hz)] 600 MHz	Synthetic δ ^{1}H [ppm, mult, *J* (Hz)] 600 MHz	Deviation (natural-synthetic) Δδ (ppm)
3	3.00 (d, 5.4)	2.99 (d, 5.4)	0.01
6	3.55 (d, 18.1)	3.53 (d, 17.8)	0.02
-	2.80 (d, 18.1)	2.78 (d, 17.8)	0.02
9	7.21 (d, 7.9)	7.20 (dd, 7.5, 1.2)	0.01
10	6.80 (t, 7.9)	6.79 (td, 7.5, 1.0)	0.01
11	7.08 (t, 7.9)	7.07 (td, 7.7, 1.2)	0.01
12	6.63 (d, 7.9)	6.61 (d, 7.8)	0.02
14	1.89 (dd, 14.7, 5.4)	1.90 (ddd, 14.7, 5.6, 2.3)	-0.01
-	1.85 (dd, 14.7, 4.5)	1.85 (ddd, 14.7, 4.3, 1.5)	-
15	2.79 (m)	2.79 (m)	-
16	3.17 (d, 11.3)	3.17 (d, 11.2)	-
18	1.21 (d, 6.4)	1.19 (d, 6.5)	0.02
19	3.71 (q, 6.4)	3.69 (q, 6.5)	0.02
21β	2.77 (d, 13.6)	2.77 (d, 13.3)	-
21α	2.56 (d, 13.6)	2.55 (d, 13.3)	0.01
NMe	2.44 (s)	2.44 (s)	-

Table 47: Comparison of 13C NMR spectroscopic data of natural and synthetic alstolactine A

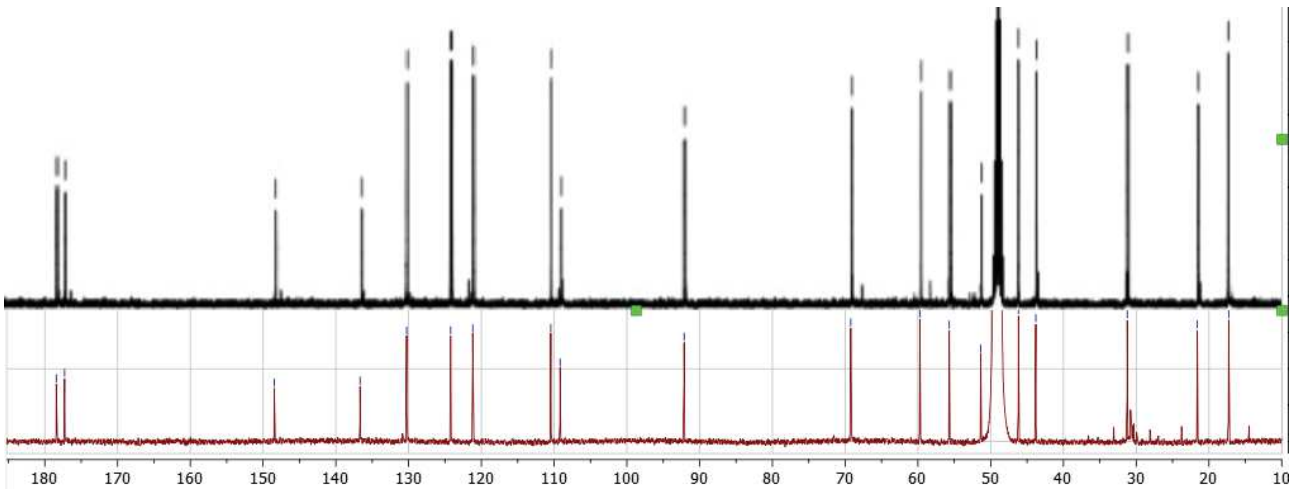


alstolactine A

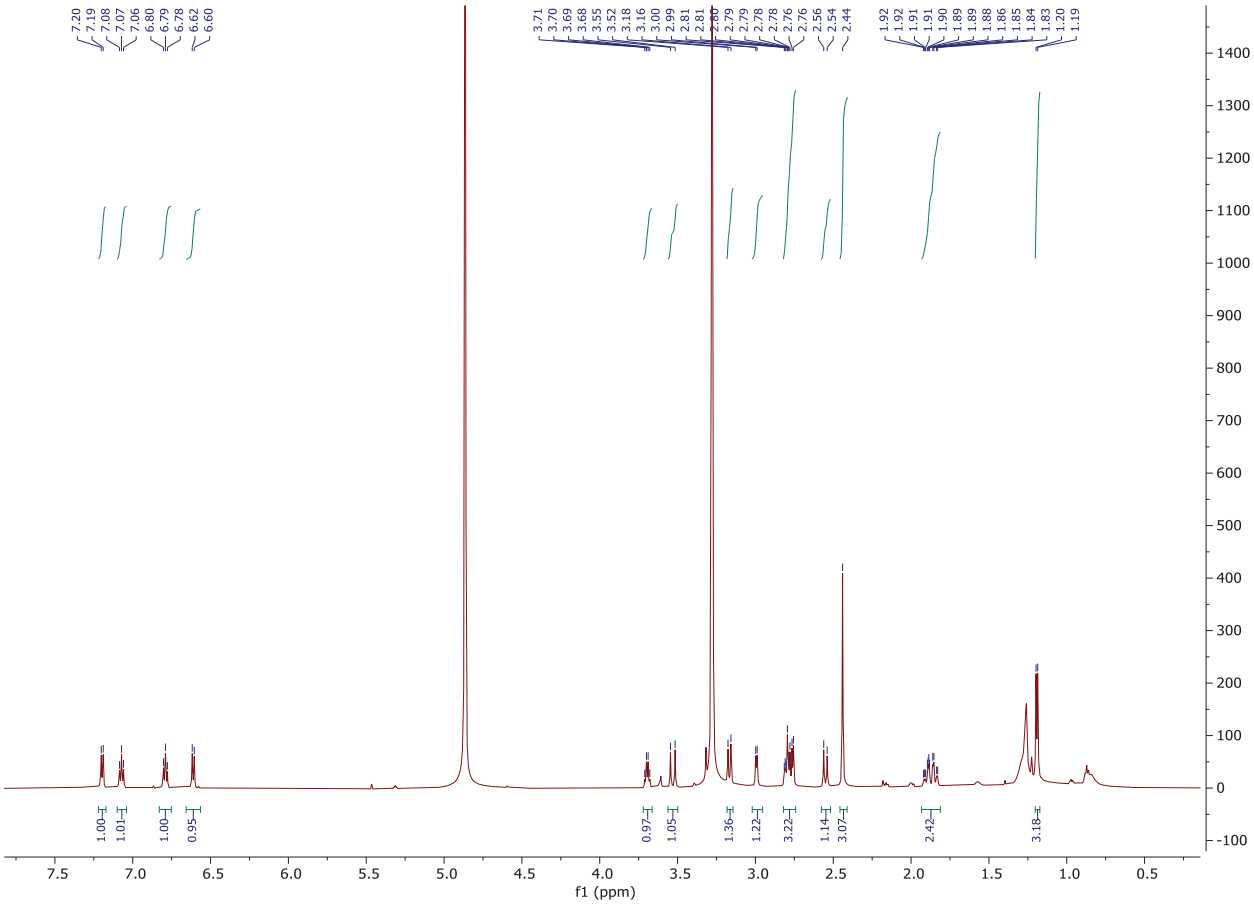
Position	Natural δ ^{13}C [ppm] 100 MHz	Synthetic δ ^{13}C [ppm] 151 MHz	Deviation (natural-synthetic) Δδ (ppm)
2	109.1	109.2	-0.1
3	59.6	59.7	-0.1
5	177.2	177.3	-0.1
6	43.8	43.8	-
7	51.3	51.4	-0.1
8	136.6	136.7	-0.1
9	124.2	124.2	-
10	121.2	121.2	-
11	130.2	130.3	-0.1
12	110.5	110.5	-
13	148.4	148.5	-0.1
14	21.6	21.6	-
15	31.2	31.2	-
16	49.1	49.1	-
17	178.4	178.4	-
18	17.3	17.3	-
19	69.2	69.2	-
20	92.1	92.1	-
21	55.6	55.7	-0.1
N-Me	46.2	46.2	-



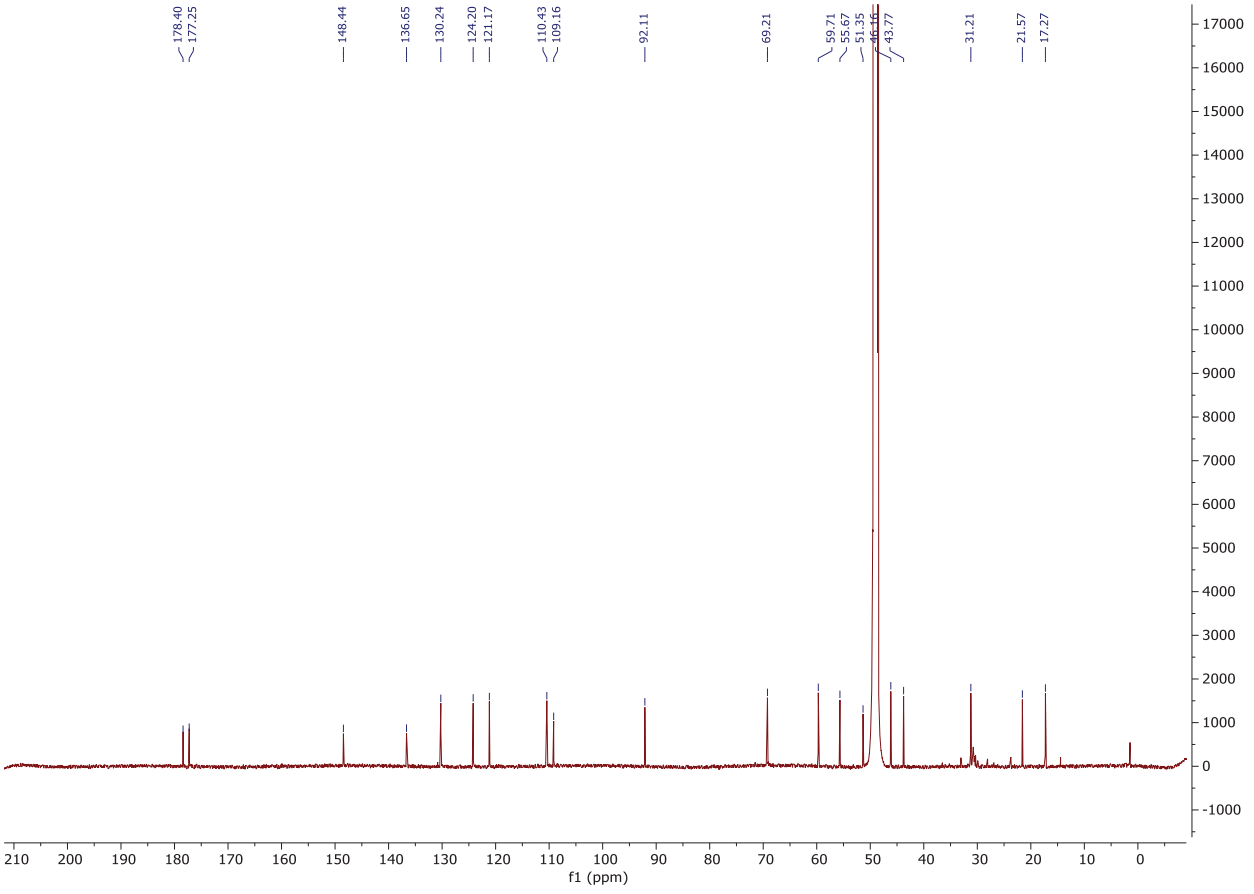
Scheme 160: Alstolactine A comparison spectra ^{1}H NMR. Top (black): natural, Bottom (red): synthetic



Scheme 161: Alstolactine A comparison spectra ^{13}C NMR. Top (black): natural, Bottom (red): synth



Scheme 162: Alstolactine A ^{1}H NMR spectra.



Scheme 163: Alstolactine A ^{13}C NMR spectra.

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Profile

- ✓ Solid background in synthetic organic chemistry
- ✓ Strong problem-solving and organizational skills
- ✓ Excellent laboratory ability: from 1 mg to 100 g scale
- ✓ Experienced in structural characterization
- ✓ Dedicated and highly motivated

Education

- ***2015-2019*** – PhD in Total Synthesis of Natural Products, Prof. Jieping Zhu lab, EPFL, Switzerland.
- ***2013-2015*** – Masters degree in Chemistry with honors. Major of promotion. Paris Sud University.
- ***2012-2013*** – Professional degree in Organic and bioorganic chemistry. IUT Orsay; Paris Sud University.
- ***2010-2012*** – Technical degree in general chemistry. IUT Castres; Paul Sabatier University.

Research Experiences

- ***PhD (4 years), EPFL, Prof. Jieping Zhu Group*** – Total synthesis of complex indole natural products from the Akuammiline family: Alstolactine A, B, C & Scholarisine K, L, M.
  - Working independently on a 23 steps sequence for the construction of highly hindered/cage-like and functionalized natural products.
  - Development and optimization of challenging reactions.

- ***Internship 2nd Master project (6 months), ICSN-CNRS, Robert Dodd Group*** – PIFA-mediated regioselective ethoxyiodination of enamides with potassium iodide.
  - Synthesis of starting materials, optimization of the reaction and scope exploration.
  - Led to a scientific publication, 1st author, *Org. Biomol. Chem*. **2016**, *14*, 8448–8451 and to a poster presentation at the ICSN symposium.

- ***Internship 1st Master project (5 months),*** **Toronto University, Prof. Mark Lautens Group** – Enantioselective Rhodium(I)-Catalyzed Domino Double Intramolecular Cyclization.
  - Convergent and linear multi-steps synthesis of desired intermediates (6 to 8 steps).
  - Optimization: Methodology using rhodium to catalyze indole or benzofuran polycyclic scaffolds containing one stereogenic center.

- ***Apprenticeship (1 year), Sanofi, Department of Isotope Chemistry and Metabolites Synthesis*** – Biodistribution of proteins.
  - Synthesis of fluorescent probes (cyanine family) with high level of polarity and unsaturation.
  - Bioconjugation of mAb (monoclonal antibody) with small molecules.

◆ ***Internship Technical degree (3 months),*** **Helsinki University, Prof. Kristiina Wähälä** – Total synthesis of plant and mammalian lignans structures.

- Synthesis of Enterolactone & Matairesinol (9 steps each).

Management

◆ ***During the PhD:***

- Mentoring of a full-time master student during 5 months.
- Teaching assistant for practical organic chemistry courses (6-8 students, 1 day per week for 5 semesters).
- In charge of the total synthesis exercices for Masters degree.
- Responsible for the relocation of our research group (19 members) into new laboratories (planification and management).

Tasks in the Laboratory

◆ ***During the PhD:***

- Responsible for the Supercritical Fluid Chromatography (SFC): Training of new users, apparatus maintenance and replacement of defective parts.
- In charge of the glassware & equipment stocks: Providing the necessary for each collaborators, ordering missing equipment and sending broken apparatus to reparation.

Languages

- **English:** Professional working proficiency.
- **Spanich**: Basic knowledge.
- **French:** Mother tongue.

References

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