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Entwicklung stereoselektiver Synthesen von naturstoffinspirierten Substanzbibliotheken durch Lewissäure und –basenkatalyse.

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Development of Stereoselective Routes to Natural Product Inspired Compound Collections *via* Lewis Acid and -Base Catalysis

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By

Adithi Danda

From Hyderabad, India

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Declaration/Erklärung

The work described in this Dissertation was performed from February 2011 to October 2015 at the Max Plank Institute of Molecular Physiology Dortmund under the guidance of Prof. Dr. Herbert Waldmann

I hereby declare that I performed the work independently and did not use any other but the indicated aids.

Die vorliegende Arbeit wurde in der Zeit von February 2011 bis October 2015 am Max-Plank-Institut für Molekulare Physiologie Dortmund unter der Anleitung von Prof. Dr. Herbert Waldmann durchgeführt.

Hiermit versichere ich an Eides statt, dass ich die vorliegende Arbeit selbstständing und nur mit den angegebenen Hilfsmitteln angefertigt habe.

Dortmund 2015

Adithi Danda

To my loving parents

and Brother

Dekan:

Erster Gutachter: Prof. Dr. Herbert Waldmann

Zweiter Gutachter: Prof. Dr. Norbert Krause

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Chapter 1

General Introduction

1. General Intoduction

One of the leading objectives of chemical biology is the identification of bioactive small molecules that serve as efficient tools for studying biological phenomena [1]. The chemical space covered by small molecules is really huge and due to time and matter constraints it is unfeasible to cover it by means of organic synthesis [2, 3]. Therefore it is crucial to identify and explore the biologically relevant fraction of the chemical space.

Natural products are a major source of inspiration as they co-evolved with proteins and are chemical entities that often show biological activities. The pronounced biological activity shown by natural products while participating in their biological role is attributed to their interaction with multiple proteins as substrates and targets. Nature is very economical in its design and synthesis of proteins and metabolites and exploits only a small fraction of the chemical space. Thus the chemical space used by natural products is not only compatible with protein structural space but also the size of such structural regions in the chemical space is limited. Thus the space used by natural products is enriched with bioactive structures that are regarded as biologically relevant and prevalidatd [4]. Natural products bind to a variety of proteins during biosynthesis and often show diverse biological activities. These insights suggest that the structural parameters required for binding to evolutionary protein binding sites may lie in the core scaffold of the natural product which is fine tuned by substituent decoration. Thus scaffolds characteristic of natural product classes are ideal starting points for compound library synthesis for chemical biology and medicinal chemistry investigations [5-7].

Natural product based synthesis employs the core structure of natural product as scaffolds for library synthesis. Natural product derived molecules employ frameworks identical to the core structure of a natural product in which different substituents are introduced at exactly the same positions as predetermined by nature. But in case of natural product inspired synthesis closely related frameworks of natural products can be employed in library synthesis. In this approach the relative positions, nature of substituents as well as the relative stereochemistry patterns can be varied, which enables to cover a larger chemical space of a particular structural class [8].

To satisfy the ever increasing number and types of biological targets, bioactive small molecules must be available in the form of libraries of pure and well characterized molecules.

Hence there is great demand for efficient synthetic methodologies that can yield libraries of bioactive small molecules in fewer chemical steps and in a stereoselective manner.

This thesis is based on the synthesis of natural product inspired compound collections. The second chapter describes the synthesis of compound collection based on indole derived indoloquinolizine and related analogs like harmicine scaffolds. The third chapter describes the asymmetric synthesis of a compound collection based on the tetrahydroxanthone scaffold.

Chapter 2

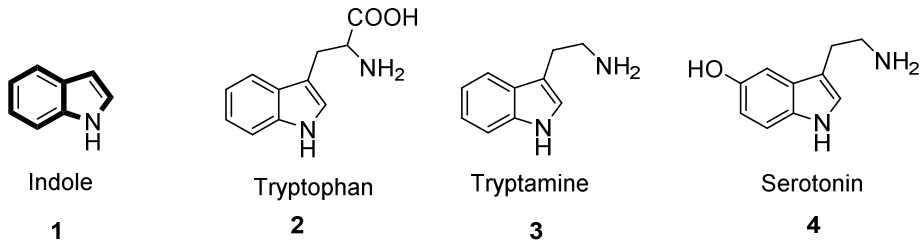
A General Catalytic Reaction Sequence to Alkaloid-Inspired Indole Polycycles

Adithi Danda, Kamal Kumar and Herbert Waldmann**

Chem. Comm., 2015, **51**, 7536 - 7539

2.1 Introduction

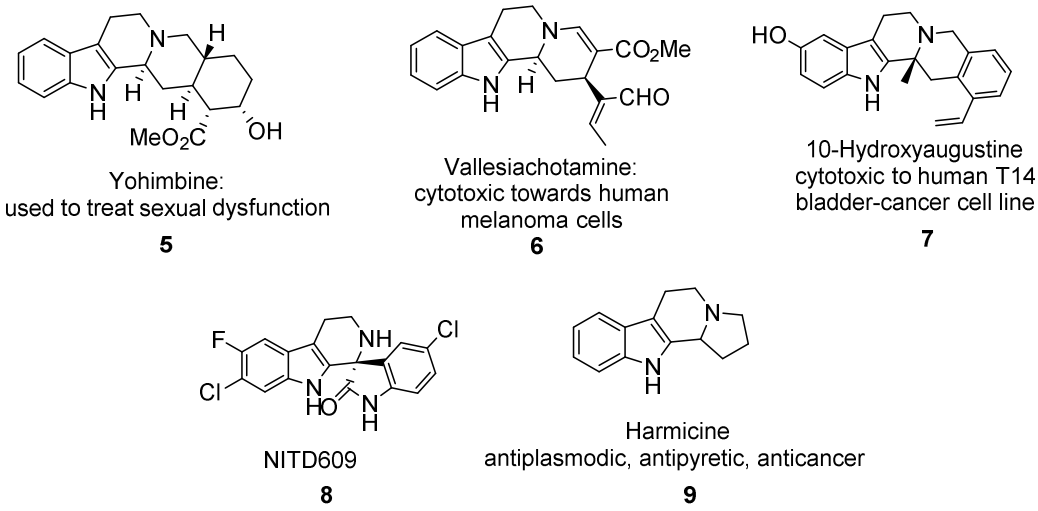
The indole subunit (**1**) is a near-ubiquitous component of biologically active natural products, and its study has been a major focus of research for generations [9-12]. The indole scaffold is termed as a "privileged scaffold" because of its ability to bind to multiple receptors, which has led to substituted indoles being termed as privileged structures which have applications across a wide range of therapeutic areas [13-16].



Scheme 1 - Naturally occuring indole structures

The indole ring system has become an important building block or intermediate in the synthesis of vast number of biologically active natural and synthetic products which comprise of simple to complex indole derived scaffolds, having a wide range of therapeutic targets, such as anti-inflammatories, phosphodiesterase inhibitors, 5-hydroxytryptamine receptor agonists and antagonists, cannabinoid receptors agonists, HMG-CoA reductase inhibitors and many more [17-19].

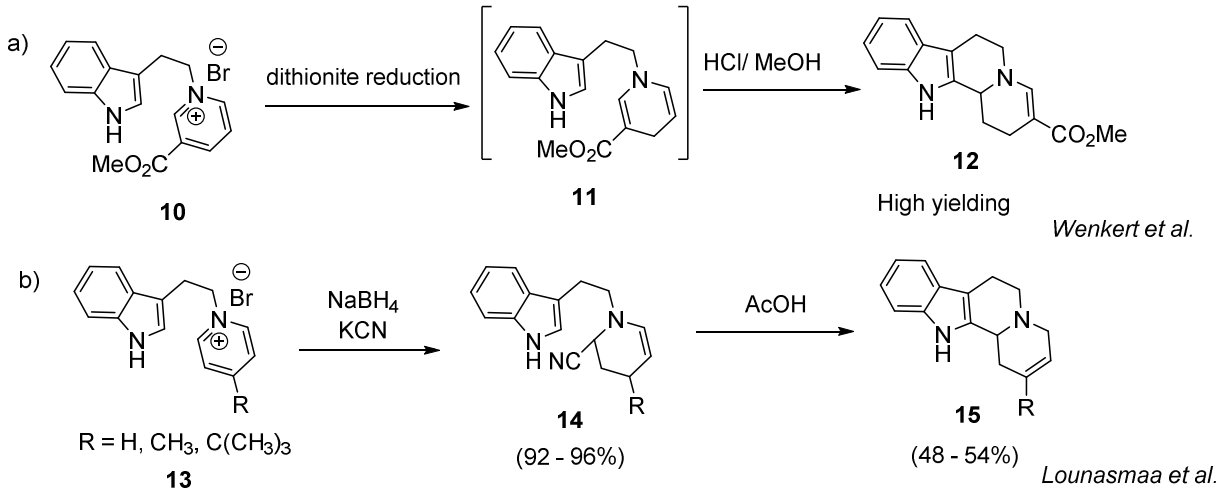
An important class of indole derived scaffolds are the tetracyclic tetrahydro-*β*-carboline ring systems like harmicine, indoloquinolizine and related analogues as depicted in Scheme 2. The indoloquinolizine scaffold and analogues have the tetrahydro-*β*-carboline ring fused to a 6-membered ring as the core scaffold e.g. yohimbine (**5**), vallesiachotamine (**6**) and 10-hydroxyaugustine (**7**) while the harmicine alkaloid [20] (**9**) has the tetrahydro-*β*-carboline ring fused to a 5-membered ring as the core scaffold as depicted in Scheme 2. Establishing new methodologies for the facile synthesis of the indole derived indoloquinolizine and related analogues is a highly demanding and challenging goal for the synthetic organic community. Compound collections built upon these complex scaffolds might afford diversly bioactive small molecules as drug and probe candidates.



Scheme 2 - Natural and synthetic small molecules with the tetracyclic tetrahydro-*β*-carboline as core scaffold

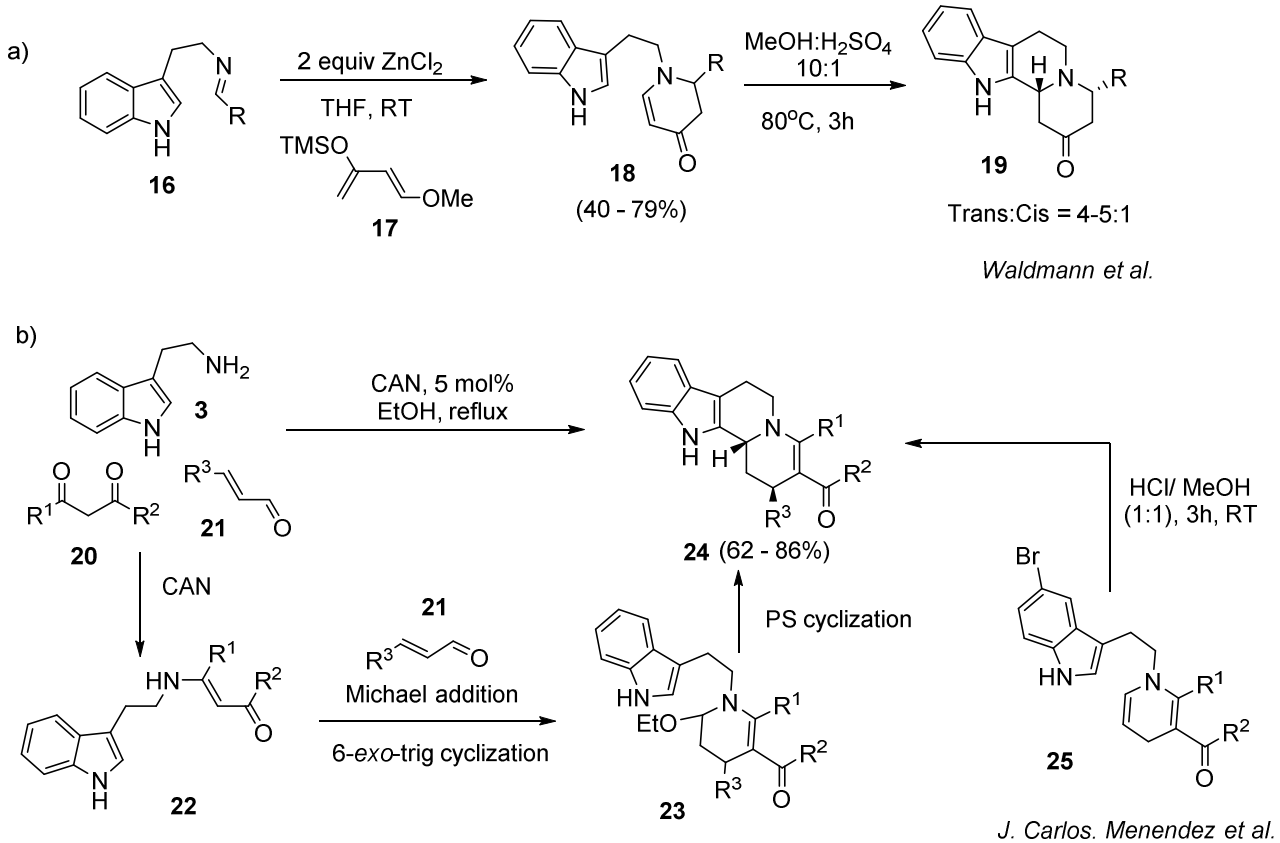
Selected examples from the methods known for the synthesis of the indoloquinolizine and harmicine scaffolds are depicted in the following section.

In *1976 Wenkert et al.* [21] reported a general two step procedure for the synthesis of indoloquinolizine wherein a dithionite reduction of the pyridinium salt (**10**) (formed by alkylation of the appropriate pyridines with trytophyl bromide) resulted in a 1,4-dihydropyridine derivative (**11**), which without isolation is converted into the tetracyclic indoloquinolizine (**12**) on mild acid treatment in high yields. Despite the presence of two enamine units in the intermediate the reaction proceeded regiospecifically (Scheme 3a). This was followed by a report in *1989* by *Lounasmaa et al.* [22] where they reported the reduction of the pyridinium salts (**13**) with $NaBH_4$ followed by cyanide trapping resulting in α-aminonitriles (**14**) which on treatment with AcOH yielded the desired indoloquinolizine (**15**) in moderate yield (Scheme 3b).



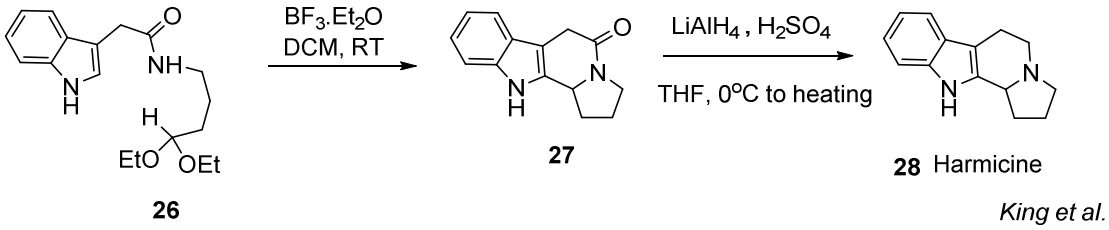
Scheme 3 – Indoloquinolizine synthesis starting from pyridinium salts

In *1992 Waldmann et al.* [23] reported the synthesis of indolo[2,3-a]quinolizidin-2-ones (**19**) (Scheme 4a), wherein a Schiff base derived from tryptamine (**16**) reacted with a Danishefskys diene (**17**) in the presence of $ZnC1_2$ to give enaminone (**18**) which was subjected to an acid catalyzed cyclization resulting in indolo[2,3-a]quinolizidin-2-ones **(19**) in *trans/cis* ratio of 4-5 : 1 and in moderate to high yields. These tetracyclic aminoketones may serve as viable intermediates in the construction of complex alkaloids. In *2013 J. Carlos Menndez et al.* [24] reported a cerium(IV) ammonium nitrate (CAN)-catalyzed sequential multicomponent reaction between tryptamine (**3**), α,β-unsaturated aldehydes (**21**), and β-dicarbonyl compounds (**20**) affording highly substituted indolo[2,3-a]quinolizines (**24**) in moderate to good yields in a single synthetic operation. The reaction mechanism proceeded *via* CAN catalyzed formation of β-enaminone (**22**) derived from tryptamine and the β-dicarbonyl compound, which underwent a Michael addition with the α,β-unsaturated aldehyde (**21**) followed by a 6-*exo*-trig cyclization resulting in a hemiaminal (**23**) which undergoes a Pictet-Spengler cyclization affording the indoloquinolizine in excellent diastereoselectivity. In case of an electon deficient indole ring the reaction lead to *N*-indolylethyl-1,4-dihydropyridines (**25**), which was cyclized to the corresponding indolo[2,3-a]quinolizines (**24**) in the presence 1:1 mixture of 35% aqueous HCl in methanol as depicted in Scheme 4b.



Scheme 4 – Synthesis of indoloquinolizines *via* enaminones

In *2007 King* [25] developed a racemic synthesis of harmicine, *via* a simple three-step procedure in which the indole amide (**26**) (obtained from *N,N'*-dicyclohexylcarbodiimide (DCC) coupling between indole-3-acetic acid and 4-aminobutyraldehyde diethyl acetal, 95% yield) was treated with $BF_3 \cdot Et_2O$, forming an acyliminium salt which then underwent a Pictet-Spengler reaction to give δ-lactam (**27**). Reduction of δ-lactam with alane (formed *in situ* from $LiAlH_4$ and sulfuric acid) gave the desired (±)-harmicine (**28**) in 69% overall yield (Scheme5).

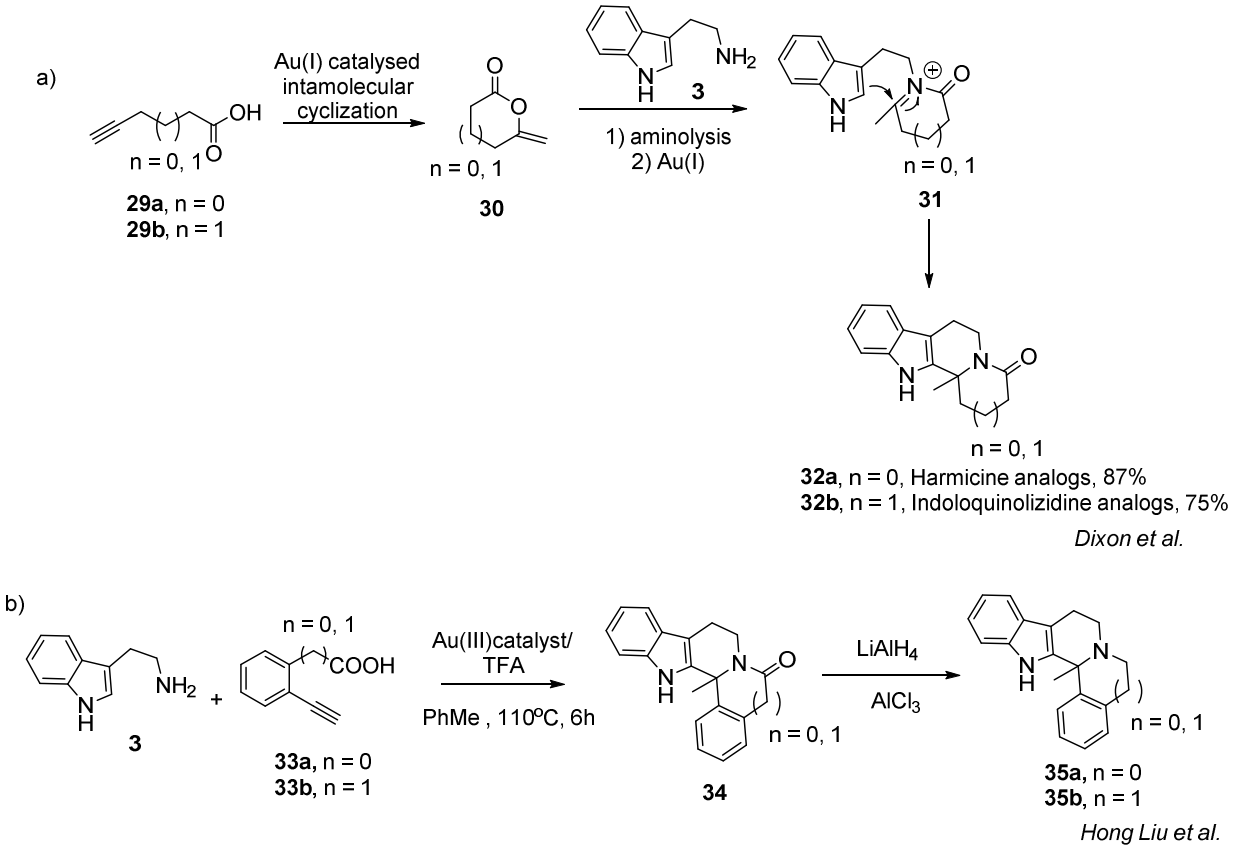


Scheme 5 - Synthesis of harmicine *via N*-acyliminium stratergy

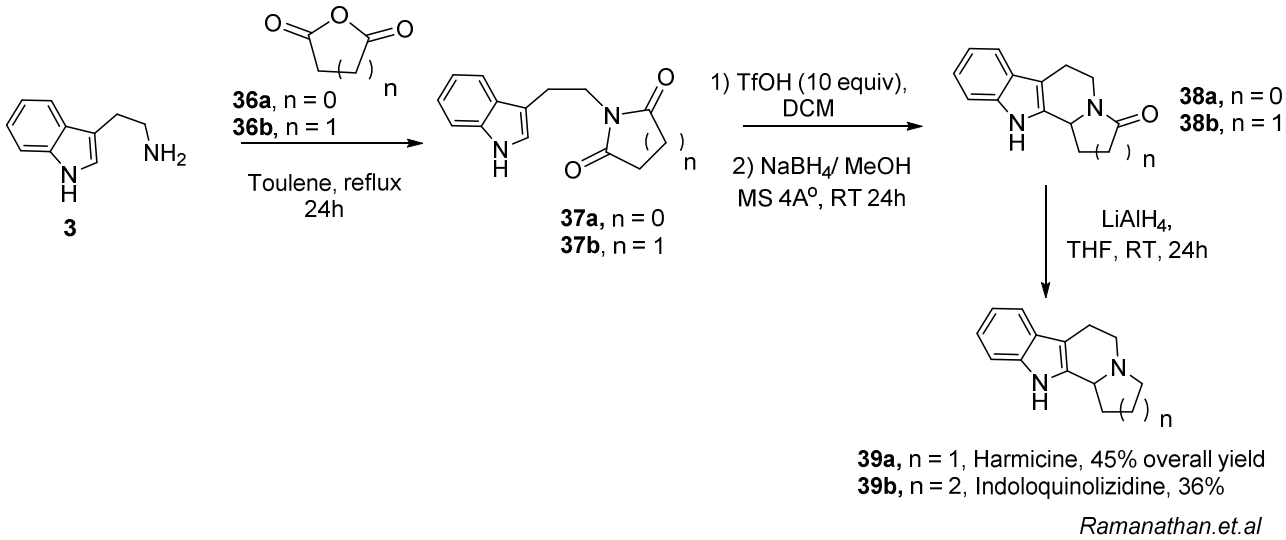
In *2007 D. J. Dixon et al*. [26] also came up with a *N*-acyliminium ion stratergy for the synthesis of harmicine and indoloquinolizidine analogs. They developed a Au(I) ($Au(PPh_3)OTf$ (1mol%)) catalyzed one pot cascade sequence between linear alkynoic acids (**29**) and tryptamine (**3**), wherein a cyclic enol ester (**30**) (formed by gold activation of the alkyne (**29**) followed by intramolecular cyclization with the carboxylic acid) would undergo aminolysis with tryptamine (**3**) followed by bronsted acid (Au(I) itself) catalyzed *N*-acylimminium ion formation (**31**). Finally nucleophillic addition of the indole onto the iminium ion **31** provided the desired product (**32**). High yields were obtained when both hexynoic (**29b**) and pentnoyic (**29a**) acids were employed (Scheme 6a). In *2013 Hong Liu et al.* [27] reported a similar one pot cascade polycylization reaction where non-linear aromatic 2-ethnyl benzoic acid (**33b**) or 2-ethnyl phenyl acetic acids (**33a**) were employed in place of linear alkynoic acids with tryptamine (**3**) in the presence of Au(I) ($Au[P(t\text{-}Bu)_2(o\text{-}biphenyl)][CH_3CN]SbF_6$) (5mol%) and TFA (20mol%) resulting in the formation of polycylic analogues of harmicine (**35a**) and indoloquinolizidine (**35b**) in good to moderate yields. The reaction mechanism was similar to the one described by *Dixon et al*. (Scheme 6b).

In *2012 Ramanathan et al.* [28] reported a Bischler–Napieralski approach towards harmicine synthesis, where instead of $POCl_3$, triflic acid in combination with molecular sieves (MS) was used for the dehydrative cyclization of imides. (±)-Harmicine (**39a**) was obtained in this manner, wherein condensation of tryptamine (**3**) with succinic anhydride (**36a**), followed by imide (**37a**) cyclization using the triflic acid/MS protocol followed by *in situ* reduction with

$NaBH_4$ yielded the γ-lactam (**38a**). The lactam was finally reduced with $LiAlH_4$ yielding the desired harmicine alkaloid (**39a**). Use of glutaric anhydride **(36b)** in place of succinic anhydride would lead to indoloquinolizidine (**39b**) based scaffolds following the similar procedure as depicted in scheme 7.



Scheme 6 – Synthesis of polycylic harmicine and indoloquinolizine analouges using linear and non-linear alkynoic acids

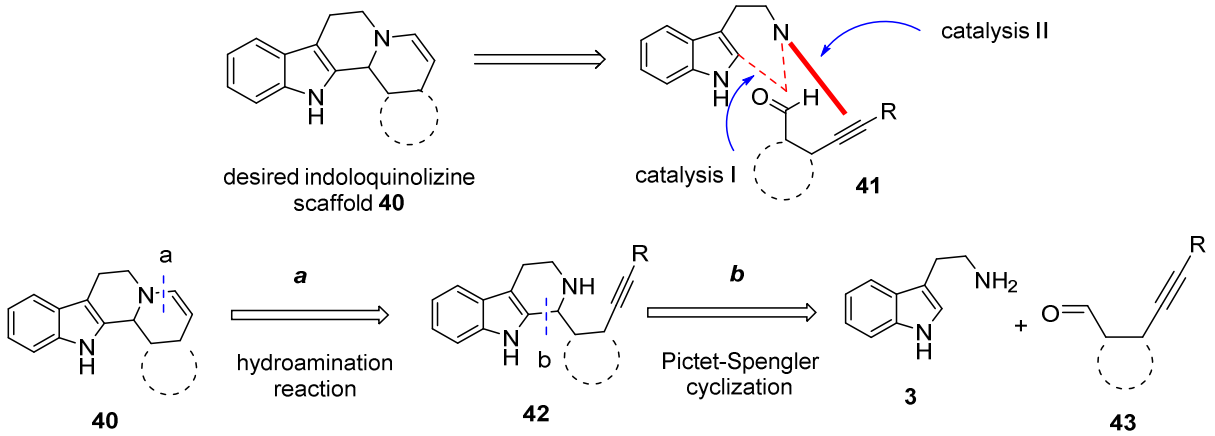


Scheme 7- Bischler–Napieralski approach towards harmicine alkaloids.

2.2 Aim of the project

Organic synthesis has exploited only a limited natural product space in its collection of small molecules. Efficient synthesis of complex natural product based frameworks and compound libraries based on these scaffolds are formidable challenges. However novel and privileged polycyclic frameworks might yield molecules with the most diverse physical, chemical and biological properties. The fusion of several rings leads to geometrically well-defined rigid polycyclic structures and thus holds the promise of a high functional specialization resulting from the ability to orient substituents in three dimensional space. Therefore, efficient methodologies resulting in polycyclic structures from biologically active heterocyclic templates are of interest to both organic and medicinal chemists.

In view of importance of the indoloquinolizine scaffold as a biologically active heterocyclic template, and a keen interest in finding new methods that are not only viable for synthesis but would also generate more diversity around the indoloquinolizine scaffold, a retrosynthetic approach for the synthesis of the desired indoloquinoizine scaffold **40** was devised as depicted in Scheme 8.



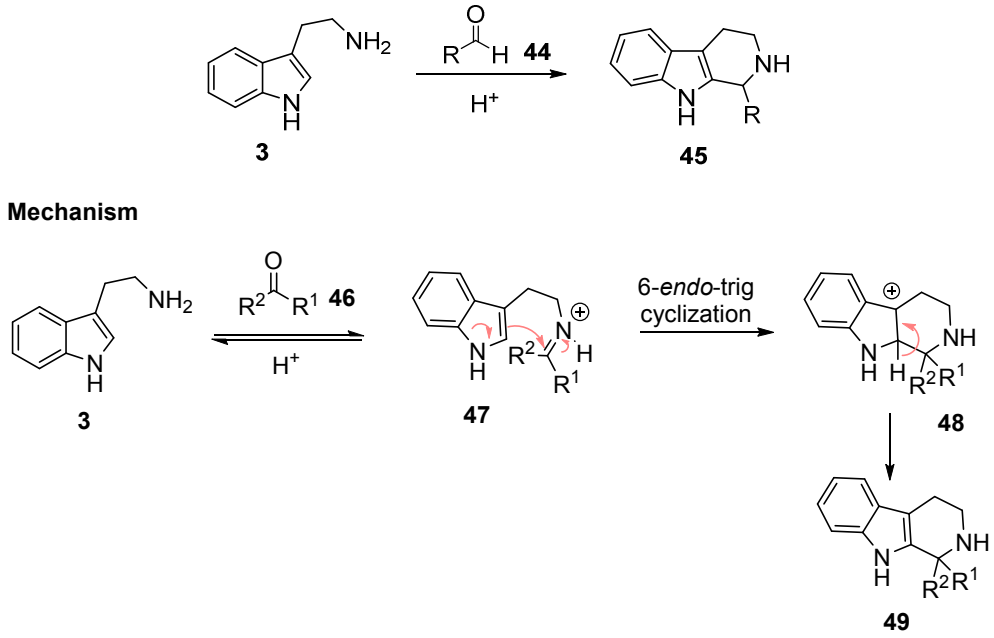
Scheme 8 - Retrosynthetic analysis of the indoloquinolizine scaffold.

The desired indoloquinolizine **40** was dissected at two points on retrosynthetic analysis. The first dissection at point **a** yielded the tetrahydro-*β*-carboline ring tethered to an alkyne (**42**). The compound **42** on being further dissected at point **b** yielded simple precursors whose synthetic equivalents turned out to be tryptamine (**3**) and acetylenic aldehydes (**43**). It was envisioned that the acetylenic aldehydes and tryptamines would cyclize in a Pictet-Spengler reaction to yield the tetrahydro-*β*-carboline (**42**), which under suitable

reaction conditions would undergo hydroamination to provide the desired indoloquinolizine (**40**).

2.3 Pictet-Spengler cyclization

The reaction was discovered in 1911 by Ame Pictet and Theodor Spengler. The Pictet-Spengler reaction, in its simplest form, consists of the condensation of a beta-arylethylamine with a carbonyl compound to yield a tetrahydroisoquinoline or tetrahydro-*β*-carboline. This reaction is best carried out under acidic or neutral conditions, although examples under basic conditions are also reported [29-31].



Scheme 9 – General mechanism of the Pictet-Spengler cyclization

The mechanism of the reaction begins with the protonation of the carbonyl oxygen (**46**) by the acid which is subsequently attacked by the amine of the tryptamine (**3**). Proton transfer steps and loss of water molecule results in a protonated imine intermediate (**47**), which then undergoes a 6-*endo*-trig cyclization reaction followed by a final deprotonation restoring the aromaticity of the indole ring and resulting in the tetrahydro-*β*-carboline product (**49**) (Scheme 9).

Nucleophillic aromatic rings such as indole and pyrrole result in good yields of the product under mild conditions, while the less nucleophilic aromatic rings such as benzene or indoles

with electron withdrawing substituents on the benzene ring give poor yields even under harsh conditions.

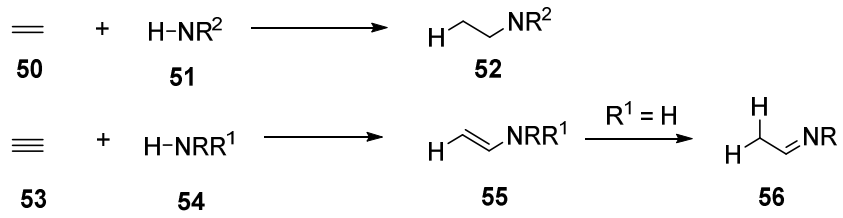
The PS reaction has been established as one of the most powerful methods for the synthesis of 1,2,3,4-tetrahydro-*β*-carboline and tetrahydroisoquinoline cores. The tetrahydro-*β*-carboline template possesses multiple sites for modification, allowing it to be ideally suited for combinatorial elaboration; hence combinations of various reactions with Pictet–Spengler condensation in a sequential tandem fashion have been studied by several research groups for synthesis of complex indole scaffolds. [32, 33]

The importance of this reaction as one of the key steps in the synthesis of indole alkaloids having the *β*-carboline core incorporated in them has led synthetic organic chemists to find new catalysts or condensation agents as well as methods for the synthesis of this heterocycle. Over the years this reaction has been extensively modified to different variants and promoted by various catalysts described in many reviews. A few examples of the achiral catalyst employed in the PS reaction over the years; we have protic acids like TFA [34], HCl [35], H_2SO_4 [36]; Lewis acids like $BF_3.Et_2O$ [37], $AuCl_3$/AgOTf [38] and lately lanthanide triflates [39-41] have also come up as efficient Lewis acid catalysts; halosilanes like chlorotrimethylsilane [42] and molecular iodine [43] are also used as efficient condensation agents for the PS reaction. The PS cyclization reaction has also been subjected to different conditions from classic room temperature and heating conditions, to being subjected to microwave [44] and ultrasound treatment [45] to obtain better conversions and yields.

In accordance with the retrosynthetic analysis and based on a sound literature overview, the Pictet-Spengler cyclization was found to be the key method for the synthesis of the tetrahydro-*β*-carboline core required to lead to the desired indoloquinolizine scaffold (**40**).

2.4 Hydroamination of alkynes

Hydroamination of alkynes is one of the most desirable transformations in organic chemistry. It represents the most atom economic process for the formation of enamines (**55**) and imines (**56**) which are important building blocks in organic synthesis (Scheme 10). Hydroamination is the direct addition of ammonia or primary and secondary amines across a carbon-carbon multiple bond of an alkene (**50**), alkyne (**53**), diene, or allene.



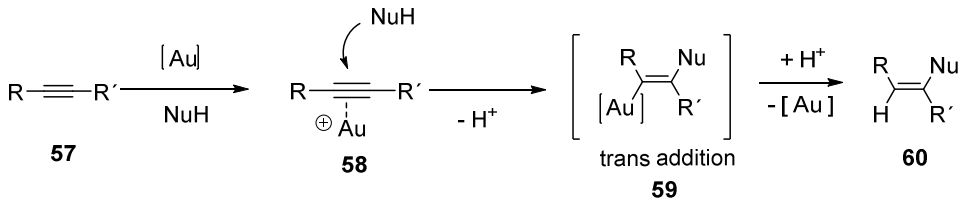
Scheme 10 – Hydroamination reaction of alkyne and alkene

Amines generally do not react spontaneously with alkynes (as long as they are not activated by electron withdrawing substituents) due to electrostatic reasons as both species may be regarded as electron rich. As a consequence, hydroaminations of alkynes is generally achieved in the presence of electrophilic catalysts.

Over the years there have been many reviews on the hydroamination of alkynes, stating the developments with regard to newer catalysts (especially metals) used to catalyze this reaction [46-49]. As a short overview of the different metals used over the years from these reviews, we have stoichiometric Hg, Ca compounds, late transition metals like Ir, Pt, Rh, Ru, Ni and Pd; group 4 metals (early transition metals) Ti , Zr and Hf ; Lanthanides (La, Sm and Nd) and actinides (U and Th). Some of the drawbacks encounterd with the use of these metals are as follows; Hg and Th are higly toxic elements, lanthanide and actinide metals as well as early transition metals are higly sensitive to air and moisture needing higly anerobic conditions, and lastly as compared to early transition metals the late transition metals show decreased sensitivity to air and moisture as well as better functional group tolerance, but are expensive.

An important metal that came up during the quest for finding a better catalyst for the hydroamination reaction was gold [50]. Gold catalysis has lately from the year 2000 attracted great interest. A few characteristic that have rendered gold catalyzed reactions synthetically attractive are the diverse range of reactions it can catalyze, mild reaction conditions, Au(I) is generally tolerant of oxygen, minimum use of additives, straight forward workups, easily available precatalysts, orthogonal reactivity to many transition metal cataylzed processes as well as providing significant increase in the molecular complexity of the formed product.

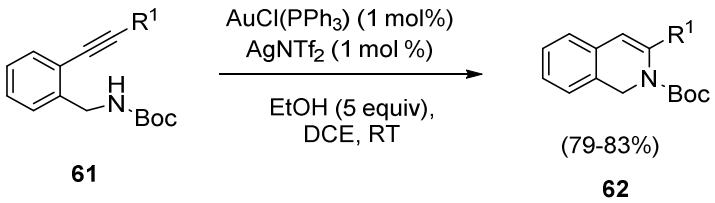
Gold complexes behave as strong Lewis-acids with exceptional ability to activate π-systems which has been attributed to relativistic effects [51]. A diverse range of transformations in gold catalysis is based on the activation of the alkyne by gold salts and complexes especially for nucleophilic attacks as depicted in Scheme 11. The nucleophile adds trans to the coordinating gold complex (**58**) and results in a Markonikov product (**60**) in most cases.



Scheme 11 – Activation of alkyne towards nucleophillic attack

Gold catalyzed intramolecular hydroamination of alkynes has been identified as an important synthetic reaction for the synthesis of various five- and six-membered N-heterocycles such as indoles, pyrroles, quinolones, and isoquinolines in an efficient and atom-economic manner and has received considerable attention. A few examples of the hydroamination rection *via* gold catalyzed 6-*endo*-dig cyclization in literature are described below.

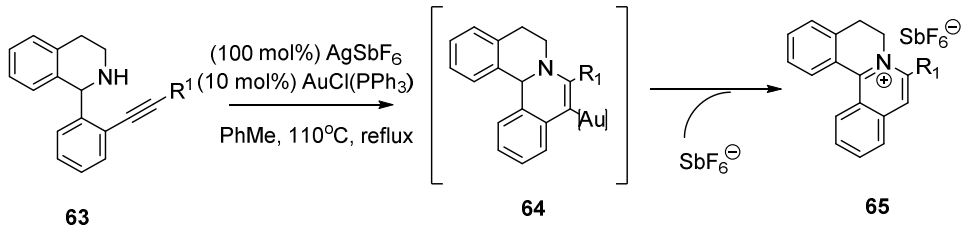
In *2008 Takemoto et al*. [52] reported the synthesis of hydroisoquinoline *via* a Au(I) catalyzed hydroamination reaction, wherein *N*-Boc-*o*-alkynylbenzylamine (**61**) on treatment with 1mol% of $Au(PPh_3)NTf_2$ in 1,2-dichloroethane as solvent with 5 equivs of EtOH at room temperature, underwent hydroamination reaction *via* 6-*endo*-dig mode yielding the desired 1,2-dihydroisoquinoline (**62**). The reaction resulted in good yields with aromatic substituents on the alkyne but was not effective for alkyl substituents. Other protecting groups such as Cbz, Ms in place of Boc were also well tolerated. This reaction also showed the importance of EtOH as an additive for the acceleration of the desired hydroamination reaction (Scheme 12).



Scheme 12 - Synthesis of 1,2-dihydroisoquinolines through hydroamination

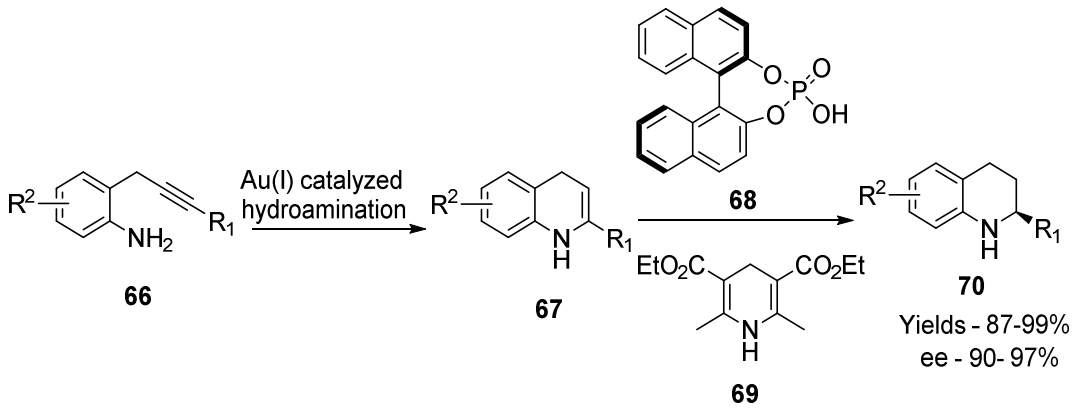
In *2010 Hong Lui et al.* [53] reported a silver and gold mediated intramolecular cyclization (hydroamination in this case) to substituted tetracyclic isoquinolizinium hexafluorostilbates (**65**). A mixture of *o*-alknyl phenyl tetrahydroisoquinoline (**63**) with 100mol% $AgSbF_6$ and 10mol% $Au(PPh_3)Cl$ in toluene as solvent was refluxed for 12h yielding the desired tetracyclic isoquinolizinium stilbates (**65**). Mechanistically the reaction proceeded by the initial activation of the alkyne by the gold catalyst followed by nucleopillic attack by amine (hydroamination reaction) *via* 6-*endo*-dig mode forming the intermediate (**64**), which on subsequent oxidative aromatization followed by complexation with hexafloroantimonate

anion generated the desired stilbates (**65**). The reaction tolerated aromatic as well as aliphatic substitutents on the alknyl group (Scheme 13).



Scheme 13- Synthesis of tetracyclic isoquinolizinium hexafluorostilbates

In *2009 Liu-Zhu Gong et al.* [54] developed a reaction which directly transformed 2-(2-propynyl) aniline (**66**) derivatives into tetrahydroquinolines (**70**) in one operation with excellent enantioselectivity under the relay catalysis of an achiral Au complex ($Au(PPh_3)CH_3$ (5mol%) and a chiral phosphoric acid (**68**). The reaction was a consecutive catalytic process consisting of a Au-catalyzed intramolecular hydroamination (*via* 6-*endo*-dig cyclization) furnishing the 1,4-dihydroquinoline **67**, followed by isomerization of **67** by chiral bronsted acid (**68**) and ultimately the assymetric transfer hydrogenation with a Hantzsch ester (**69**) producing optically active **70**. The reaction tolerated aromatic and aliphatic substituents on the alkyne as well as electron donating and withdrawing substituents on the aniline moiety resulting in very good yields and enantioselectivities (Scheme 14).



Scheme 14- Synthesis of tetrahydroquinolines with good enantioselectivity

Inspired by these above results on gold catalyzed intramolecular hydroamination of alkynes *via* 6-*endo*-dig cyclization and many other reports in literature describing similar reactions,

gold was pursued as a catalyst for the hydroamination step in the reaction sequence leading to the desired indoloquinolizine (**40**) as in Scheme 8.

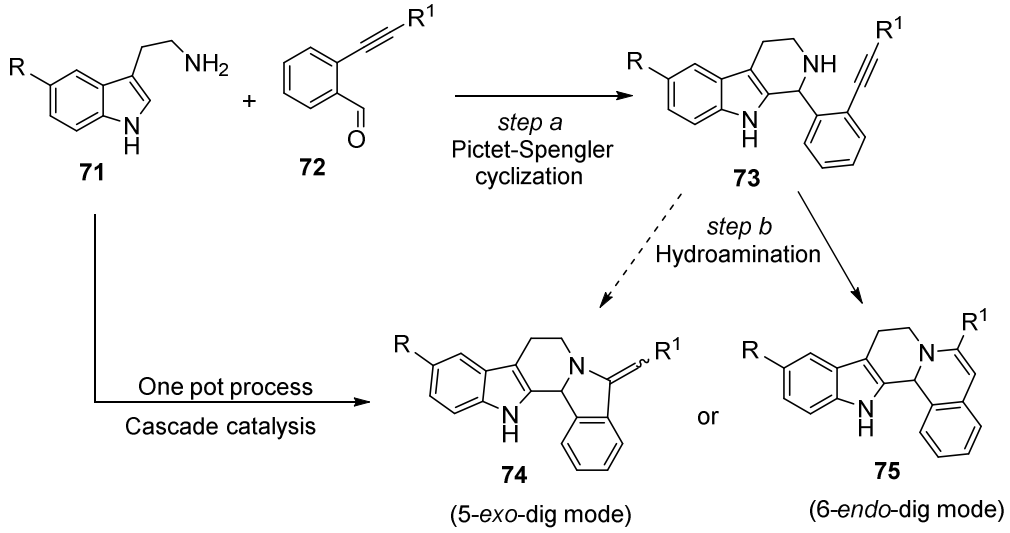
2.5 Results and Discussion

Based on a sound literature overview on the devised retrosynthetic approach (as in Scheme 8), Pictet-Spengler cyclization was employed for the synthesis of the tetrahydro-*β*-carboline core (**42**) followed by the gold catalyzed hydroamination reaction yielding the desired indoloquinolizine core (**40**).

Hereafter is described the synthesis of precursors and optimizations leading to the three different indole based scaffolds achieved in the course of this project.

2.5.1 Synthesis of indoloquinolizine based indole scaffold

In accordance with the retrosynthetic plan *o*-alknyl benzaldehydes **72** and tryptamines **71** were employed as starting precursors to achieve the synthesis of the desired indoloquinolizine scaffold (**75**). The starting materials were expected to cyclize in an Pictet-Spengler reaction (*step a*) to yield the tetrahydro-*β*-carbolines (**73**), which under suitable reaction conditions would undergo a hydroamination reaction (*step b*) with the alkyne to give the desired indoloquinolizine scaffold **75** (Scheme 15).

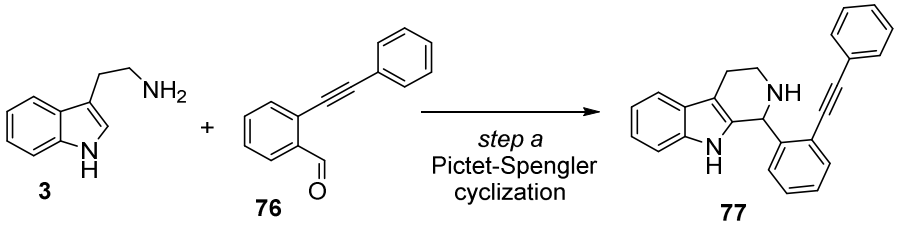


Scheme 15- Proposed route for the synthesis of the desired indoloquinolizine

2.5.1.1 Optimization of individual steps (*a* and *b*)

Optimization of Pictet-Spengler cyclization *step a*

In an attempt to find a suitable catalyst for the Pictet-Spengler cyclization, *o*-alknyl phenyl benzaldehyde **76** and tryptamine **3** were used as model substrates. The starting materials were subjected to acid catalysis which is a classic condition for effecting the Pictet-Spengler reaction (Scheme 16) as depicted in Table 1 and Table 2.



Scheme 16 – Pictet-Spengler cyclization for the synthesis of **77**

Table 1 Optimization of the Pictet-Spengler cyclization step catalyzed *via* Brϕnsted acids

Entry	Catalyst (equiv)	Temperature (^{0}C)	Solvent	Time (h)	Result / Yield[a] (%) of 77
1	TFA (1)	RT	DCM	24h	20
2		50	Toulene	24h	40
3	Benzoic acid[b] (1)	RT to 50	Toulene	24h	NR
4	*p*-TSA[b] (1)	RT to 50	Toulene	24h	30
5	TfOH[b] (0.5)	RT to 50	Toulene	12h	< 10

[a]Isolated yield of the Pictet-Spengler product, [b]The RM was stirred at RT for 12 h followed by heating at 50^{0}C for 12h

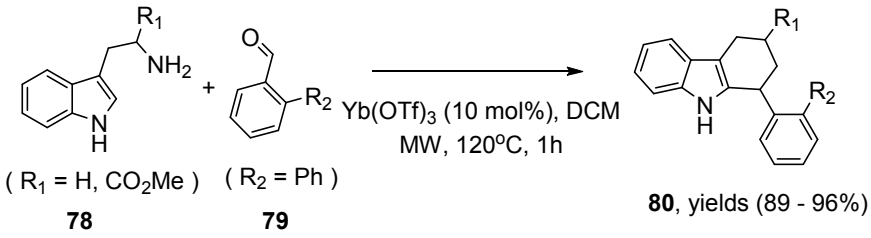
Treatment of the starting materials with 1 equiv of trifloroacetic acid in DCM (Table 1, entry 1) led to only 20% yield of the PS product (**77**) and even heating the reaction mixture to 50^{o}C in toluene (entry 2) resulted only in 40% yield of **77**. Meanwhile other Brϕnsted acids such as *p*-TSA did not improve the yield of **77** (entry 4), while benzoic acid resulted in no reaction (entry 3). Subjecting the starting materials to a stronger Brϕnsted acid such as TfOH (entry 5) also resulted in low yield of the PS product (**77**).

Table 2 Optimization of the Pictet-Spengler cyclization step catalyzed *via* Lewis acids

Entry	Catalyst (mol%)	Tempeature (^oC)	Solvent	Time (h)	Result / Yield[a] (%) of 77
1	$BF_3.Et_2O$ (1 equiv)	RT to 50	Toulene	24	Low yielding
2	$Yb(OTf)_3$ (10)	MW, 120	DCM	1	12
3	$Yb(OTf)_3$ (10), IL[b]	RT	DCM	24	65
4	$Yb(OTf)_3$ (10), IL[b]	MW, 120	DCM	1	74

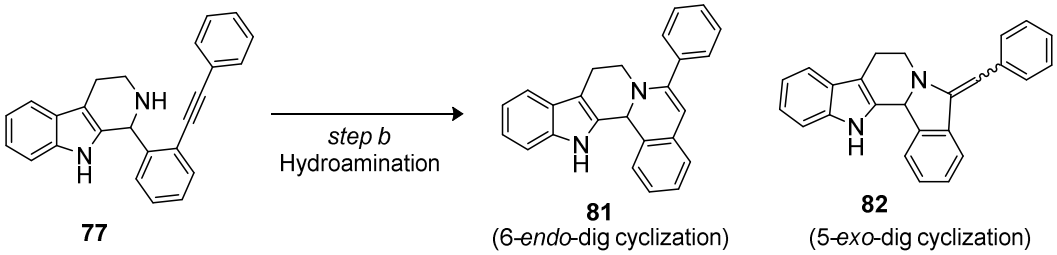
[a]Isolated yield of the PS product, MW – Microwave, [b]IL- ionic liquid [bmim]Cl-$AlCl_3$ – (0.32 ml/ mmol of **3**)

Without much success with Brϕnsted acids as catalyst for the PS cyclization, Lewis acid catalysts were next employed to catalyze the PS cyclization (Table 2). As depicted in Table 2 treating the starting materials with 1 equiv of $BF_3.Et_2O$ resulted in low yields of **77**. During optimization, a literature overview on catalysts employed for PS cyclization, led to reports on the use of lanthanide triflates as Lewis acid catalysts by *Ganesan et al.* [39]



This study established $Yb(OTf)_3$ as a highly effective achiral Lewis acid catalyst for PS cyclization of tryptophans and tryptamine (**78**) with the latter needing the addition of 50 mol% of ionic liquid [bmim]Cl-$AlCl_3$. Motivated by the above results starting materials **3** and **76** were treated with 10 mol% of $Yb(OTf)_3$ and subjected to microwave irradiation resulting in very low yield of the PS product (Table 2, entry 2). However addition of 50 mol% of ionic liquid to the reaction mixture at room temperature enhanced the yield of **77** to 65% (entry 3) and on microwave irradiation the yield of **77** was further improved to 74% (entry 4). Thus $Yb(OTf)_3$ proved to be an effective catalyst for the PS cyclization with substrates **3** and **76** in the presence of ionic liquid as an additive.

Optimization of the hydroamination *step b*



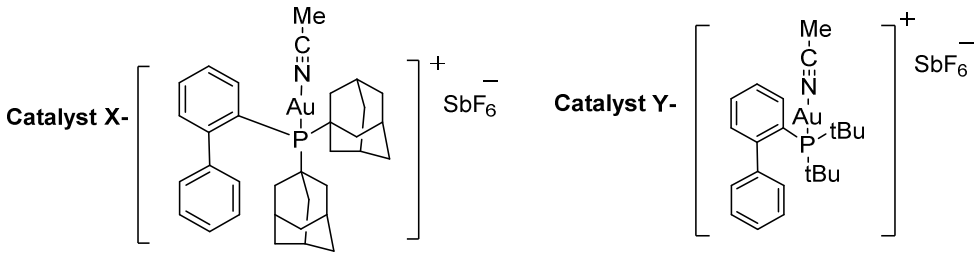
Scheme 18 – Hydroamination step resulting in the desired indoloquinolizine.

With successful optimization of the first step ie the Pictet-Spengler cyclization the next task was to find a suitable catalyst for the second step i.e. intramolecular hydroamination of the alkyne in **77** with the secondary amine *via* a 6-*endo*-dig mode of cyclization yielding product **81** or *v*ia 5-*exo*-dig mode of cyclization yielding product **82**. The PS product **77** was screened with a few homogeneous silver and gold catalysts at room temperature in particular the latter due to its high alkynophilicity for terminal and internal triple bonds rendering them active for nucleophillic attack.

Table 3 Optimization of the hydroamination *step b*.

Entry	Catalyst (mol %)	Solvent	Time (h)	Yield[a] (%) of 81
1	AgOTf (10)	DCE	24	trace
2	$AgSbF_6$ (10)	DCE	24	trace
3	$AuCl(SMe_2)$ (10)	DCE	1	25
4	$Au(PPh_3)OTf$ (10)	DCE	1	40
5	$Au(PPh_3)SbF_6$(10)	DCE	1	35
6	$AuCl_3$ (10)	DCE	1	37
7	Cat Y	DCE	1	62
8	Cat X	DCE	1	42
9	Cat Y	CH_3CN	1	48
10		Toulene	1	NR

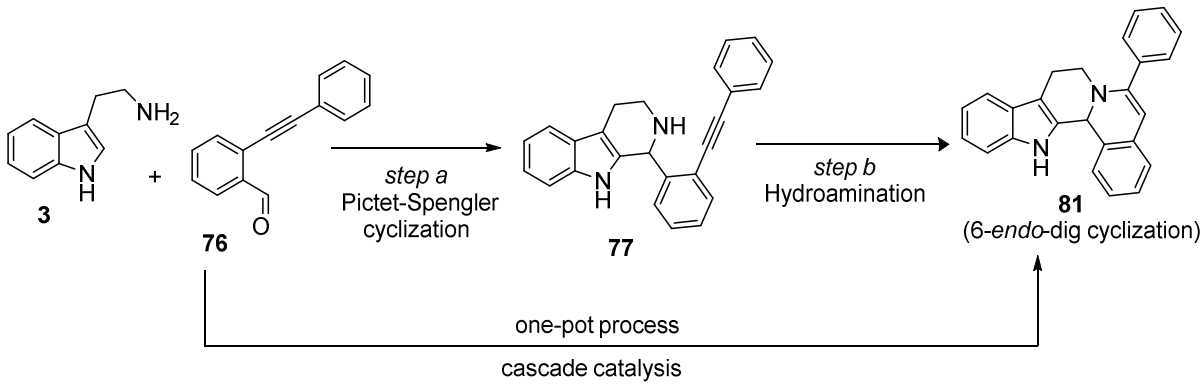
[a]Isolated yield , all the reactions were performed at 0.1 mmol scale in 2 ml of solvent



As depicted in Table 3 both silver salts AgOTf and $AgSbF_6$ (Table 3, entry1 and 2) failed to provide any hydroamination product. The reaction was next examined with selected gold complexes. Treatment of **77** with 10 mol% of $AuCl(SMe_2)$ at room temperature resulted in 25% yield of the hydroamination product **81**, but even on heating the reaction mixture to 50^oC the reaction never went to completion. Resorting to cationic Au(I) phosphine complexes (entry 4) $Au(PPh_3)OTf$ generated *in situ* resulted in an improvement in the yield of **81.** Under the same reaction conditions $Au(PPh_3)SbF_6$ (entry 5) and $AuCl_3$ (entry 6) were similarly effective at room temperature. The use of stable cationic Au(I) complexes with bulky biphenyl-based phosphines ie catalysts **Y** and **X** (entries 7 and 8) at room temperature were found to be effective hydroamination catalysts. In DCE Catalyst **Y** provided a good yield (62%) of the indoloquinolizine **81**. However its catalytic efficiency in CH_3CN was comparatively lower. Owing to very low solubility of catalyst **Y** in toluene no hydroamination product was observed. The screenings with gold complexes in all cases resulted exclusively in the formation of 6-*endo*-dig product **81** (confirmed through ^1H NMR) and no 5-*exo*-dig product **82** was observed. Two important observations noted while monitoring the reaction were, firstly longer reaction times resulted in reduced yields of **81** and secondly loss of compound **81** was observed over normal silica gel column chromatography. Basified silica gel didn't show any improvement in the yields, due to which the crude reaction mixture was subjected to fast column chromatographic purification. These observations were attributed to the lower stability of the hydroamination product **81**.

2.5.1.2 Attempted one-pot synthesis of indoloquinolizine 81.

With successful optimization of the two individual steps (*a* and *b*), the next challenge was to develop a one-pot synthesis yielding product **81**, with both the catalytic cycles working sequentially (Scheme 19).



Scheme 19 - One-pot process for the synthesis of indoloquinolizine **81**

Table 4 Efforts for the one-pot cascade synthesis of indoloquinolizine 81

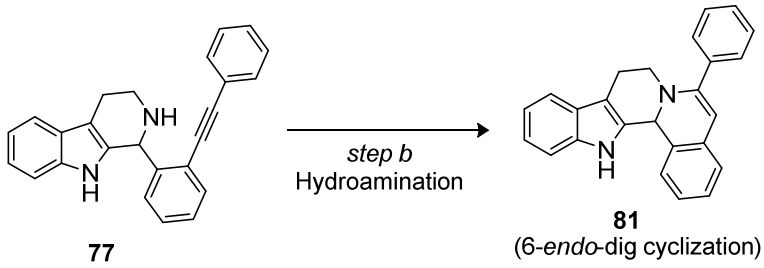
Entry	Catalyst (mol %)	Solvent	Temp (^{o}C)	Time (h)	Yield[a] (%)	
					77	**81**
1	$Yb(OTf)_3$ (10)+ IL[b]	DCM	MW, 120	1	74	-
2	Cat Y (10)	DCE	RT	1	-	62
3	$Yb(OTf)_3$ (10)+IL[b] + Cat Y (10)	DCM	RT	24	50	-
4	$Yb(OTf)_3$ (10)+IL[b] + Cat Y (10)	DCE	reflux	24	30	-
5	$Yb(OTf)_3$ (10) +IL[b] + Cat Y (10)	DCE	MW, 120	1.5	28	-
6[c]	$Yb(OTf)_3$ (10) +IL[b] + Cat Y (10)	DCE:EtOH (5 equiv)	MW, 120	1.5	20	-
7[c]	$Yb(OTf)_3$ (10) +IL[b] + Cat Y (10)	*i*-PrOH	MW, 120	1.5	15	-
8	$Yb(OTf)_3$ (10) +IL[b] + $Au(PPh_3)OTf$ (10)	DCE	RT to reflux	24	20	-
9	$Yb(OTf)_3$ (10)+TMSCl (1 equiv)	DCM:THF (4:1)	RT	24	75	-
10	$Yb(OTf)_3$ (10) +TMSCl (1 equiv) + Cat Y (10)	DCM:THF (4:1)	RT to reflux	24	30	-

.[a]Isolated yield, [b]IL- Ionic liquid [bmim]Cl.$AlCl_3$ (0.32ml/ mmol of **3**), [c]these reactions were also performed at RT but failed to provide the hydroamination product.

As shown in Table 4 the catalysts for the optimized conditions (entries 1 and 2) of steps *a* and *b* were mixed and screened under different conditions to establish a cascade/one-pot process. A mixure of the substrates **3** and **76** in the presence of 10mol% of $Yb(OTf)_3$ and ionic liquid along with catalyst Y (10 mol%) in DCM at room temperature (entry 3) resulted only in the

PS product **77** and no hydroamination product **81** was observed. Refluxing the reaction mixture in 1,2-dichloroethane (entry 4) or subjecting it to microwave irradiation (entry 5) at 120^{o}C also resulted only in product **77.** Use of solvents like *i*PrOH or DCE with 5 equivalents of ethanol also failed to provide the product **81** (entries 7 and 6). Use of Au(PPh$_3$)OTf as a catalyst in place of catalyst **Y** also resulted in the Pictet-Spengler adduct **77** (entry 8). Using 1 equivalent of TMSCl as an additive with Yb(OTf)$_3$ in place of ionic liquid, which is also known to catalyse the PS reaction (entry 9), resulted in product **77**.

An important criterion for a cascade reaction is the compatibility between the reacting substrates, solvent and especially the different catalysts involved. Literature reports showed Au as a catalyst working in harmony with Yb complexes [55] as well as with ionic liquids [56]. In order to check the compatibility of the various reacting species in the present system (Scheme 20) some control experiments were set up to realize the conversion of the Pictet-Spengler product **77** into indoloquinolizine **81** as depicted in Table 5.



Scheme 20 – Control experiments to realize the conversion of **77** into **81.**

Table 5 Control experiments

Entry	Condition	Yield[a] (%) 81
1.	PS Product + Cat Y (10 mol%)	62
2.	PS Product + Cat Y (10 mol%) + Yb(OTf)$_3$ (10 mol%)	59
3.	PS Product + IL[b] + Cat Y (10 mol%)	NR
4.	PS Product + IL[b] + Cat Y (10 mol%) + Yb(OTf)$_3$ (10 mol%)	NR

[a]Isolated yield, [b]IL- Ionic liquid [bmim]Cl.AlCl$_3$ (0.32ml/ mmol of **3**), the reactions were carried out in DCE as solvent at 0.1 mmol scale,

Addition of 10 mol% of Yb(OTf)$_3$ (entry 2) to the reaction mixture (in entry 1) resulted in product **81** without much difference in the yield of the isolated product. Surprisingly addition

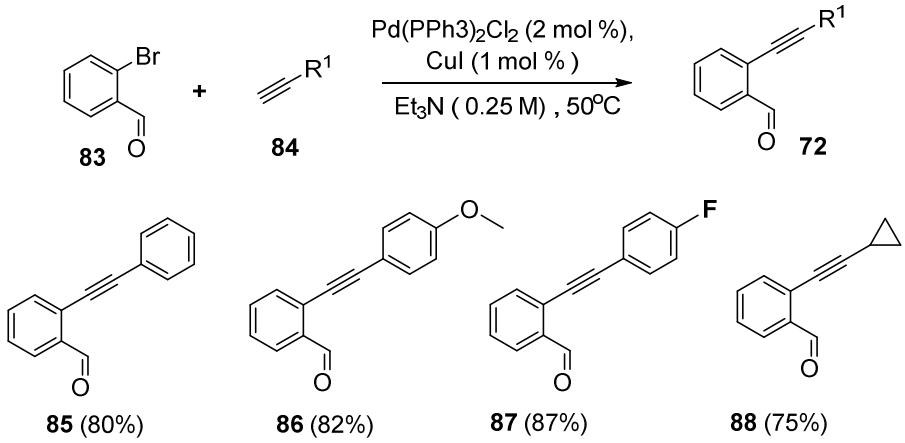
of (IL) ionic liquid [bmim]Cl.$AlCl_3$ (0.32ml/ mmol of **3**) (entry 3) to the reaction mixture (in entry 1) failed to give the hydroamination product **81** either at room temperature or by refluxing the reaction mixture in DCE. Similar results were also observed when 1 equivalent of TMSCl was used as an additive in place of the ionic liquid. Based on the above observations it was concluded that ionic liquid was important for the Pictet-Spengler cyclization but was not compatible with the hydroamination step and hence impeded the one-pot process (entry 4). Thus a two-step reaction sequence was developed to synthesize the desired indoloquinolizine **81**.

2.5.1.3 Scope of the Reaction

With successful optimization of a two-step protocol for the synthesis of indoloquinolizine **81**, the scope of this two-step procedure was investigated.

Synthesis of *O*-Alknyl benzaldehydes

o-Alknyl benzaldehydes were prepared following the known procedure [57] in which *o*-bromo benzaldehyde and the corresponding terminal alkyne were subjected to a Sonogashira reaction resulting in the desired *o*-alkynyl benzaldehydes (Scheme 21).

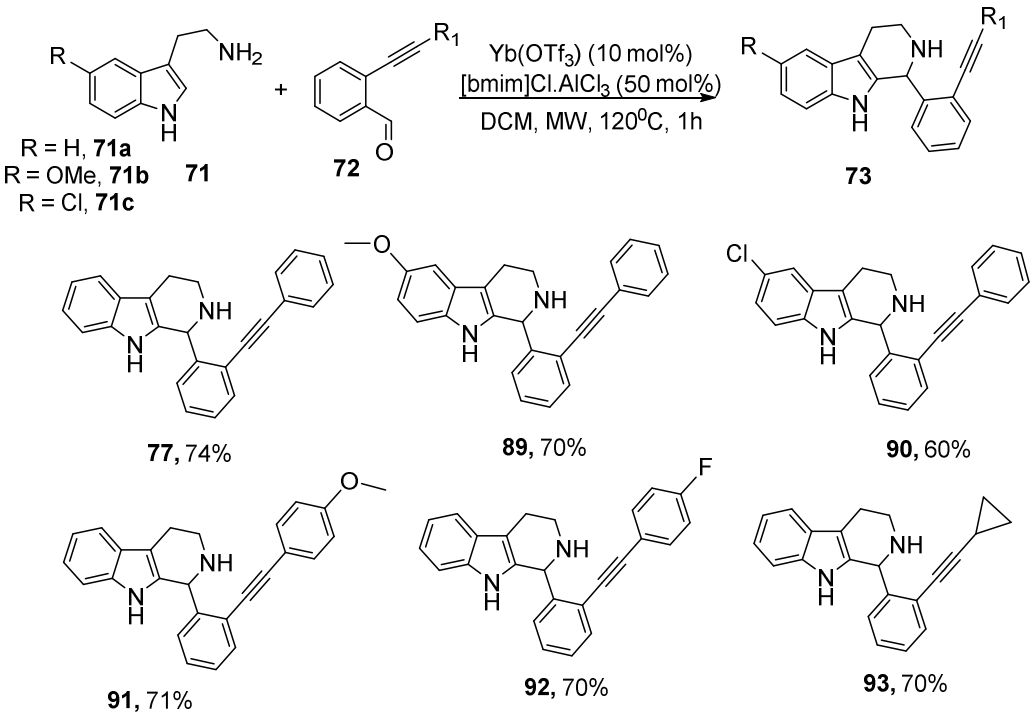


Scheme 21 – Scope of the sonogashira reaction, isolated yields depicted in brackets

Using the literatue procedure four different alknyl benzaldehydes with the acetylene bearing neutral (**85**), electron rich (**86**) and electron poor (**87**) aryl moiety as well as a cyclopropyl (**88**) moiety were prepared in good yields.

Scope of the Pictet-Spengler cyclization (*step a*)

Using the optimized reaction conditions developed for the Pictet-Spengler cyclization (*step a*), a mixture of tryptamine/5-substituted tryptamines (**71a-c**) and *o*-alkynyl benzaldehydes (**85-88**) were treated with 10 mol% $Yb(OTf)_3$ and ionic liquid (0.32ml/ mmol of **3**) and the reaction mixture was subjected to microwave irradiation at 120^{o}C yielding the Pictet-Spengler products **73** (Scheme 22).

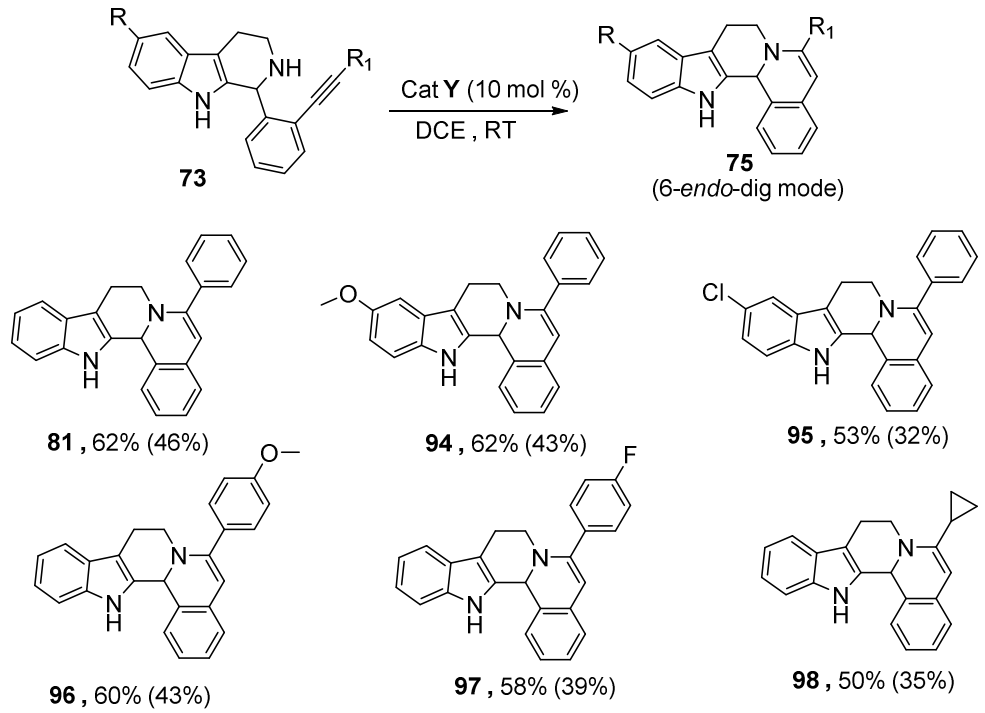


Scheme 22- Scope of the Pictet-Spengler reaction, depicting isolated yields

As depicted in Scheme 22, the reaction tolerated neutral (**71a**) and electron rich 5-OMe (**71b**) tryptamines yielding the corresponding PS products in good yields. Surprisingly electron poor 5-Cl tryptamine (**71c**) which is known to be a poor substrate for PS cyclization requiring harsh conditions and resulting in lower yields of the PS product as compared to its electron rich counterparts, under the optimized condition resulted in moderate yield of **90**. This demonstrated the synthetic utility of the reaction sequence. Varying substituents on the acetylene also provided good yields of the corresponding PS products (**91-93**).

Scope of the hydroamination reaction (*step b*)

The pure PS products **73** were treated with 10 mol% of catalyst Y in 1,2-dichloroethane as solvent at room temperature and the reaction was monitored using TLC for completion. The hydroamination reaction followed the 6-*endo*-dig mode of cyclization yielding product **75** (Scheme 23).



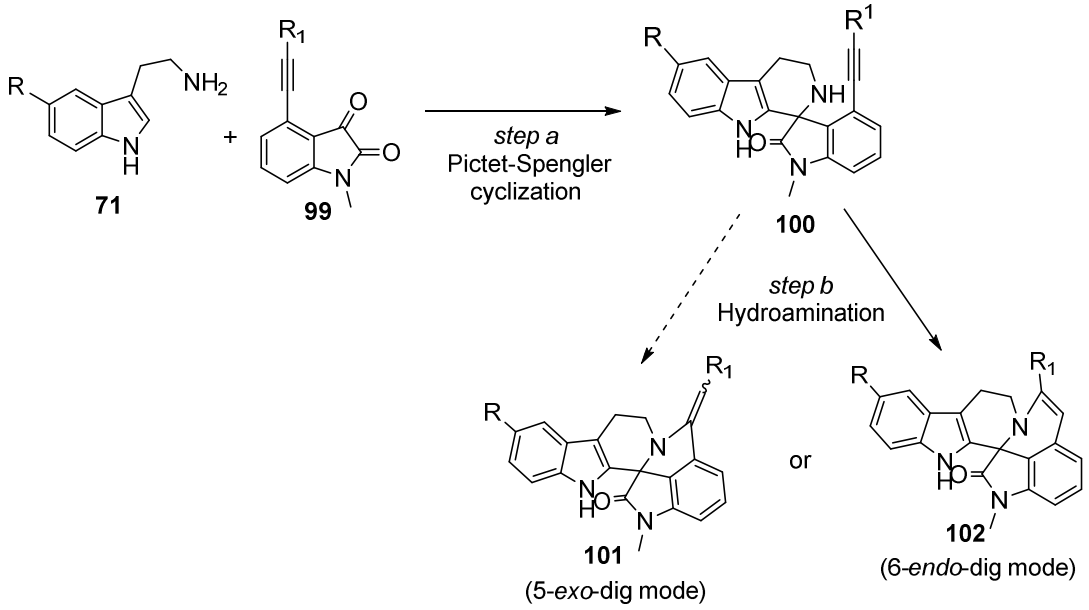
Scheme 23- Scope of the hydroamination reaction, yields in brackets depict combined yields over two synthetic steps

As depicted in Scheme 23 the reaction sequence tolerated tryptamines with electron rich and poor substitutents on the indole ring affording products (**81, 94-95**) in moderate yields. Electron rich (**96**) and poor aryl groups (**97**) on the acetylene were similarly effective, pleasingly cyclpropyl group on the acetylene also resulted in moderate yields of **98**.

Thus, the synthesis of the first indole derived **Indoloquinolizine scaffold 75** *via* a catalytic two-step process with varied substarte scope was successfully achieved.

2.5.2 Synthesis of tetrahydro-*β*-carboline ring fused to a spirooxindole ring system giving rise to hexacyclic indoloquinolizines

Having successfully established the synthesis of indoloquinolizines **75**, the utility of this two step process was investigated for the synthesis of more complex hexacyclic indoloquinolizines embodying a tetrahydro-*β*-carboline ring fused to a spirooxindole ring system. In this system instead of acetylenic aldehydes (**72**) acetylenic istains (**99**) were employed with typtamines (**71**)



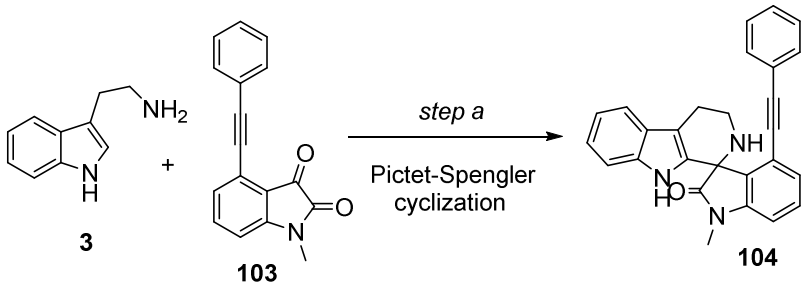
Scheme 24- A two step protocol for the synthesis of hexacyclic indoloquinolizines.

As depicted in Scheme 24, it was expected that tryptamines (**71**) and acetylenic isatins (**99**) would cyclize in a Pictet-Spengler reaction to yield products **100,** which on treatment with a gold catalyst would undergo a hydroamination reaction either *via* a 6-*endo*-dig mode of cyclization yielding product **102** or a 5-*exo*-dig mode of cyclization yielding product **101**.

2.5.2.1 Optimization of the individual steps (*a* and *b*)

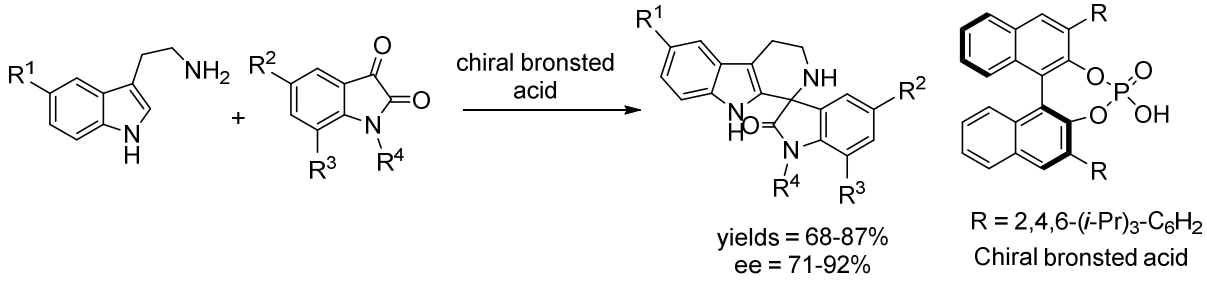
Optimization of the Pictet-Spengler cyclization (*step a*)

For the reaction optimization tryptamine (**3**) and *N*-methyl 4-ethnyl phenyl isatin (**103**) were employed as model substrates.



Scheme 25 –Pictet-Spengler cyclization step for synthesis of **104**

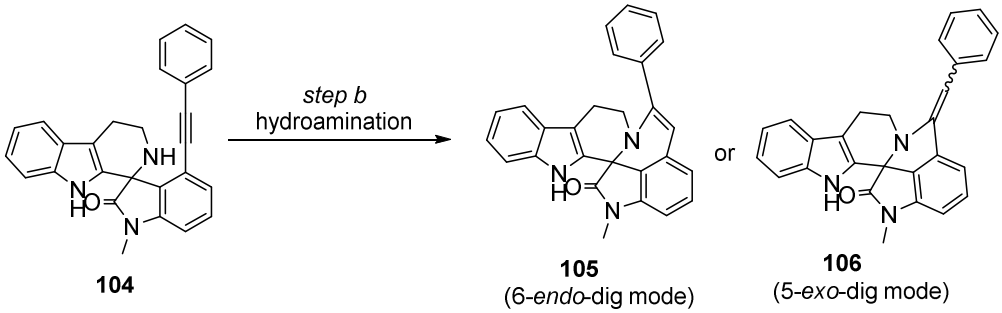
Initially the model substrates **3** and **103** were subjected to reaction conditions optimized for the synthesis of PS product **73** (Scheme 22), wherein the starting materials (**3** and **103**) were treated with 10 mol% of $Yb(OTf)_3$ and ionic liquid [bmim]Cl.$AlCl_3$ (0.32ml/ mmol of **3**) in DCM. Subsequently the reaction mixture was subjected to microwave irradiation at 120^{o}C for 1h resulting in the PS product **104** in a moderate yield of 55%.



In literature [58] reports of isatins undergoing PS cyclization with tryptamines in the presence of (*S*)-BINOL derived phosphoric acids as catalysts with good yields and enantioselectivities, inspired the use of TFA as an achiral Bronsted acid catalyst in the PS cyclization (as depicted in Scheme 25). As expected on treating the starting materials (**3** and **103**) with 1 equivalent of TFA for 24h at 50^{o}C enhanced the yield of **104** to 76% in DCE, use of toluene as a solvent further improved the yield to 81%. Heating the reaction mixture to higher temperature of 80^{o}C did not show any improvement in the yield of **104**. These results established TFA as an acid catalyst for the PS cyclization in this system.

Optimization for the Hydroamination (*step b*)

With TFA optimized as an acid catalyst for the PS cyclization (*step a*), finding a suitable gold catalyst for the hydroamination step (*step b*) was the next task.



Scheme 26 – The plausible hydroamination products that can be formed on treatment of **104** with Au catalyst**.**

The PS product **104** was initially treated with 10 mol% of catalyst **Y** (the optimized catalyst for the hydroamination reaction yielding indoloquinolizines **75** (Scheme 23), yielding the desired hydroamination product **105** with no traces of product **106** (deterimed *via* crude ^{1}H NMR). In the proton NMR of the isolated hydroamination product **105** presence of a side product 6-8% (determined by ^{1}H NMR) rendered the isolation of the pure compound **105** difficult. Hence, in order to avoid the formation of this undesired side product a small screening of the PS product **104** with selected gold complexes was set up as depicted in Table 6.

Table 6 Optimization of the hydroamination *step b*

Entry	Catalyst (mol %)	Temperature (^{o}C)	Solvent	Time (h)	Yield[a] (%) of 105
1	$Au(PPh_3)OTf$ (10)	RT	DCE	2	43
2	$Au(PPh_3)SbF_6$ (10)	RT	DCE	2	30
3	$AuCl_3$ (10)	RT	DCE	2	50
4	$AuCl(SMe_2)$ (10)	RT	DCE	2	76
5		RT	Toulene	2	65
6		RT	CH_3CN	2	50

[a]Isolated yield of product **105**

All the gold complexes employed in the screening resulted in the formation of the hydroamination product **105** exclusively as a single diastereomer and formation of product **106** was not observed. As seen in Table 6 Au(I) phosphine complexes $Au(PPh_3)OTf$ (entry 1) and $Au(PPh_3)SbF_6$ (entry 2) resulted in moderate yields of **105** at room temperature. Use of

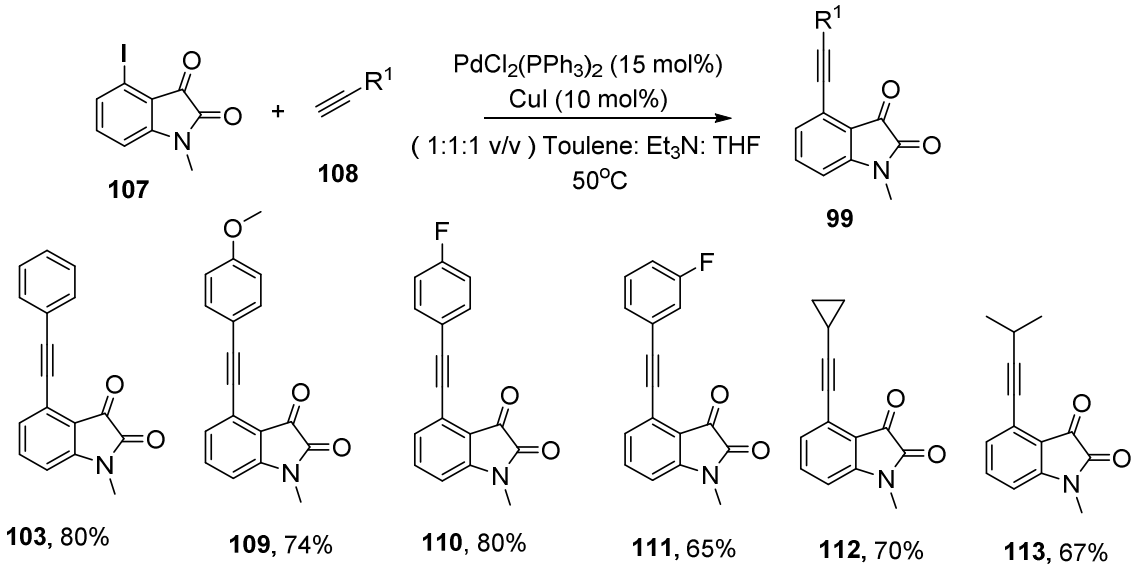
$AuCl_3$ showed slight improvement in yield (entry 3), but pleasingly catalyst $AuCl(SMe_2)$ enhanced the yield of the product to 76% at room temperature. The efficiency of catalyst $AuCl(SMe_2)$ was maximum in DCE (entry 4) as solvent and dropped in toluene (entry 5) and acetonitrile (entry 6). Based on these results $AuCl(SMe_2)$ turned out to be the best catalyst for the hydromaination reaction yielding product **105**. As was the case with indoloquinolizines (**75**) loss of compound was witnessed with longer reaction times as well as during purification using normal silica gel columns. In order to isolate the product **105** in maximum yield, the reaction was monitored by TLC for completion and the crude reaction mixture was subjected to fast column chromatography for purification.

2.5.2.2 Scope of Reaction

With catalysts optimized for both the individual steps (*a* and *b*), the scope of the reaction was investigated.

Synthesis of Starting Materials

Alknyl isatins were synthesized by Sonogashira coupling reaction between 4-Iodo-*N*-methyl isatin (**107**) and the corresponding terminal alkyne (**108**) in the presence of $PdCl_2(PPh_3)_2$ and CuI as catalysts in a 1:1:1 mixture of degassed Toulene: Et_3N: THF as solvent at 50°C. 4-Iodo-N-methyl isatin was prepared according to the literature procedure [59] in 51% yield.

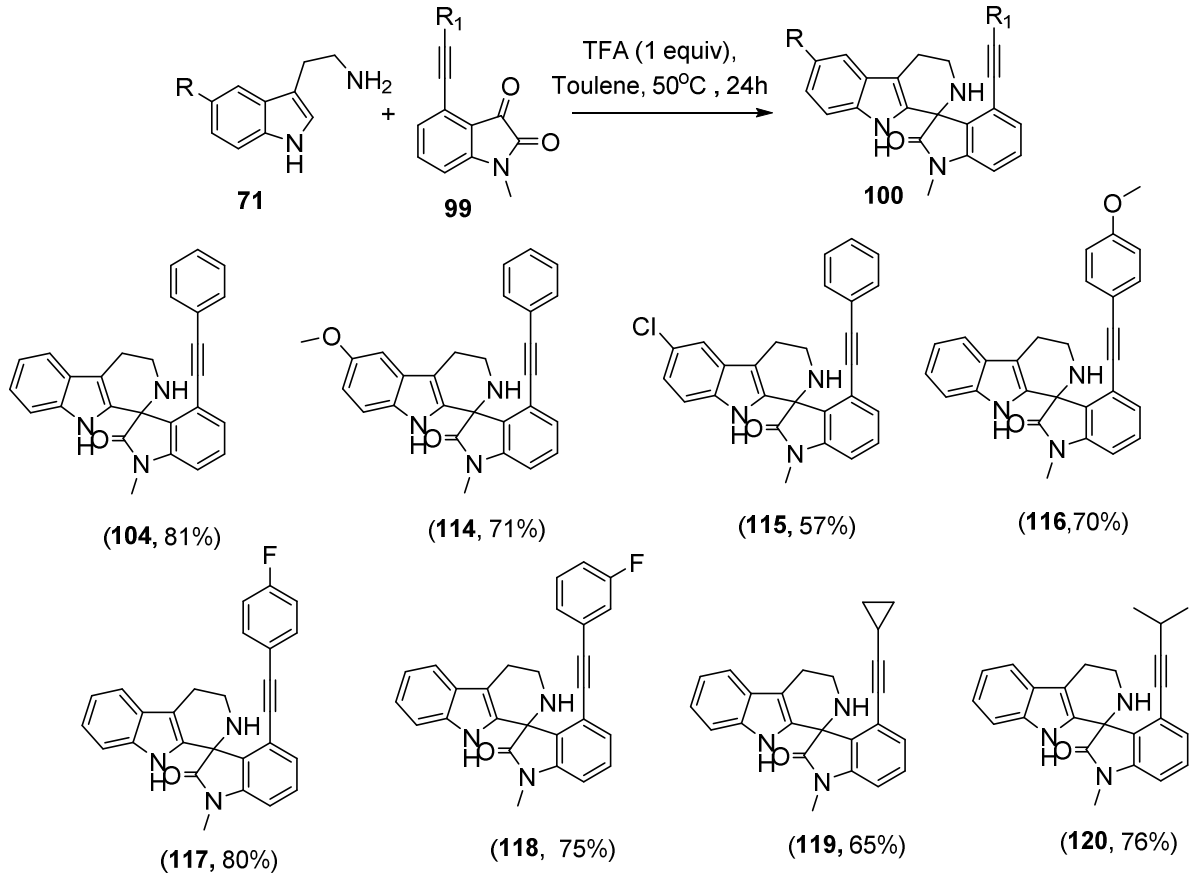


Scheme 27 – Scope of the Sonogashira reaction along with isolated yields

The reaction showed tolerance for varied groups on the acetylene, such as neutral (**103**) and electron donating (**109**) aryl groups, electron withdrawing groups such as floro at para (**110**) and meta (**111**) position resulted in good to moderate yields respectively. Cyclopropyl (**112**) and isopropyl (**113**) groups on the acetylene were also obtained in moderate yields. In total six of these songashira coupling products were prepared (Scheme 27).

Scope of the Pictet-Spengler cyclization (*step a*)

The synthesized Sonogashira products **99** along with tryptamine/ 5-OMe tryptamine were treated with 1equiv of TFA in toluene at 50^{o}C for 24h yielding the PS products **100** (Scheme 28).



Scheme 28 – Scope of the PS cyclization reaction with isolated yields

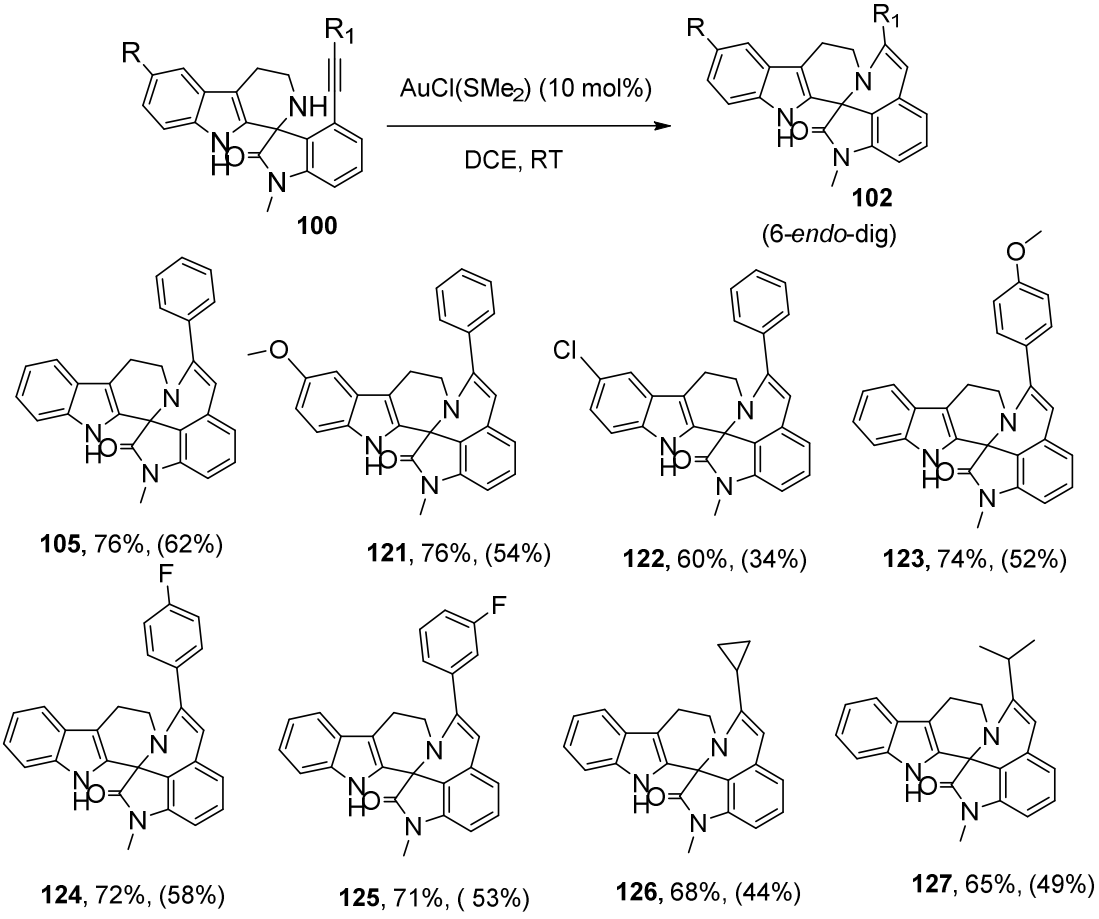
As depicted in Scheme 28 the reaction tolerated varied substituents on the acetylene from electron donating (**116**) and withdrawing (**117, 118**) aryl groups to cyclopropyl (**119**) and isopropyl (**120**) groups, resulting in good to moderate yields of the PS product. Electron donating 5-OMe group on tryptamine resulted in 71% yield of the PS product (**114**), while the

electron withdrawing 5-Cl group on tryptamine resulted in trace amounts of the PS product under the optimized reaction condition. Refluxing the reaction mixture in toluene also resulted in trace amounts of **115**. Resorting to $Yb(OTf)_3$ and ionic liquid [bmim]Cl.$AlCl_3$ as a catalyst system for the PS cyclization resulted in moderated yields of the desired product **115** (57%). Hence PS product **115** was obtained following the procedure established for formation of PS product **73** (Scheme 22).

In a nutshell the reaction tolerated varied substituents on the acetylene as well as electron donating and neutral tryptamines; its only limitation was the inefficiency of TFA as an acid catalyst with electron withdrawing substituents on tryptamine.

Scope of the hydroamination reaction (*step b*)

The isolated PS products **100** were treated with 10 mol% $AuCl(SMe_2)$ in 1,2-dichloroethane at room temperature, affording the desired hydroamination product **102** *via* 6-*endo*-dig cyclization.

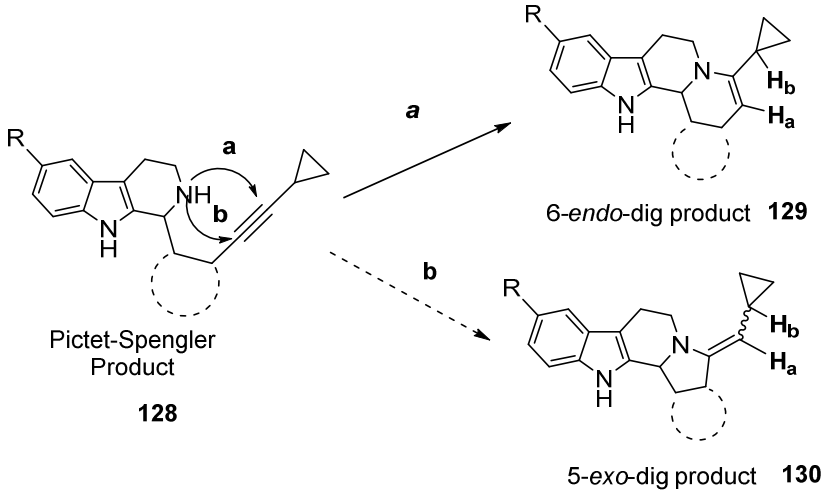


Scheme 29 – Scope of the hydroamination reaction, yields depicted in the brackets are over two reaction steps

As depicted in Scheme 29 the hydroamination products (**102**) were obtained in good to moderate yields giving the desired hexacyclic spirooxindole scaffold. The reaction resulted in good yields with neutral and electron rich tryptamines whereas electron poor 5-Cl tryptamine led to a drop in the yield of **122** (60%). Substituents on the acetylene with electron donating (**123**) and withdrawing (**124, 125**) substituents on the aryl group were equally effective. Similarly cyclopropyl and isopropyl groups on the acetylene also gave the desired products **126** and **127** respectively in good yields.

With this we successfully achieved the synthesis of the second Indole derived **hexacyclic indoloquinolizine scaffold 102**, showing a varied substrate scope.

2.5.3 Characterization of products 75 and 102 formed *via* 6-*endo*-dig cyclization of the corresponding Pictet-Spengler products.



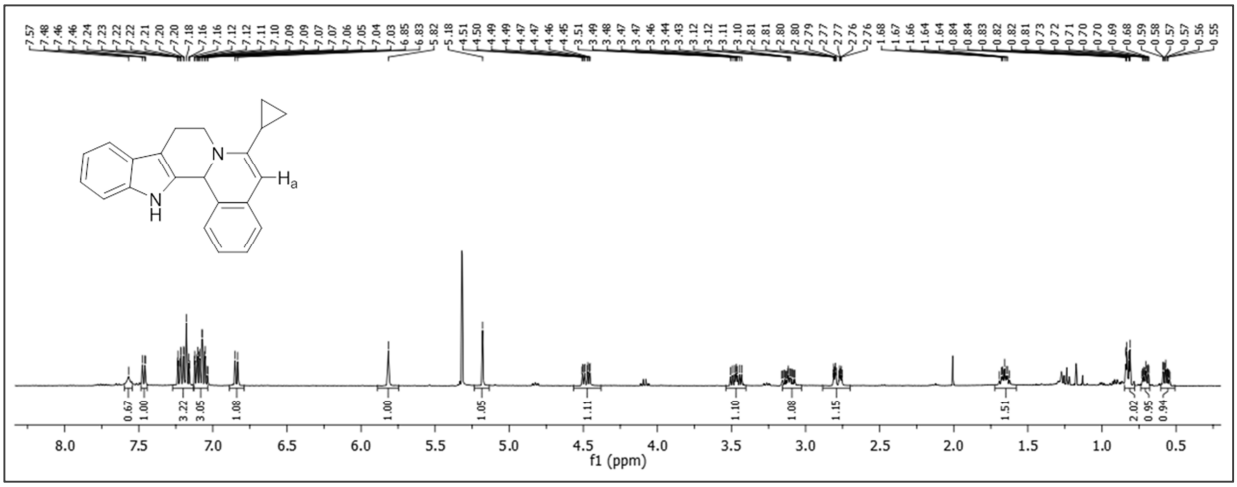
Scheme 30 – NMR evidence for the formation of 6-*endo*-dig product

As depicted in Scheme 30 the Pictet-Spengler product (**128**) would potentially undergo a hydroamination reaction either *via* a 6-*endo*-dig mode (*path a*) giving rise to an endocyclic 6 membered ring (**129**) or *a* 5-*exo*-dig mode (*path b*) giving rise to an exocyclic 5-membered ring (**130**). The isolated product in both the scaffolds (**75** and **102**) was confirmed to be a 6-*endo*-dig product *via* proton NMR. In order to explain this result substrates with the cyclopropyl group on the acetylene in both the scaffolds ie **98** and **126** were chosen. As shown in Scheme 30, in product **130** the enamine proton H_a is allylic to proton H_b resulting in

a splitting of both protons due to allylic coupling, whereas in product **129** absence of an allylic proton for the enamine proton H_a would result in the enamine proton not being split.

The ^1H NMR spectrum of **98** showed a singlet at 5.82 ppm (Figure 1) and **126** showed a singlet at 5.27 ppm (Figure 2) for the H_a proton in each case. The presence of the enamine proton as a singlet in the NMR spectrum of both substrates ruled out the formation of the 5-*exo*-dig product and strongly suggested that the hydroamination reaction proceeds *via* a 6-*endo*-dig pathway resulting in products **98** and **126**.

Figure 1: NMR spectra of 98 in deuterated DCM



Section of the NMR spectrum showing the enamine proton H_a as a singlet.

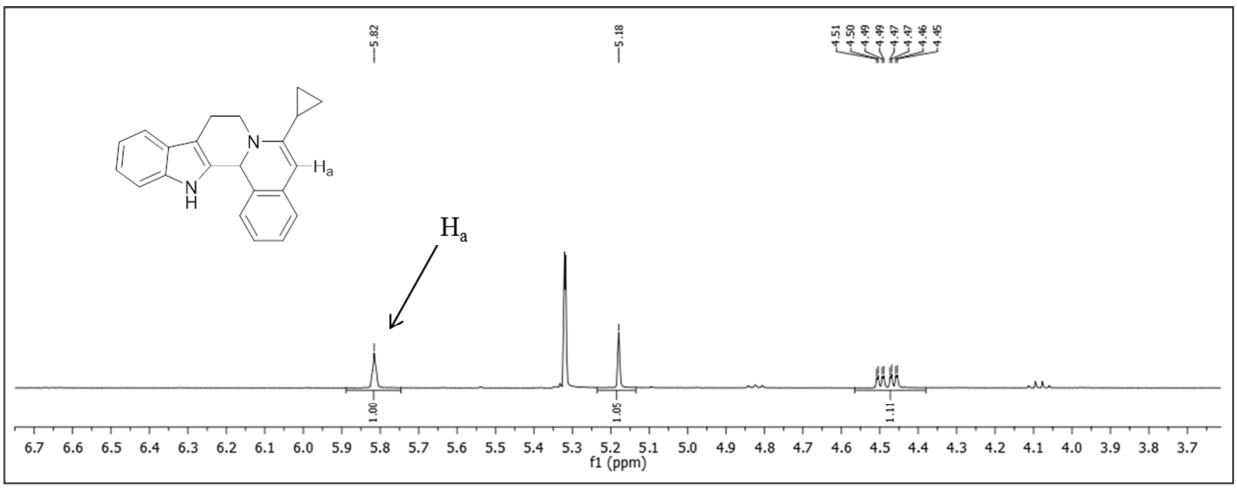
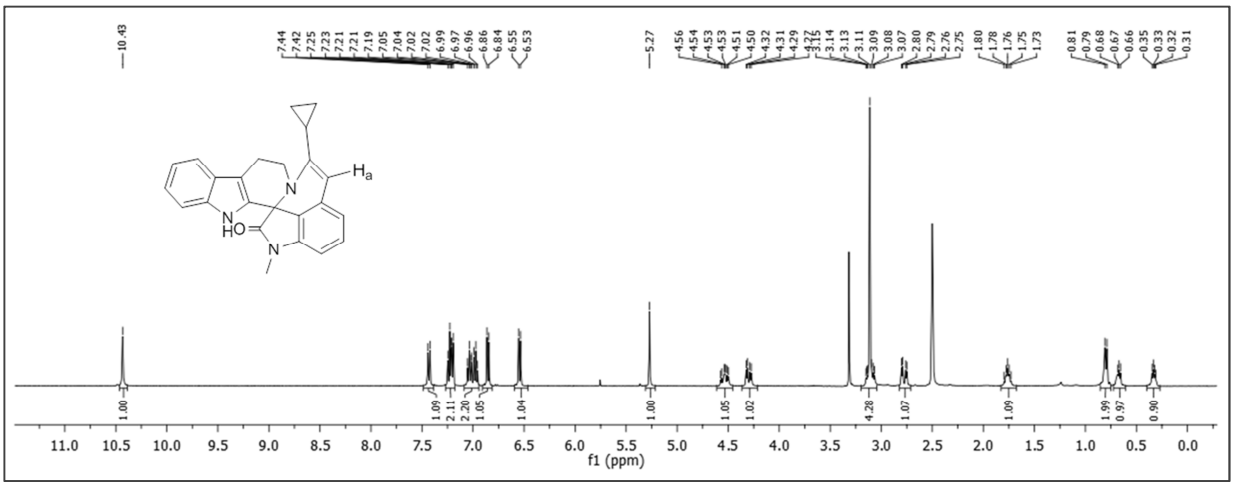
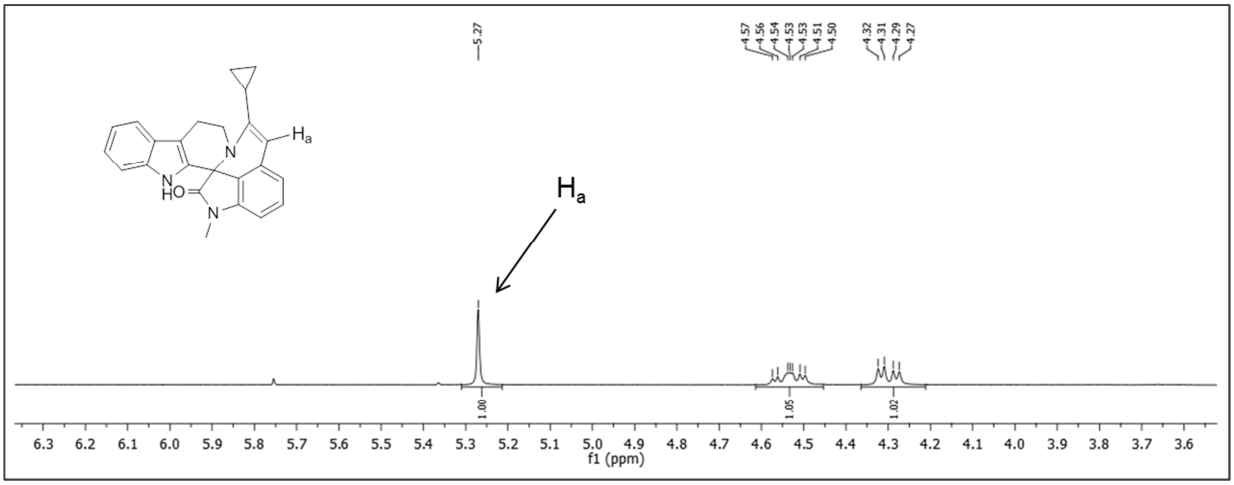


Figure 2: NMR spectra of 126 in deuterated DMSO



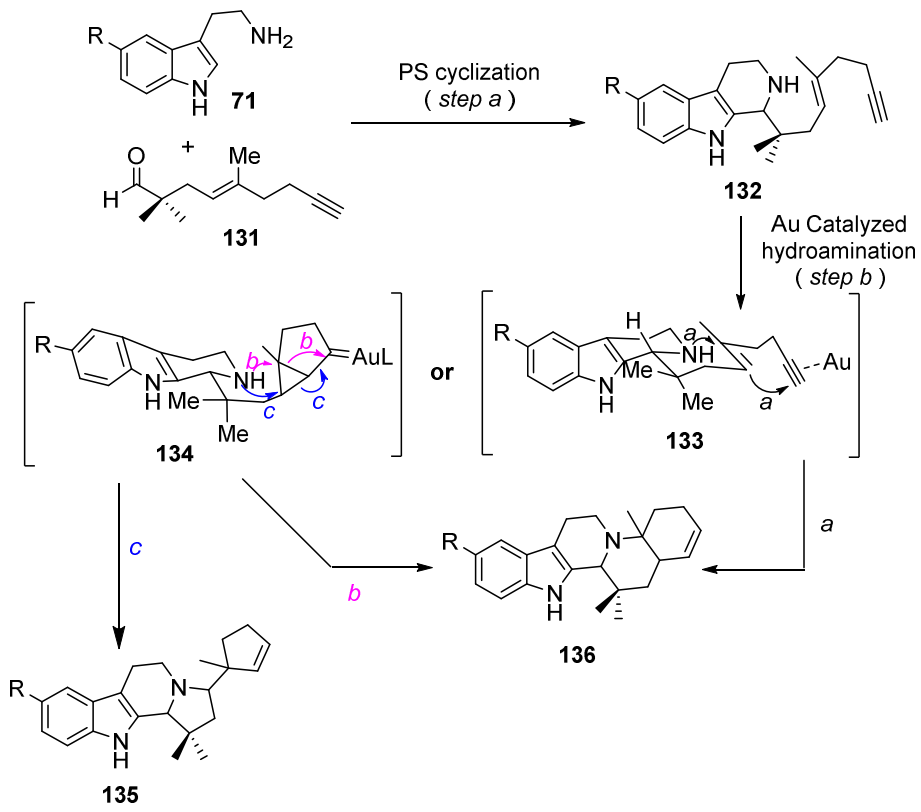
Section of the NMR spectrum showing the enamine proton H_a as a singlet.



2.5.4 Cascade polycylization of a designed *β*-carboline embodying a 1,5-enyne providing analogs of the harmicine alkaloid.

Cycloisomerization of 1,n-enynes has emerged as an efficient tool for the synthesis of complex structures in an easy one-pot process using a wide range of transition metal complexes [60-62]. Selective activation of alkynes, wide range of functional group tolerance and mild reaction conditions are important properties that have established Au as a versatile catalyst for the intramolecular enyne metathesis for substrates with carbon-carbon triple bonds [63-66].

A variety of internal nucleophiles like phenols, carboxylic acids, sulfonamides, hydroxyl functions have been successfully employed in the gold mediated polycyclization of 1,5-enynes [63, 64, 67, 68]. However presence of a tetrahydro-*β*-carboline core as an internal nucleophile in gold mediated 1,5-enyne polycylizations is not known. In view of generating polycylic indole scaffolds with higher structural complexity a gold mediated polycylization of substarte **132** (having a tetrahydro-*β*-carboline core appended to a 1,5-enyne) was investigated. Herein the secondary amine in the tetrahydro-*β*-carboline core (**132**) was expected to behave as the terminating nucleophile in the polycylization process.

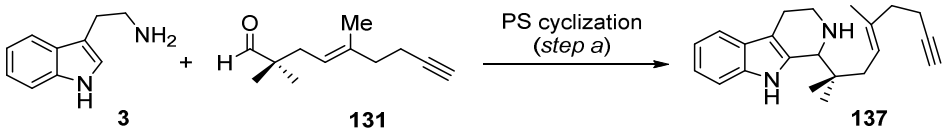


Scheme 31 – Proposed route for the polycyclization of the designed substarte **132**.

The designed model substate **132** has a tetrahydro-*β*-carboline tethered to a 1,5-enyne with a (*E*) configured alkene. This substrate could be obtained by a PS cyclization between tryptamine **71** and the non-enolisable aldehyde **131**. A successful polycylization of **132** would ensure efficient access to indole polycycles with higher structural complexity. It was assumed that activation of the alkyne in the PS product **132** by gold complexes would trigger the addition of the alkene and a concomitant addition of the secondary amine in **132** to the more stabilized carbocationic position on the alkene *(path a*) to provide the yohimbine based alkaloid scaffold **136**. Alternatively a step wise process leading to the nucleophilic opening of the cyclopropyl gold carbene **134**, can either yield scaffold **136** (*path b*) or the harmicine analogue **135** (path c) (Scheme 31) [67].

2.5.4.1 Optimization of the reaction steps (*a* and *b*)

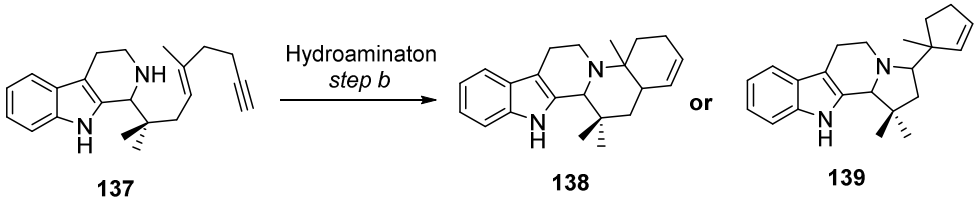
Optimization of the Pictet-Spengler cyclization *step a*



Scheme 32 - Pictet-Spengler cyclization *step a*.

Model substrates tryptamine (**3**) and non-enoliazable aldehyde (**131**) were subjected to the two previously optimized conditions for PS cyclizations to get scaffolds **73** (Scheme 22) and **100** (Scheme 28). In one condition the starting materials (**3** and **131**) were treated with 1equiv of TFA in toulene at 50^{o}C for 24h which resulted in 50% yield of the PS product **137**. Alternatively a mixture of the starting materials with 10mol% of $Yb(OTf)_3$ and ionic liquid [bmim]Cl.$AlCl_3$ (0.32ml/ mmol of **3**) in DCM was subjected to microwave irradiation for 1h at 120^{o}C resulting in 70% yield of **137**. Use of DCE as solvent further enhanced the yield of **137** to 84%. These results proved that $Yb(OTf)_3$ and ionic liquid as a catalyst system were more effective in inducing the PS cyclization as compared to TFA in this system.

Optimization of the hydroamination *step b*



Scheme 33 – Gold mediated double cyclization of **137** leading to either of the plausible products.

A reaction screening for the catalytic double cyclization cascade was then attempted with Pictet-Spengler product **137** employing various gold complexes.

Table 7 Screening of the Au mediated double cyclization cascade of PS product 137

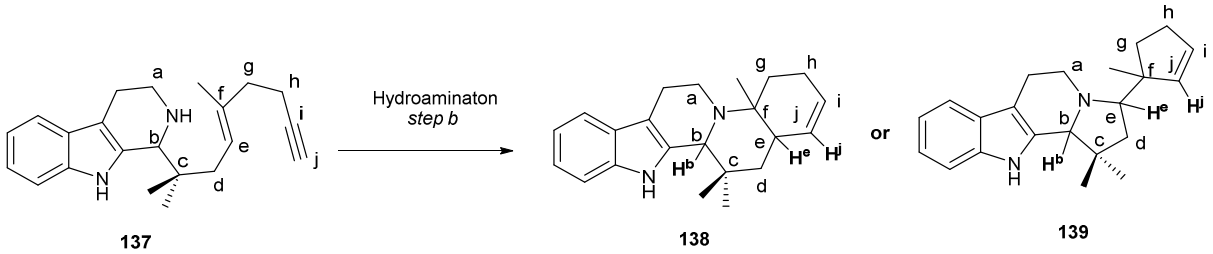
Entry	Catalyst (mol%)	Solvent	Temp (^oC)	Time (h)	Yield[a] (%)	dr[b]
1	$Au(PPh_3)OTf$ (10)	DCE	80	24	30	1 : 1.5
2	$AuCl_3$ (10)	DCE	80	24	20	1 : 1.4
3	$Au(PPh_3)NTf_2$ (10)	DCE	80	24	33	1 : 1.4
4	$AuCl(SMe_2)$ (10)	DCE	80	24	43	1 : 1.4
5	$AuCl(SMe_2)$ (10)	*i*-PrOH	80	24	15	1 : 1.2
6	$AuCl(SMe_2)$ (10)	AcN	80	24	30	1: 1.3
7	$AuCl(SMe_2)$ (10)	1.4-dioxne	80	24	24	1 : 1.2
8	Catalyst Y (10)	DCE	80	24	53	1 : 2
9	Catalyst Y (10)	DCE	80, MW	1	70	1 : 1.6
10	Catalyst Y (10)	DCE	120, MW	1	68	1 : 1.4
11	Catalyst Y (10)	DCE:Ethanol(5eq)	80, MW	1	43	1 : 1.2

[a]Isolated yield of **139** (both the diastereomers together), [b]dr minor: major diastereomer determined using crude ^1H NMR spectra.

As depicted in Table 7 the cascade double cyclization in the presence of Au(I)phosphine complexes $Au(PPh_3)OTf$ (entry 1) and $Au(PPh_3)NTf_2$ (entry 3) resulted in harmicine analogs **139** embodying a cyclopentyl ring in moderate yields as a mixture of diastereomers. The same reaction at room temperature for 24h gave very low yield of product **139**. Use of $AuCl_3$ (entry 2) gave no improvement in yields, but $AuCl(SMe_2)$ as a catalyst enhanced the yield of **139** with best results in DCE (entry 4) as solvent. Intrestingly catalyst **Y** was again most effective for the synthesis of **139** when the reaction was perfomed at 80^oC in DCE under microwave heating (entry 9). Subjecting the reaction mixture to 120^oC in microwave (entry 10) resulted in lower yield of the product. In the optimization microwave heating (entry 9) at 80^oC for 1 h proved to be more effective as compared to conventional heating (entry 8) at 80^oC for 24h. The screening resulted in **139** as a mixture of diastereomers and formation of product **138** was not observed.

2.5.4.2 Characterization of product 139 *via* NMR

The double cyclization cascade reaction (Scheme 34) during optimization always resulted in the formation of product **139** as a mixture of diastereomers and formation of product **138** was not observed. The major and minor products formed in the double cyclization cascade reaction were diasteromers was established *via* a study of the NMR data of both the diastereomers which included ^{1}H, ^{13}C and 2-D NMRs such as *g*HMBC, *g*HSQC and *g*COSy experiments.

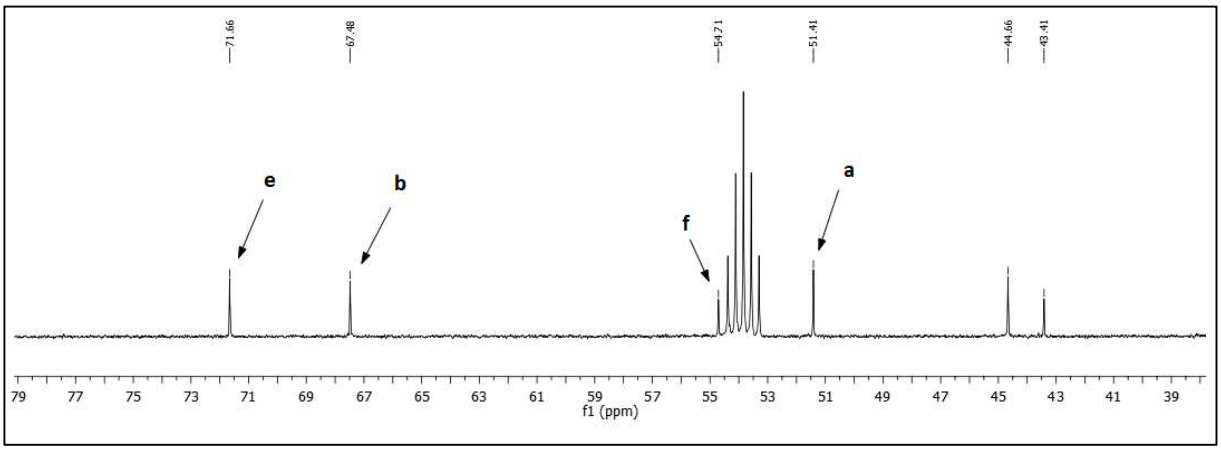


Scheme 34 – Plausible products of the gold mediated double cyclization of **137**

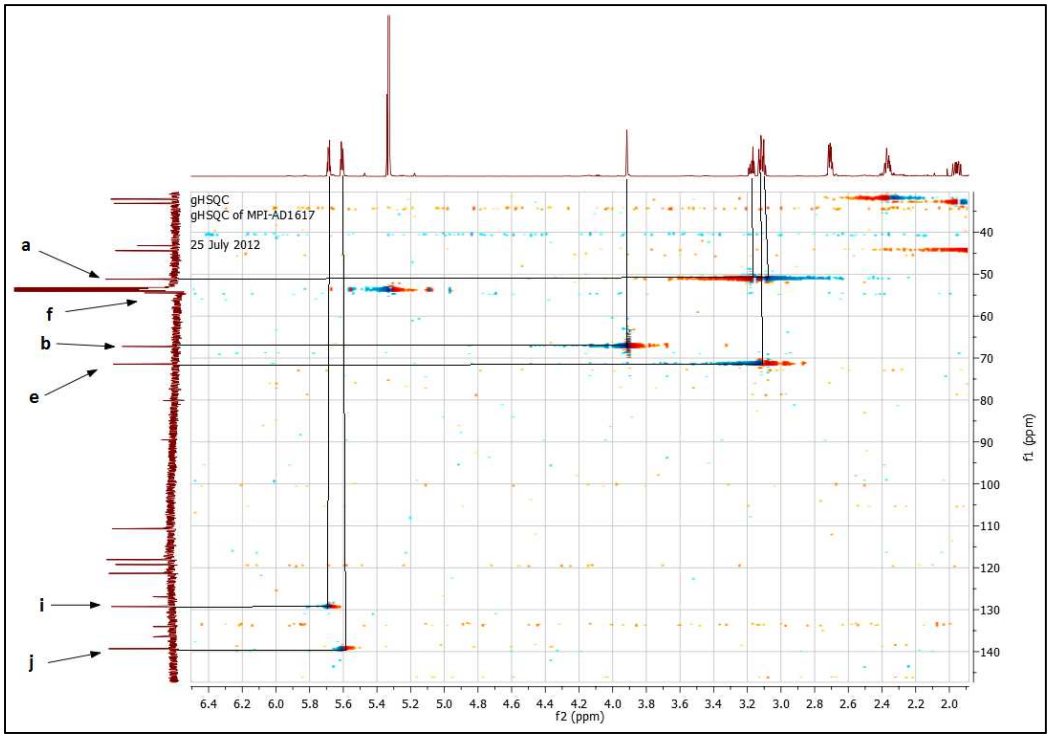
The NMR spectra of the major diastereomer of the double cyclization product was used to explain the formation of product **139**

Figure 3 – ^{13}C, *g*HSQC and *g*COSY spectra of the major diastereomer of the double cyclization product.

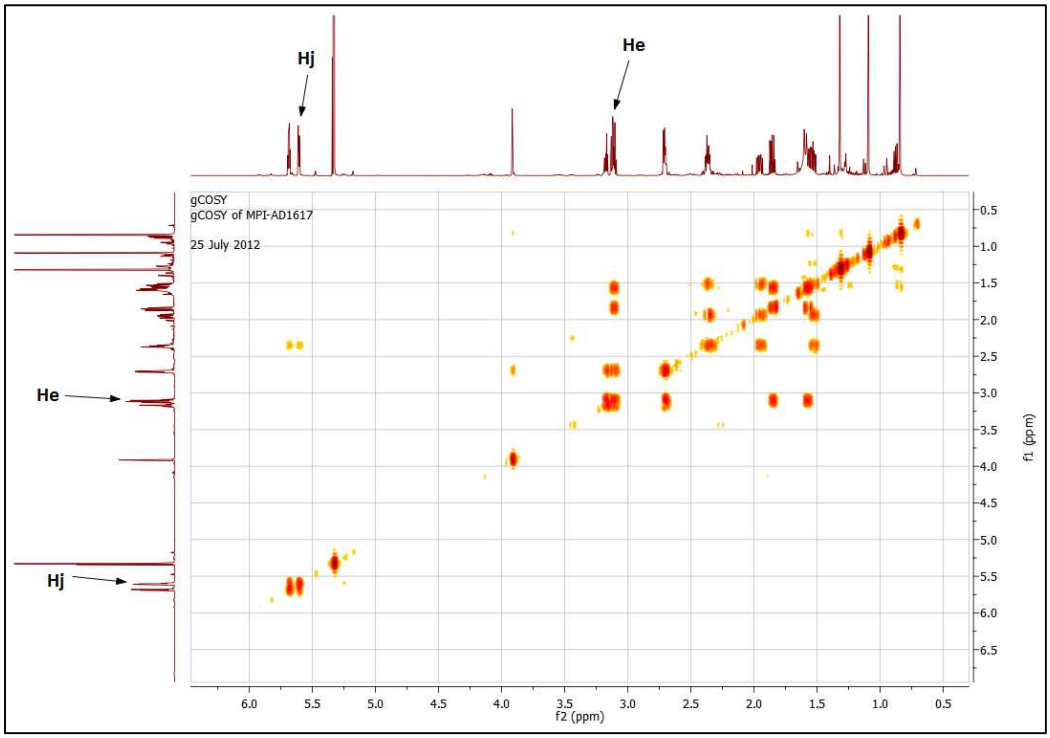
Section of the ^{13}C NMR spectrum of the major diastereomer, showing carbons **e** (71.46 ppm), **b** (67.48 ppm), **f** (54.71) and **a** (51.41 ppm)



Section of the *g*HSQC spectrum of the major diastereomer showing carbons; **b** and **e** (are not quaternary carbons); carbon **f** (is a quaternary carbon); double bond carbons **i** and **j**



Section of the *g*COSY spectrum of the major diastereomer, showing an absence of *g*COSY coupling between protons $\mathbf{H}^{e}$ and $\mathbf{H}^{j}$

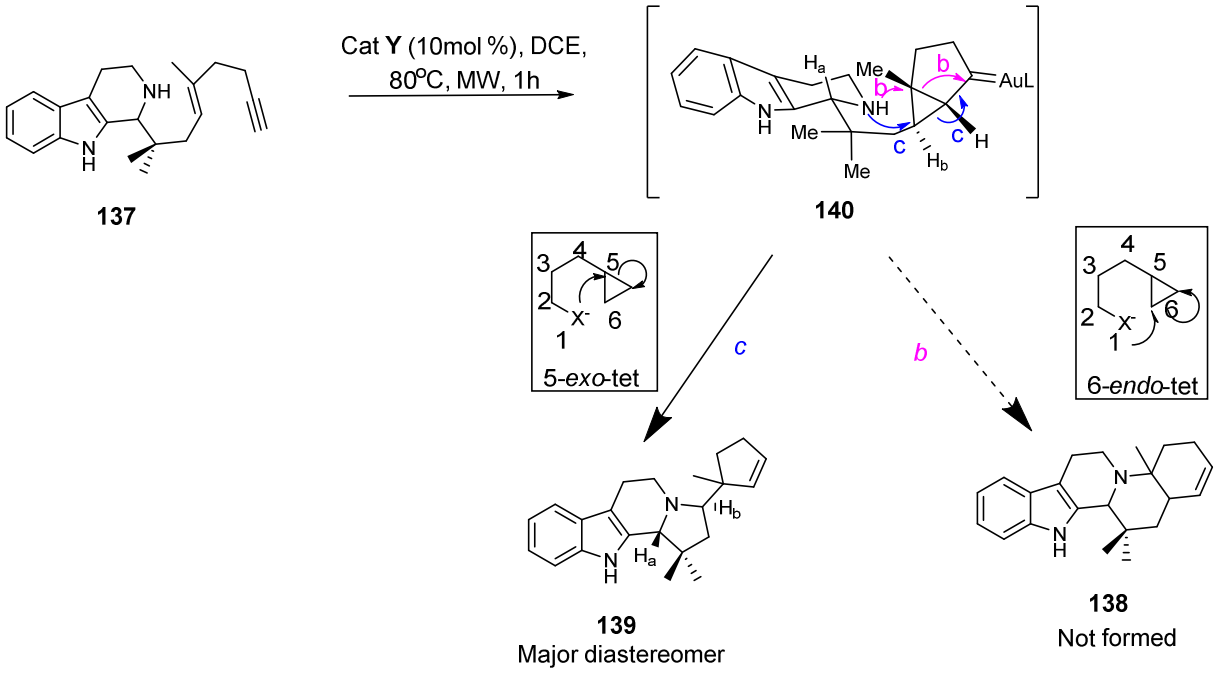


The spectra of the major diastereomer formed in the double cyclization cascade reaction (Scheme 34) depicted in Figure 3 favored the structure of product **139** due to the following conclusions; a) as depicted in the ^{13}C and *g*HSQC spectra of the major diastereomer both carbons **b** and **e** were not quaternary carbons and both of them appeared downfield (at 71ppm and 67ppm respectively) due to the deshielding effect caused by the electronegative nitrogen atom present at α position to both the carbons as in product **139**; b) absence of a *g*COSY coupling (J^3 coupling) between protons $\mathbf{H^e}$ and $\mathbf{H^j}$ (in the *g*COSY spectrum) that are attached to carbons (**e** and **j** respectively) α to each other in product **138** further supported the structure of product **139**

The above results helped us establish the formed double cyclization product as **139** for the major diastereomer. The structure of the minor diastereomer was also assigned on the basis of similar analysis of the NMR spectra.

The *syn* configuration for the minor diastereomer of **139** was established by a n*O*e signal between $\mathbf{H^b}$ and $\mathbf{H^e}$, whereas absence of this n*O*e signal in the major diastereomer of **139** pointed towards an *anti* configuration (see **Experimental Part 5.2.3.1** for 1-D NMR spectra).

2.5.4.3 Mechanism of the reaction



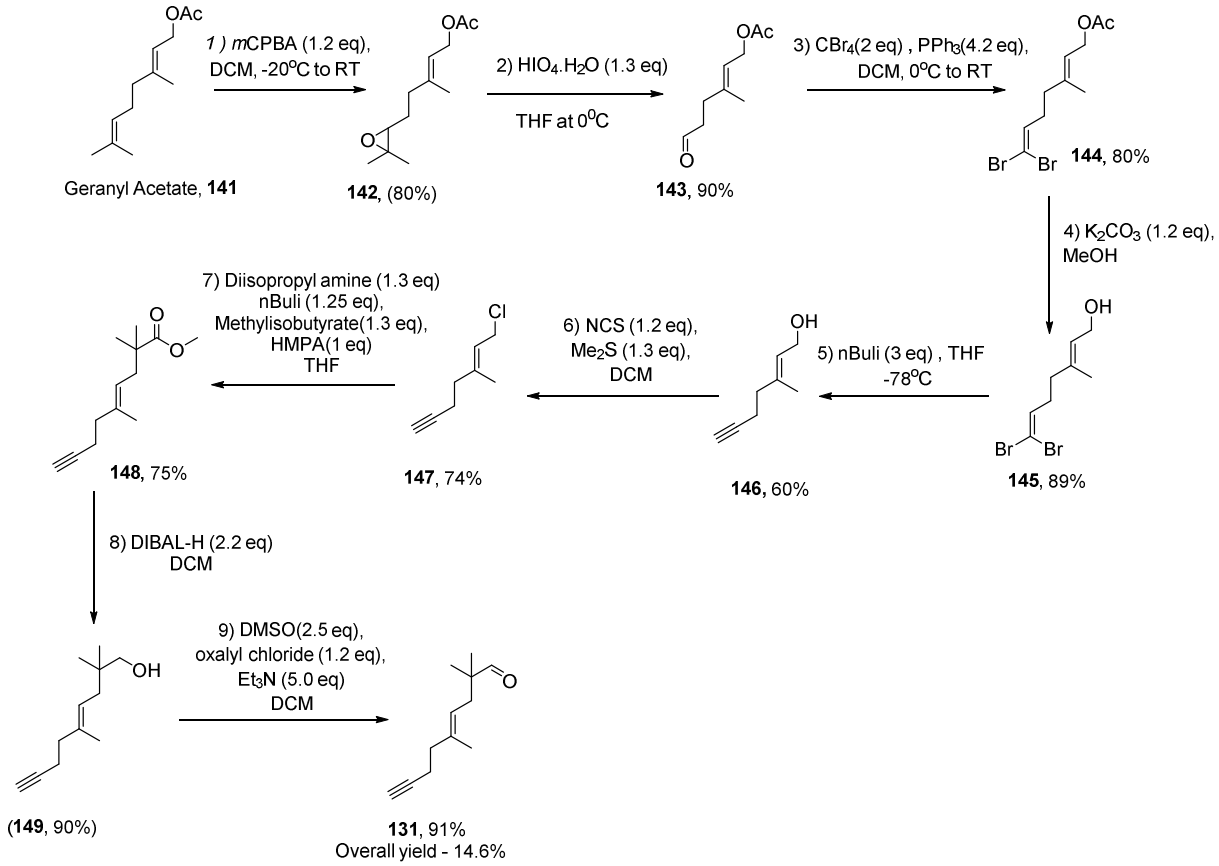
Scheme 35- Proposed mechanism for the formation of product **139**.

A mechanism was delineated to explain the double cyclization cascade reaction. In accordance with the proposal in Scheme **31**, the results indicate that the polycyclization cascade was a stepwise process that occured *via* gold mediated 6-*endo*-dig cyclization furnishing the cyclopropyl gold carbene intermediate (**140**). The selective formation of harmicine analogues **139** suggests that the ring-closure by addition of the secondary amine in a 5-*exo*-tet mode was favoured over a 6-*endo*-tet pathway which is in accordance with Baldwin´s rules, affording analogs of harmicine alkaloid **139** (Scheme 35).

2.5.4.4 Scope of the double cyclization cascade reaction

Synthesis of the aldehyde 131

The aldehyde **131** was synthesized starting from geranyl acetate over nine reaction steps with an overall yield of 14.6%



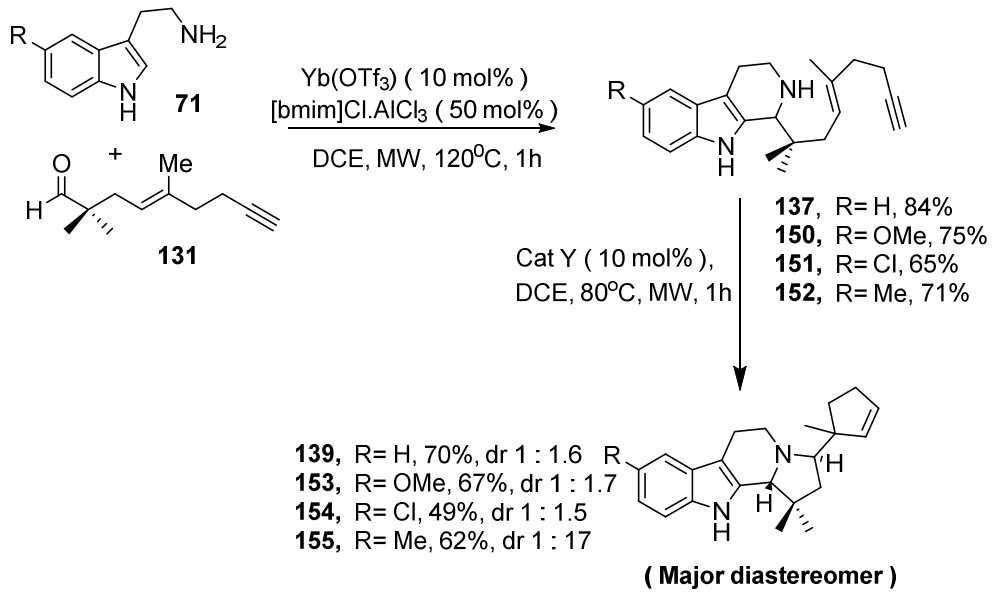
Scheme 36 - Synthetic scheme for aldehyde **131**

Commerially available geranyl acetate (**141**) which already possesses a trisubstituted alkene with (*E*) configuration was initially subjected to epoxidation with *m*CPBA followed by

epoxide ring opening in the presence of HIO_4 giving aldehyde **143** in 72% overall yield starting from geranyl acetate. The aldehyde **143** was subjected to Correy –Fuchs reaction resulting in the dibromoolefin (**144**) in 80% yield. Treatment of the dibromoolefin (**144**) to an acetate hydrolysis-elimination reaction resulted in product **146** in 54% overall yield. The compound **146** was subsequently transformed into the corresponding allylic chloride **147**, treatment of the chloride with lithium methyl isobutyrate enolate resulted in **148** with 55% overall yield starting from **146**. Subsequent reduction of the methyl ester in **148** to alcohol with DIBAL-H followed by swern oxidation resulted in the final aldehyde **131** in overall yield of 82% starting from **148** (Scheme 36)**.**

Scope of the polycyclization cascade reaction.

Tryptamines (**71**) with varied substituents at 5 position along with aldehyde **131** were subjected to the optimized conditions for both the steps.



Scheme 37 – Substarte scope for the double casade cylization reaction.

As depicted in Scheme 37 the reaction tolerated electron donating and withdrawing substituents on the tryptamine for both the steps resulting in good to moderate yields of the harmicine analogs (**139, 153-155**) as a mixture of diastereomers.

With this, the synthesis of the third indole derived scaffold **135** yielding **analogs of the harmicine alkaloid** *via* a two step protocol was achieved.

2.5 Summary

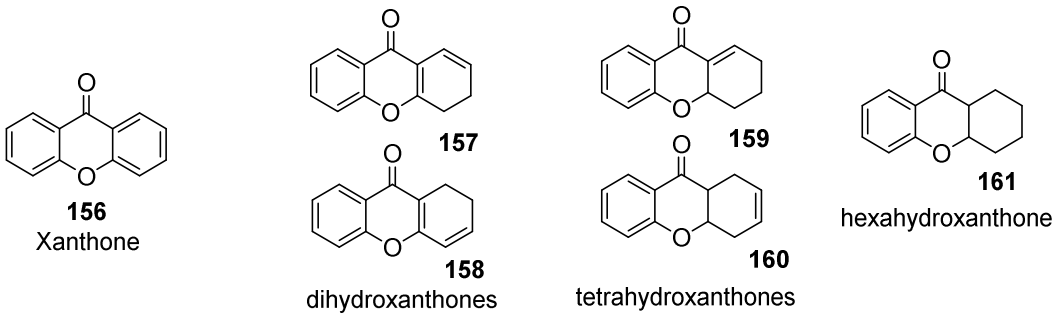
In conclusion we successfully developed a two-step catalytic process, involving a Pictet-Spengler cyclization step followed by hydroamination reaction yielding the desired indoloquinolizine (**75**) and hexacyclic indoloquinolizine (**102**) scaffolds. A Au(I) catalyzed cascade polycylization was also developed to get access to complex analogs of the harmicine alkaloid (**135**) *via* the two-step protocol.

Chapter 3

Bifunctional *N*-Acyl-Aminophosphine Catalyzed Asymmetric [4+2] Annulation of Allenoates and 3-Cyano Chromones.

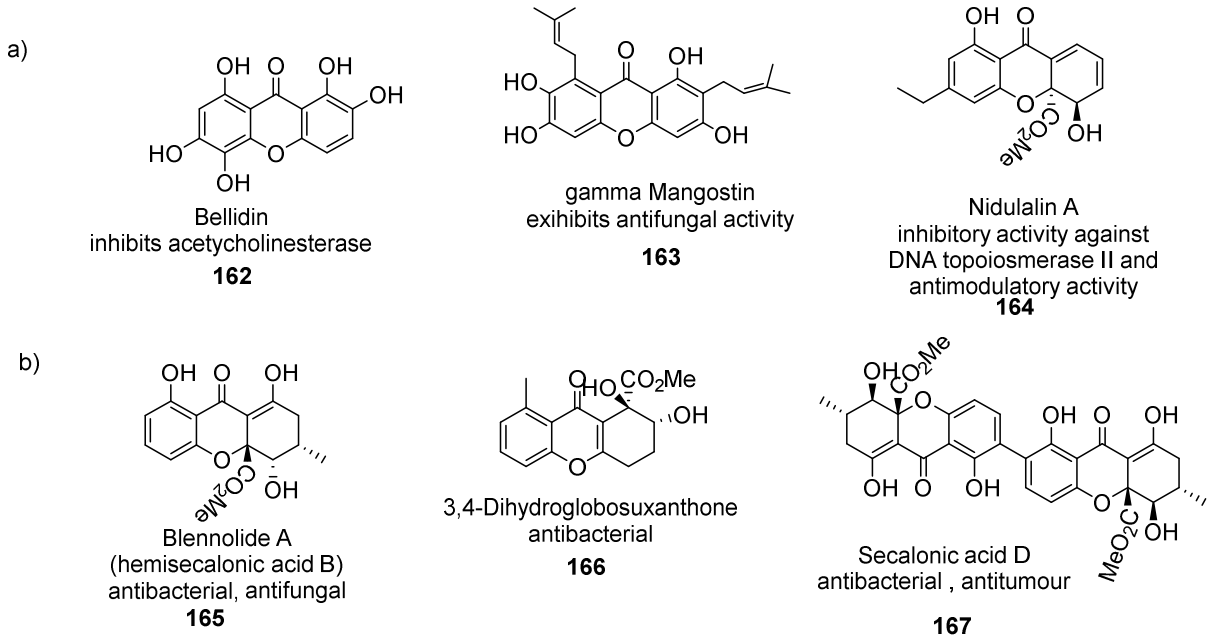
3.1 Introduction

The Xanthone nucleus **156** comprises of a class of oxygenated heterocycles with 9*H*-xanthen-9-one or xanthone as the parent compound. They are usually found as secondary metabolites in higher plants, fungi and lichens. Xanthone monomers occur as either fully aromatized dihydro- (**157, 158**), tetrahydro- (**159, 160**), or more rarely as hexahydroderivatives (**161**) as depicted in Scheme 38 [69-71].



Scheme 38 - Xanthone monomers.

Xanthones have also been reccognised as "privileged structures" because of their ability to interact with a diverse range of target biomolecules resulting in pronounced biological activity within a broad spectrum of diseased states such as antimitotic, antimalarial, antiplatelet, antitumour, antioxidant etc. They also behave as adrenergic blocking agents, calcium agonists and are also known to show effects on enzymes such as acetylcholinesterase, aldose reductase, aromatase etc.[72, 73]



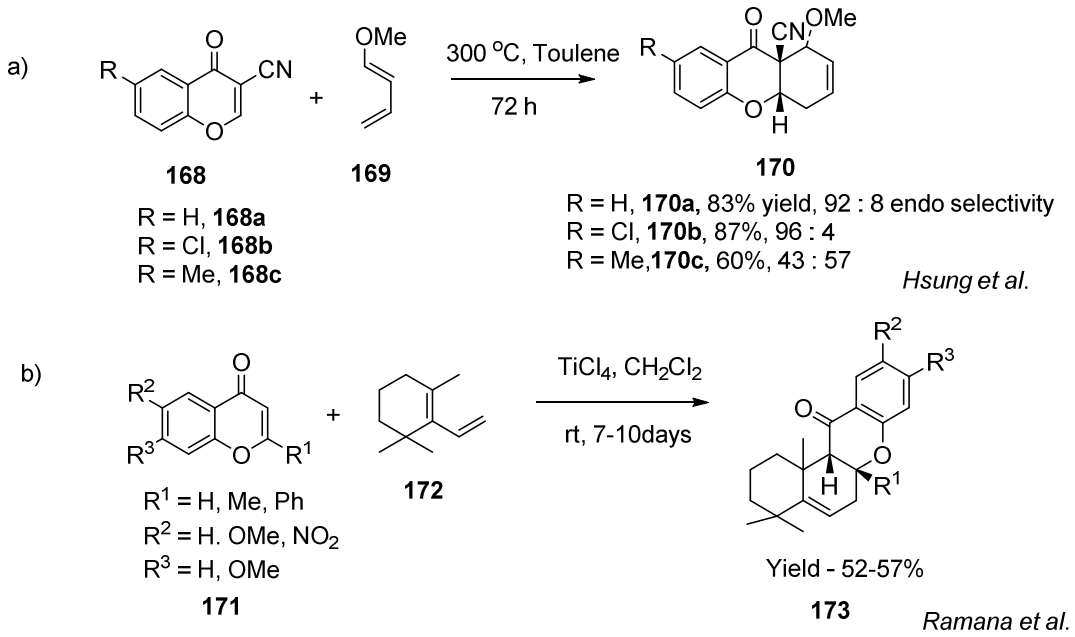
Scheme 39 – a) Naturally occuring xanthone dervatives, b) Natural products with the tetrahydroxanthone units

A few examples of biologically active xanthone analogues are depicted in Scheme 39a and b (**162-167**). Scheme 39b in particular represents natural products containing the tetrahydroxanthone unit as for example in blennolide A [74] (**165**), 3,4-dihydroglobosuxanthone (**166**) and secalonic acids (**167**) [75]. The study of xanthones and its derivatives has been of interest not only from a descriptive or synthetic point of view but also from a biological and pharmacological point of view. In literature the total synthesis of xanthone based natural products has mostly been limited to fully aromatized xanthones, whereas synthesis of the more challenging partially saturated xanthone core is less frequently reported [76].

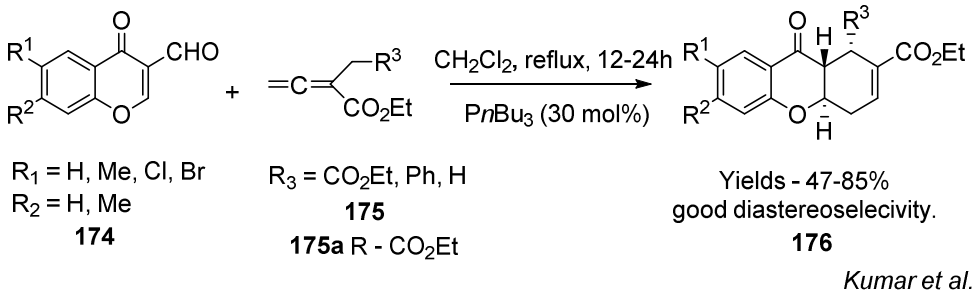
Selected examples from the literature for the synthesis of tetahydroxanthenone scaffold **160** and its derivatives are described in the following section.

In *1997 Hsung et al.* [77] reported a highly stereoselective [4+2] cycloaddition reaction of 3-cyanochromones (**168**) with electron rich dienes wherein the dienophile 3-cyano chromone (**168a**) and 1-methoxy-1,3-butadiene (**169**) in toluene were heated to 300^{o}C in a sealed tube yielding the tetrahydroxanthone scaffold (**170a**), in good yields and with good *endo* selectivity. Presence of substituents at C-6 position of the chromone ring significantly affected the rate of the reaction and the *endo* selectivity. Electron withdrawing groups such as bromine or chlorine (**168b**) at C-6 position resulted in shorter reaction times, lower reaction temperatures and high *endo* selectivity (**170b**). On the contrary electron-donating groups such as the methyl group (**168c**) reduced the stereoselectivity and needed higher temperatures and longer reaction times (**170c**) (Scheme 40a). In *2011 Ramana et al.* [78] reported a successful Diels-Alder reaction of 1,3,3-trimethyl-2-vinyl-1-cyclohexene (**172**) with chromones (**171**) in the presence of $TiCl_4$ as a Lewis acid resulting in the formation of the tetracyclic tetrahydroxanthones (**173**). The reaction was regio- and stereoselective (Scheme 40b).

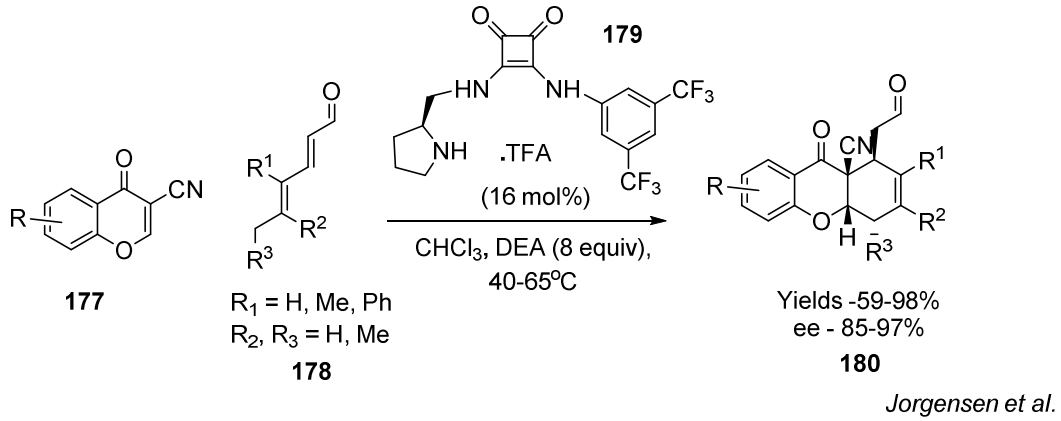
In *2011 Kumar et al.* [79] reported a phosphine catalyzed [4+2] annulation of electron deficient 3-formyl chromones (**174**) and α-alkyl substituted allenes (**175**) that followed a deformylation reaction resulting in the tricyclic cyclohexene-fused-chromone ring (**176**) in moderate to good yields and with good diastereoselectivites. The reaction tolerated differently substituted chromones and allenes. The stereodecorated common scaffold (**176**) was also subjected to further transformations to yield other naturally occurring benzopyrone and related scaffolds (Scheme 41).



Scheme 40 – Tetrahydroxanthone synthesis *via* Diels-alder reactions.



Scheme 41 – Phosphine catalyzed [4+2] annulation resulting in the tetrahydroxanthone scaffold.



Scheme 42 - Enantioselective synthesis of tetrahydroxanthones

In *2012 Jorgensen et al.* [80] reported a trienamine mediated enantioselective synthesis of tetrahydroxanthones which was based on a [4+2] cycloaddition between 2,4-dienals (**178**) and 3-cyanochromones (**177**) as dineophiles. The substrates were treated with H-bond directing squaramide based organocatalyst (**179**) in the presence of *N*,*N*-diethylacetamide (DEA) as an additive in chloroform at 60^{o}C yielding the tetrahydroxanthone scaffold (**180**). The reaction tolerated differently substituted chromones as well as substituted 2,4-dienals resulting in products (**180**) with good yields, high enantioselectivities and with excellent diastereoselectivities (>20:1) (Scheme 42).

3.2 Aim of the Project

The pronounced biological properties exhibited by the optically active tetrahydroxanthenone derivatives, their wide occurrence in nature and lack of asymmetric synthetic protocols to build this scaffold, inspired the development of a synthetic methodology that would offer a stereoselective access to a compound collection based on this naturally occurring scaffold.

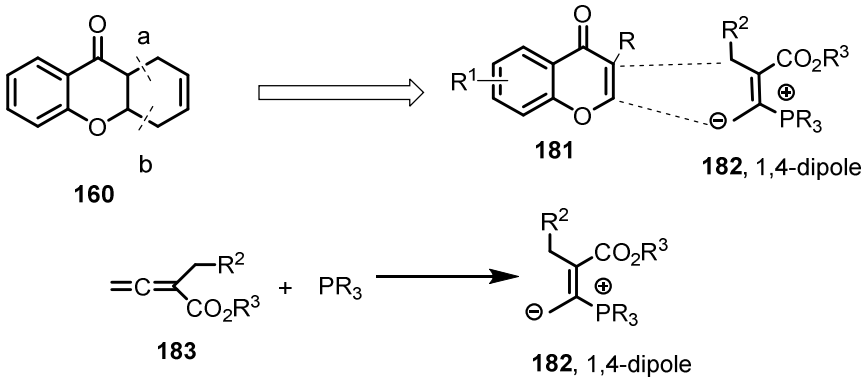
The importance of the preparation of optical isomers of small molecules is obvious from the fact that biological activity is often associated with one of the enantiomers in compounds of natural and synthetic origin. There are several methods known to obtain enantiomerically pure compounds like the classical chemical resolution procedure, but unfortunately it suffers from the disadvantage of obtaining a theoretical maximum of 50% yield of the optical isomer. The same problem exists with enzymatic resolution wherein the racemic mixture is treated with reagents of biological origin. In contrast asymmetric synthesis is a method that can provide a theoretical yield of 100% of one of the enantiomer [81]. The importance and practicality of asymmetric synthesis for obtaining enantiomerically pure compounds has been acknowledged by synthetic organic chemists, and is also visible by the explosive boom in newer and more efficient methods being developed in this regard in the last decades [82-85].

As already mentioned before (Scheme **41**) in *2011 Kamal et al.* reported a novel racemic synthesis of the tetrahydroxanthone scaffold (**160**) *via* P*n*Bu$_3$ catalyzed [4+2] annulation of electron deficient chromone and allenes [79]. Absence of an asymmetric variant of the above reaction inspired the development of an asymmetric synthesis of a compound collection embodying the tetrahydroxanthone scaffold by using nucleophillic chiral phosphine catalysts [86-88].

Nucleophillic phosphine catalysis of allenes with electrophiles like electron deficient alkenes, imines, ketones etc. is one of the most powerful and straight forward methods for the synthesis of highly functionalized carbo- and heterocyclic structural motifs present in bioactive natural products [89-96]. The tremendous growth in nucleophilic phosphine as a Lewis base catalyst over the years is attributed to several important features such as a) the reactions are highly atom-economical and usually do not produce any byproducts, b) unique and fine tunable properties of trivalent phosphines, c) the reactions are metal-free allowing the reaction to be performed on large scale , d) the reaction topologies can be controlled by judicious choice of phosphine catalyst as well as structural variations of starting materials and e) trivalent phosphines are also known for their ability to stabilize adjacent carbanions to form ylides and also their ability to behave as a good leaving group.

Despite that progress in the field of asymmetric organophosphine catalyzed reactions has been slow [86, 97] and remains unsubstantiated mainly due to the lack of suitable chiral catalysts available. Also the major part of successful work in asymmetric cycloaddition between electrophiles and allenes belongs to [3+2] [98-102] cycloaddition reactions whereas the [4+2] [103-108] variants need to be further explored. All these challenges acted as a motivation in developing a phoshine catalyzed asymmetric synthesis of the tetrahydroxanthone scaffold (**160**).

As depicted in Scheme 43, the tetrahydroxanthone scaffold (**160**) could be dissected at positions a and b leading to simple precursors ie electron deficient chromones (**181**) and a 1,4-dipole (**182**) that can be generated from α-substituted allenes (**183**) in the presence of an organophosphine catalyst (Scheme 43).

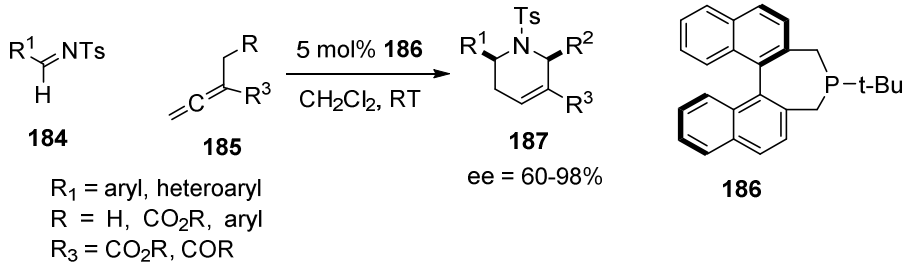


Scheme 43 - Retrosynthetic approach for the synthesis of tetrahydroxanthone derivatives.

Chromones bearing electron withdrawing substituents at C-3 position are quite reactive molecules and behave as Michael acceptors, heterodienes, as well as dienophiles. A number of chromones have been reported to undergo nucleophilic addition reactions giving rise to heterocyclic compounds as condensation products [77, 78, 109-111]. The electron deficient allene on the other hand behaves as a 1,4-dipole synthon when treated with catalytic tertiary phosphines and traps various dipolarophiles in [4+2] annulations.

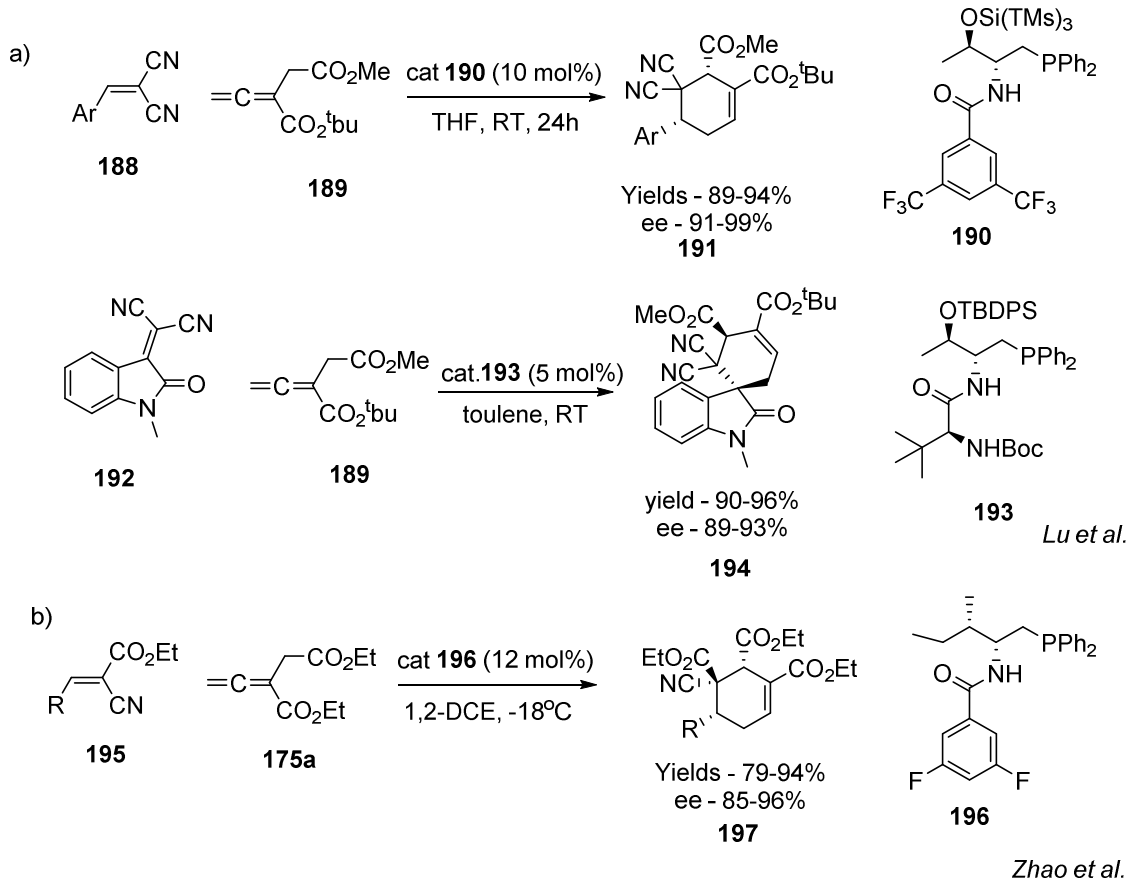
A few selected examples from literature depicting the assymetric [4+2] cycloaddition reaction between activated olefins and allenes catalyzed by organophosphine catalysts.

In *2005 Fu et al.* [108] reported an asymmetric synthesis of piperidine derivatives (**187**) *via* [4+2] annulation of imines (**184**) and allenes (**185**) catalyzed by the chiral phosphine (**186**). The reaction tolerated a range of imines resulting in excellent diastereo- and enantioselectivities. The [4+2] annulation proceeded best if the allene beared an R group that can stabilize an anion (eg ester or aryl). For an unsubstituted allene (R = H) moderate enantioslectivity was observed (Scheme 44).



Scheme 44 – Chiral phosphine (**186**) catalyzed [4+2] annulation of imines and allenes furnishing piperidine derivatives (**187**)

In 2012 *Lu et al.* [112] reported the first highly enantioselective [4+2] annulation of activated dicyano alkenes (**188**) with α-alkyl substituted allene (**189**) catalyzed by amino-acid based bifunctional phosphine (**190**) yielding optically enriched functionalized cyclohexenes (**191**). The reaction tolerated different aryl groups on the alkene resulting in moderate to good diastereoselectivities and excellent enantioselectivities. However alkenes derived from aliphatic aldehydes failed to provide the desired annulation. Similar reaction of isatin derived alkene (**192**) with allene (**189**) in the presence of a dipeptide based phosphine catalyst (**193**) afforded 3-spirocyclohexene-2-oxindole (**194**) in high yields with excellent diastreo- and enantioselectivities (Scheme 45a).



Scheme 45– Phosphine catalyzed assymetric [4+2] annulation between activated alkenes and α-alkyl substituted allenes.

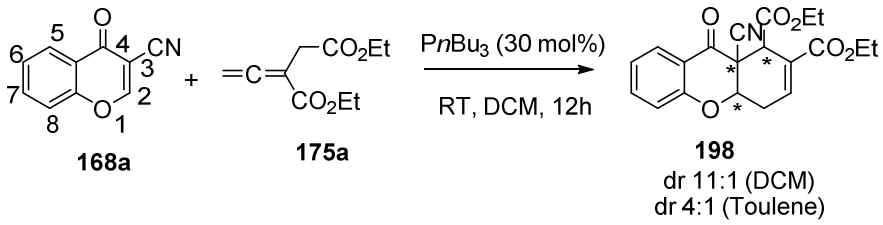
In the same year *Zhao et al.* [113] described a similar [4+2] cycloaddition reaction between activated alkenes (**195**) and α-alkyl substituted buta-2,3-dienoate (**175a**) in the presence of *N*-acyl aminophosphine catalyst (**196**) yielding the optically enriched cyclohexene adducts (**197**) with three contiguous stereogenic centres. The reaction tolerated differently substituted olefins yielding the corresponding adducts in good yields as well as with excellent diastreo- and enantioselectivities. Interestingly aliphatic substituent such as isopropyl in place of the R group (in **195**) also resulted in 92% yield and 97% ee. This result stands out as in the previous study alkenes derived from aliphatic aldehydes were unable to undergo the [4+2] annulation (Scheme 45b).

3.3 Results and Discussion

In view of the biological importance of the tetrahydroxanthone scaffold and its derivatives, a study on developing an organophosphine catalyzed assymetric [4+2] cycloaddition reaction between electron deficient chromones (**181**) and α-alkylsubstituted allenes (**183**) as depicted in Scheme 43 was initiated.

Phosphine catalyzed [4+2] cycloaddition reaction with 3-cyano chromone 168a and α-alkyl substituted allene 175a.

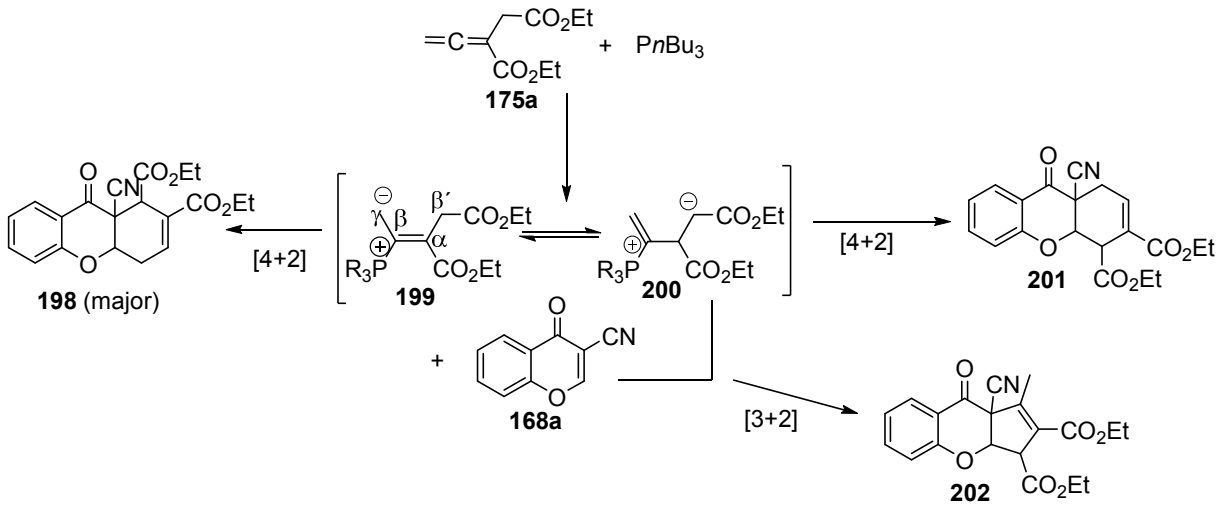
3-Cyano chromone (**168a**) was chosen over 3-formyl chromone (Scheme 41) along with α-alkyl substituted buta-2,3-dienoate **175a** (Scheme 46) for the optimization of the [4+2] annulation reaction for primarily 2 reasons; a) the inherent instability of the β-formyl group tends to negatively influence the yield and diastereomeric ratio of the ensuing product and b) a cyano function would create an all-carbon-quaternary center in the desired tetrahydroxanthones which is a formidable synthetic challenge. Initially the reaction of **175a** and **168a** was tested with 30 mol% of P*n*Bu$_3$ as catalyst in DCM at room temperature for 12h. The cycloadduct (**198**) was obtained in 75% isolated yield and with good diastereoselectivity (11:1). Heating the reaction to reflux in DCM improved the yields to 90% but reduced the diastereoselctivity to 9:1. Use of toluene as a solvent for the reaction at room temperature for 12h resulted in 80% yield of (**198**) but with a loss in diastereoselectivity (4:1). These results indicate the importance of the role of solvent in the [4+2] annulation, especially on the diastereoselectivity of the reaction.



Scheme 46- P*n*Bu$_3$ catalyzed [4+2] annualtion reaction of 3-cyano chromone with allene **175a**.

Characterization of the [4+2] annulation product 198 *via* NMR

Nucleophillic addition of P*n*Bu$_3$ to allene **175a**, results in the formation of the phosphonium dienolate intermediate **199**, which can add to 3-cyano chromone *via* the γ-carbon yielding the [4+2] annulation product **198**. Although it seems quite difficult, a conjugate addition of the phosphonium enolate in isomeric form **200** to 3-cyanochromone would furnish the [4+2] adduct **201**. A similar conjugated addition of the ylide **200** may trap the chromone in a [3+2] annulation yielding adduct **202**.



Scheme 47 – Possible products formed on phosphine catalyzed annulation of **175**a and **168a**

The major and minor products formed in the [4+2]-annulation reaction were diastereomers of compound **198** resulting from the γ-addition of allene derived zwitterion. This was established *via* a study of NMR spectra of both the diastereomers which included ^{1}H, ^{13}C and 2-D NMRs such as gHSQC and gCOSy experiments.

Proton NMR of the major diastereomer was used to explain the formation of a [4+2] adduct (either **198** or **201**) and not a [3+2] adduct **202**. The presence of CH_2 protons H^a in the ^{1}H NMR spectra of **198**, as well as absence of a methyl peak as a singlet in the spectrum ruled out the formation of the [3+2] product **202** (Figure 6, ^{1}H NMR).

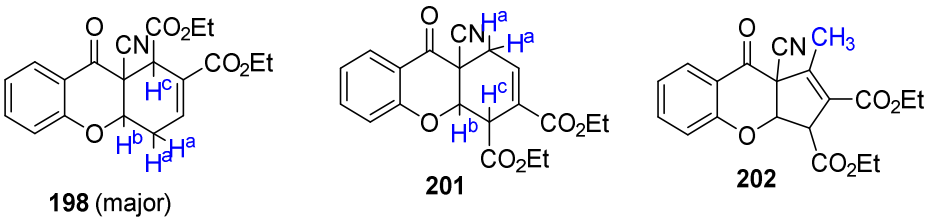
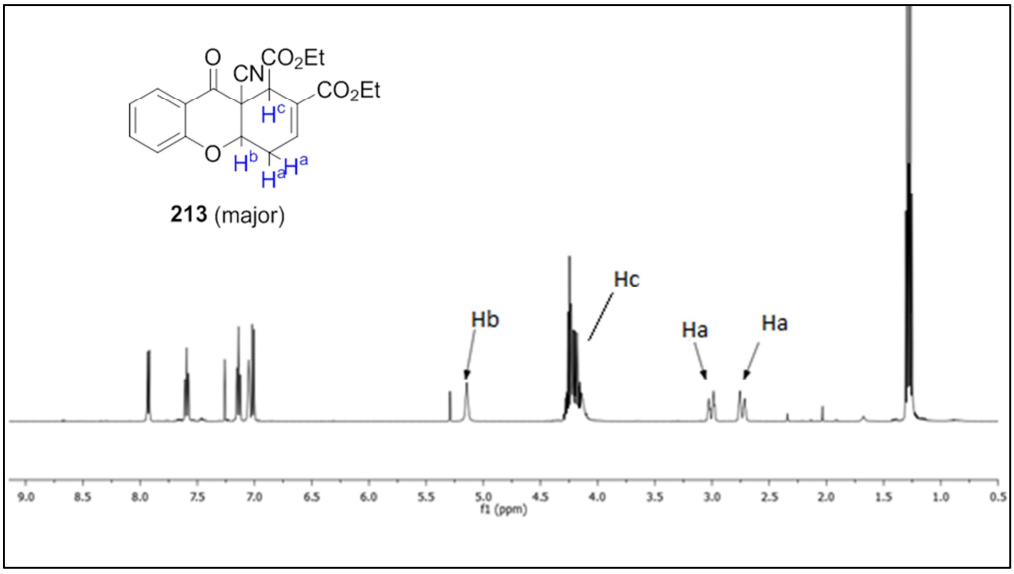
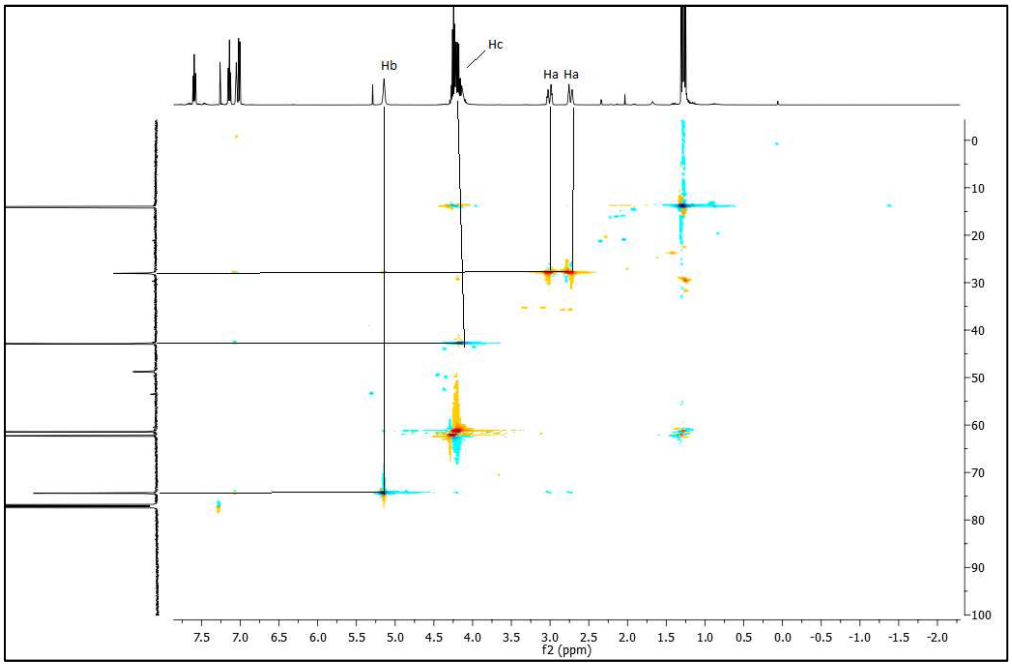


Figure 4 – Possible products of the phosphine catalyzed annulation

Figure 5 – ^{1}H NMR and *g*HSQC spectra of the major diastereomer formed in the [4+2] annulation reaction.



Section of the proton NMR spectrum of the major diastereomer formed in the [4+2] annulation reaction depicting protons H^a, H^b and H^c.

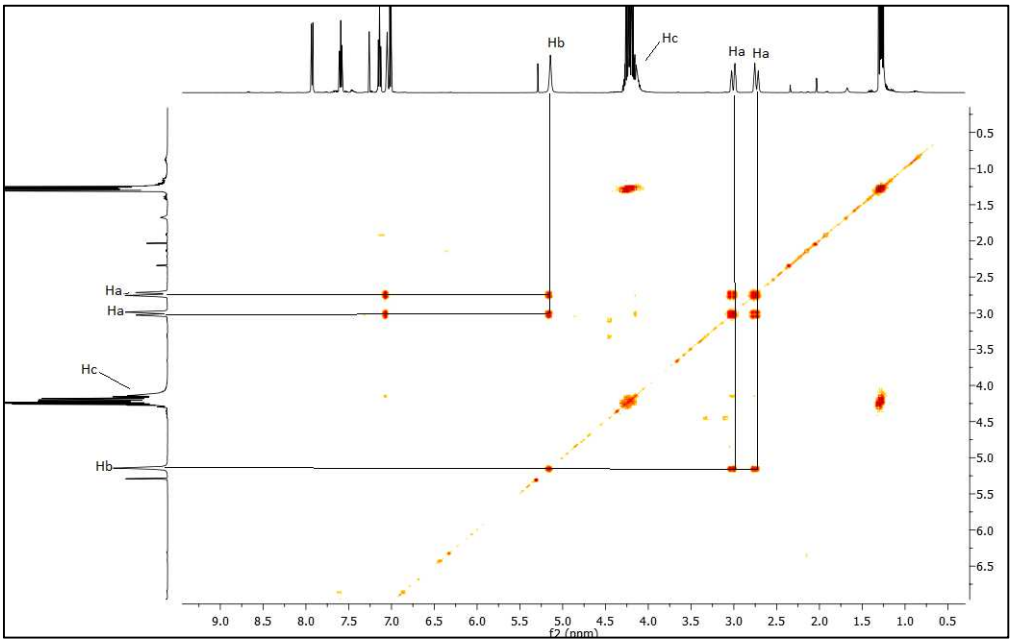


Section of the *g*HSQC spectrum of the major diastereomer formed in the [4+2] annulation reaction depicting protons H^a as CH_2 protons.

2-D *g*COSY spectra (Figure 6) of the major diastereomer was used to explain the formation of the [4+2] γ-addition product **198**. As seen in Figure 6 a strong *g*COSY coupling between the CH_2 protons (H^a) and proton H^b (J^3 coupling), and an absence of a *g*COSY coupling in the

spectrum between protons H^b and H^c that are attached to carbons α to each other in product **201**, helped us establish the [4+2] adduct as a γ-addition product **198** for the major diastereomer.

Figure 6 – Section of *g*COSY spectra of the major diastereomer **198** depicting gCOSY coupling between protons H^a and H^b, and absence of gCOSY copling between protons H^b and H^c



The structure of the minor diastereomer was also assigned on the basis of similar analysis of NMR spectra and further corroborated by single crystral X-ray structure of one of the adducts formed during our asymmetric reaction development.

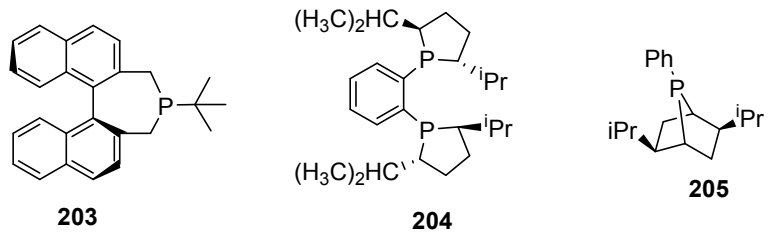
3.3.1 Optimization of the phosphine catalyzed asymmetric [4+2] annulation reaction between 3-cyano chromone and α-substituted allene esters.

With promising results with the racemic version of the [4+2] annulation we went ahead to optimize the asymmetric version of the reaction.

Chiral organophosphine catalysts

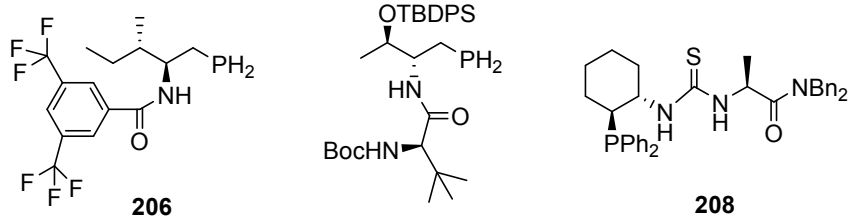
The chiral organophosphine catalysts found in literature can be divided in two broad categories i.e. a) chiral phosphines without additional functionalities, b) chiral phosphines with hydrogen bond donors as depicted in Scheme 48 [114].

a) Chiral phosphines without additonal functionality



203 **204** **205**

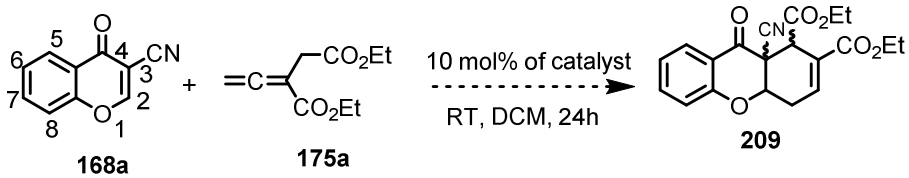
b) Chiral phosphines with hydrogen bond doners



206 **207** **208**

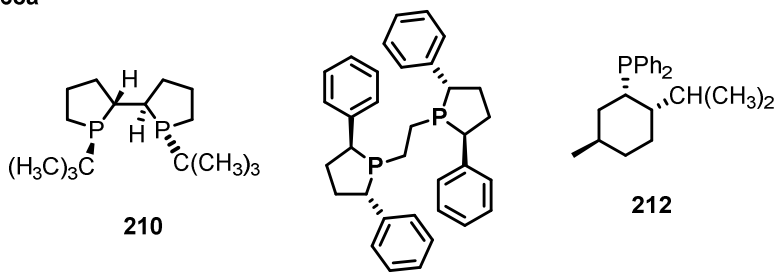
Scheme 48 – Chiral phosphines used in nucleophilic phosphine catalysis

[4+2] annulation of 3-cyano chromone with allenoate 175a catalyzed by chiral phosphines without additional functionality.



168a **175a** **209**

Catalysts :-



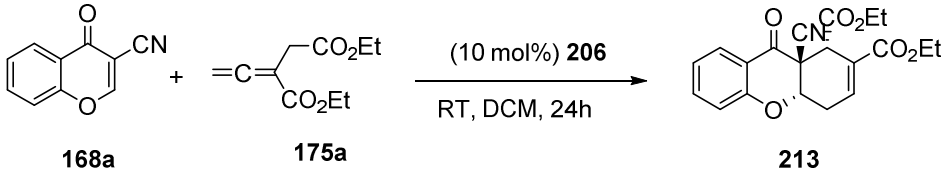
210 **211** **212**

Scheme 49 – [4+2] annulation in the presence of chiral organophosphine catalysts without additional functionality.

In the initial screening starting materials 3-cyano chromone (**168a**) and α-alkyl substituted buta-2,3-dienoate **175a** were treated with 10 mol% of chiral phosphines (as depicted in Scheme 49) along with catalyst **203** and **204** (Scheme 48) in DCM at room temperature for 24h. All the chiral catalysts without additional functionality failed to provide the desired [4+2]

adduct **209**. Neither refluxing the reaction mixture in DCM for 24h nor changing the solvent to toluene (at room temperature or reflux) resulted in the desired [4+2] adduct.

[4+2] annulation of 3-cyano chromone with allenoate 175a catalyzed by chiral phosphines with H-bond doners.



168a **175a** **213**

Scheme 50 – [4+2] annulation in the presence of chiral phosphine **206**

With no success with chiral phosphine catalysts without additional functionality (**203-204, 210-212**), chiral phosphines with hydrogen-bond doner functions were next employed to catalyze the [4+2] annulation (Scheme 50). Based on previous reports by *Lu et al.* [112] and *Zhao et al.* [113] (as depicted in Scheme 45) amino-acid derived chiral phosphines were employed as organophoshine catayst in the desired [4+2] annulation between 3-cyano chromone and allene **175a** [115]. Treatment of a mixture of **168a** and **175a** with 10 mol% of the catalyst **206** (*L-iso*leucine based aminophosphine) in DCM at room temperature for 24h yielded the desired [4+2] annulation product **213** in 52% yield, with moderate diastereoselectivity 1: 3.5 and excellent enantioselectivity (93%) for the major diastereomer. The asymmetric version of the [4+2] annulation yielded both the diastereomers as [4+2] γ-addition products similar to the ones in the racemic reaction (established *via* proton NMR), however with a reversal of preferred diastereoselectivity ie the major diastereomer in the racemic reaction, turned out to be the minor one in the asymmetric variant of the reaction. Encouraged by the initial result with catalyst **206**, a small library of amino-acid derived phosphine catalysts were synthesized to further improve the result.

3.3.2 Synthesis of amino acid derived phosphine catalysts

α-amino acid derived aminphosphines and there *N*-protected counterparts have been used as efficient chiral ligands in metal catalyzed reactions. Their modular backbones and bifunctional structures have also established them as efficient organocatalysts in recent years.

The general structural design of the amino-acid derived phosphine is depicted in Figure 7 which consists of a modular chiral backbone and tunable H-binding site which is mostly responsible for the assymetric induction and a highly nucleophillic phosphine site.

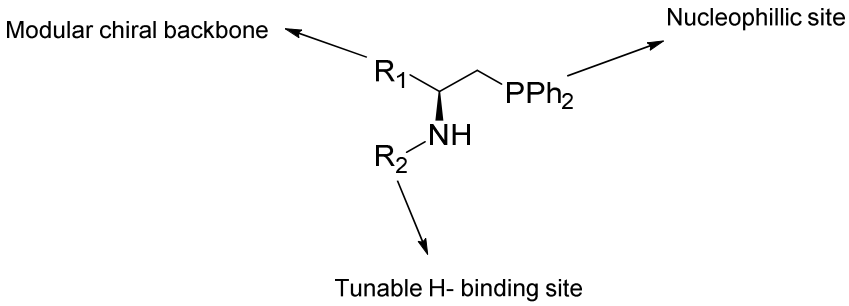
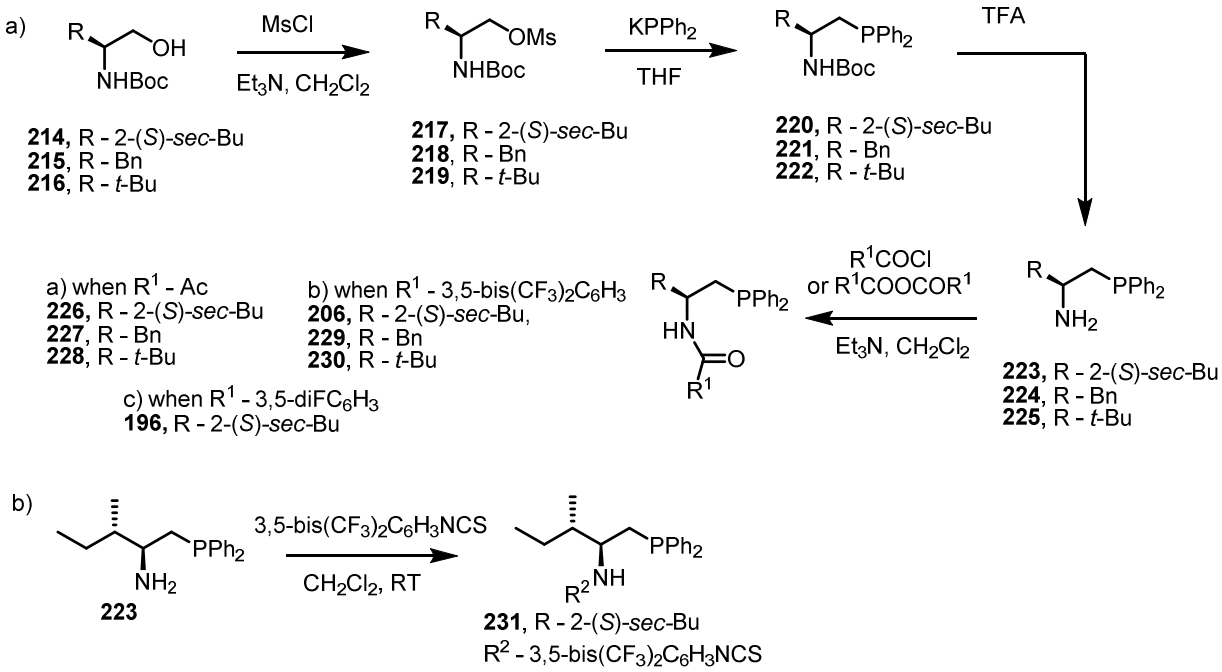


Figure 7 – Structural design for the amino-acid derived phosphine catalysts

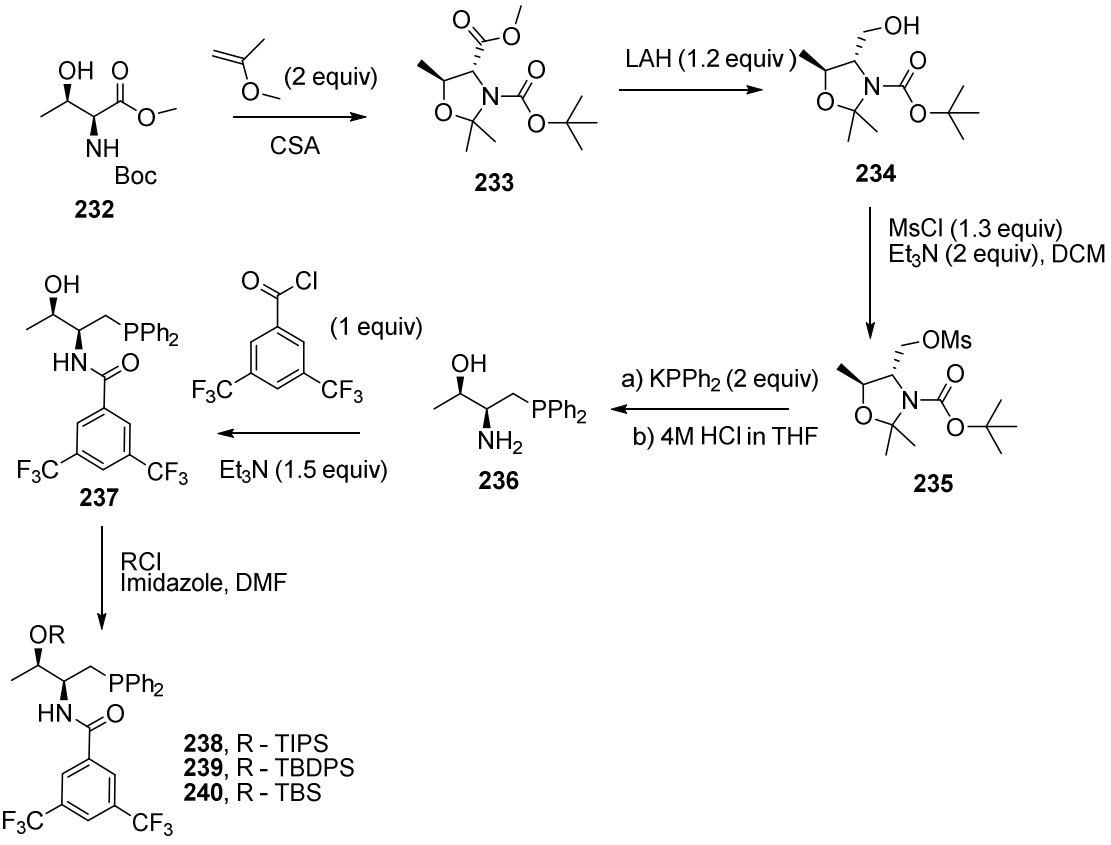
Based on the general structural design a small library of aminophosphines was synthesized to make a reaction screening and identify the best catalyst.



Scheme 51 – a) Synthetic scheme for the preparation of isoleucine-, valine-, phenyl alanine derived aminophosphines; b) synthesis of aminophosphine **231** from the corresponding free amine.

As depicted in Scheme 51, *L*-isoleucine-, *L*-tertleucine-, *L*-phenyl alanine based *N*- acyl aminophosphines could be easily accessed from the corresponding *N*-Boc protected amino alcohols in four synthetic steps. The amino alcohols (**214- 216**) were initially subjected to *O*-

mesylation using MsCl (**217-219**), followed by treatment with potassium diphenylphosphine yielding the boc-protected aminophosphines (**220-222**). The boc-protected aminophosphines on treatment with TFA yielded the free amines (**223-225)**, which were subjected to treatment with various acid chlorides or anhydrides resulting in a) acetyl-protected (**226-228**); b) 3,5-(bistrifloromethyl)benzoyl protected (**206, 229-230**) and lastly c) 3,5-diflorobenzoyl (**196**) protected aminophosphines. Thiourea protected aminophosphine **231** was obtained by treating the corresponding free amine (**223**) with 3,5-bistrifloromethyl phenyl isothiocyanate at room temperature in DCM as solvent.

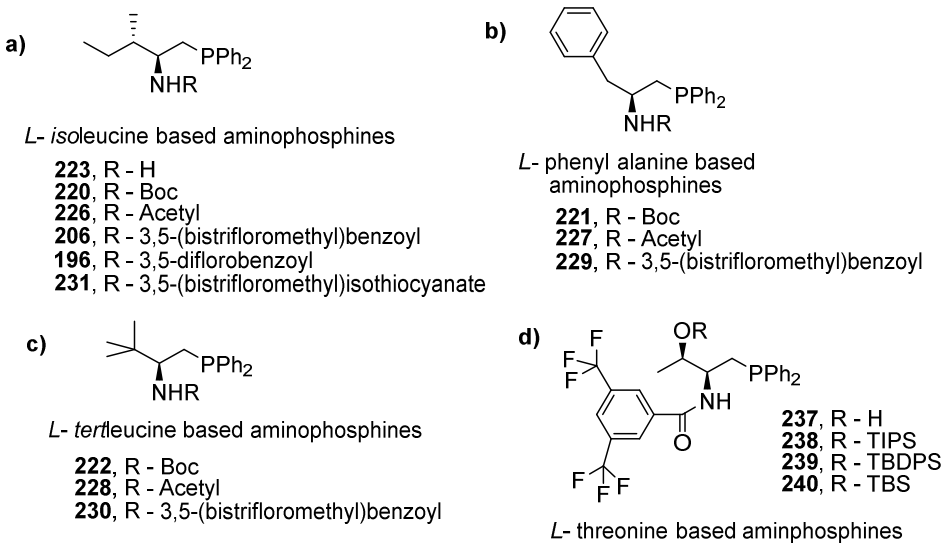


Scheme 52 – Synthetic procedure for the synthesis of *L*-threonine based aminophosphines.

The *L*- threonine based aminophosphines were synthesized according to the procedure depicted in Scheme 52. Commercially available *N*-Boc-*L*-threonine methyl ester (**232**) was treated with methoxypropene in the presence of camphor sulphonic acid yielding the oxazolidine ring (**233**), which was subjected to LAH reduction followed by mesylation furnishing the mesyl protected oxazolidine alcohol (**234**) [116]. Compound **234** was treated with potassium diphenyl phosphine followed by treatment with 4M HCl in THF yielding the aminophosphine **236**. The free amine in **236** was subjected to amide protection with 3,5-

(bistrifloromethyl) benzoyl chloride yielding aminophosphine (**237**), followed by *o*-silylation with varied acid chlorides providing aminophosphines **238- 240**.

Following the synthetic procedures stated in Scheme 51 and 52 a small library of amino-phosphines was synthesized as depicted in Scheme 53.



Scheme 53- Amino acid derived *N*-acyl aminophosphines.

3.3.3 Asymmetric [4+2] annulation of 3-cyano chromone with allenoate 175a catalyzed by amino-acid derived phosphines.

The catalytic efficiency of the amino-acid derived phosphines (Scheme 53) for the [4+2] annulation between 3-cyano chromone and allenoate **175a** was studied and the results are presented in Table 8. The reactions were performed with 10 mol% of catalyst in DCM (resulting in 1M concentration of the reaction mixture) at room temperature for 24h.

The influence of different *N*-protecting groups (Brønsted acid moieties) on the [4+2] annulation was examined with catalysts derived from *L*-isoleucine. Phosphines with free amine group (Table 8, entry 1) and strong hydrogen bond donating group ie thiourea (entry 2) failed to provide sufficient activation for the reaction and no [4+2] product **213** was formed. Phosphines with less acidic acetyl (entry 3) and carbmate (entry 4) groups were found to be better catalyst yielding the [4+2] adduct **213** with good enantioselectivites but poor yields and diastereoselectivities. Aminophosphine (**206**) bearing the 3,5(bistrifloromethyl)benzoyl group (entry 5) turned out to be the best in the group furnishing the cycloadduct **213** in moderate yield (52%) and diastereoselectivity (1: 3.5) but with excellent enantioselectivity (93%). Examination of catalysts with other chiral back bones such as *L*-phenyl alanine (entries 7-9),

*L-tert*leucine (entries 10-12), did not result in any improvement. It appears that the 3,5(bistrifloromethyl)benzoyl group (entries 9 and 12) is a more efficient *N*-protecting group as compared to the carbmate (entries 7 and 10) and acetyl (entries 8-11). Among the three aminophosphines derived catalysts *L-iso*leucine (entry 5, **206**), *L-tert*leucine (entry 12, **230**) and *L*-phenyl alanine (entry 9, **229**) bearing the 3,5-(bistrifloromethyl)benzoyl group, the one with *L*-isoleucine chiral backbone (**206**) was found to be the best catalyst in this asymmetric [4+2] annulation reaction.

Table 8 – [4+2] annulation catalyzed by amino-acid derived phosphines.

Entry	Catalyst (10 mol%)	Yield[a] %	dr[b] (minor: major)	ee[c] (%)
1	**223**	NR	-	-
2	**231**	NR	-	-
3	**226**	29	1 : 1.7	87
4	**220**	30	1 : 1.2	72
5	**206**	52	1 : 3.6	93
6	**196**	60	1 : 3.5	91
7	**221**	< 15	ND	ND
8	**227**	29	1 : 1.5	85
9	**229**	32	1 : 2	89
10	**222**	25	1 : 1	57
11	**228**	30	1 : 1.2	63
12	**230**	55	1 : 3	93
13	**238**	NR	-	-
14	**237**	83	1 : 3.5	95

[a] isolated yield of product 213, [b] Determined *via* ^{1}H NMR analysis of the crude poduct,[c] enantioselectivity of the major diastereomer was determined by chiral HPLC.

o-silylated (TIPS) *L*-threonine based phoshine amide (entry 14, **238**) that also supported by the 3,5-(bistrifloromethyl)benzoyl group turned out to be the most effective catalyst yielding the [4+2] cycloadduct with excellent enantioselectivity (95%) and enhanced yield (83%). Unfortunately the reaction still suffered from poor diastereoselectivity. *L*-threonine based phoshine amide with a free –OH group (entry 13, **237**) failed to catalyze the above [4+2] annulation reaction.

3.3.4 Effect of solvent on the [4+2] annulation.

A catalyst screen in the earlier section revealed *L*- threonine based phosphine amide (**238**) to be the most effective catalyst for the above annulation yielding the [4+2] adduct **213** in good yield and with excellent enantioselectivity, but unfortunately the reaction suffered from poor diastereoselectivity. In order to improve the diastereoselectivity of the above reaction (Scheme 50) the effect of solvents on the aminophosphine **238** catayzed [4+2] annulation was investigated. The reaction was stirred at room temperature for 24 h, with 1 M concentration of the reaction mixture.

Table 9 – Effect of solvent on the [4+2] annulation catalyzed by aminophosphine 238.

Entry	Solvent	Yield[a] %	dr[b] (minor: major)	ee[c] (%)
1	CH_2Cl_2	83	1 : 3.5	95
2	THF	51	1 : 5.6	93
3	Toulene	43	1 : 4.5	97
4	Ether	<20	1 : 1.8	ND
5	1,4-dioxane	81	1 : 11	96.7
6	Ethyl acetate	35	1 : 4.8	93

[a] isolated yield of product 213, [b] Determined *via* ^{1}H NMR analysis of the crude poduct,[c] enantioselectivity of the major diastereomer determined by chiral HPLC.

As depicted in Table 9, non-polar solvents such as DCM (entry 1), toluene (entry 3) and 1,4-dioxane (entry 5) resulted in better yields, enantioselectivities and diastereoselectivities as compared to polar aprotic solvents such as THF (entry 2) and ethyl acetate (entry 6). The most prominent effect was displayed by 1,4-dioxane which yielded the [4+2] adduct in excellent enantioselectivity of 96.7%, high yield (81%) and importantly with very high diastereoselectivity (1:11).

With solvent playing an important role in the reaction, the effect of solvent concentration on the [4+2] annulation reaction was studied as depicted in Table 10, in the presence of 10 mol% of catalyst **238** at room temperature for 24 h.

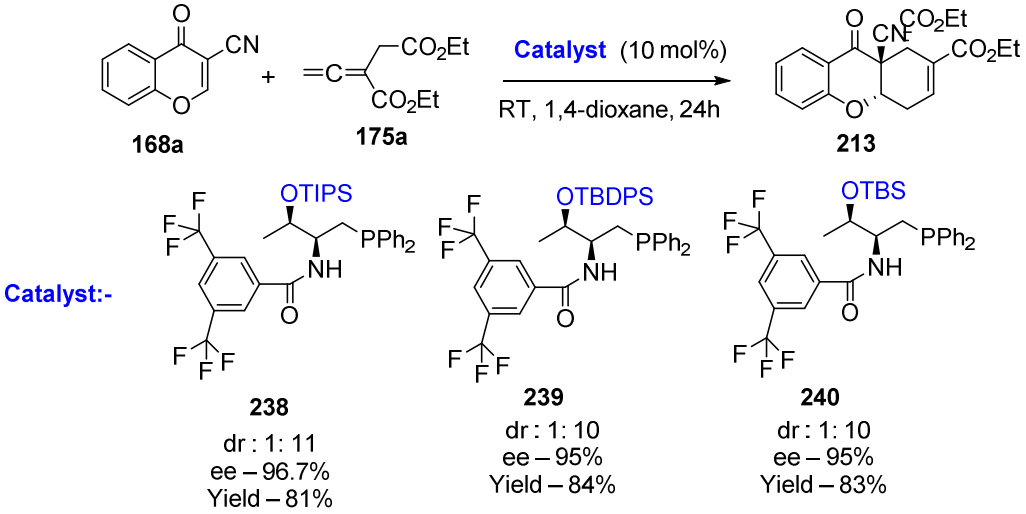
Table 10 – Effect of solvent concentration on the [4+2] annulation catalyzed by aminophosphine 238

Entry	Molarity	Yield[a] %	dr[b] (minor: major)	ee[c] (%)
1	1 M	81	1 : 11	96.7
2	2 M	72	1 : 11	96.6
3	0.5 M	61	1 : 11	95

[a] isolated yield of product 213, [b] Determined *via* ^{1}H NMR analysis of the crude poduct,[c] enantioselectivity of the major diastereomer determined by chiral HPLC.

All the earlier optimizations were carried out at 1 M concentration of the reaction mixture, increasing the concentration to 2 M (entry 2) or decreasing the concentration to 0.5 M (entry 3) in both the cases resulted in a drop in the yield of the [4+2] annulation product without affecting the diastereo- and enantioselectivity. Hence further studies were performed with 1 M solvent concentration of the reaction mixture. Pleasingly addition of molecular sieves 3Å to the reaction mixture in entry 1 Table 10 resulted in an increase in the yield (93%) of the [4+2] adduct **213** without any change in the enantio- and diastereoselevtivity.

3.3.5 Effect of *o*-protecting groups (on the *L*- threonine based phosphine amide) on the [4+2] annulation.



Scheme 54 – Effect of *o*-protecting groups (on *L*- threonine based phoshine amides) on the [4+2] annulation (ee is depicted for major diastereomer and was determined using chiral HPLC).

As depicted in Scheme 54, all the *O*-silylated *L*- threonine based phoshine amides bearing the 3,5-(bistrifloromethyl)benzoyl group were equally effective and yielded the [4+2] adduct in excellent enantio-and diastereoselectivity. The reactions were performed in 1,4-dioxane

(resulting in 1M concentration of the reaction mixture), with 10 mol% catalyst loading at room temperature for 24 h in the presence of 3Å molecular sieves.

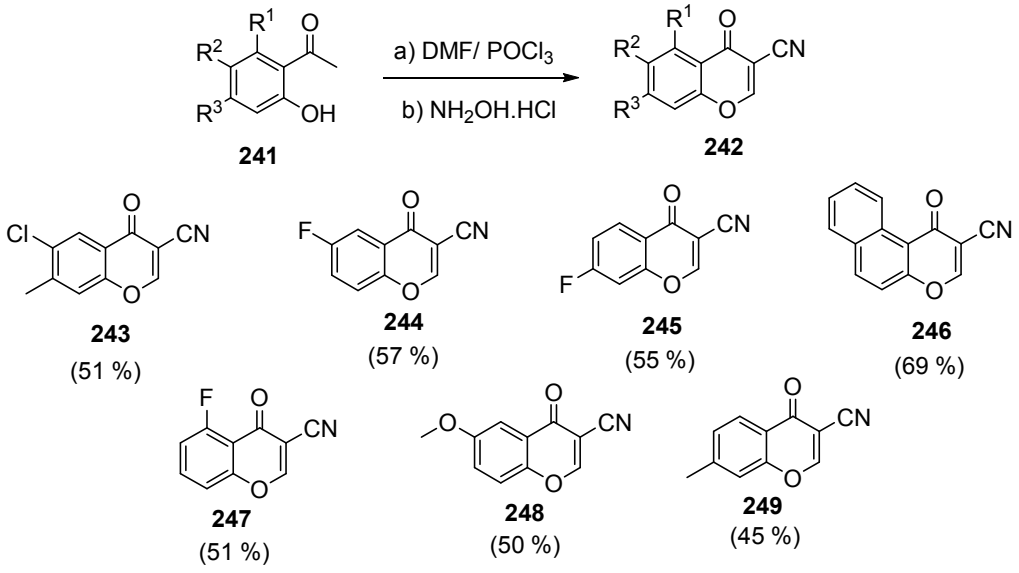
In accordance with the above results reaction conditions for the enantioselective [4+2] annulation of 3-cyano chromones with allenoates was established. According to the reaction protocol, 3-cyano chromone and 10 mol% of the catalyst **238** in the presence of 3Å molecular sieves were dissolved in 1,4-dioxane (resulting in 1 M concentration of the reaction mixture), followed by addition of 1.3 equiv of allene ester **175a** to the reaction mixture. The reaction mixture was stirred at room temperature for 24 h under an inert atmosphere yielding the desired [4+2] adduct **213**, which could be purified using silica gel column chromatography.

3.3.6 Scope of the asymmetric [4+2] annulation.

Having established the optimal conditions for the [4+2] annulation reaction, the generality and scope of this reaction was explored.

3.3.6.1 Synthesis of 3-cyano chromones

Differently substituted 3-cyano chromones were synthesized according to the procedure depicted in Scheme 55, wherein various 2-hydroxy acetophenones were subjected to a Vilsmeier-Haack reaction with DMF and $POCl_3$ at 0^oC, followed by addition of hydroxyl amine hydrochloride to the reaction mixture at room temperature yielding the corresponding 3-cyano chromones in moderate to good yields [117].

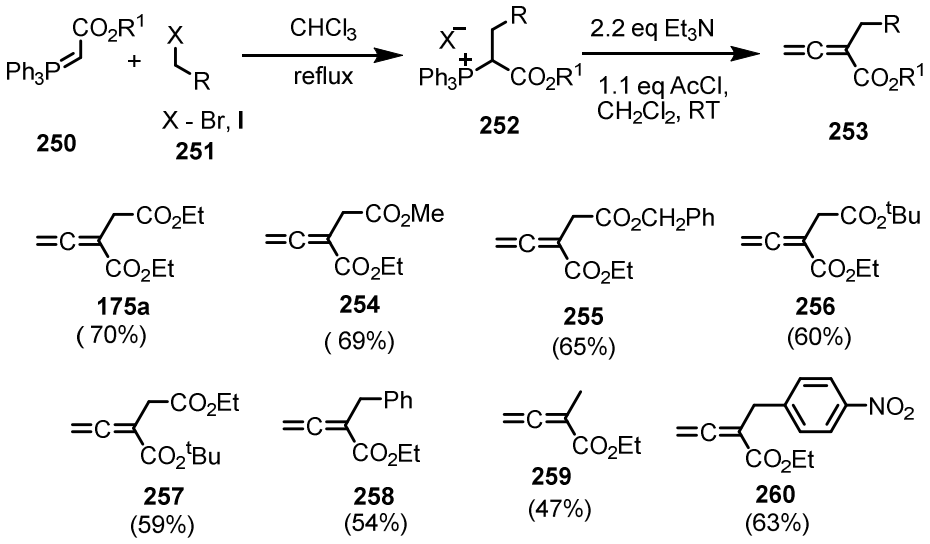


Scheme 55 – General procedure for the synthesis of 3-cyano chromones, isolated yields in brackets.

The reaction tolerated electron withdrawing substituents (**244, 245, 247**) and electron donating substituents (**246, 248, 249**) at positions R^1, R^2 and R^3 yielding the desired 3- cyano chromones **242** in moderate yields.

3.3.6.2 Synthesis of α-substituted allenes.

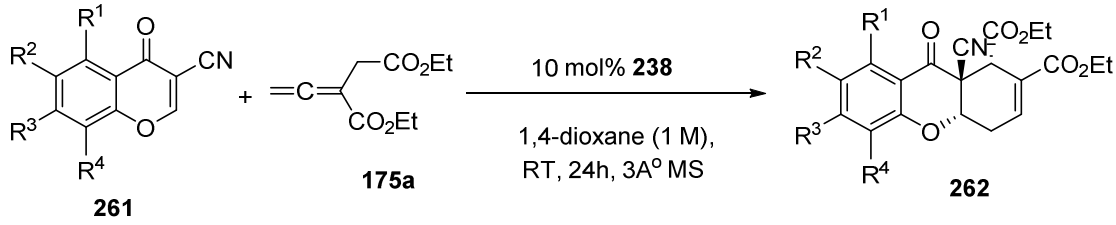
α-Substitued allene esters were prepared *via* a Wittig reaction between triphenyl phosphonium salt **250** and an acid halide **251** as depicted in Scheme 56.



Scheme 56 - General procedure for the synthesis of allenes, isolated yields over 2 steps in brackets.

The reaction tolerated variations at positions R and R^1, yielding the desired allenes **253** in good to moderate yields.

3.3.6.3 Scope of the asymmetric [4+2] annulation reaction: Employing substituted electron deficient chromones.



Scheme 57 – Scope of the reaction using varied cyano chromones

Table 11 – Scope of the [4+2] annulation with varied chromones.

Entry	Product	R^1	R^2	R^3	R^4	Yield[a] %	dr[b] (minor: major)	ee[c] (%)
1	**213**	H	H	H	H	93	8 : 92	96
2	**263**	H	F	H	H	91	10 : 90	95
3	**264**	H	Cl	H	H	91	9 : 91	96
4	**265**	H	Br	H	H	92	9 : 91	96
5	**266**	H	Me	H	H	81	20 : 80	93
6	**267**	H	$CH(CH_3)_2$	H	H	80	25 : 75	86
7[d]	**268**	H	OMe	H	H	60	20 : 80	96
8[e]	**269**	Benzene		H	H	81	16 : 84	91
9	**270**	H	H	Me	H	83	16 : 84	91
10	**271**	H	H	F	H	89	16 : 84	96
11	**272**	H	Cl	Me	H	89	16 : 84	95
12	-	F	H	H	H	NR	-	-
13	-	H	Cl	H	Cl	NR	-	-

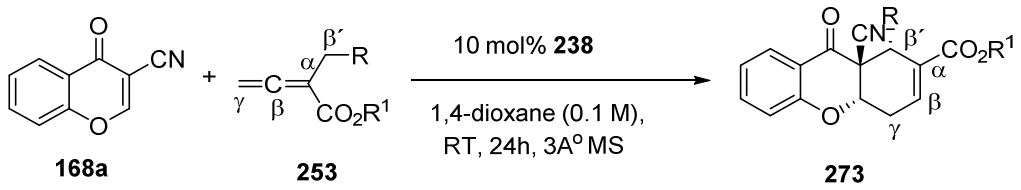
[a] isolated yields of product **262** (both the diastereomers together), [b] Determined *via* ^{1}H NMR analysis of the crude poducts,[c] enantioselectivity of the major diastereomer was determined by chiral HPLC, [d] 20 mol% of catalyst **238** at RT for 48h, [e]15mol% of catalyst **238** at RT for 48h.

A careful study of the scope of the reaction with varied cyanochromones revealed the following (Table 11), in general substrates bearing electron withdrawing and donating substituents on the phenyl ring of the chromone yielded the [4+2] adducts with excellent enantoselectivities and yields. The C-6 position of the chromone ring (ie R^2) showed good tolerance for both electron donating and withdrawing substituents. While the electron withdrawing substituents at R^2 (Table 11, entries 2-4) yielded the [4+2] adducts in excellent yields, as well as enantio-and diastereoselectivities, the electron donating counterparts (entries 5-6) showed a loss in yield and diastreosoelectivity. Presence of highly electron donating substituents at R^2 like methoxy (entry 7) and naphthalene based cyano chromones (entry 8) required higher catalyst loading (20 mol% and 15 mol% respectively) and longer reaction times (48h for both at room temperature), yielding the corresponding cycloadducts with excellent enantoselectivities and in moderate yields and diasteroselectivites. Heating the reaction mixture to 50^{o}C for 24h did not show any improvement in either the yields or

reaction times in both the cases. Such results imply the importance of having sufficiently electron deficient chromones that can behave as Michael acceptors. Electron donating (entry 9) and withdrawing substituents (entry 10) at C-7 position on the chromone ring (ie R^3) behaved similarly yielding the [4+2] adduct in good yields and diastereoselectivites and with excellent enantioselectivities. Suprisingly electron withdrawing substituents at 5 and 8 positions (Floro and chloro group respectively) of the chromone ring ie R^1 and R^4 failed to provide the the [4+2] annulation product. Heating the reaction mixture uptill 80°C also showed no effect on the reaction in both the cases.

3.3.6.4 Scope of the asymmetric [4+2] annulation: Employing α-substituted allene esters.

With an established scope of the [4+2] annulation with varied cyanochromones, the feasibility of the [4+2] reaction was checked with differently α-substituted allenes as depicted in Scheme 58.



Scheme 58 – [4+2] annulation of cyano chromone with differently α-substituted allenes.

All the synthesized allenes as in Scheme 58 along with 3-cyano chromone were subjected to [4+2] annulation using the optimized reaction condition as depicted in Table 12.

Employing various allenoates (Table 12, entries 1-5) in the [4+2] reaction with 3-cyano chromone resulted in the desired adducts **273** in good yields and with excellent enantioselectivities. Increase in the stearic bulk of the substituents on the ester moiety led to slightly lower diastereoselectivity (entry 3, 4 and 5). α-benzyl allene ester (entry 6) as well as α-methyl allene ester (entry 7) in the reaction with 3-cyano chromone failed to provide the desired [4+2] adducts. Heating the reaction mixture to 80°C or increasing catalyst loading had no effect in both the cases. Lastly an electron poor aromatic ring *p*-NO_2Ph (entry 8) in place of the ester moiety at the *β*-postion of the allenoate resulted in low yield of the cycloadduct **278** (determined *via* NMR) with almost no diastereoselectivity. These results led to the following conclusions; presence of an electron-poor moiety like an ester group at the β´-position of the

allenoate increases steric hinderance at that position thus favours the γ-addition to the C-2 position of the chromone. Secondly presence of an ester group increases the acidity of the β´proton and thus facilitates the reaction discourse towards cyclization by attack of chromonyl enolate on the β´-postion of allene (Scheme 59, mechanism).

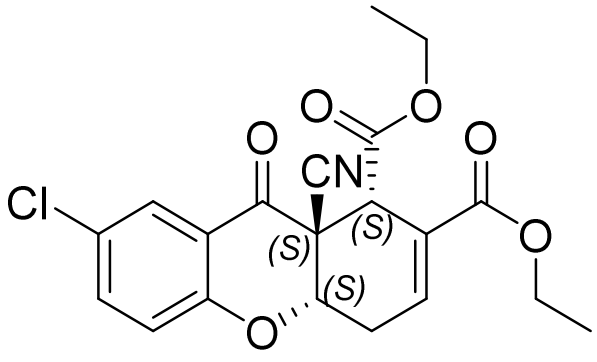
Table 12 – Scope of the [4+2] annulation with allenes.

Entry	Product	R	R^1	Yield[a] %	dr[b] (minor: major)	ee[c] (%)
1	**213**	CO_2Et	CO_2Et	93	8 : 92	96
2	**274**	CO_2Me	CO_2Et	88	10 : 90	96
3	**275**	CO_2Bn	CO_2Et	91	14 : 86	97
4	**276**	$CO_2{}^tBu$	CO_2Et	89	14 : 86	96
5	**277**	CO_2Et	$CO_2{}^tBu$	85	16 : 84	94
6	-	Ph	CO_2Et	NR	-	-
7	-	H	CO_2Et	NR	-	-
8	**278**	*p*-NO_2Ph	CO_2Et	< 15	46 : 54	ND

[a]isolated yields of both the diastereomers together (**273**), [b] Determined *via* ^{1}H NMR analysis of the crude poducts,[c] enantioselectivity of the major diastereomer determined by chiral HPLC.

3.3.7 Absolute configuration of the [4+2] annulation product 264 (major diastereomer)

The absolute configuration of the annulation products was unambiguously assigned by determining the X-ray crystal structure of the major diastereomer of **264,** formed in the reaction of 6-Cl-3-cyanochromone and allene ester **175a** catalyzed by 10 mol% of amino phosphine **238**.



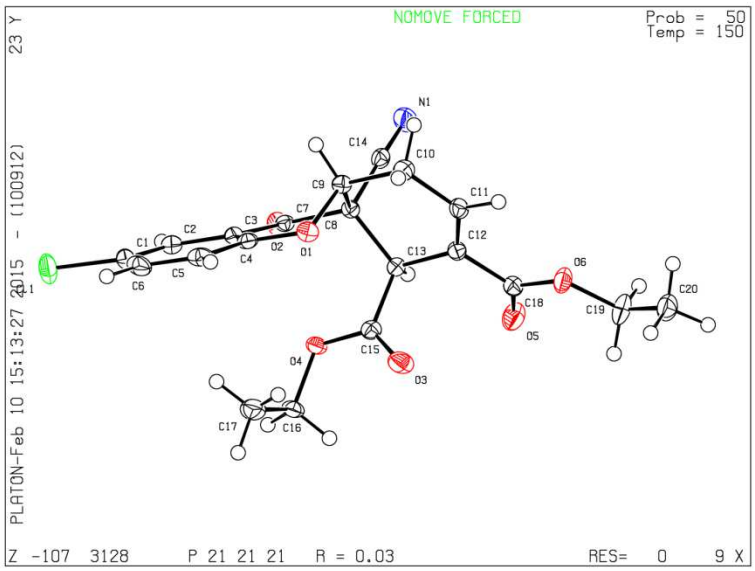
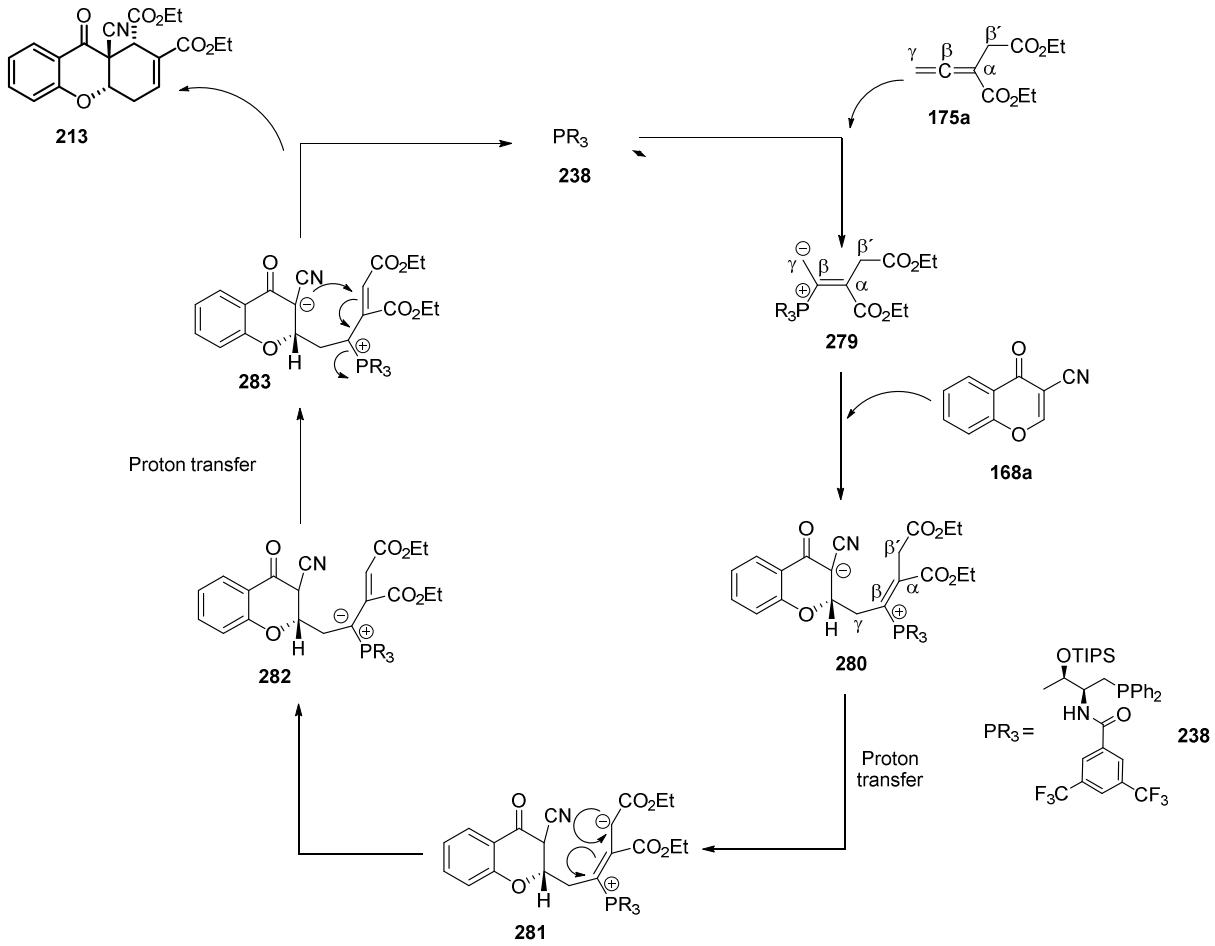


Figure 8 - Absolute configuration of molecule **264**

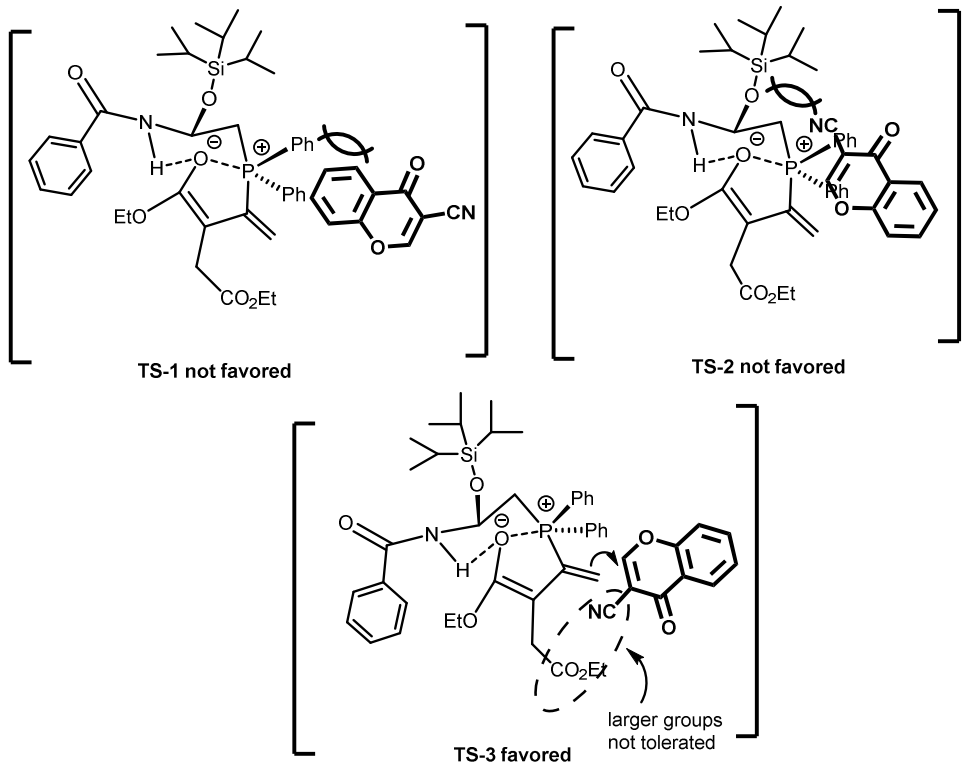
The Crystals of compound **264** were obtained by dissolving 20mg of the compound **264** in 0.5ml of DCM + 0.5ml of isohexane + 0.05ml of *i*-propanol. The solution was left to stand in a quiet corner for the solvent to evaporate slowly and yield the desired crystal.

3.3.8 Proposed mechanism for the [4+2] annulation.

The first step of the annulation reaction involves the formation of the phosphonium enolate **279**, by the nucleophillic addition of the aminophosphine to allene **175a**. A γ-addition of the dienolate specie **279** to the electron deficient chromone ring **168a** leads to the formation of the zwitterionic specie **280**. In light of previous studies [101, 103, 113] a possible transition state for intermediate **280** is proposed in Scheme 60. The stabilization of the transition state is assisted by hydrogen bonding interaction between the amide NH of the catalyst and the enolate and a P-O interaction. A *si*-face attack by the dienolate on the chromone is preferred (TS-3, Scheme 60) to avoid the stearic bulk of the triisopropyl group (catalyst backbone) as well as the two phenyl rings on the phosphine (TS-2 and 1, Scheme 60). Two consecutive proton transfer steps shuffle the proton on the β´-carbon to the β-carbon leading to the formation of an allyphosphonium zwitterionic specie **283.** A conjugated addition of the chromonyl enolate followed by β-elimination of the aminophosphine furnishes the [4+2] cycloadduct **213** in excellent enantio-and diastereoselectivity (96% ee and dr - 1:11 respectively).



Scheme 59 – Mechanism of the [4+2] annulation between 3-cyano chromone and allene **175a**.

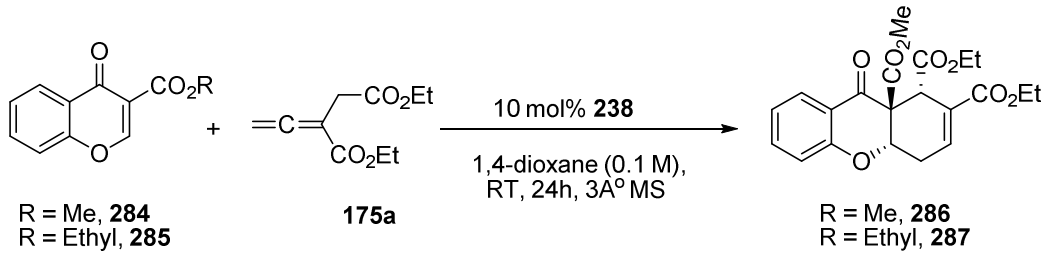


Scheme 60 – Possible transition state for **280**

3.3.9 Feasability of the [4+2] annulation with 3-methyl ester chromone and allene ester 175a

After studying the [4+2] annulation with various 3-cyano- chromones, the feasibility of the reaction with 3-methyl ester substituted chromone (**284**) as depicted in Scheme 61 was checked

The 3-Methyl ester chromone (**284**) with allenoate **175a** was subjected to the [4+2] annulation using the optimized reaction conditions for 3-cyano chromones. The reaction resulted in very low yield of the [4+2] cycloadduct **286** (<20%, determined *via* NMR) with no diastereoselectivity (1: 1.5).



Scheme 61 – [4+2] annulation between 3-methyl ester chromone and allenoate **175a**

Increasing catalyst loading to 20 mol% or heating the reaction to higher temperatures (60^{o}C and 80^{o}C) showed only slight improvement in the yields of the reaction. Attempts with few more aminophosphines with different chiral backbones and having the 3,5(bistrifloromethyl)benzoyl group as the *N*-protecting group (**206, 229, 230**) and also the ones derived from *L*-isoleucine having different *N*-protecting groups (**220, 226**), resulted in low or trace amounts of the [4+2] adduct **286**. The feasibility of the [4+2] annulation in different solvents in the presence of 10 mol% of aminophosphine **238** was checked. Only in case of DCM as solvent the reaction showed around ~35% yield (determined *via* NMR) but with no diastereosectivity (1: 1). Lastly using ethyl ester chromone (**285**) with allenoate **175a** for the [4+2] annulation also showed similar results like the methyl ester substituted chromone. Although its difficult to predict the cause of the low reactivity of the ester substituted chromones **284-285** as compared to cyano substituted chromones, we assume that in a highly packed transition state of the complex **280** (TS-3, Scheme 60) does not prefer any bigger group that sterically interacts with the α-substitution on the allene ester resulting in very low yield of the product.

3.4 Summary

In summary, an enatioselective [4+2] annulation reaction between electron deficient and differently substituted 3-cyano chromones and α-substituted allenoates catalyzed by amino acid derived phosphine catalyst was developed. The reaction yielded enantiomerically pure tetrahydroxanthones supporting three consecutive chiral centers including an all carbon quaternary center. A small compound collection following the optimized reaction conditions was built and shall be explored for its biological properties.

Chapter 4

Summary

4.1 Summary

Natural product inspired compound collections embody structural scaffolds derived from biologically relevant and prevalidated fractions of chemical structure space explored by nature. These structural scaffolds are also referred to as *privileged* given the fact that the number of structural motifs of protein and natural products is limited. The probability that compound libraries inspired by natural products, will be biologically relevant is high and is also a viable guiding principle for the identification of small molecules for chemical biology and medicinal chemistry research.

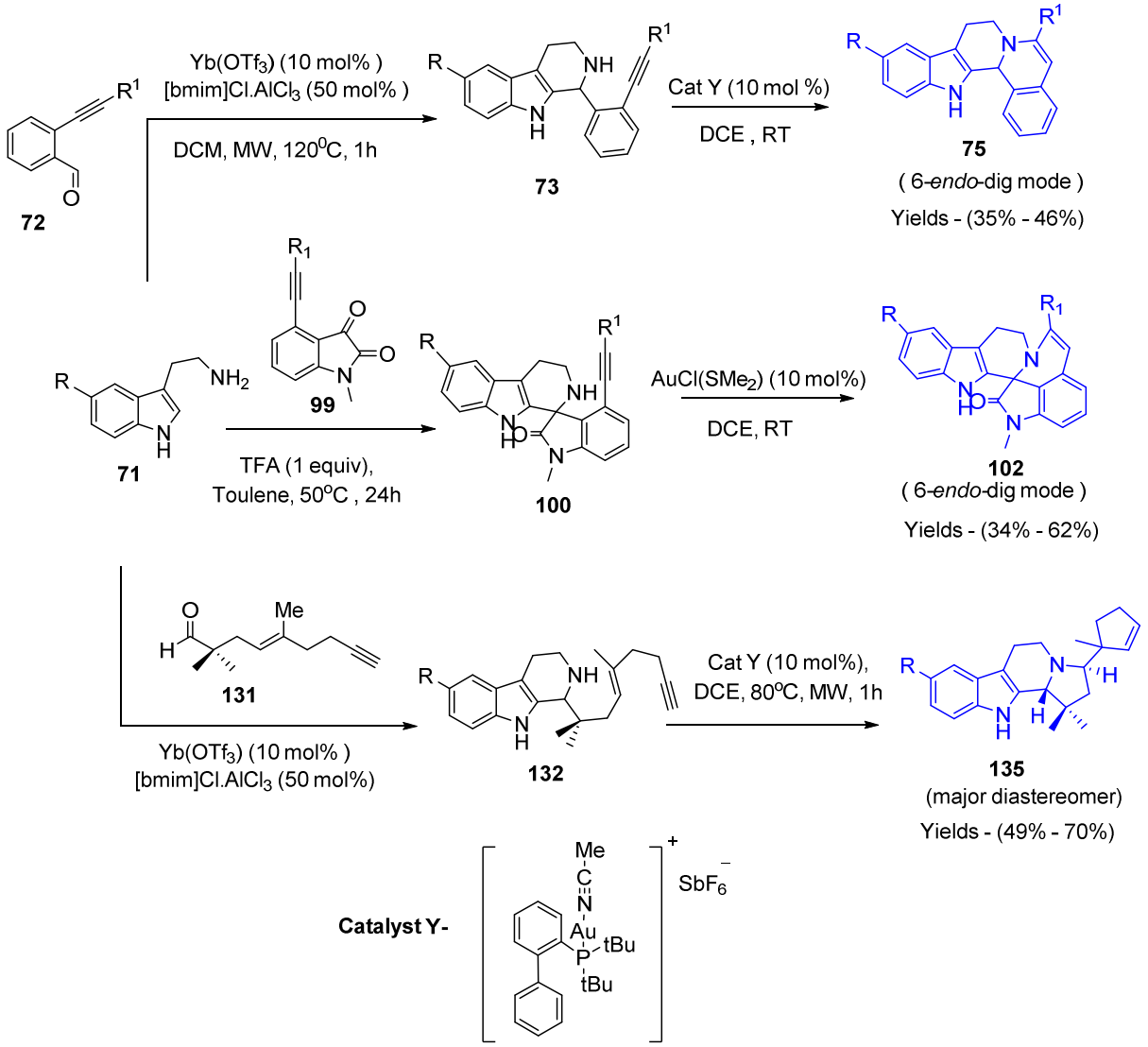
This present work addresses the synthesis of compound libraries inspired by natural product scaffolds. The synthesis of a small library of indole derived indoloquinolizine and related scaffolds and the synthesis of an asymmetric compound collection based on the tetrahydroxanthone scaffold was developed.

A compound library based on indole derived indoloquinolizine and related scaffolds.

In view of the importance of the indoloquinolizine scaffold and related analogs like the harmicine scaffold as biologically active heterocyclic templates which occur widely in the alkaloid world, a two-step reaction sequence was devised, which involves a Pictet-Spengler cyclization followed by a Au(I) catalyzed intramolecular hydroamination reaction of acetylenes to access the desired indole derived scaffolds (**75, 102, 135**).

The synthesis of the indoloquinolizine scaffold **75,** was achieved *via* a two-step protocol, wherein acteylenic aldehydes (**72**) and tryptamines (**71**) cyclized in a Pictet-Spengler reaction catalyzed by (10 mol%) of $Yb(OTf)_3$ in the presence of ionic liquid [bmim]Cl-$AlCl_3$ (0.32 ml/ mmol of tryptamine) yielding the corresponding tetrahydro-*β*-carbolines (**73**). Treatment of the pure adducts **73** with (10 mol%) of the gold catalyst **Y** afforded the desired indoloquinolizines **75** (Scheme 62). The reaction showed tolerance for aryl and alkyl substituents on the acetylene yielding the corresponding indoloquinolizines **75** in moderate to good yields. Notably electron poor tryptamines like 5-chloro tryptamine (**71c**) that are poor substrates for the Pictet-Spengler cyclization also yielded the desired indoloquinolizine (**95**) in moderate yield under the conditions of the developed protocol.

With encouraging results with indoloquinolizines (**75**), the utility of this two-step protocol for the synthesis of hexacyclic indoloquinolizines (**102**) (Scheme 62) was examined. Herein acetylenic isatins (**99**) and tryptamines (**71**) were subjected to Pictet-Spengler cyclization in the presence of 1 equiv of TFA yielding the desired Pictet-Spengler adducts (**100**), which on treatment with (10 mol%) $AuCl(SMe_2)$ yielded the desired hexacyclic indoloquinolizines (**102**) in good yields over two synthetic steps. Only in case of 5-chloro tryptamine (**71c**) the Pictet-Spengler cyclization with TFA resulted in very poor yields of **115** and hence resorting to Ytterbium catalysis resulted in moderate yields of **115** (57%). The reaction in this case also showed good tolerance for varied aryl and alkyl substituents on the acetylene.



Scheme 62 – Three different indole based scaffolds (**75, 102, 135**) were synthesized, a) the yields are depicted over two reaction steps for scaffolds **75** and **102**, b) the yields depicted for scaffolds **135** are for the gold catalyzed polyclization cascade step.

In view of generating polycylic indole scaffolds with higher structural complexity acetylenic aldehyde of type **131** with tryptamines **71** were employed in the devised two-step protocol. The Pictet-Spengler cyclization between substrates **131** and **71** catalyzed by (10 mol%) $Yb(OTf)_3$ in the presence of ionic liquid [bmim]Cl-$AlCl_3$ (0.32 ml/ mmol of tryptamine) yielded the tetrahydro-*β*-carbolines (**132**) tethered to a 1,5 enyne with (*E*)- configured alkene. The designed substrates **132** on treatment with gold catalyst **Y** (10 mol%) underwent a double cascade polycyclization yielding harmicine analogs **135** as a mixture of diastereomers in good yields (Scheme 62). The reaction tolerated both electron donating and withdrawing substituents on the indole ring of the tryptamine.

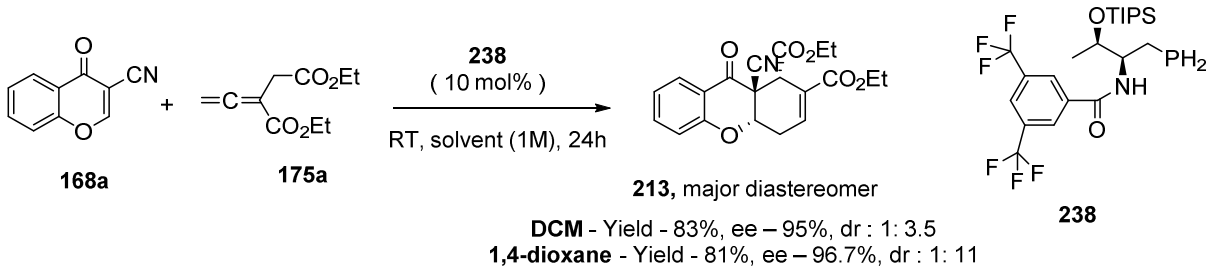
In conclusion a two-step catalytic reaction sequence was developed to afford indole derived indoloquinolizines (**75**) and hexacyclic indoloquinolizine scaffolds (**102**). A Au(I) catalyzed cascade polycylization gave efficient access to complex analogs of the harmicine alkaloid (**135**).

_N_-acyl aminophosphine catalyzed asymmetric [4+2] annulation of allenoates and 3-cyanochromones yielding enantiomerically pure tetrahydroxanthones.

The wide occurrence of the tetrahydroxanthone scaffold in nature and among pharmacologically active compounds, as well as the profound biological activities showcased by the optically active tetrahydroxanthone derivatives inspired the development of a synthetic methodology that offers an easy stereoselective access to this class of compounds. We relied on an organophosphine mediated [4+2] annulation between electron deficient cyano chromones and α-allene esters yielding the desired optically active tetrahydroxanthone scaffold (**289**).

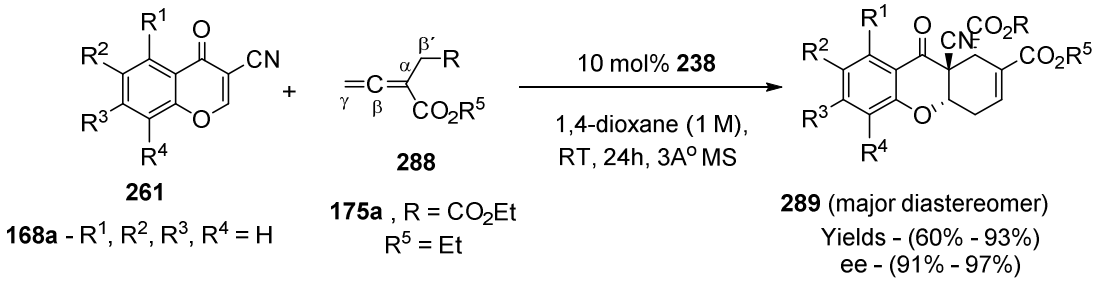
Initially electron deficient 3-cyanochromone **168a** and α-allene ester **175a** were treated with various chiral organophosphines for catalyzing the [4+2] annulation. Amino acid derived aminophosphine (**206**) was found to be effective in catalyzing the [4+2] annulation affording the desired tetrahydroxanthone scaffold (**213**) as two diastereomers. The asymmetric version of the [4+2] annulation yielded both diastereomers as [4+2] γ-addition products similar to the ones in the racemic version of the reaction (determined *via* NMR), however with a reversal of preffered diastereoselectivity. A small library of aminophosphines was synthesized and screened for their catalytic efficiency in the [4+2] annulation between 3-cyano chromone **168a** and allenoate **175a**. *L*-threonine derived aminophosphine **238** with

3,5(bistrifloromethyl)benzoyl group as the *N*-protecting group was found to be most effective in catalyzing the [4+2] annulation reaction affording the [4+2] adduct **(213**) in excellent enantioselectivity (95%) and yield (83%) but with moderate diastereoselectivity (1: 3.5) in DCM as solvent. Solvent played an important role in improving the diastereoselectivity of the reaction, wherein carrying out the [4+2] annulation in 1,4-dioxane (1M concentration of the reaction mixture) afforded the [4+2] adduct **213** in excellent enantioselectivity 96.7%, high yield (81%) and most importantly with very high diastereoselectivity (1:11) (Scheme 63). Lastly addition of 3Å molecular sieves to the reaction mixture further improved the yield to 93% without any change in enantio- and diastereoselectivity.



Scheme 63 – [4+2] annulation catalyzed by chiral aminophosphine **238** in different solvents, the enantioselectivity of the major diastereomer was determined by chiral HPLC.

With an optimized reaction condition for the [4+2] annulation, the scope of this reaction was investigated. Initially differently substituted cyanochromones **(261)** were employed for the [4+2] annulation with allenoate **175a**. The reaction showed good tolererance for electron donating and withdrawing substituents at R^2 (C-6 position) and R^3 (C-7 position) position on the chromone, yielding the [4+2] adducts **(289)** in excellent yields and enantioselectivities and with good to moderate diastereoselectivities (Scheme 64). Electron withdrawing substituents at position R^1 and R^4 failed to provide the desired [4+2] adduct. Next α-substituted allene esters (**288**) were tested for the [4+2] annulation with cyano chromone (**168a**) yielding the [4+2] adducts **(289)** in good yields and excellent enantioselectivities. A slight drop in diastereoselectivity was observed with increase in the stearic bulk of substituents on the ester moiety (R and R^5). α-benzyl and α-methyl allene esters failed to provide the desired [4+2] adduct **289**.



Scheme 64 – [4+2] annulation with differently substituted 3-cyano chromones and α-substituted allene esters, the enantioselectivity of the major diastereomer was determined by chiral HPLC.

In conclusion we successfully developed a *N*-acyl amino acid derived asymmetric [4+2] annulation reaction between differently substituted 3-cyano chromones and α-substituted allenoates, affording enantiomerically pure tetrahydroxanthones supporting three consecutive chiral centers including an all carbon quaternary center.

4.2 Zusammenfassung

Von Naturstoffen inspirierte Substanzbibliotheken inkorporieren biologisch relevante und prävalidierte Bereiche des chemischen Strukturraums. Da die Anzahl an natürlichen Strukturmotiven von Proteinen und Naturstoffen begrenzt ist, werden die Grundgerüste solcher Substanzbibliotheken als *privilegiert* bezeichnet. Die Wahrscheinlichkeit, dass die von solchen privilegierten Grundgerüsten inspirierten Substanzbibliotheken biologisch relevante Wirkung zeigen, ist hoch. Somit ist die Synthese von naturstoffinspirierten Substanzbibliotheken ein leistungsfähiges Prinzip zur Identifikation biologisch aktiver niedermolekularer Substanzen für die chemische Biologie und die medizinalchemische Forschung.

Die vorliegende Arbeit beschäftigt sich mit der Synthese von solchen naturstoffinspirierten Substanzbibliotheken. Sie beschreibt die Synthese einer kleinen Indol-basierten Indochinolizin-Bibliothek und verwandten Grundgerüsten und die Synthese einer asymmetrischen, auf dem Tetrahydroxanthongerüst basierenden Substanzkollektion.

Eine auf dem Indolgerüst basierende Substanzbibliothek von Indolochinolizinen und verwandten Strukturen.

Im Hinblick auf die biologische Relevanz des Indolochuinolizingerüsts und verwandter Analoga wie Harmicin als aktive heterozyklische Strukturen mit weiter Verbreitung in der Welt der Alkaloide wurde eine zweistufige Reaktionssequenz zum Aufbau dieser Strukturen (**75, 102, 135**) entwickelt. Diese beinhaltet eine Pictet-Spengler Zyklisierung, gefolgt von einer Au(I)-katalysierten intramolekularen Hydroaminierung von Acetylenen.

Das Indolochinolizin **75** wurde in zwei Stufen erhalten, wobei acetylenische Aldehyde (**72**) und Tryptamine (**71**) durch eine Pictet-Spengler Reaktion unter $Yb(OTf)_3$-Katalyse (10 mol%) in Anwesenheit der ionischen Flüssigkeit [bmim]Cl-$AlCl_3$ (0.32 ml/mmol des Tryptamins) zu Tetrahydro-β-carbolinen (**73**) zyklisiert wurden. Behandlung der aufgereinigten Produkte **73** mit 10 mol/% des Goldkatalysators **Y** führte zum gewünschten Indolochinolizin **75** (Abbildung 62) in moderater bis guter Ausbeute. Die Reaktion tolerierte sowohl Aryl- als auch Alkylsubstituenten am Acetylen. Auch elektronenarme Tryptamine wie 5-Chlorotryptamin (**71c**), die nur schlechte Substrate für die Pictet-Spengler Zyklisierung

sind, führten zum gewünschten Indolochinolizin (**95**) in moderaten Ausbeuten unter diesen Bedingungen.

Aufgrund der erfolgreichen Synthese von Indolochinolizinen (**75**) wurde die oben dargestellte Reaktionssequenz auf die Synthese von hexazyklischen Indolochinolizinen (**102**, Abbildung 62) übertragen. Dazu wurden acetylenische Isatine (**99**) und Tryptamine (**71**) in der Anwesenheit von TFA durch Zyklisierung zum gewünschten Pictet-Spengler-Produkt (**100**) umgesetzt. Dieses führte nach anschließender Behandlung mit 10 mol/% $AuCl(SMe_2)$ zum gewünschten hexazyklischen Indolochinolizin (**102**) in zwei Schritten und mit guten Ausbeuten. Nur im Falle des 5-Chlorotryptamins gelang die Zyklisierung in Anwesenheit von TFA nicht und es wurde auf Ytterbiumkatalyse zurückgegriffen, womit **115** in moderater Ausbeute von 57% erhalten wurde. Auch in diesem Fall zeigte die Reaktion große Toleranz gegenüber verschiedenen Alkyl- und Arylsubstituenten am Acetylen.

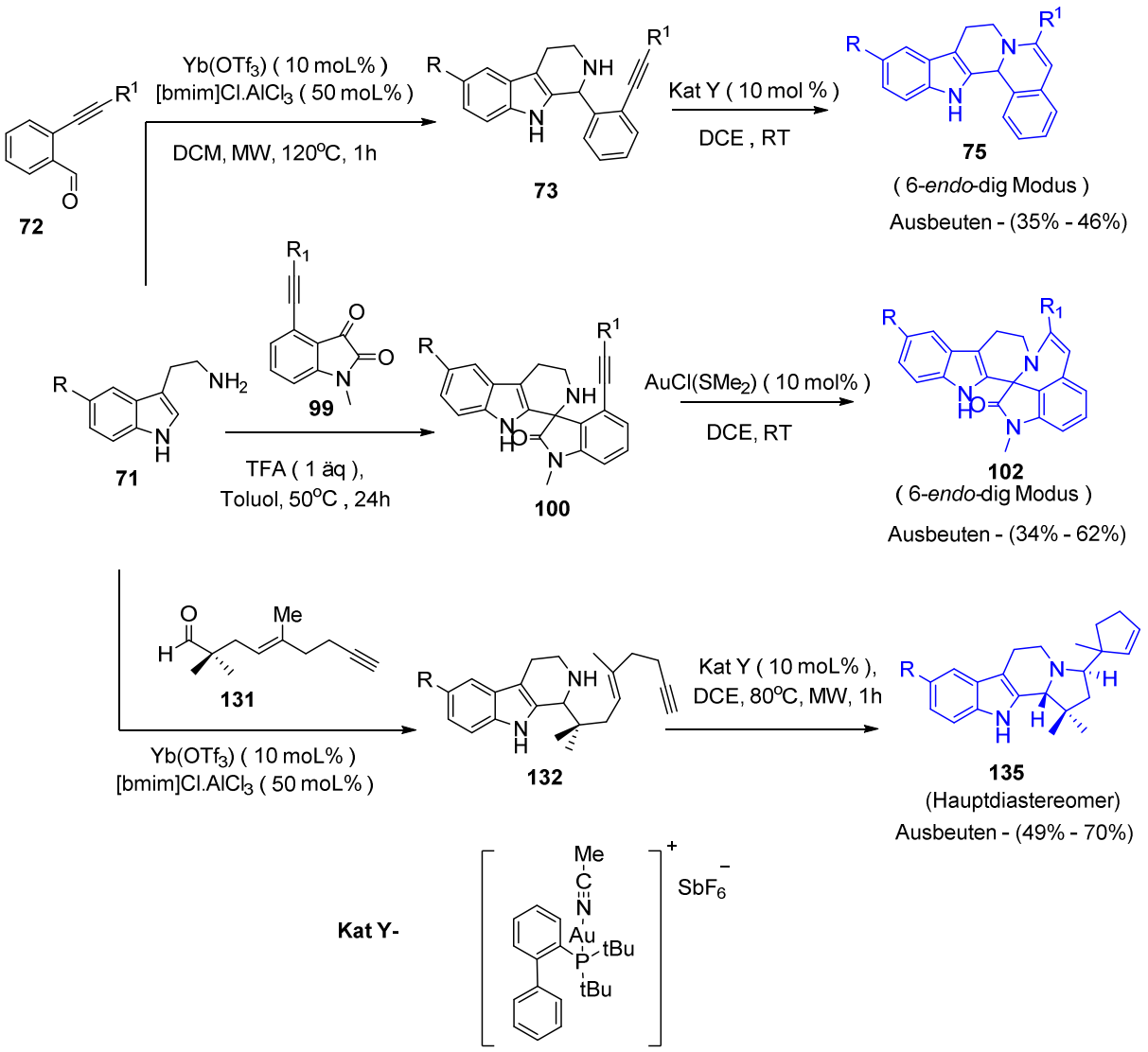


Abbildung 62 – Drei im Rahmen dieser Dissertation hergestellte Indol-basierte Strukturen (**75**, **102**, **135**), a) Ausbeuten für **75** und **102** wurden über zwei Stufen, b) Ausbeuten für **135** nach der goldkatalysierten Zyklisierung.

Um polyzyklische Indolstrukturen mit höherer struktureller Vielfalt herzustellen, wurden acetylenische Aldehyde des Typs **131** mit Tryptaminen des Typs **71** den entwickelten Reaktionsbedingungen unterworfen. Die Pictet-Spengler Zyklisierung von **131** und **71** führte unter $Yb(OTf)_3$ –Katalyse (10 mol/%) in Anwesenheit der ionischen Flüssigkeit [bmim]Cl-$AlCl_3$ (0.32 ml/ mmol Tryptamin) zu dem mit einem 1,5 Eninverknüpften Tetrahydro-β-carbolin **132** mit (*E*)-Konfiguration der Doppelbindung. **132** vollzog bei Behandlung mit 10 mol% des Goldkatalysators **Y** eine zweifache Polycyclisierungskaskadenreaktion zum Harmicinanalogon **135** als Diastereomerengemisch und mit guter Ausbeute (Abbildung 62). Die Reaktion tolerierte sowohl elektronenziehende als auch elektronenschiebende Substituenten am Indolring des Tryptamins.

Zusammenfassend wurde eine katalytische Reaktionssequenz zur Synthese von Indol-basierten Indochinolizin- (**75**) und hexazyklischen Indochinolizingerüststrukturen (**102**) in zwei Stufen entwickelt. Eine Au(I)-katalysierte Polyzyklisierungskaskade erlaubt den Zugang zu komplexen Harmicinanaloga (**135**).

***N*-Acylaminophosphin-katalysierte asymmetrische [4+2]-Anellierung von Allenoaten und 3-Cyanochromonen zur Synthese enantiomerenreiner Tetrahydroxanthonen.**

Da das Tetrahydroxanthongerüsts in der Natur und unter pharmakologisch aktiven Verbindungen und insbesondere von optisch aktiven Tetrahydroxanthonderivaten weit verbreitet ist wurde eine Syntheseroute zu entwickelt, die einen einfachen stereoselektiven Zugang zu dieser Substanzklasse ermöglicht. Eine Organophosphin-vermittelte [4+3]-Anellierungsreaktion zwischen elektronenarmen Cyanochromonen und α-Allenoaten führte zu dem gewünschten optisch aktiven Tetrahydroxanthongerüst **289**.

Hierbei wurde das elektronenarme 3-Cyanochromon **168a** mit dem α-Allenester **175a** mit diversen chiralen Organophosphinen umgesetzt. Aminosäurebasierte Aminophosphine stellten sich dabei als effektive Katalysatoren für die [4+2]-Annelierung zur Herstellung des gewünschten Tetrahydroxanthongerüsts **213** als Gemisch zweier Diastereomere heraus. Die

asymmetrische Version dieser Reaktion führte zur Bildung beider Diastereomere als [4+2] γ-Additionsprodukte, ähnlich wie die racemische Version (Bestimmung durch NMR), allerdings unter Inversion der relativen Stereochemie. Zudem wurde eine kleine Kollektion von Aminophosphinen hergestellt und auf ihre katalytische Effizienz in der beschriebenen Annelierungsreaktion getestet. Mit dem *L*-Threonin-basierten, mit 3,5-(Bistrifloromethyl)-benzoylamid versehenen Aminosphosphin **238** konnte das [4+2]-Addukt **213** in Dichlormethan in exzellenter Enantioselektivität von 95% und mit einer Ausbeute von 83%, jedoch lediglich mit moderater Diastereoselektivität (1: 3.5) erhalten werden. Die Wahl des Lösungsmittels erwies sich als kritischer Faktor bezüglich der Diastereoselektivität heraus. So konnte in 1,4-Dioxan (1M Konzentration des Reaktionsgemisches) eine exzellente Enantioselektivität von 96.7%, eine gute Ausbeute von 81% und eine sehr hohe Diastereoselektivität von 1:11 erreicht werden. Durch Zugabe von 3Å-Molekularsieb konnte die Ausbeute unter Erhalt der Enantio- oder Diastereoselektivität auf 93% gesteigert werden.

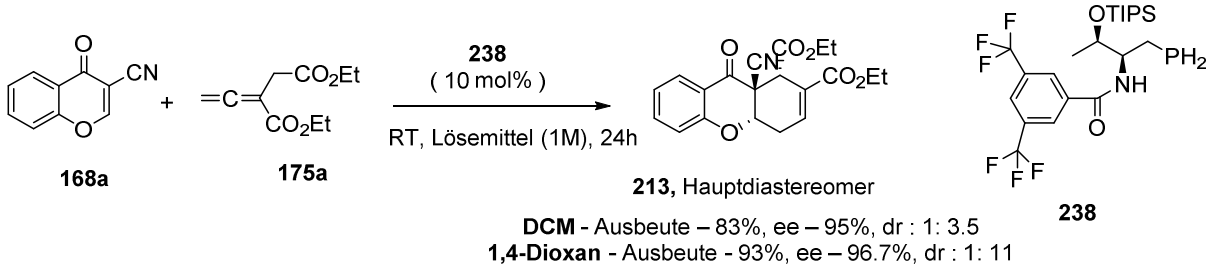


Abbildung 63 – Durch das chirale Aminophosphin **238** katalysierte [4+2]-Annelierung in verschiedenen Lösemitteln. Die Enantioselektivität wurde mittels chiraler HPLC bestimmt.

Die optimierte Reaktion mit Allenoat **175a** zeigte hohe Toleranz sowohl gegenüber elektronenziehenden als auch elektronenschiebenden Substituenten R^2 (C-6 Position) und R^3 (C-7 Position) des Chromons. Dabei wurden die gewünschten [4+2]-Addukte **289** in exzellenten Ausbeuten, guter Enantioselektivität und mit guter bis moderater Diastereoselektivität erhalten. Mit elektronenziehenden Substituenten an der R^1- oder R^4-Position wurde kein [4+2]-Addukt gefunden. In Bezug auf verschieden α-substituierte Allenoate (**288**) wurden, dass bei der Reaktion mit Cyanochromon **168a** gute Ausbeuten bei exzellenter Enantioselektivität erreicht werden. Eine leichte Verringerung der Diastereoselektivität wurde in Anwesenheit von Substituenten am Ester mit großem sterischen Anspruch beobachtet. Bei Verwendung von α-Benzyl- and α-Methylallenestern fand keine [4+2]-Annelierung statt.

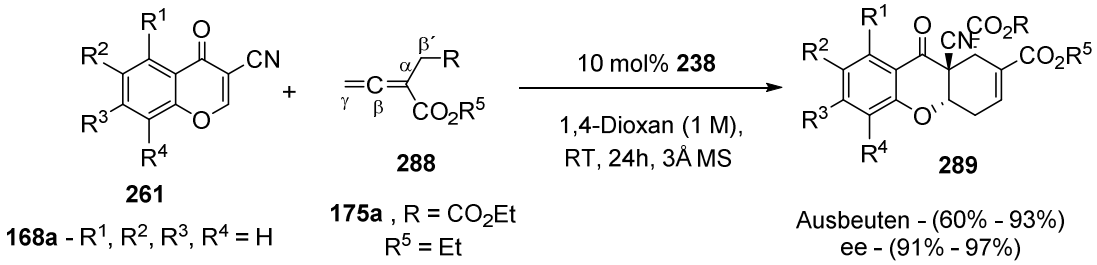


Abbildung 64 – [4+2]-Annelierung mit verschieden substituierten 3-Cyanochromonen mit α-substituierten Allenestern. Die Enantioselektivität für das Hauptdiastereomer wurde mittels chiraler HPLC bestimmt.

Zusammenfassend wurde eine asymmetrische *N*-Acylaminophosphin-katalysierte [4+2]-Annelierungsreaktion zwischen verschieden substituierten 3-Cyanochromonen und α-substituierten Allenoaten zu enantiomerenreinen Tetrahydroxanthonen mit drei Stereozentren entwickelt, von denen eins ein quartäres Kohlenstoffatom trägt.

Chapter 5

Experimental Part

5. Experimental Part

5.1 General Methods and Materials

Techniques: All reactions involving air or moisture sensitive reagents or intermediates were carried out under argon atmosphere. All the glassware's were dried by heat gun under high vaccum prior to use. Concentration of the reaction mixture was performed under reduced pressure at 40^{o}C at the appropriate pressure. Purified compounds were further dried under high vacuum.

Solvents and reagents: Dichloromethane and Triethyl amine was distilled from CaH_2. Dry acetonitrile, toluene and 1,4-dioxane, diehyl ether and ethyl acetate stored over molecular sieves were received from Aldrich and Acros and used without any further purification. All other solvents or reagents were purified according to standard procedures or were used as received from Aldrich, ABCR, Alfa-Aesar, Acros, Fluka, and TCI.

TLC: TLC was performed using precoated Merck silica gel 60 F254 glass plates, detection of compounds were performed by UV254 light and/or dipping into a solution of KMnO4 (1.5 g in 400 mL H_2O, 5 g $NaHCO_3$) followed by heating with a heat gun.

Flash Chromatography: Was performed using silica gel Merck 60 (40-63 μm), argon pressure approximately 0.5 bar, eluent is given in parantheses.

^{1}H-NMR and ^{13}C-NMR: Were recorded on a Bruker DRX400 (400 MHz) and Bruker DRX600 (600 MHz), using $CDCl_3$ or DMSO-d_6 or CD_2Cl_2 as solvent. Data are reported in the following order: chemical shift (δ) values are reported in ppm with the solvent resonance as internal standard ($CDCl_3$: δ = 7.26 ppm for ^{1}H, δ = 77.16 ppm for ^{13}C), (DMSO-d_6: δ = 2.50 ppm for ^{1}H, δ = 39.52 for ^{13}C), (CD_2Cl_2: δ = 5.32 ppm for ^{1}H, δ = 53.84 for ^{13}C), multiplicities are indicated br s (broadened singlet), s (singlet), d (doublet), t (triplet), q

(quartet), m (multiplet), dd (doublet of doublet), dt (doublet of triplet); coupling constants (*J*) are given in Hertz (Hz).

MS: HRMS (ESI): Spectra were recorded on a LTQ Orbitrap mass spectrometer coupled to an Acceka HPLC-System (HPLC column: Hypersyl GOLD, 50 mm x 1 mm, particle size 1.9 µm, ionization method: electron spray ionization.

GC: Were recorded on a gas chromatograph (Agilent 7890 A, column DB-5MS) with downstream mass spectrometer (Agilent 5975 inert XL MSD)

Microwave Reactions: were performed using CEM Intellivent Explorer 541416 machine at the desired temperature using 300 W power and 14 mbar pressure.

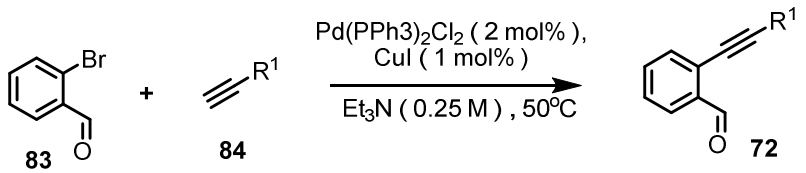
Melting points: Were measured on a melting point device 540 by Büchi. All melting points are uncorrected.

5.2 Experimental part for chapter 2

5.2.1 Synthesis of indoloquinolizine based indole scaffold

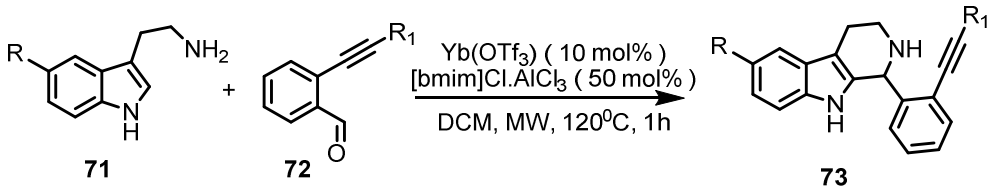
General Procedure 1 (GP1) for the synthesis of *o*-alkynyl benzaldehydes 72.

2-bromobenzaldehyde **83** (1 equiv) was dissolved in Et_3N (0.25 M) and the reaction mixture was degassed for 5 min by argon bubbling. Then CuI (1 mol%) and $PdCl_2(PPh3)_2$ (2 mol%) were introduced and the mixture was further degassed for 10 min by argon bubbling. Finally, the corresponding alkyne **84** (1.2 equiv) was added and the reaction was stirred at 50 °C and monitored *via* TLC. After completion of the reaction, it was quenched by addition of distilled water and was extracted by CH_2Cl_2 (3 times). The combined organic layers were washed with brine, dried over MgSO4, filtrated and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography using silica gel with ethyl acetate and petroleum ether as eluents.



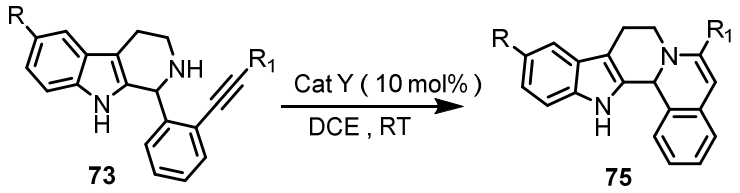
General Procedure 2 (GP2) for the synthesis of Pictet-Spengler Derivatives 73

To a mixture of the corresponding tryptamine/5-substituted tryptamine **71** (0.36 mmol), *O*-alkynyl benzaldehyde **72** (1.2 equiv, 0.43 mmol) and $Yb(OTf_3)$ (10 mol%, 22.51 mg) was added dry DCM (1.2 ml) under an argon atmosphere with stirring, followed by the addition of ionic liquid $[bmim]Cl.AlCl_3$ (0.32 ml/mmol). The reaction mixture was then subjected to microwave irradiation for 60 min at 120 ^oC. The crude reaction mixture was directly purified by column chromatography using basified silica gel with methanol and dichloromethane as eluents.

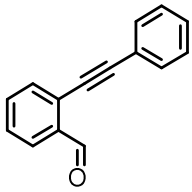


General Procedure 3 (GP3) for the gold catalyzed hydroamination reaction yielding indoloquinolizines 75.

To a solution of the tetrahydro-β-carboline **73** (0.1 mmol) in dry DCE (2 ml) under argon atmosphere was added the gold Cat Y (10 mol%, 7.72 mg) and the reaction mixture was stirred at RT until the completion of the reaction monitored *via* TLC. The solvent was removed in vacuo and the crude reaction mixture was purified by flash chromatography using silica gel with petroleum ether and ethyl acetate as eluents.

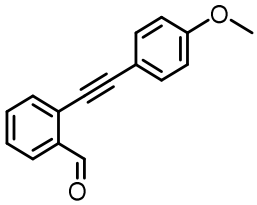


2-(Phenylethynyl) benzaldehyde (85)



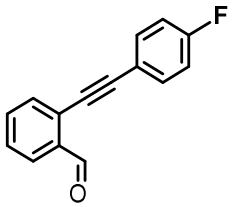
Compound **85** was synthesized according to the **GP1** as a yellowish liquid in 80% yield, R_F = 0.55 (5% EtOAc/ Petroleum ether); ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 10.66 (d, *J* = 0.8 Hz, 1H), 7.96 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.67 – 7.64 (m, 1H), 7.61- 7.55 (m, 3H), 7.48 – 7.43 (m, 1H), 7.41 – 7.37 (m, 3H); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 191.8, 136.0, 133.9, 133.3, 131.8, 129.2, 128.7, 128.6, 127.4, 127.0, 122.4, 96.4, 85.0; HRMS (ESI)**:** Calculated for $C_{15}H_{10}O$ [M+H$^+$]: 207.08044, Found: 207.08144.

2-((4-Methoxyphenyl)ethynyl)benzaldehyde (86)



Compound **86** was synthesized according to the **GP1** as a pinkish solid in 86% yield, R_F = 0.56 (5% EtOAc/ Petroleum ether); ^{1}H NMR (400 MHz, 25 °C, CD_2Cl_2): δ 10.63 (s, 1H), 7.91 (d, *J* = 7.9 Hz, 1H), 7.67 – 7.57 (m, 2H), 7.55 – 7.51 (m, 2H), 7.45 (t, *J* = 7.5 Hz, 1H), 6.96 – 6.89 (m, 2H), 3.84 (t, *J* = 1.4 Hz, 3H); ^{13}C NMR (100 MHz, 25 °C, CD_2Cl_2): δ 191.4, 160.3, 135.6, 133.6, 133.1, 132.9, 128.1, 127.0, 127.0, 114.2, 114.0, 96.2, 83.6, 55.2; HRMS (ESI)**:** Calculated for $C_{16}H_{12}O_2$ [M+H$^+$]: 237.09101, Found: 237.09215.

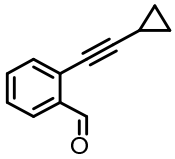
2-((4-Fluorophenyl)ethynyl)benzaldehyde (87)



Compound **87** was synthesized according to the **GP1** as a brownish yellow solid in 87% yield, R_F = 0.54 (5% EtOAc/ Petroleum ether); ^{1}H NMR (400 MHz, 25 °C, CD_2Cl_2): δ 10.67 – 10.57 (m, 1H), 7.96 – 7.88 (m, 1H), 7.69 – 7.55 (m, 4H), 7.51 – 7.45 (m, 1H), 7.15 – 7.08 (m, 2H); ^{13}C NMR (100 MHz, 25 °C, CD_2Cl_2): δ 191.7, 163.3 (d, J_{C-F} = 250.2 Hz),

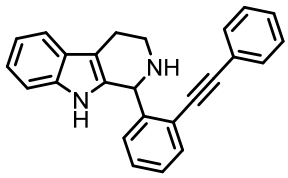
136.3, 134.2, 134.1 (d, *J* = 8.5 Hz), 133.6, 129.1, 127.7, 126.8, 119.0 (d, *J* = 3.5 Hz), 116.2 (d, *J* = 22.3 Hz), 95.3, 85.1; HRMS (ESI): Calculated for $C_{15}H_9FO$ [M+H$^+$]: 225.07102, Found: 225.07181.

2-(Cyclopropylethynyl)benzaldehyde (88)



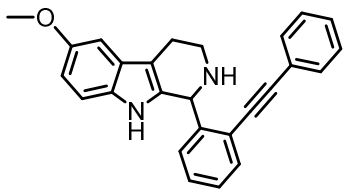
Compound **88** was synthesized according to the **GP1** as a yellowish liquid in 88% yield, R_F = 0.6 (5% EtOAc/ Petroleum ether); ^{1}H NMR (400 MHz, 25 °C, CD_2Cl_2): δ 10.53 – 10.43 (m, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.57 – 7.45 (m, 2H), 7.42- 7.33 (m, 1H), 1.58 – 1.48 (m, 1H), 0.97- 0.91 (m, 2H), 0.89 – 0.81 (m, 2H); ^{13}C NMR (100 MHz, 25 °C, CD_2Cl_2): δ 192.1, 136.5, 134.0, 133.6, 128.1, 127.2, 101.6, 71.7, 9.1, 0.5; HRMS (ESI)**:** Calculated for $C_{12}H_{10}O$ [M+H$^+$]: 171.08044, Found: 171.08065.

Compound 77



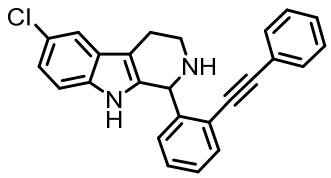
Compound **77** was synthesized according to the **GP2** as a sticky reddish brown solid in 74% yield, R_F = 0.43 (10% MeOH/ DCM); ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 7.75 (s, 1H, NH), 7.54 (m, 1H), 7.47 (m, 1H), 7.40 (m, 2H), 7.28-7.23 (m, 3H), 7.23-7.15 (m, 2H), 7.15-7.09 (m, 2H), 7.07-7.01 (m, 2H), 5.74 (s, 1H), 3.23 (m, 1H), 3.07 (m, 1H), 2.81 (m, 2H), 2.20 (bs, 1H, NH); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 143.7, 136.0, 134.0, 132.8, 131.7, 128.8, 128.69, 128.67, 128.5, 127.9, 127.4, 122.9, 122.6, 121.7, 119.4, 118.2, 110.9, 110.4, 94.5, 87.1, 55.4, 42.2, 22.5; HRMS (ESI)**:** Calculated for $C_{25}H_{21}N_2$ [M+H$^+$]: 349.16993, Found: 349.17088.

Compound 89



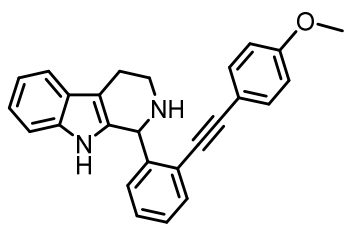
Compound **89** was synthesized according to the **GP2** as a sticky reddish brown solid in 70% yield, R_F = 0.45 (10% MeOH/ DCM); ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 7.61 (m, 1H), 7.57 (s, 1H, NH), 7.47 (m, 2H), 7.35-7.27 (m, 5H), 7.23 (m, 1H), 7.13 (dd, *J* = 8.7, 0.5 Hz, 1H), 7.0 (d, *J* = 2.4 Hz, 1H), 6.8 (dd, *J* = 8.7, 2.5 Hz, 1H), 5.81 (s, 1H), 3.87 (s, 3H), 3.33 (m, 1H), 3.18 (m, 1H), 2.86 (m, 2H), 2.05 (bs, 1H, NH); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 154.2, 143.6, 134.9, 132.9, 131.7, 131.1, 128.8, 128.73, 128.70, 128.5, 127.9, 127.8, 122.9, 122.7, 111.64, 111.61, 110.2, 100.6, 94.5, 87.1, 56.1, 55.6, 42.4, 22.6; HRMS (ESI): Calculated for $C_{26}H_{23}N_2O$ [M+H$^+$]: 379.18049, Found: 379.18026 .

Compound 90



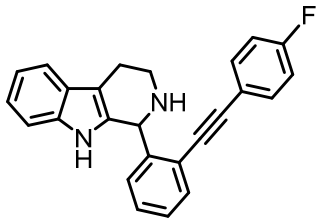
Compound **90** was synthesized according to the **GP2** as a sticky reddish brown solid in 60% yield, R_F = 0.47 (10% MeOH/ DCM); **^{1}H** NMR (400 MHz, 25 °C, CD_2Cl_2): δ 8.14(s, 1H, NH), 7.63(m, 1H), 7.49(d, *J* = 1.4 Hz, 1H), 7.45(m, 2H), 7.37-7.24(m, 5H), 7.20(dd, *J* = 7.2, 0.6 Hz, 1H), 7.11(dd, *J* = 8.6, 0.6 Hz, 1H), 7.04 (m, 1H), 5.76 (s, 1H), 3.27 (m, 1H), 3.09 (m, 1H), 2.84 (m, 1H), 2.75 (m, 1H), 2.23 (bs, 1H, NH); **^{13}C** NMR (100 MHz, 25 °C, CD_2Cl_2): δ 143.9, 136.4, 134.7, 133.1, 131.9, 129.1, 129.0, 128.9, 128.89, 128.85, 128.2, 125.1, 123.1, 122.9, 121.8, 117.9, 112.2, 110.3, 94.7, 87.3, 55.8, 42.5, 22.6; HRMS (ESI)**:** Calculated for $C_{25}H_{20}N_2Cl$ [M+H$^+$]: 383.13095, Found: 383.13142.

Compound 91



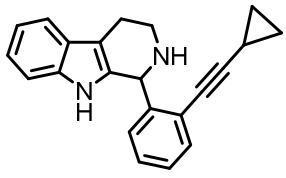
Compound **91** was synthesized according to the **GP2** as a sticky reddish brown solid in 71% yield, R_F = 0.48 (10% MeOH/ DCM); ^{1}H NMR (400 MHz, 25 °C, CD_2Cl_2): δ 7.92 (s, 1H, NH), 7.61 (m, 1H), 7.42 (m, 2H), 7.29 (m, 2H), 7.26-7.18 (m, 3H), 7.08 (m, 2H), 6.87 (m, 2H), 5.80 (s, 1H), 3.81 (s, 3H) 3.30 (m, 1H), 3.13 (m, 1H), 2.85 (m, 2H), 2.03 (bs, 1H, NH); ^{13}C NMR (100 MHz, 25 °C, CD_2Cl_2): δ 160.2, 143.8, 136.1, 134.5, 133.2, 132.6, 128.6, 128.5, 127.8, 123.0, 121.6, 119.3, 118.2, 115.0, 114.2, 113.7, 110.9, 110.2, 94.5, 86.0, 55.63, 55.53, 42.4, 22.6; HRMS (ESI)**:** Calculated for $C_{26}H_{23}N_2O$ [M+H$^+$]: 379.18049, Found: 379.18131.

Compound 92



Compound **92** was synthesized according to the **GP2** as a sticky reddish brown solid in 70% yield, R_F = 0.46 (10% MeOH/ DCM); ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 7.8 (s, 1H, NH), 7.61(m, 1H), 7.55 (m, 1H), 7.42 (m, 2H), 7.28 (m, 2H), 7.23-7.18 (m, 2H), 7.13 (m, 2H), 7.02 (m, 2H), 5.78 (s, 1H), 3.32 (dt, *J* = 12.2, 5.1 Hz, 1H), 3.16 (m, 1H), 2.88 (m, 2H), 2.24 (bs, 1H, NH); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 162.7(d, *J* = 250.2 Hz, CF), 143.6, 136.0, 133.9, 133.6 (d, *J* = 8.4 Hz, 2CH), 132.8, 128.9, 128.7, 127.9, 127.4, 122.5, 121.8, 119.5, 119.0 (d, *J* = 3.5 Hz), 118.3, 115.8 (d, *J* = 22.1 Hz, 2CH), 110.9, 110.4, 93.4, 86.8, 86.7, 55.6, 42.3, 22.5; HRMS (ESI)**:** Calculated for $C_{25}H_{20}N_2F$ [M+H$^+$]: 367.16050, Found: 367.16184.

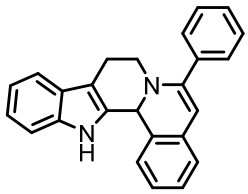
Compound 93



Compound **93** was synthesized according to the **GP2** as a sticky reddish brown solid in 70% yield, R_F = 0.46 (10% MeOH/ DCM); ^{1}H NMR (400 MHz, 25 °C, CD_2Cl_2): δ 7.96 (s, 1H, NH), 7.52 (m, 1H), 7.47 (dd, *J* = 7.5, 1.1 Hz, 1H), 7.26-7.12 (m, 5H), 7.07 (m, 2H), 5.65 (s, 1H), 3.26 (dt, *J* = 12.1, 5 Hz, 1H), 3.10 (m, 1H), 2.88 (m, 1H), 2.80 (m, 1H),

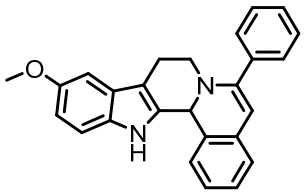
2.22 (bs, 1H, NH), 1.48 (m, 1H), 0.88 (m, 2H), 0.76 (m, 2H); ^{13}C NMR (100 MHz, 25 °C, CD_2Cl_2): δ 144.2, 136.3, 134.8, 133.0, 128.6, 128.1, 127.9, 127.7, 123.6, 121.7, 119.4, 118.3, 111.1, 110.2, 99.1, 73.7, 55.5, 42.5, 22.8, 9.02, 8.97, 0.58; HRMS (ESI)**:** Calculated for $C_{22}H_{21}N_2$ [M+H$^+$]: 313.16993, Found: 313.17066.

Compound 81



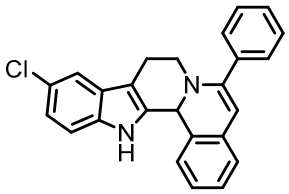
Compound **81** was synthesized according to the **GP3** as a orangish red solid in 62% yield, R_F = 0.47 (5% EtOAc/Petroleum ether); ^{1}H NMR (400 MHz, 25 °C, CD_2Cl_2): δ 8.03 (bs, 1H, NH),7.68 (m, 2H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.4 (m, 4H), 7.26 (m, 1H), 7.21 (m, 2H), 7.13 (dd, *J* = 13, 4.7 Hz, 2H), 7.11 (m, 1H), 6.25 (s, 1H), 5.53 (s, 1H), 3.23 (m, 1H), 3.14 (m, 1H), 2.86 (m, 1H), 2.66 (m, 1H); ^{13}C NMR (100 MHz, 25 °C, CD_2Cl_2): δ 149.9, 137.4, 136.6 134.5, 132, 129.6, 128.9, 128.8, 128.3, 128, 127.7, 126.7, 125.2, 124.2, 122.1, 119.8, 118.5, 111.3, 109.6, 108.3, 57.3,43.1, 22.2 ; HRMS (ESI)**:** Calculated for $C_{25}H_{21}N_2$ [M+H$^+$]: 349.16993, Found: 349.17038.

Compound 94



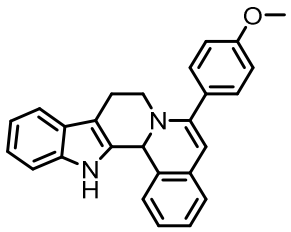
Compound **94** was synthesized according to the **GP3** as a orangish red solid in 62% yield, R_F = 0.45 (5% EtOAc/Petroleum ether); ^{1}H NMR (400 MHz, 25 °C, CD_2Cl_2): δ 8.07 (bs, 1H, NH), 7.64 (d, *J* = 8.7 Hz, 2H), 7.53 (d, *J* = 7.5 Hz,1H), 7.41 (d, *J* = 8 Hz, 1H), 7.29-7.08 (m, 6H), 6.95 (d, *J* = 8.6 Hz, 2H), 6.26 (s, 1H), 5.45 (s, 1H), 3.85 (s, 3H), 3.13 (m, 2H), 2.89 (m, 1H), 2.67 (dd, *J* = 15.3, 3.9 Hz, 1H); ^{13}C NMR (100 MHz, 25 °C, CD_2Cl_2): δ 160.6, 149.7, 136.6, 134.8, 131.9, 129.7, 129.6, 129.3, 128.1, 127.7, 126.4, 125.1, 124.0, 122.1, 119.8, 118.6, 114.2, 111.3, 109.7, 107.5, 57.1, 55.7, 42.7, 22.3; HRMS (ESI): Calculated for $C_{26}H_{23}ON_2$ [M+H$^+$]: 379.18049, Found: 379.18127.

Compound 95



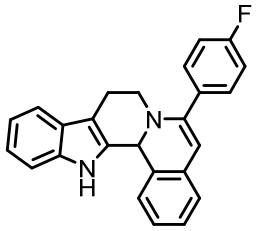
Compound **95** was synthesized according to the **GP3** as a yellowish orange solid in 53% yield, R_F = 0.46 (5% EtOAc/Petroleum ether); ^{1}H NMR (400 MHz, 25 °C, $(CD_3)_2SO$): δ 11.37(s, 1H, NH), 7.74 (dd, *J* = 8.1, 1.3 Hz, 2H), 7.51 (d, *J* = 2.0 Hz, 1H), 7.48-7.38 (m, 4H), 7.31-7.20 (m, 3H), 7.11 (dd, *J* = 8.6, 2.1 Hz, 2H), 6.62 (s, 1H), 5.35 (s, 1H), 3.00-2.79 (m, 3H), 2.62 (m, 1H); ^{13}C NMR (100 MHz, 25 °C, $(CD_3)_2SO$): δ 148.4, 135.9, 134.7, 133.3, 133.2, 129.6, 128.7, 128.6, 127.6, 127.5, 127.0, 126.6, 125.2, 123.8, 123.1, 120.8, 117.1, 112.6, 109.2, 107.5, 55.8, 41.3, 21.4; HRMS (ESI)**:** Calculated for $C_{25}H_{20}N_2Cl$ [M+H$^+$]: 383.13095, Found: 383.12930.

Compound 96



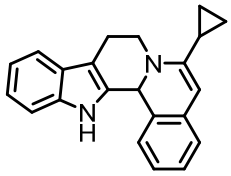
Compound **96** was synthesized according to the **GP3** as a orangish yellow solid in 60% yield, R_F = 0.43 (5% EtOAc/Petroleum ether), ^{1}H NMR (400 MHz, 25 °C, CD_2Cl_2): δ 7.88 (bs, 1H, NH), 7.68 (dd, *J* = 8, 1.6 Hz, 2H), 7.45-7.36 (m, 3H), 7.29-7.24 (m, 2H), 7.2 (m, 2H), 7.14 (d, *J* = 7.3 Hz, 1H), 6.97 (d, *J* = 2.4 Hz,1H), 6.82 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.22 (s, 1H), 5.51 (s, 1H), 3.84(s, 3H), 3.24 (m, 1H), 3.14 (m, 1H), 2.81 (m, 1H), 2.62 (m, 1H); ^{13}C NMR (100 MHz, 25 °C, CD_2Cl_2): δ 154.3, 149.7, 137.2, 134.2, 132.7, 131.4, 129.3, 128.7, 128.6, 128, 127.9,127.8,126.4, 125, 124, 111.7,111.6, 109.2, 107.9, 100.6, 57.2, 55.9, 43, 22; HRMS (ESI)**:** Calculated for $C_{26}H_{23}ON_2$ [M+H$^+$]: 379.18049, Found: 379.18130.

Compound 97



Compound **97** was synthesized according to the **GP3** as a orangish red solid in 58% yield, R_F = 0.45 (5% EtOAc/Petroleum ether)**,** ^{1}H NMR (400 MHz, 25 °C, CD_2Cl_2): δ 8.03(bs, 1H, NH), 7.69 (m, 2H), 7.53 (dd, *J* = 7.8, 0.5 Hz, 1H), 7.40 (m, 1H), 7.28 (m, 1H), 7.24-7.15 (m, 4H), 7.15-7.09 (m, 3H), 6.27 (s, 1H), 5.47 (s, 1H), 3.12 (m, 1H), 2.87 (m, 1H), 2.66 (dt, *J* = 15.4,4.3 Hz, 1H); ^{13}C NMR (100 MHz, 25 °C, CD_2Cl_2): δ 163.4(d, *J* = 247.2 Hz, CF), 148.9, 136.6, 134.4, 133.5 (d, *J* = 3.2 Hz), 131.8, 129.8 (d, *J* = 8.2 Hz, 2CH), 129.7, 128.3, 127.7, 126.8, 125.2, 124.2, 122.1, 119.8, 118.6, 115.7 (d, *J* = 21.6 Hz, 2CH), 111.3, 109.6, 108.6, 57.1, 42.8, 22.2 ; HRMS (ESI)**:** Calculated for $C_{25}H_{20}N_2F$ [M+H$^+$]: 367.16050, Found: 367.16107.

Compound 98

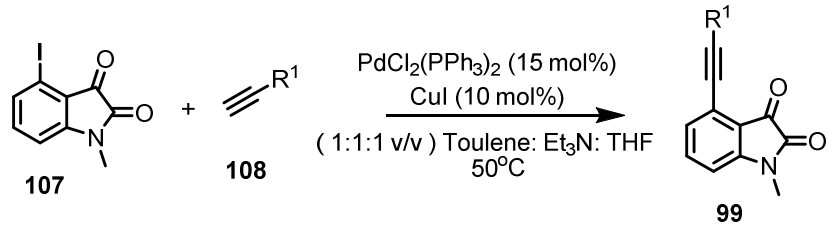


Compound **98** was synthesized according to the **GP3** as a orangish red solid in 50% yield, R_F = 0.45 (2.5% EtOAc/Petroleum ether)**,** ^{1}H NMR (400 MHz, 25 °C, CD_2Cl_2): δ 7.56 (s, 1H, NH), 7.46 (m, 1H), 7.25-7.15 (m, 3H), 7.13-7.02 (m, 3H), 6.84 (d, *J* = 7.6 Hz, 1H), 5.82 (s, 1H), 5.18 (s, 1H), 4.48 (m, 1H), 3.46 (m, 1H), 3.12 (m, 1H), 2.78 (m, 1H), 1.66 (m, 1H), 0.82 (m, 2H), 0.71 (m, 1H), 0.56 (m, 1H); ^{13}C NMR (100 MHz, 25 °C, CD_2Cl_2): δ 150.1, 135.9, 134.8, 134.0, 128.7, 128.2, 126.9, 125.5, 125.0, 123.4, 121.8, 119.7, 118.2, 111.3, 108.8, 97.7, 59.0, 45.2, 21.7, 12.9, 6.5, 6.2; HRMS (ESI)**:** Calculated for $C_{22}H_{21}N_2$ [M+H$^+$]: 313.16993, Found: 313.16868.

5.2.2 Synthesis of tetrahydro-*β*-carboline ring fused to a spirooxindole ring system giving rise to hexacyclic indoloquinolizines

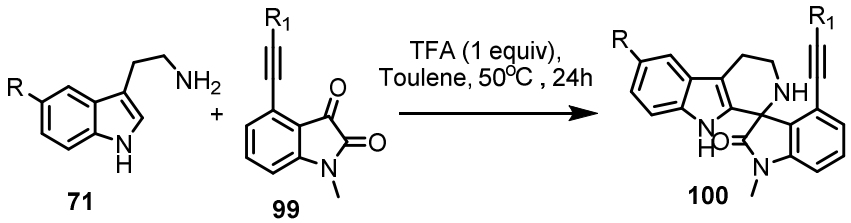
General Procedure 4 (GP4) for the synthesis of alknyl isatins 99.

To a mixture of 4-Iodo-*N*-methylisatin [59] (500 mg, 1.74 mmol) and $PdCl_2(PPh_3)_2$ (15 mol%, 182.49 mg) under an argon atmosphere was added anhydrous Et_3N (12 mL), anhydrous Toluene (12 mL), anhydrous THF (12 mL) followed by the addition of the corresponding terminal alkyne (1.4 equiv, 2.43 mmol). The above reaction mixture was stirred at RT for 10 mins before the addition of CuI (10 mol%, 33.13 mg). The resulting reaction mixture was heated to 50 ^oC and stirred at that temperature until the completion of the reaction (monitored *via* TLC). The solvent was then removed *in vacuo* and the residue was purified by flash column chromatography using silica gel to yield the corresponding Sonogashira product as orange or red solids.



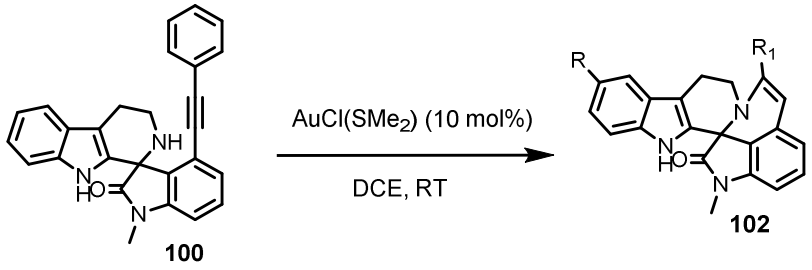
General Procedure 5 (GP5) for the synthesis of Pictet-Spengler Derivatives 100

To a mixture of Tryptamine/5-OMe Tryptamine (0.25 mmol) and the corresponding Sonogashira product **99** (0.25 mmol) under an argon atmosphere was added 5 mL of toluene and the reaction mixture was stirred at RT for 5 mins followed by the addition of TFA (1 equiv, 0.25 mmol) . The resulting reaction mixture was heated to 50 ^oC for 24 h. The solvent was then removed in *vacuo* and the residue was purified by flash column chromatography using basified silica gel with methanol and dichloromethane as eluents.

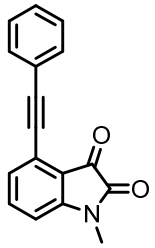


General Procedure 6 (GP6) for the gold catalyzed hydroamination reaction yielding hexacyclic indoloquinolizines 102.

To a solution of the Pictet-Spengler compound **100** (0.1 mmol) in dry DCE (2 mL) under an argon atmosphere was added the gold catalyst $AuCl(SMe_2)$ (10 mol%, 0.01 mmol). The reaction mixture was stirred at RT until the completion of the reaction (monitored *via* TLC). The solvent was then removed in *vacuo* and the crude reaction mixture was purified by flash chromatography (silica gel) using petroleum ether and ethyl acetate as eluents.

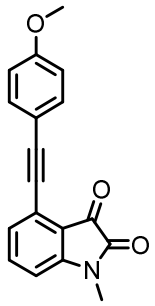


1-Methyl-4-(phenylethynyl)indoline-2,3-dione (103)



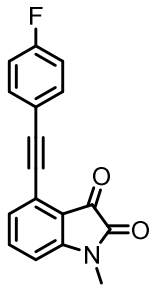
Compound **103** was synthesized according to the **GP4** as a red solid in 80% yield, R_F = 0.30 (30% EtOAc/Petroleum ether)**;** m.p. – 175.3- 175.6^{o}C; ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 7.68 (m, 2H), 7.54 (m, 1H), 7.39 (m,1H), 7.20 (dd, *J* = 7.9, 0.8 Hz, 1H), 6.82 (dd, *J* = 7.9, 0.7 Hz, 1H), 3.26 (s, 3H); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 181.2, 158.1, 151.3, 137.3, 132.5, 129.5, 128.6, 127.4, 122.3, 122.1, 117.2, 109.1, 98.26, 85.6, 26.3; HRMS (ESI): Calculated for $C_{17}H_{12}O_2N$ [M+H^{+}]: 262.08626, Found: 262.08669.

4-((4-Methoxyphenyl)ethynyl)-1-methylindoline-2,3-dione (109)



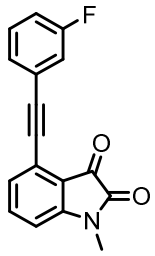
Compound **109** was synthesized according to the **GP4** as a reddish orange solid in 74% yield, R_F = 0.32 (30% EtOAc/Petroleum ether); m.p. – 178.3- 178.5^{o}C; ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 7.63(m, 2H), 7.51 (m, 1H), 7.16 (dd, *J* = 8.0, 0.8 Hz, 1H), 6.91 (m, 2H), 6.78 (dd, *J* = 7.9, 0.7 Hz, 1H), 3.84 (s, 3H), 3.25 (s, 3H); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 181.3, 160.8, 158.3,151.5, 137.3, 134.3, 127.2, 122.7, 117.1, 114.5, 114.4, 108.7, 99.0, 85.0, 55.58, 26.4; HRMS (ESI): Calculated for $C_{18}H_{14}O_3N$ [M+H$^+$]: 314.07876, Found: 314.07906.

4-((4-Fluorophenyl)ethynyl)-1-methylindoline-2,3-dione (110)



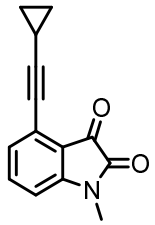
Compound **110** was synthesized according to the **GP4** as a red solid in 80% yield, R_F = 0.36 (30% EtOAc/Petroleum ether); m.p. – 202.2- 202.7 ^{o}C; ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 7.68 (m, 2H), 7.54 (td, *J* = 7.9, 1.0 Hz, 1H), 7.18 (dd, *J* = 7.9, 0.7 Hz, 1H), 7.09 (m, 2H), 6.83 (m, 1H), 3.26 (d, *J* = 0.9 Hz, 3H); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 181.33, 163.47 (d, *J* = 251.6 Hz, CF), 158.16, 151.6, 137.4, 134.6 (d, *J* = 8.6 Hz, 2CH), 127.3, 122.0, 118.6(d, *J* = 3.6 Hz), 117.3, 116.1 (d, *J* = 22.2 Hz, 2CH), 109.2, 97.2,85.4, 26.4; HRMS (ESI): Calculated for $C_{17}H_{11}O_2NF$ [M+H$^+$]: 280.07683, Found: 280.07728.

4-((3-Fluorophenyl)ethynyl)-1-methylindoline-2,3-dione (111)



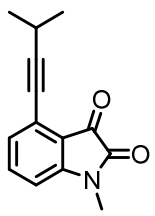
Compound **111** was synthesized according to the **GP4** as a red solid in 65% yield, R_F = 0.35 (30% EtOAc/Petroleum ether); m.p. – 192.6- 192.9 ^{o}C; ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 7.56 (td, *J* = 7.9, 1.1 Hz, 1H), 7,47 (m, 1H), 7.36 (m, 2H), 7.21 (dd, *J* = 7.9, 0.8 Hz, 1H), 7.11 (m, 1H), 6.86 (dd, *J* = 7.9, 0.7 Hz, 1H), 3.27 (d, *J* = 1.0 Hz, 3H); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 181.2, 162.5 (d, *J* = 247.1 Hz, CF), 158.0, 151.6, 137.5, 130.3(d, *J* = 8.5 Hz), 128.53 (d, *J* = 3.1 Hz), 127.5, 124.2 (d, *J* = 9.5 Hz), 121.6, 119.2 (d, *J* = 22.1 Hz), 117.4, 117.0 (d, *J* = 21.2 Hz), 109.6, 96.6, 86.2, 26.4; HRMS (ESI)**:** Calculated for $C_{17}H_{14}O_2NF$ [M+H^{+}]: 280.07683, Found: 280.07705.

4-(Cyclopropylethynyl)-1-methylindoline-2,3-dione (112)



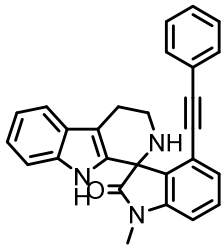
Compound **112** was synthesized according to the **GP4** as a reddish orange solid in 70% yield, R_F = 0.41 (30% EtOAc/Petroleum ether); m.p. – 162.9- 163.3 ^{o}C; ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 7.46 (m, 1H), 7.02 (dt, *J* = 10.8, 5.4 Hz, 1H), 6.74 (dd, *J* = 7.9, 0.7 Hz, 1H), 3.22 (s, 3H), 1.54 (m, 1H), 0.99 (m, 4H); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 181.2, 158.2, 151.3, 137.1, 127.6, 123.2, 117.5, 108.2, 104.5, 72.4, 26.3, 9.7, 0.9; HRMS (ESI)**:** Calculated for $C_{14}H_{12}O_2N$ [M+H^{+}]: 226.08626, Found: 226.08631.

1-Methyl-4-(3-methylbut-1-yn-1-yl)indoline-2,3-dione (113)



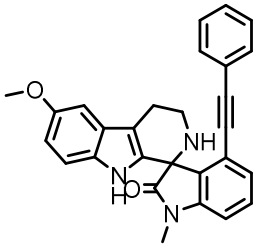
Compound **113** was synthesized according to the **GP4** as a reddish orange solid in 67% yield, R_F = 0.42 (30% EtOAc/Petroleum ether); m.p. – 155.7- 155.9 °C; ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 7.47 (m, 1H), 7.06 (m, 1H), 6.76 (dd, *J* = 7.9, 0.7 Hz, 1H), 3.23 (s, 3H), 2.88 (dt, *J* = 13.8, 6.9 Hz, 1H), 1.32 (m, 6H); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 181.2, 158.1, 151.3, 137.1, 127.8, 123.1, 117.5, 108.5, 105.8, 76.2, 26.3, 22.6, 21.7; HRMS (ESI)**:** Calculated for $C_{14}H_{14}O_2N$ [M+H$^+$]: 228.10191, Found: 228.10232.

Compound 104



Compound **104** was synthesized according to the **GP5** as a reddish brown solid in 81% yield, R_F = 0.45 (10% MeOH/DCM); ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 7.57 (m, 1H), 7.48 (s, 1H, NH), 7.36 (dd, *J* = 10.4, 5.4 Hz, 1H), 7.25-7.11 (m, 7H), 6.87 (dd, *J* = 8.3, 1.3 Hz, 3H), 3.95 (m, 1H), 3.31 (m, 1H), 3.24 (s, 3H), 2.92 (m, 1H), 2.78 (m, 1H), 2.35 (bs, 1H, NH); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 175.9, 144.7, 136.3, 131.7, 131.1, 130.1, 129.3, 128.7, 128.2, 127.6, 126.6, 122.4, 122.0, 120.0, 119.7, 118.5, 113.4, 111.2, 108.5, 95.4, 83.9, 61.2, 39.9, 26.6, 22.5; HRMS (ESI)**:** Calculated for $C_{27}H_{22}ON_3$ [M+H$^+$]: 404.17574, Found: 404.17563.

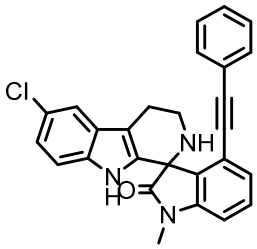
Compound 114



Compound **114** was synthesized according to the **GP5** as a reddish brown solid in 71% yield, R_F = 0.48 (10% MeOH/DCM); ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 7.29 (m, 1H), 7.26 (s, 1H, NH), 7.15 (m, 1H), 7.06 (m, 3H), 7 (dd, *J* = 8.7, 0.5 Hz, 1H), 6.94 (d, *J* = 2.4 Hz, 1H), 6.81 (m, 3H), 6.71 (dt, *J* = 8.8, 2.2 Hz, 1H), 3.88 (m, 1H), 3.81 (s, 3H), 3.25 (m,

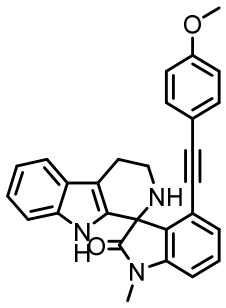
1H), 3.17 (s, 1H), 2.8 (m, 1H), 2.66 (m, 1H), 1.95 (bs, 1H, NH); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 175.9, 154.3, 144.7, 131.7, 131.5, 131.2, 130.2, 130.1, 128.7, 128.2, 128.0, 126.6, 122.0, 120.1, 113.3, 112.3, 111.7, 108.5, 100.6, 95.4, 83.9, 61.3, 56.1, 39.9, 26.6, 22.6; HRMS (ESI)**:** Calculated for $C_{28}H_{24}O_2N_3$ [M+H$^+$]: 434.18630, Found: 434.18655.

Compound 115



Compound **115** was synthesized according to the **GP2** as a reddish brown solid in 57% yield, R_F = 0.5 (10% MeOH/DCM); ^{1}H NMR (400 MHz, 25 °C, CD_2Cl_2): δ 7.95 (s, 1H, NH), 7.53 (m, 1H), 7.37 (m, 1H), 7.28 (m, 1H), 7.19 (m, 3H), 7.07 (m, 2H), 6.91 (m, 3H), 3.81 (m, 1H), 3.23 (m, 1H), 3.18 (s, 3H), 2.83 (m, 1H), 2.72 (m, 1H), 2.30 (bs, 1H, NH); ^{13}C NMR (100 MHz, 25 °C, CD_2Cl_2): δ 175.9, 145.1, 134.8, 131.77, 131.75, 131.2, 130.5, 129.1, 128.8, 128.6, 126.8, 125.5, 122.7, 122.2, 120.2, 118.1, 113.3, 112.5, 109.0, 95.4, 84.3, 61.4, 39.9, 26.7, 22.6; HRMS (ESI)**:** Calculated for $C_{27}H_{21}ON_3Cl$ [M+H$^+$]: 438.13677, Found: 438.13722.

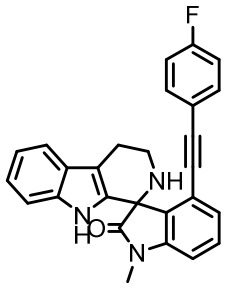
Compound 116



Compound **116** was synthesized according to the **GP5** as a reddish brown solid in 70% yield, R_F = 0.49 (10% MeOH/DCM); ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 7.57 (m, 1H), 7.43 (s, 1H, NH), 7.34 (t, *J* = 7.9 Hz, 1H), 7.2 (m, 1H), 7.13 (m, 3H), 6.86 (dd, *J* = 7.9, 0.8 Hz, 1H), 6.8 (m, 2H), 6.65 (m, 2H), 3.96 (m, 1H), 3.77 (s, 3H), 3.33 (m ,1H), 3.25 (s, 3H), 2.93 (m, 1H), 2.78 (m, 1H), 1.99 (bs, 1H, NH); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 175.9, 160.0, 144.7, 136.3, 133.2, 130.8, 130.1, 129.4, 127.6, 126.5, 122.4, 120.5, 119.7,

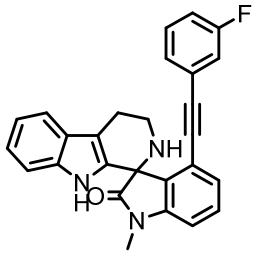
118.4, 114.1, 113.9, 113.4, 111.2, 108.2, 95.7, 82.8, 61.2, 55.4, 39.9, 26.6, 22.5; HRMS (ESI)**:** Calculated for $C_{28}H_{24}O_2N_3$ [M+H$^+$]: 434.18630, Found: 434.18640.

Compound 117



Compound **117** was synthesized according to the **GP5** as a reddish brown solid in 80% yield, R_F = 0.51 (10% MeOH/DCM); ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 7.55 (m, 1H), 7.48 (s, 1H, NH), 7.36 (t, *J* = 7.9 Hz, 1H), 7.19 (m , 1H), 7.16-7.11 (m, 3H), 6.88 (dd, *J* = 7.9, 0.8 Hz, 1H), 6.83-6.78 (m, 3H), 3.95 (m, 1H), 3.32 (m, 1H), 3.25 (s, 3H), 2.93 (m, 1H), 2.74 (m, 1H), 2.09 (bs, 1H, NH); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 175.8, 162.7 (d, *J* = 250.5 Hz, CF), 144.8, 136.3, 133.6 (d, *J* = 8.5 Hz, 2CH), 131.1, 130.2, 129.3, 127.5, 126.5, 122.5, 120.0, 119.7, 118.4, 118.1 (d, *J* = 3.4 Hz), 115.6 (d, *J* = 22.1 Hz, 2CH), 113.3, 111.2, 108.6, 94.3, 83.6, 61.2, 39.8, 26.7, 22.5; HRMS (ESI)**:** Calculated for $C_{27}H_{21}ON_3F$ [M+H$^+$]: 422.16632, Found: 422.16615.

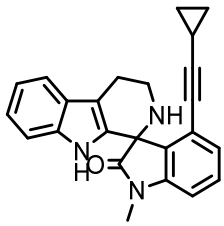
Compound 118



Compound **118** was synthesized according to the **GP5** as a reddish brown solid in 75% yield, R_F = 0.49 (10% MeOH/DCM); **^{1}H** NMR (400 MHz, 25 °C, CD_2Cl_2): δ 7.75 (s, 1H, NH), 7.60 (m, 1H), 7.38 (dd, *J* = 10.3, 5.5 Hz, 1H), 7.20-7.10 (m, 5H), 6.97 (m, 1H), 6.92 (dd, *J* = 7.9, 0.9 Hz, 1H), 6.72 (m, 1H), 6.62 (m, 1H), 3.85 (m, 1H), 3.26 (m, 1H), 3.21 (s, 3H), 2.91(m, 1H), 2.78 (m, 1H), 2.09 (bs, 1H, NH); **^{13}C** NMR (100 MHz, 25 °C, CD_2Cl_2): δ 175.9, 162.3(d, *J* = 246.2 Hz, CF), 145.0, 136.3, 131.6, 130.2, 130.0 (d, *J* = 8.6 Hz), 129.7, 127.6 (d, *J* = 3 Hz), 127.3, 126.6, 124.0 (d, *J* = 9.5 Hz), 122.5, 119.8, 119.5, 118.5, 118.2(d, *J* = 23.0 Hz), 116.1(d, *J* = 21.2 Hz), 113.2, 111.1, 109.1, 93.6 (d, *J* = 3.4 Hz),

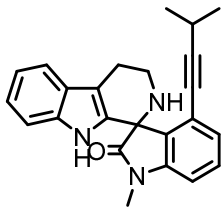
85.1, 61.3, 39.8, 26.5, 22.6; HRMS (ESI)**:** Calculated for $C_{27}H_{21}ON_3F$ [M+H$^+$]: 422.16632, Found: 422.16617.

Compound 119



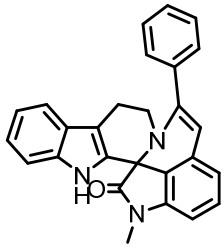
Compound **119** was synthesized according to the **GP5** as a reddish brown solid in 65% yield, R_F = 0.51 (10% MeOH/DCM); ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 7.54(m, 1H), 7.29 (m, 2H), 7.18-7.06 (m, 3H), 7.01 (d, *J* = 7.9 Hz, 1H), 6.81 (d, *J* = 7.9 Hz, 1H), 3.97 (m, 1H), 3.36 (m, 1H), 3.21 (s, 3H), 2.96 (m, 1H), 2.88 (m, 1H), 2.03 (bs, 1H, NH), 1.06 (m, 1H), 0.54 (m, 2H), 0.22 (m, 1H), -0.01(m, 1H); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 175.9, 144.5, 136.3, 131.0, 129.9, 129.5, 127.4, 126.8, 122.2, 120.9, 119.5, 118.5, 113.0, 111.0, 107.7, 100.3, 70.6, 61.1, 39.7, 26.6, 22.4, 8.5, 8.4, 0.05; HRMS (ESI): Calculated for $C_{24}H_{22}ON_3$ [M+H$^+$]: 368.17574, Found: 368.17656.

Compound 120



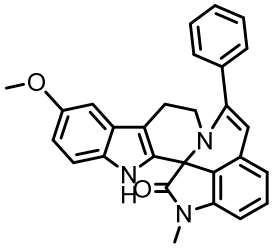
Compound **120** was synthesized according to the **GP5** as a reddish brown solid in 76% yield, R_F = 0.51 (10% MeOH/DCM); ^{1}H NMR (400 MHz, 25 °C, CD_2Cl_2): δ 7.73 (s, 1H, NH), 7.55 (m, 1H), 7.31 (m, 1H), 7.11 (m, 3H), 7.04 (m, 1H), 6.82 (dd, *J* = 7.9, 0.9 Hz, 1H), 3.84 (m, 1H), 3.29 (m, 1H), 3.15 (s, 3H), 2.90 (m, 2H), 2.41 (dt, *J* = 13.8, 6.9 Hz, 1H), 2.24 (bs, 1H, NH), 0.80 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, 25 °C, CD_2Cl_2): δ 176.2, 144.9, 136.5, 131.3, 130.1, 127.6, 126.9, 122.4, 121.0, 119.6, 118.6, 113.1, 111.2, 108.2, 102.4, 74.9, 61.4, 39.9, 26.6, 22.6, 22.45, 22.41, 21.3; HRMS (ESI)**:** Calculated for $C_{24}H_{24}ON_3$ [M+H$^+$]: 370.19139, Found: 370.19219.

Compound 105



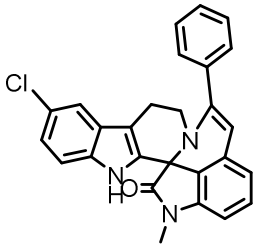
Compound **105** was synthesized according to the **GP6** as a white solid in 76% yield, R_F = 0.38 (25% EtOAc/Petroleum ether); m.p. – 277.3 – 277.8°C; ^{1}H NMR (400 MHz, 25 °C, $(CD_3)_2SO$): δ 10.51 (s, 1H, NH),7.44-7.35 (m, 4H), 7.35-7.27 (m, 3H), 7.22 (dd, *J* = 8.1, 0.8 Hz, 1H), 7.04 (m, 1H), 6.96 (m, 2H), 6.64 (d, *J* = 7.8 Hz, 1H), 5.39 (s, 1H), 4.39 (m, 1H), 3.63 (dd, *J* = 13.6, 3.9 Hz, 1H), 3.18 (s, 3H), 2.43 (m, 2H); ^{13}C NMR (150 MHz, 25 °C, $(CD_3)_2SO$): δ 176.3, 151.6, 141.9, 137.5, 136.0, 130.9, 130.5, 129.8, 127.9, 126.6, 121.4, 118.6, 117.6, 116.9, 115.7, 111.4, 109.4, 106.5, 104.5, 61.2, 42.7, 26.3, 19.8; HRMS (ESI)**:** Calculated for $C_{27}H_{22}ON_3$ [M+H$^+$]: 404.17574, Found: 404.17552.

Compound 121



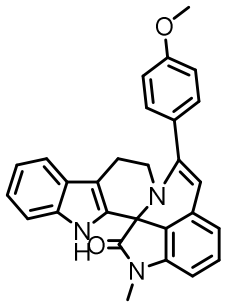
Compound **121** was synthesized according to the **GP6** as a white solid in 76% yield, R_F = 0.36 (25% EtOAc/Petroleum ether); m.p. – 315.6 – 315.7 °C; ^{1}H NMR (400 MHz, 25 °C, $(CD_3)_2SO$): δ 10.33(s, 1H, NH), 7.41(m, 3H), 7.35-7.25(m, 3H), 7.11 (d, *J* = 8.7 Hz, 1H), 6.95 (d, *J* = 7.8 Hz, 1H), 6.87 (d, *J* = 2.3 Hz, 1H), 6.69 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.64 (d, *J* = 7.8 Hz, 1H), 5.38 (s, 1H), 4.39 (m, 1H), 3.72 (s, 3H), 3.62 (m, 1H), 3.17 (s,3H), 2.42 (m, 2H); ^{13}C NMR (100 MHz, 25 °C, $(CD_3)_2SO$): δ 177.0, 153.9, 152.3, 142.6, 138.2, 131.7, 131.6, 131.2, 131.0, 128.6, 128.1, 127.6, 117.7, 116.3, 112.7, 112.1, 109.8, 107.1, 105.1, 100.3, 62.0, 56.0, 43.4, 27.0, 20.6; HRMS (ESI)**:** Calculated for $C_{28}H_{24}O_2N_3$ [M+H$^+$]: 434.18630, Found: 434.18653.

Compound 122



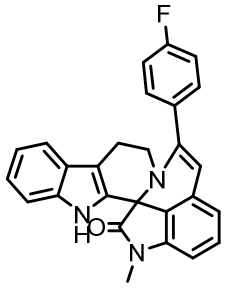
Compound **122** was synthesized according to the **GP6** as a white solid in 60% yield, R_F = 0.39 (25% EtOAc/Petroleum ether); m.p. – 302.7 – 303.0 ^{o}C; ^{1}H NMR (400 MHz, 25 °C, $(CD_3)_2SO$): δ 10.75 (s, 1H, NH), 7.46-7.37 (m, 4H), 7.35-7.27 (m, 3H), 7.22 (d, *J* = 8.6 Hz, 1H), 7.05 (dd, *J* = 8.6, 2.1 Hz, 1H), 6.98 (d, *J* = 7.8 Hz, 1H), 6.65 (d, *J* = 7.7 Hz, 1H), 5.4 (s, 1H), 4.38 (m, 1H), 3.62 (dd, *J* = 14.0, 4.7 Hz, 1H), 3.18 (s, 3H), 2.4 (m, 2H);^{13}C NMR (150 MHz, 25 °C, $(CD_3)_2SO$): δ 176.1, 151.5, 141.9, 137.4, 134.5, 131.7, 130.9, 130.6, 128.0, 127.7, 123.3, 121.3, 117.1, 116.6, 115.8, 112.9, 109.4, 106.6, 104.6, 61.1, 42.5, 26.4, 19.7; HRMS (ESI)**:** Calculated for $C_{27}H_{21}ON_3Cl$ [M+H$^+$]: 438.1367, Found: 438.13728.

Compound 123



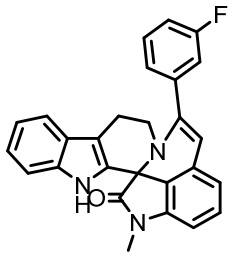
Compound **123** was synthesized according to the **GP6** as a white solid in 74% yield, R_F = 0.37 (25% EtOAc/Petroleum ether); m.p. – 275.2– 275.6 ^{o}C; ^{1}H NMR (600 MHz, 25 °C, $(CD_3)_2SO$): δ 10.51 (s, 1H, NH), 7.37 (d, *J* = 7.9 Hz, 1H), 7.32-7.20 (m, 4H), 7.04 (m, 1H), 6.96 (m, 4H), 6.62 (m, 1H), 5.33 (s, 1H), 4.38 (m, 1H), 3.79 (s, 3H), 3.62 (m,1H), 3.18 (s, 3H), 2.44 (m, 2H); ^{13}C NMR (150 MHz, 25 °C, $(CD_3)_2SO$): δ 176.4, 158.8, 151.4, 141.9, 136.0, 131.1 130.5, 129.8, 129.6, 126.6, 121.4, 118.6, 117.6, 116.8, 115.5, 113.6, 111.4, 109.4, 106.3, 103.9, 61.2, 55.1, 42.7, 26.3, 19.8; HRMS (ESI)**:** Calculated for $C_{28}H_{24}O_2N_3$ [M+H$^+$]: 434.18630, Found: 434.18621.

Compound 124



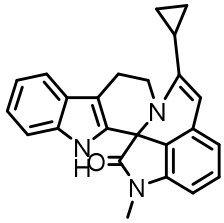
Compound **124** was synthesized according to the **GP6** as a white solid in 72% yield, R_F = 0.4 (25% EtOAc/Petroleum ether); m.p. – 285.4 – 285.7 ^{o}C; ^{1}H NMR (600 MHz, 25 °C, $(CD_3)_2SO$): δ 10.53 (s, 1H, NH), 7.38 (d, *J* = 7.7 Hz, 3H), 7.3 (t, *J* = 7.8 Hz, 1H), 7.23 (m, 3H), 7.04 (m, 1H), 6.96 (m, 1H), 6.64 (m, 1H), 5.38 (s, 1H), 4.4 (m, 1H), 3.57 (dd, *J* = 14.2, 4.9 Hz, 1H), 3.18 (s, 3H), 2.44 (m, 2H); ^{13}C NMR (150 MHz, 25 °C, $(CD_3)_2SO$): δ 176.3, 161.6 (d, *J* = 244.9 Hz, CF), 150.5, 141.9, 136.0, 133.8 (d, *J* = 3.1 Hz), 130.8, 130.5, 129.7, 126.6, 121.4, 118.6, 117.6, 116.9, 115.7, 111.4, 109.3, 106.6, 104.7, 61.2, 42.6, 26.3, 19.8; HRMS (ESI)**:** Calculated for $C_{27}H_{21}ON_3F$ $[M+H^+]$: 422.16632, Found: 422.16647.

Compound 125



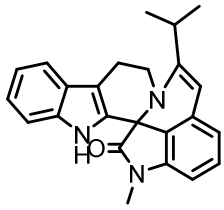
Compound **125** was synthesized according to the **GP6** as a white solid in 71% yield, R_F = 0.38 (25% EtOAc/Petroleum ether); m.p. – 279.3 – 279.7 ^{o}C; ^{1}H NMR (600 MHz, 25 °C, $(CD_3)_2SO$): δ 10.54 (s, 1H, NH), 7.46 (m, 1H), 7.39 (d, *J* = 7.9 Hz, 1H), 7.3 (m, 1H), 7.25- 7.15 (m, 4H), 7.04 (m, 1H), 6.99 (m, 1H), 6.96 (m, 1H), 6.66 (m, 1H), 5.46 (s, 1H), 4.41 (m, 1H), 3.64 (m, 1H), 3.18 (s, 3H), 2.51 (m, 1H), 2.44 (m, 1H); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 176.2, 150.23, 150.22, 141.9, 139.8(d, *J* = 8.0 Hz), 136.0, 130.6(d, *J* = 4.9 Hz), 129.7, 126.6, 123.6, 121.4, 118.6, 117.7, 117.0, 115.8, 114.8, 111.4, 109.4, 106.8, 105.2, 61.2, 42.7, 26.3, 19.9; HRMS (ESI)**:** Calculated for $C_{27}H_{21}ON_3F$ $[M+H^+]$: 422.16632, Found: 422.16645.

Compound 126



Compound **126** was synthesized according to the **GP6** as a white solid in 68% yield, R_F = 0.45 (25% EtOAc/Petroleum ether); m.p. – 302.5 – 302.8 ^{o}C; ^{1}H NMR (400 MHz, 25 °C, $(CD_3)_2SO$): δ 10.43 (s, 1H, NH), 7.43 (d, *J* = 7.6 Hz, 1H), 7.22 (m, 2H), 7.03 (dd, *J* = 11.0, 4.0 Hz, 1H), 6.97 (t, *J* = 7.4 Hz, 1H), 6.85 (d, *J* = 7.7 Hz, 1H), 6.54 (d, *J* = 7.8 Hz, 1H), 5.27 (s, 1H), 4.53 (m, 1H), 4.30 (dd, *J* = 14.2, 5.7 Hz, 1H), 3.11 (m, 4H), 2.78 (dd, *J* = 16.1, 4.7 Hz, 1H), 1.76 (m, 1H), 0.79 (m, 2H), 0.66 (m, 1H), 0.34 (m, 1H); ^{13}C NMR (100 MHz, 25 °C, $(CD_3)_2SO$): δ 176.6, 151.8, 142.0, 135.8, 131.7, 130.3, 130.2, 126.8, 121.3, 118.5, 117.5, 116.8, 115.1, 111.3, 109.5, 105.5, 98.0, 61.3, 40.1, 26.2, 20.1, 12.5, 6.6, 6.1; HRMS (ESI)**:** Calculated for $C_{24}H_{22}ON_3$ [M+H$^+$]: 368.17574, Found: 368.17698.

Compound 127



Compound **127** was synthesized according to the **GP6** as a white solid in 65% yield, R_F = 0.47 (25% EtOAc/Petrolether); m.p. – 283.5 – 283.7^{o}C; ^{1}H NMR (400 MHz, 25 °C, $(CD_3)_2SO$): δ 10.41 (s, 1H, NH), 7.41 (d, *J* = 7.7 Hz, 1H), 7.25 (dd, *J* = 12.4, 4.7 Hz, 1H), 7.19 (m, 1H), 7.02 (m, 1H), 6.96 (m, 1H), 6.87 (d, *J* = 7.8 Hz, 1H), 6.59 (d, *J* = 7.8 Hz, 1H), 5.39 (s, 1H), 4.58 (m, 1H), 3.81 (dd, *J* = 14.4, 4.9 Hz, 1H), 3.12 (s, 3H), 2.86 (m, 2H), 2.75 (dd, *J* = 16.0, 4.6 Hz, 1H), 1.06 (dd, *J* = 21.4, 6.6 Hz, 6H),^{13}C NMR (100 MHz, 25 °C, $(CD_3)_2SO$): δ 176.7, 156.7, 141.7, 135.8, 131.7, 130.5, 130.2, 126.6, 121.2, 118.5, 117.5, 116.8, 115.1, 111.3, 109.6, 105.4, 96.2, 61.4, 40.8, 27.5, 26.2, 24.5, 20.5, 20.3; HRMS (ESI)**:** Calculated for $C_{24}H_{24}ON_3$ [M+H$^+$]: 370.19139, Found: 370.19153.

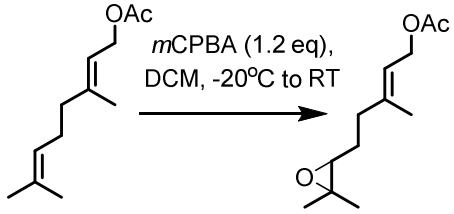
5.2.3 Cascade polycylization of a designed *β*-carboline embodying a 1,5-enyne providing analogs of the harmicine alkaloid.

Synthesis of the aldehyde 131

Procedure for the synthesis of compound 142

To a solution of geranyl acetate (5g, 25.47 mmol) in CH_2Cl_2 (80 ml) at -20^oC was dropwise added a solution of *m*CPBA (5.27g, 30.56 mmol) in CH_2Cl_2 (40 ml) over 60 mins. After stirring the reaction from -20 ^oC to RT over a period of 2 h, the reaction was quenched with saturated aqueous solution of $NaHCO_3$ (80 ml). The aqueous layer was extracted with CH_2Cl_2 (2 X 15 ml) and the combined organic layers were washed with brine dried over anhydrous $MgSO_4$. The residue was purified by flash chromatography using EtOAc and petroleum ether as eluents.

(*E*)-5-(3,3-Dimethyloxiran-2-yl)-3-methylpent-2-en-1-yl acetate (142)



Geranyl acetate, 141 **142**

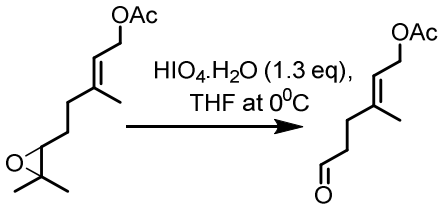
Compound **142** was obtained as a colourless oil in 80% yield, R_F = 0.48 (20% EtOAc/Petroleum ether); ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$) : δ 5.35 (td, *J* = 7.1, 1.2 Hz, 1H), 4.55 (d, *J* = 7.1 Hz, 2H), 2.66 (dd, *J* = 7.8, 4.7 Hz, 1H), 2.23 – 2.07 (m, 2H), 2.01 (s, 3H), 1.69 (s, 3H), 1.66 – 1.59 (m, 2H), 1.26 (s, 3H), 1.22 (s, 3H); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$) : δ 171.0, 141.2, 119.0, 63.9, 61.2, 58.4, 36.2, 27.1, 24.8, 21.0, 18.8, 16.5; HRMS (ESI): Calculated for $C_{12}H_{20}O_3Na$ [M+Na^+]: 235.13047, Found: 235.13150.

Procedure for the synthesis of compound 143

To a solution of periodic acid (6.9 g, 30.27 mmol) in water (30 ml) at 0 ^oC was added a solution of the compound (**142**) in THF (30 ml), after stirring the reaction mixture for 30 min the solution was diluted with an aqeous solution of $NaHCO_3$ (40 ml) and stirred for an additional 15 min. The reaction mixture was filtered througha pad of celite, and the filter cake

was washed with ether (2 X 20 ml) and the combined filterates were extracted with ether washed with water, sat $NaHCO_3$ and brine and dried over MgSO4. The residue was purified by column chromatography using EtOAc and petroleum ether as eluents.

(*E*)-3-Methyl-6-oxohex-2-en-1-yl acetate (143)



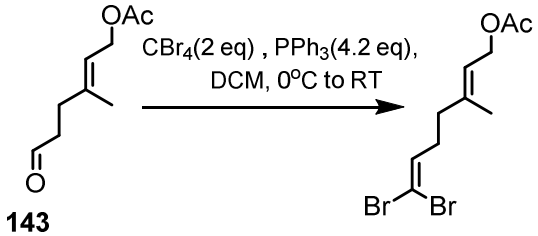
142 **143**

Compound **143** was obtained as a colourless oil in 90% yield, R_F = 0.51 (10% EtOAc/Petroleum ether); ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 9.76 (t, *J* = 1.6 Hz, 1H), 5.37 – 5.26 (m, 1H), 4.56 (dd, *J* = 7.0, 0.5 Hz, 2H), 2.62 – 2.46 (m, 2H), 2.43 – 2.30 (m, 2H), 2.03 (s, 3H), 1.72 – 1.69 (m, 3H); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 201.7, 171.0, 140.0, 119.4, 61.1, 41.8, 31.5, 21.0, 16.6.; GC-MS (m/z) : Calculated for $C_9H_{14}O_3$ - 170.09, Found: 170.02.

Procedure for the synthesis of compound 144

To a solution of triphenyl phosphine (9.62 g, 37.17 mmol) in 60 ml of CH_2Cl_2 at 0 ^{o}C was dropwise added a solution of CBr_4 (5.83 g, 17.7 mmol) in 15 ml of CH_2Cl_2. The reaction mixture was stirred for 5 mins followed by the addition of aldehyde **143** in 15 ml of CH_2Cl_2 and the resulting solution was warmed to 0 ^{o}C. After stirring for 2 h the phosphonium salts were precipitated with pentane (60 ml) and filtered through celite. The resulting organic extracts were evaporated *in vacuo* and the residue was purified by flash chromatography using ethyl acetate and petroleum ether as eluents.

(*E*)-7,7-Dibromo-3-methylhepta-2,6-dien-1-yl acetate (144)



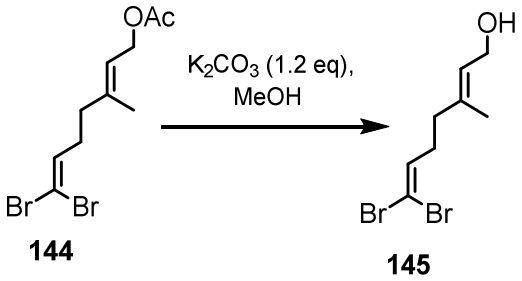
143 **144**

Compound **144** was obtained as a yellow oil in 80% yield, R_F = 0.61 (10% EtOAc/Petroleum ether); the spectral data for the obtained compound are in agreement with the reported data.[118]

Procedure for the synthesis of compound 145

To a solution of the compound **144** (3 g, 9.2 mmol) in MeOH (8 ml) was added potassium carbonate (635 mg, 4.6 mmol) at room temperature. After stirring for 30 mins the potassium carbonate was filtered off and MeOH was evaporated. The reside was extracted with ether (2 X 8 ml), washed with NH_4Cl (10 ml) and brine (15 ml) and the organic extracts were dried over MgSO4. The solvent was removed *in vacuo* and used in the next step without further purification.

(*E*)-7,7-Dibromo-3-methylhepta-2,6-dien-1-ol (145)



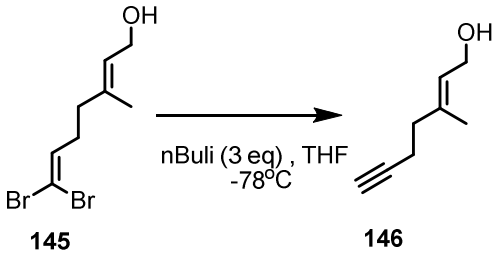
144 **145**

Compound **145** was obtained as a yellow oil in 89% yield, R_F = 0.34 (20% EtOAc/Petroleum ether); the spectral data for the obtained compound are in agreement with the reported data.[118]

Procedure for the synthesis of compound 146

To a solution of compound (**145**) (24 mmol, 6.7 g), in dry THF (35 mL) was added a solution of *n*-BuLi (2.5 M, 74.4 mmol) at -78 ^oC. After 0.5 h, the mixture was allowed to reach room temperature and then quenched with a saturated solution of NH_4Cl (35 mL) and extracted with ether (2×30 mL). The organic layer was washed twice with brine (60 mL) and dried with $MgSO_4$ and the solvent was removed under reduced pressure, the residue was then subjected to flash column chromatography using silica gel with ethyl acetate and petroleum ether as eluents.

(*E*)-3-Methylhept-2-en-6-yn-1-ol (146)



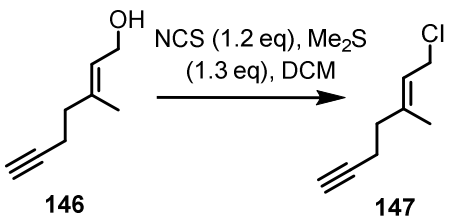
145 **146**

Compound **146** was obtained as a yellow oil in 60% yield, R_F = 0.38 (20% EtOAc/Petroleum ether); ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 5.46 (m, 1H), 4.15 (d, *J* = 6.8 Hz, 2H), 2.31 (m, 2H), 2.24 (m, 2H), 1.95 (m, 1H), 1.68 (s, 3H) ppm; ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 137.6, 124.8, 83.9, 68.8, 59.3, 38.1, 17.3, 16.2 ppm; HRMS (ESI): Calculated for $C_8H_{13}O$ [M+H$^+$]:125.09609, Found: 125.09577.

Procedure for the synthesis of compound 147

To a solution *N*-chlorosuccinimide (7.57 mmol, 1.0 g) in dry DCM (31 mL) at -30 °C was added freshly distilled dimethyl sulfide (8.20 mmol, 0.6 mL) dropwise with a syringe. The mixture was warmed to 0 °C and maintained at that temperature for 5 mins and then again cooled to -40 °C. To the resulting milky white suspension was added **146** (6.31 mmol, 0.78 g) dissolved in dry DCM (3 mL). The suspension was warmed to 0 °C and stirred at that temperature for 2 h, then the suspension was allowed to warm to room temperature, and stirring was continued for additional 15 mins. The resulting clear colorless solution is washed with NaCl (30 mL) and extracted with pentane (2 × 50 mL), the pentane extracts are further washed with NaCl (60 mL) and dried over $MgSO_4$. The residue was directly used for the next step.

(*E*)-7-Chloro-5-methylhept-5-en-1-yne (147)



146 **147**

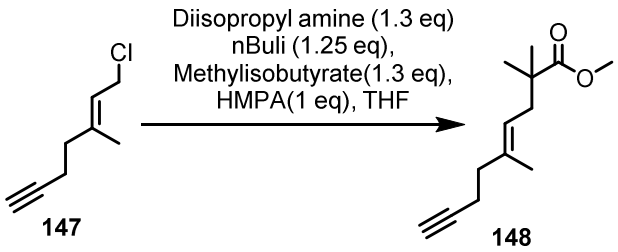
Compound **147** was obtained as a yellow oil in 74% yield, R_F = 0.48 (2.5% EtOAc/Petroleum ether); ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 5.51 (m, 1H), 4.10(dd, *J* = 7.9, 0.5 Hz, 2H),

2.36-2.25 (m, 4H), 1.96 (t, *J* = 2.5 Hz, 1H), 1.75 (m, 3H) ppm; ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 140.7, 121.7, 83.6, 69.0, 40.8, 38.1, 17.2, 16.0 ppm.

Procedure for the synthesis of compound 148

To a solution of diisopropylamine (6.5 mmol, 0.91 ml) in dry THF (12 ml) was added *n*-BuLi (2.5 M in hexane, 6.45 mmol, 2.58 mL) dropwise at 0 ^{o}C . After stirring for 10 mins the reaction mixture was cooled to -78 ^{o}C and a solution of methyl isobutyrate (6.5 mmol, 0.74 mL) in dry THF (4.5 mL) was added dropwise. The temperature was allowed to reach 0 ^{o}C for 15 mins and then decreased again to -78 ^{o}C. To the resulting reaction mixture was added a solution of **147** (5.42 mmol, 0.77 g) in dry THF (2.5 mL) and the temperature was allowed to warm to RT. The reaction mixture was diluted with ether (20 mL) and washed with NH_4Cl (2 × 30 mL) and then brine (2 × 30 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure and the crude mixture was purified by Flash Chromatography using silica gel with EA and petroleum ether as eluents.

Methyl (*E*)-2,2,5-trimethylnon-4-en-8-ynoate (148)



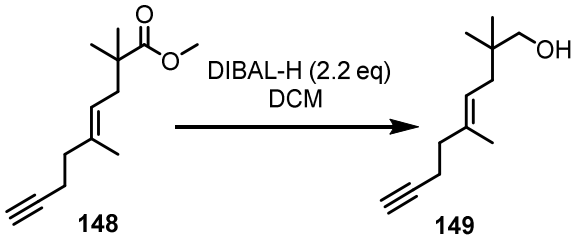
Compound **148** was obtained as a light yellow oil in 75% yield, R_F = 0.49 (5% EtOAc/Petroleum ether); ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 5.16 (m, 1H), 3.65 (s, 3H), 2.32-2.17 (m, 6H), 1.93 (t, *J* = 2.5 Hz, 1H), 1.61 (m, 3H), 1.17 (s, 6H) ppm; ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 178.4, 136.0, 121.4, 84.3, 68.6, 51.8, 43.2, 38.8, 38.6, 24.9, 17.7, 16.0 ppm; GC-MS (m/z) : Calculated for $C_{13}H_{20}O_2$ – 208.14, Found: 208.30.

Procedure for the synthesis of compound 149

To a solution of the **148** (5.3 mmol, 1.1 g) in dry DCM (53 mL) at 0 ^{o}C was added DIBAL-H (1 M in THF, 13.2 mmol, 13.2 mL), the reaction mixture was stirred for 1 h. The reaction mixture was then diluted with ether, followed by the addition of MeOH (0.5 mL) and (0.5 mL) H_2O and was warmed to room temperature and stirred for 30 mins. A saturated solution of Na^+/K^+ Tartrate (55 mL) was added to the reaction mixture and stirred for 1 h at room

temperature. The mixture was then extracted with DCM (2 × 40 mL) and the organic layers were washed with brine (80 mL) and dried over $MgSO_4$, the solvent was removed under reduced pressure and the compound purified by flash chromatography using silica gel with EA and petroleum ether as eluents.

(*E*)-2,2,5-Trimethylnon-4-en-8-yn-1-ol (149)

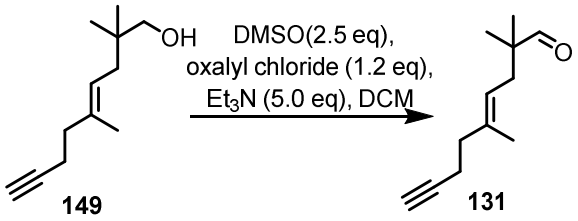


Compound **149** was obtained as a light yellow oil in 90% yield, R_F = 0.38 (25% EtOAc/Petroleum ether); ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 5.31 (m, 1H), 3.34 (s, 2H), 2.31 (m, 2H), 2.24 (t, *J* = 7.1 Hz, 2H), 1.98 (d, *J* = 7.8 Hz, 2H), 1.95 (m, 1H), 1.64 (s, 3H), 0.90 (s, 6H) ppm; ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 135.2, 122.4, 84.4, 72.0, 68.7, 38.8, 37.0, 36.4, 24.0, 17.6, 15.9 ppm; HRMS (ESI)**:** Calculated for $C_{12}H_{21}O$ [$M+H^+$]: 181.15869, Found:181.15858.

Procedure for the synthesis of compound 131

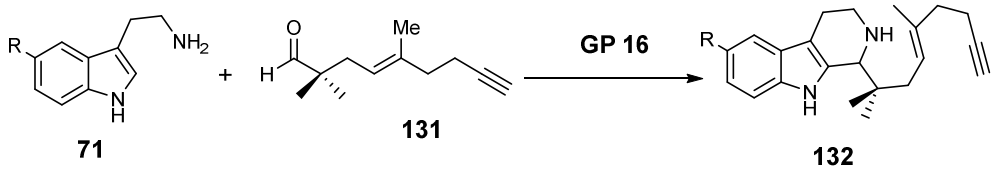
To a solution of oxalyl chloride (6 mmol, 0.51 mL) in dry DCM (39 mL) at -78 ^{0}C was added DMSO (12.5 mmol, 0.88 mL) dropwise. After stirring for 15 mins the reaction mixture was treated slowly with the compound **149** (5 mmol, 0.9 g) dissolved in dry DCM (7 mL), stirred for 20 mins and treated slowly with treithylamine (25 mmol, 0.58 mL). After 5 min the reaction was warmed to RT and stirred for additional 1 h.The reaction mixture was poured into water (45 mL) and extracted using DCM (2 × 40 mL), the organic layer was dried using $MgSO_4$ and solvent removed under reduced pressure. The reaction mixture was purified by flash chromatography using silica gel with EA and petroleum ether as eluents.

(*E*)-2,2,5-Trimethylnon-4-en-8-ynal (131)



Compound **131** was obtained as a light yellow oil in 89% yield, R_F = 0.46 (10% EtOAc/Petroleum ether); ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 9.49 (m, 1H), 5.17 (m, 1H), 2.28 (m, 2H), 2.20 (dd, *J* = 16.3, 7.1 Hz, 4H), 1.94 (m, 1H), 1.62 (s, 3H), 1.06 (s, 6H) ppm; ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 206.4, 136.5, 120.3, 84.2, 68.8, 46.7, 38.7, 35.4, 21.3, 17.6, 16.1 ppm; HRMS (ESI)**:** Calculated for $C_{12}H_{19}O$ [M+H$^+$]: 179.14304, Found:179.14268.

General Procedure 7 (GP 7) for the synthesis of Pictet-Spengler derivatives 132

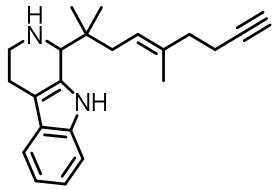


To a solution of the corresponding amine **71** (0.28 mmol) and Yb(OTf)$_3$ (10 mol%, 0.028 mmol) in dry DCE (0.6 mL), was added the aldehyde **131** (0.28 mmol) dissolved in (0.4 mL) dry DCE followed by the addition of the ionic liquid [bmim]Cl-$AlCl_3$ (0.32 mL/mmol of aldehyde). The resulting suspension was heated to 120 ^{o}C under microwave irradiation for 60 mins, 300 W power and 14 mbar pressure. The solvent was removed *in vacuo* and the crude reaction mixture was purified by flash chromatography using basified silica gel with dichloromethane and methanol as elutants.

General Procedure 8 (GP 8) for the gold-catalyzed double cyclization cascade.

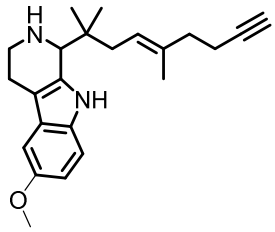
To a solution of the catalyst Y (10 mol%, 0.01 mmol) in dry DCE (1 mL) was added the corresponding Pictet-Spengler compound **132** (0.1 mmol) dissolved in 2 mL of dry DCE. The suspension was heated to 80 ^{o}C under microwave irradiaton for 60 mins. The solvent was removed *in vacuo* and the crude reaction mixture was purified using flash chromatography with petroleum ether and ethyl acetate as eluents.

Compound 137



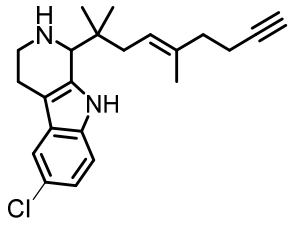
Compound **137** was synthesized according to the **GP7** as a reddish brown thick oil in 84% yield, R_F = 0.47 (10% MeOH/DCM); ^{1}H NMR (400 MHz, 25 °C, CD_2Cl_2): δ 7.98 (*br* s, 1H) , 7.48 (d, *J* = 7.7 Hz, 1H), 7.33 (d, *J* = 8 Hz, 1H), 7.13 (t, *J* = 7.5 Hz, 1H), 7.07 (m, 1H), 5.43 (t, *J* = 7.2 Hz, 1H), 4.02 (s, 1H), 3.36 (dt, *J* = 12.0, 4.0 Hz, 1H) , 2.90 (m, 1H), 2.74 (m, 2H), 2.59 (*br* s, 1H), 2.36-2.23 (m, 5H), 2.13 (dd, *J* = 14.8, 7.6 Hz, 1H) , 1.98 (m, 1H), 1.68 (s, 3H), 1.14 (s, 3H), 1.08 (s, 3H) ppm; ^{13}C NMR (100 MHz, 25 °C, ,CD_2Cl_2): δ 136.1, 135.9, 134.7, 127.6, 122.5, 121.7, 119.4, 118.1, 112.1, 110.9, 84.7, 68.9, 60.8, 43.8, 39.8, 39.0, 38.2, 25.5, 24.9, 23.2, 17.8, 16.2 ppm; HRMS (ESI)**:** Calculated for $C_{22}H_{29}N_2$ [M+H$^+$]: 321.23253, Found: 321.23308.

Compound 150



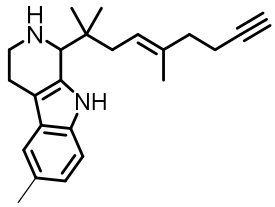
Compound **150** was synthesized according to the **GP7** as a reddish brown thick oil in 75% yield, R_F = 0.45 (10% MeOH/DCM); ^{1}H NMR (400 MHz, 25 °C, CD_2Cl_2): δ 7.86 (*br* s, 1H) , 7.20 (d, *J* = 8.8 Hz, 1H), 6.93 (d, *J* = 2.4 Hz, 1H), 6.76 (dd, *J* = 8.8, 2.4 Hz, 1H), 5.40 (t, *J* = 7.2 Hz, 1H), 4.04 (s, 1H), 3.82 (s, 3H), 3.39 (dt, *J* = 12.0, 4.0 Hz, 1H), 3.10 (*br* s, 1H), 2.92 (m, 1H), 2.72 (m, 2H), 2.35-2.21 (m, 5H), 2.12 (dd, *J* = 14.4, 7.2 Hz, 1H), 1.98 (t, *J* = 2.4 Hz, 1H), 1.66 (s, 3H), 1.13 (s, 3H), 1.09 (s, 3H) ppm; ^{13}C NMR (100 MHz, 25 °C, CD_2Cl_2): δ 154.4, 136.1, 134.9, 131.2, 127.9, 122.3, 111.8, 111.64, 111.63, 100.4, 84.6, 68.9, 60.9, 56.1, 43.8, 39.8, 39.0, 38.1, 25.4, 24.9, 22.8, 17.8, 16.2 ppm; HRMS (ESI)**:** Calculated for $C_{23}H_{31}N_2O$ [M+H$^+$]: 351.24309, Found: 351.24369.

Compound 151



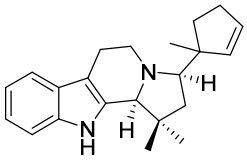
Compound **151** was synthesized according to the **GP7** as a reddish brown thick oil in 65% yield, R_F = 0.5 (10% MeOH/DCM); ^{1}H NMR (400 MHz, 25 °C, CD_2Cl_2): δ 8.01 (*br* s, 1H) , 7.43 (d, *J* = 2.0 Hz, 1H), 7.24 (m, 1H), 7.07 (dd, *J* = 8.6, 2.0 Hz, 1H), 5.40 (td, *J* = 7.4, 1.2 Hz, 1H), 3.96 (t, *J* = 1.7 Hz , 1H), 3.31 (m, 1H) , 2.86 (m, 1H), 2.65 (m, 2H), 2.34-2.21 (m, 5H), 2.09 (dd, *J* = 14.4, 7.2 Hz, 1H), 1.95 (t, *J* = 2.6 Hz, 1H), 1.87 (*br* s, 1H), 1.66 (s, 3H), 1.12 (s, 3H), 1.05 (s, 3H) ppm; ^{13}C NMR (100 MHz, 25 °C, CD_2Cl_2): δ 136.9, 135.9, 134.4, 128.8, 124.9, 122.4, 121.6, 117.6, 112.1, 111.9, 84.6, 68.8, 60.7, 43.6, 39.8, 39.0, 38.2, 25.6, 25.0, 23.3, 17.8, 16.1 ppm; HRMS (ESI)**:** Calculated for $C_{22}H_{28}N_2Cl$ [M+H$^+$]: 355.19355, Found: 355.19429.

Compound 152



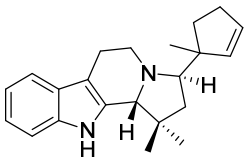
Compound **152** was synthesized according to the **GP7** as a reddish brown thick oil in 71% yield, R_F = 0.45 (10% MeOH/DCM); ^{1}H NMR (400 MHz, 25 °C, CD_2Cl_2): δ 7.88 (*br* s, 1H) , 7.26 (s, 1H), 7.21 (d, *J* = 8.2 Hz, 1H), 6.96 (d, *J* = 8.0 Hz, 1H), 5.41 (t, *J* = 7.3 Hz, 1H), 4.02 (s, 1H), 3.37 (dt, *J* = 12.1, 4.1 Hz, 1H), 3.02 (*br* s, 1H), 2.90 (m, 1H), 2.70 (m, 2H), 2.44 (s, 3H), 2.35-2.22 (m, 5H), 2.12 (dd, *J* = 14.5, 7.3 Hz, 1H) , 1.98 (m, 1H), 1.67 (s, 3H), 1.13 (s, 3H), 1.08 (s, 3H) ppm; ^{13}C NMR (100 MHz, 25 °C, CD_2Cl_2): δ 135.8, 134.9, 134.4, 128.6, 127.8, 123.2, 122.5, 117.8, 111.6, 110.5, 84.7, 68.8, 60.9, 43.8, 39.8, 39.1, 38.2, 25.5, 24.9, 23.3, 21.5, 17.8, 16.2; HRMS (ESI)**:** Calculated for $C_{23}H_{31}N_2$ [M+H$^+$]: 335.24818, Found: 335.24877.

Compound 139: Yield: 70%, dr 1 : 1.6, synthesized using the general procedure **GP8**



Minor Diastereomer:

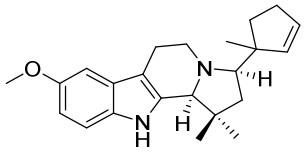
Obtained as a light yellow oil**;** R_F = 0.6 (20% EtOAc/Petroleum ether); ^{1}H NMR (400 MHz, 25 °C, CD_2Cl_2): δ 7.79 (*br* s, 1H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.10 (m, 1H), 7.04 (m, 1H), 5.64 (m, 1H), 5.58 (m, 1H), 3.62 (dd, *J* = 11.1, 5.8 Hz, 1H), 3.23 (s, 1H), 2.83 (m, 1H), 2.65 (m, 2H), 2.41 (m, 2H), 2.27-2.12 (m, 2H), 1.78 (dd, *J* = 12.8, 9.2 Hz, 1H), 1.7 (m, 1H), 1.56 (dd, *J* = 12.8, 8.0 Hz, 1H), 1.37 (s, 3H), 1.03 (s, 3H), 0.97 (s, 3H) ppm; ^{13}C NMR (100 MHz, 25 °C, CD_2Cl_2): δ 140.9, 136.3, 134.9, 128.6, 127.6, 121.3, 119.5, 118.2, 111.0, 110.7, 71.8, 69.9, 52.1, 48.8, 45.2, 37.5, 34.6, 32.1, 29.1, 26.3, 23.4, 23.1 ppm; HRMS (ESI)**:** Calculated for $C_{22}H_{29}N_2$ [M+H$^+$]: 321.23253, Found: 321.23253.



Major Diastereomer:

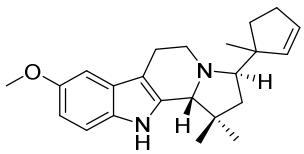
Obtained as a yellow oil; R_F = 0.35 (20% EtOAc/Petroleum ether); ^{1}H NMR (400 MHz, 25 °C, CD_2Cl_2): δ 7.79 (*br* s, 1H), 7.47 (d, *J* =7.8 Hz, 1H), 7.33 (d, *J* = 7.9 Hz, 1H), 7.11 (m, 1H), 7.05 (m, 1H), 5.68 (m, 1H), 5.60 (m, 1H), 3.92 (s, 1H), 3.14 (m, 3H), 2.71 (m, 2H), 2.36 (m, 2H), 1.97 (m, 1H), 1.86 (dd, *J* = 12.5, 7.3 Hz, 1H), 1.55 (m, 2H), 1.32 (s, 3H), 1.09 (s, 3H), 0.84 (s, 3H) ppm; ^{13}C NMR (100 MHz, 25 °C, CD_2Cl_2): δ 139.5, 136.7, 134.2, 129.4, 127.1, 121.5, 119.4, 118.3, 111.0, 110.9, 71.6, 67.4, 54.7, 51.4, 44.6, 43.4, 33.3, 32.3, 27.9, 25.0, 23.9, 22.1 ppm; HRMS (ESI)**:** Calculated for $C_{22}H_{29}N_2$ [M+H$^+$]: 321.23253, Found: 321.23280.

Compound 153: Yield: 67%, dr 1 : 1.7, synthesized using the general procedure **GP8**



Minor Diastereomer:

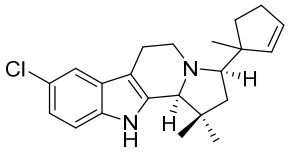
Obtained as a yellow oil; R_F = 0.57 (20% EtOAc/Petroleum ether), ^{1}H NMR (400 MHz, 25 °C, CD_2Cl_2): δ 7.67 (*br* s, 1H), 7.20 (dd, *J* = 8.8, 0.4 Hz, 1H), 6.90 (d, *J* = 2.4 Hz, 1H), 6.73 (dd, *J* = 8.8, 2.4 Hz, 1H), 5.64 (m, 1H), 5.57 (m, 1H), 3.82 (d, 3H, *J* = 0.7 Hz, 3H), 3.61 (m, 1H), 3.21 (s, 1H), 2.80 (m, 1H), 2.61 (m, 2H), 2.40 (m, 2H), 2.26-2.11 (m, 2H), 1.77 (dd, *J* = 12.9, 9 Hz, 1H), 1.69 (m, 1H), 1.55 (dd, *J* = 12.9, 7.9 Hz, 1H), 1.35 (s, 3H), 1.02 (s, 3H), 0.96 (s, 3H) ppm; ^{13}C NMR (100 MHz, 25 °C, CD_2Cl_2): δ 154.4, 140.8, 135.8, 131.3, 128.6, 128.0, 111.5, 110.9, 110.5, 100.7, 71.9, 69.9, 56.1, 52.1, 48.8, 45.2, 37.5, 34.6, 32.1, 29.1, 26.3, 23.4, 23.2 ppm; HRMS (ESI)**:** Calculated for $C_{23}H_{31}N_2O$ [M+H$^+$]: 351.24309, Found: 351.24360.



Major Diastereomer:

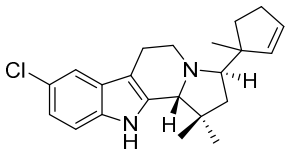
Obtained as a yellow oil; R_F = 0.34 (20% EtOAc/Petroleum ether); ^{1}H NMR (400 MHz, 25 °C, CD_2Cl_2): δ 7.67 (*br* s, 1H), 7.21 (d, *J* =.8.7 Hz, 1H), 6.94 (d, *J* = 2.4 Hz, 1H), 6.75 (dd, *J* = 8.7, 2.5 Hz, 1H), 5.68 (m, 1H), 5.60 (m, 1H), 3.89 (s, 1H), 3.83 (s, 3H), 3.14 (m, 3H), 2.67 (dd, *J* = 6.3, 4.5 Hz, 2H), 2.36 (m, 2H), 1.96 (m, 1H), 1.85 (dd, *J* = 12.5, 7.3 Hz, 1H), 1.54 (m, 2H), 1.30 (s, 3H), 1.09 (s, 3H), 0.84 (s, 3H) ppm; ^{13}C NMR (100 MHz, 25 °C, CD_2Cl_2): δ 154.4, 139.5, 135.2, 131.7, 129.4, 127.6, 111.5, 111.1, 110.7, 100.7, 71.6, 67.5, 56.1, 54.7, 51.4, 44.6, 43.4, 33.3, 32.3, 27.9, 25.0, 23.9, 22.2 ppm; HRMS (ESI)**:** Calculated for $C_{23}H_{31}N_2O$ [M+H$^+$]: 351.24309, Found: 351.24357.

Compound 154: Yield: 49%, dr 1 : 1.5, synthesized using the general procedure **GP8**



Minor Diastereomer:

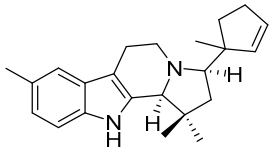
Obtained as a yellow oil; R_F = 0.61 (20% EtOAc/Petroleum ether); ^{1}H NMR (400 MHz, 25 °C, CD_2Cl_2): δ 7.85 (*br* s, 1H), 7.41 (s, 1H), 7.25 (d, *J* = 8.5 Hz, 1H), 7.05 (dd, *J* = 8.6, 1.7 Hz, 1H), 5.64 (m, 1H), 5.56 (m, 1H), 3.61 (dd, *J* = 11.0, 6.1 Hz, 1H), 3.21 (s, 1H), 2.79 (m, 1H), 2.62 (m, 2H), 2.40 (m, 2H), 2.26-2.09 (m, 2H), 1.78 (dd, *J* = 12.9, 9.1 Hz, 1H), 1.69 (m, 1H), 1.56 (dd, *J* = 14.2, 6.6 Hz, 1H), 1.36 (s, 3H), 1.02 (s, 3H), 0.96 (s, 3H) ppm; ^{13}C NMR (100 MHz, 25 °C, CD_2Cl_2): δ 140.8, 136.7, 134.6, 128.8, 128.7, 125.1, 121.3, 117.8, 112.0, 110.6, 71.7, 69.8, 52.1, 48.6, 45.1, 37.5, 34.5, 32.1, 29.1, 26.3, 23.4, 23.0 ppm; HRMS (ESI)**:** Calculated for $C_{22}H_{28}N_2Cl$ [M+H$^+$]: 355.19355, Found: 355.19403.



Major Diastereomer:

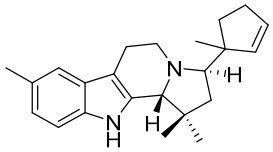
Obtained as a yellow oil; R_F = 0.36 (20% EtOAc/Petroleum ether); ^{1}H NMR (400 MHz, 25 °C, CD_2Cl_2): δ 7.86 (*br* s, 1H), 7.44 (s, 1H), 7.26(dd, *J* = 8.5, 0.5 Hz, 1H), 7.07 (m, 1H), 5.68 (m, 1H), 5.59 (m, 1H), 3.90 (s, 1H), 3.13 (m, 3H), 2.67 (m, 2H), 2.36 (m, 2H), 1.94 (m, 1H), 1.85 (dd, *J* = 12.5, 7.4 Hz, 1H), 1.54 (m, 2H), 1.31 (s, 3H), 1.08 (s, 3H), 0.83 (s, 3H) ppm; ^{13}C NMR (100 MHz, 25 °C, CD_2Cl_2): δ 139.4, 136.1, 135.0, 129.6, 128.3, 125.0, 121.5, 117.8, 112.0, 110.8, 71.5, 67.3, 54.6, 51.1, 44.6, 43.4, 33.3, 32.3, 27.9, 24.9, 23.9, 22.0; HRMS (ESI)**:** Calculated for $C_{22}H_{28}N_2Cl$ [M+H$^+$]: 355.19355, Found: 355.19399

Compound 155: Yield: 62%, dr 1 : 1.7, synthesized using the general procedure **GP8**



Minor Diastereomer:

Obtained as a yellow oil; R_F = 0.58 (20% EtOAc/Petroleum ether); ^{1}H NMR (400 MHz, 25 °C, CD_2Cl_2): δ 7.68 (*br* s, 1H), 7.20 (m, 2H), 6.92 (d, *J* = 8.3 Hz, 1H), 5.64 (d, *J* = 5.6 Hz, 1H), 5.57 (d, *J* = 5.5 Hz, 1H), 3.60 (dd, *J* = 10.7, 5.9 Hz, 1H), 3.21 (s, 1H), 2.79 (m, 1H), 2.61 (m, 2H), 2.40 (m, 5H), 2.25-2.11 (m, 2H), 1.77 (dd, *J* = 12.9, 9.0 Hz, 1H), 1.70 (m, 1H), 1.55 (dd, *J* = 12.9, 7.8 Hz, 1H), 1.35 (s, 3H), 1.02 (s, 3H), 0.96 (s, 3H) ppm; ^{13}C NMR (100 MHz, 25 °C, CD_2Cl_2): δ 140.9, 135.0, 134.6, 128.7, 128.6, 127.9, 122.8, 118.0, 110.6, 110.2, 71.9, 69.9, 52.1, 48.8, 45.2, 37.5, 34.6, 32.1, 29.1, 26.3, 23.4, 23.1, 21.5 ppm; HRMS (ESI)**:** Calculated for $C_{23}H_{31}N_2$ [M+H$^+$]: 335.24818, Found: 335.24871.

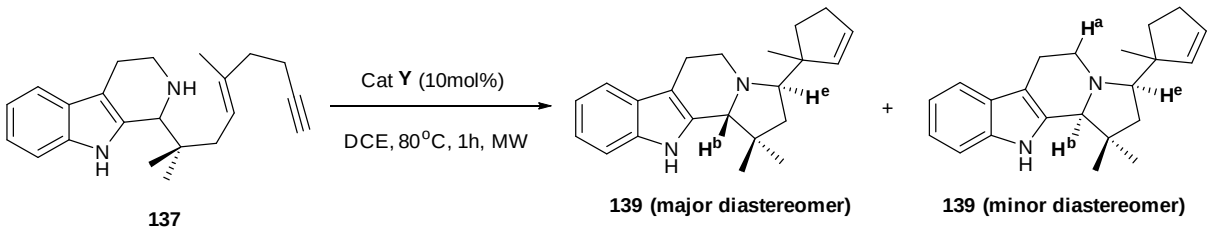


Major Diastereomer:

Obtained as a yellow oil; R_F = 0.33 (20% EtOAc/Petrolether); ^{1}H NMR (400 MHz, 25 °C, CD_2Cl_2): δ 7.68 (*br* s, 1H), 7.26 (s, 1H), 7.21(d, *J* = 8.2 Hz, 1H), 6.94 (d, *J* = 8.2 Hz, 1H), 5.68 (m, 1H), 5.60 (m, 1H), 3.89 (s, 1H), 3.13 (m, 3H), 2.67 (m, 2H), 2.43 (s, 3H), 2.36 (m, 2H), 1.96 (m, 1H), 1.85 (dd, *J* = 12.5, 7.3 Hz, 1H), 1.55 (m, 2H), 1.30 (s, 3H), 1.09 (s, 3H), 0.83 (s, 3H) ppm; ^{13}C NMR (100 MHz, 25 °C, CD_2Cl_2): δ 139.5, 135.0, 134.4, 129.4, 128.7, 127.4, 123.0, 118.1, 110.5, 110.4, 71.6, 67.5, 54.7, 51.4, 44.6, 43.5, 33.3, 32.3, 27.9, 25.0, 23.9, 22.1, 21.5 ppm; HRMS (ESI): Calculated for $C_{23}H_{31}N_2$ [M+H$^+$]: 335.24818, Found: 335.24844.

5.2.3.1 1-D NOE experiments for product 139

The double cyclization cascade reaction of PS product **137** yielded product **139** as a mixture of diastereomers (Scheme 65). The *syn*-configuration for the **minor diastereomer** of **139** was established by observation of a n*O*e signal between H^b and H^e (Figure 9), whereas absence of this n*O*e signal in the **major diastereomer** of **139** pointed towards an *anti*-configuration (Figure 10).

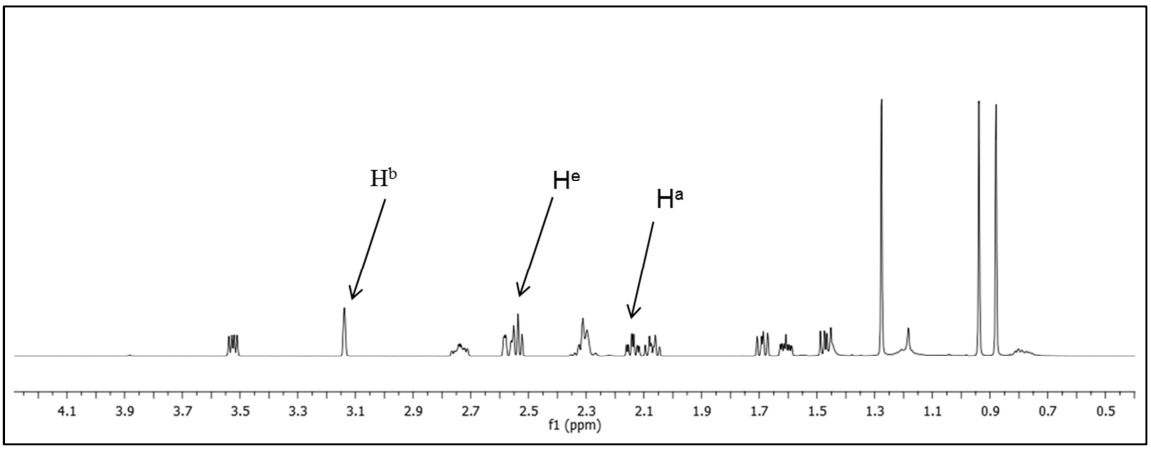


Scheme 65- Gold mediated double cyclization cascade of **137** affords product **139** as a mixture of diastereomers.

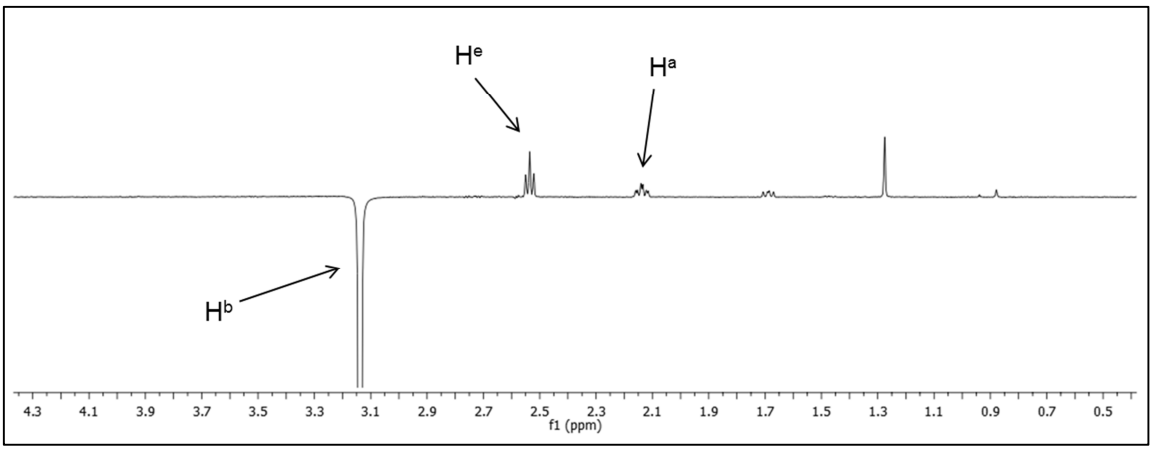
n*O*e coupling 139 (minor diastereomer)

Figure 9- Proton NMR spectra of **139 (minor diastereomer)** in deteurated DCM, depicting signal enhancement due to n*O*e coupling beween protons H^e and H^b

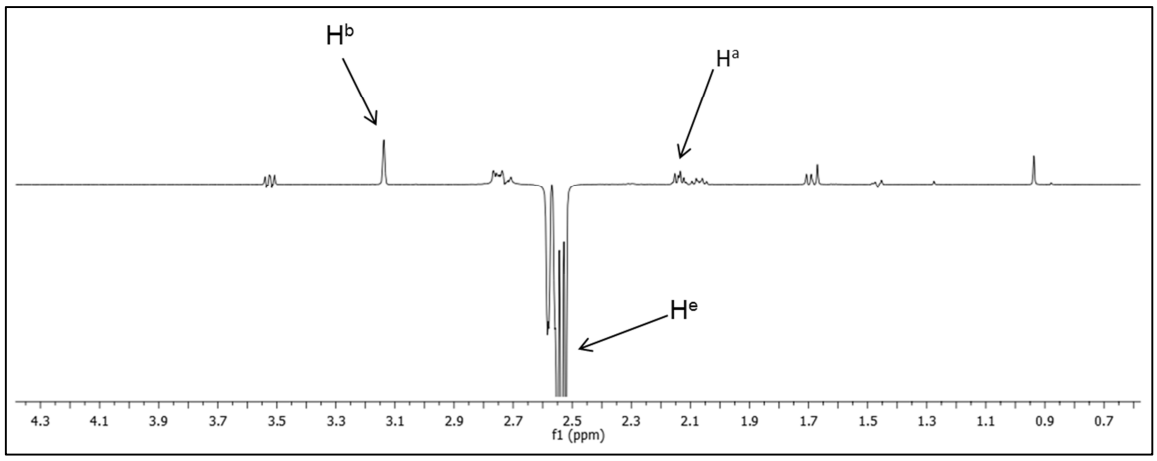
Section of the proton NMR spectrum of **139** (minor diastereomer) depicting protons H^a, H^b and H^e

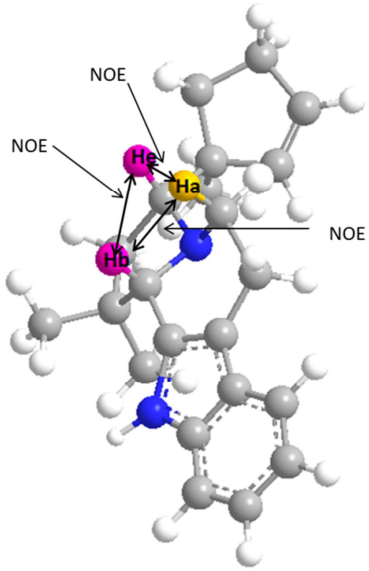


Proton H^b on irradiation shows 2% n*O*e signal enhancement *via* H^e and 1% n*O*e signal enhancement *via* H^a



Proton H^e on irradiation shows 3% n*O*e signal enhancement *via* H^b and 2% n*O*e signal enhancement *via* H^a





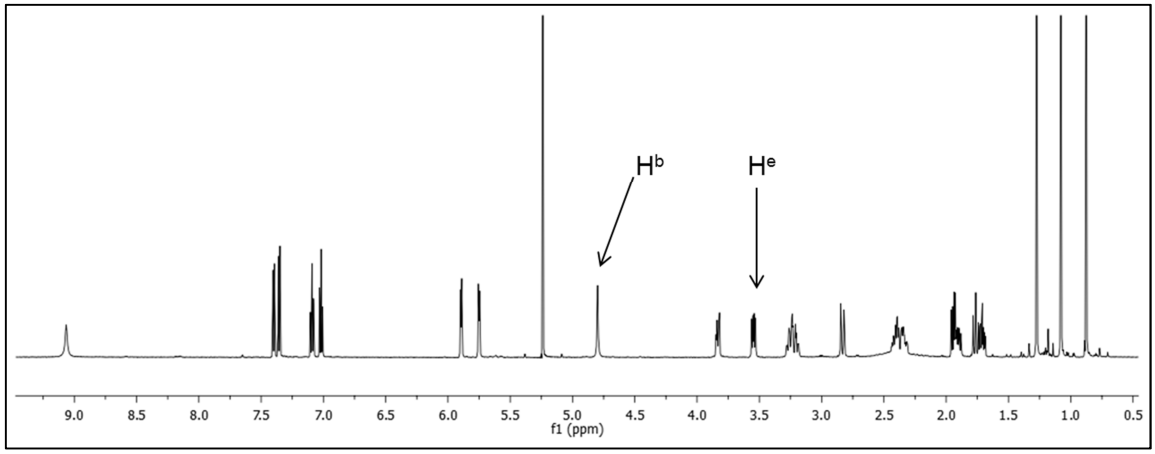
3D model depicting the n*O*e coupling for the minor diastereomer of **139**

n*O*e coupling 139 (major diastereomer)

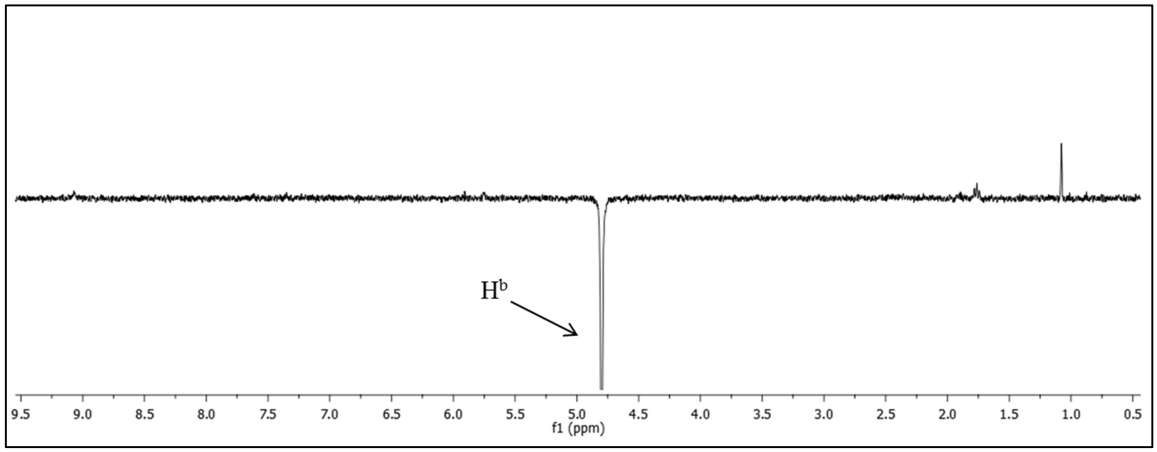
A TFA salt of the major diastereomer was used to determine the n*O*e coupling, in which protons H_b and H_e were well separated as seen in Figure 10.

Figure 10 – Proton NMR spectrum of TFA salt of major diastereomer in deteurated DCM, depicting absence of signal enhancement due to n*O*e coupling beween protons H^e and H^b

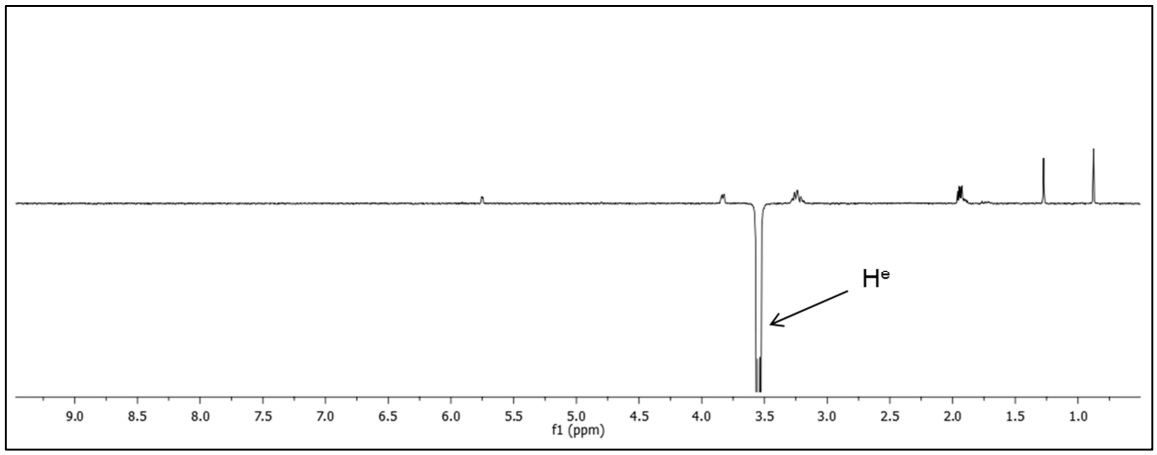
Proton NMR spectrum of **139** (major diastereomer) depicting protons H^b and H^e



Proton H^b on irradiation shows no n*O*e signal enhancement *via* H^e



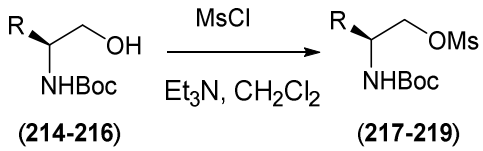
Proton H^e on irradiation shows no n*O*e signal enhancement *via* H^b



5.3 Experimental part for chapter 3

5.3.1 Synthetic scheme for the preparation of isoleucine-, valine-, phenyl alanine derived aminophosphines.

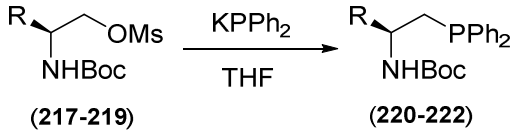
General Procedure 9 (GP9) for the preparation of mesylates (217- 219)



(**214-216**) (**217-219**)

To an ice-cooled solution of the commercially available boc-protected amino alcohol (**214-216**) (13.8 mmol) and triethylamine (15.18 mmol, 1.1 equiv) in DCM (55 mL), a solution of methanesulfonyl chloride (14.35 mmol, 1.04 equiv) in DCM (27 mL) was added dropwise over a period of 30 min, After completion of the reaction monitored *via* TLC, the solvent was evaporated under *vacuo* and ethyl acetate (30 mL) and water (30 mL) were added to the residue. The organic layer was washed with aqueous 5% $NaHCO_3$ (50 mL) and brine (50 mL), and dried over Na_2SO_4. The organic solvent was evaporated to give the corresponding mesylates (**217- 219**) as white solids in quantitative yields.

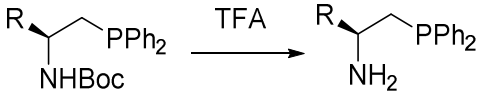
General Procedure 10 (GP10) for the preparation of boc-protected aminophosphines (220- 222)



(**217-219**) (**220-222**)

Potassium diphenylphosphide (0.5 M THF solution, 63 mL, 28 mmol), was added dropwise to a solution of a corresponding mesylate (**217- 219**) (13.27 mmol) in THF (30 mL) at -40 °C under argon. The reaction mixture was stirred at that same temperature overnight.The solution was allowed to warm to room temperature and was filtered through celite. The reaction mixture was concentrated *in vacuo*. The residue was purified by silica gel column chromatography with EtOAc and petroleum ether as eluents to give the desired boc-protected aminophosphine (**220- 222**) as a viscous liquid.

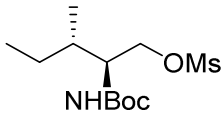
General Procedure 11 (GP11) for the preparation of aminophosphines (223- 225)



(**220-222**) (**223-225**)

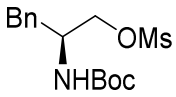
To a solution of the boc-protected aminophosphine (**220- 222**) (3.68 mmol) in CH_2Cl_2 (68 mL) was added trifluoroacetic acid (13.5 mL, 177.15 mmol) at 0 °C under argon. The solution was stirred at 0 °C for 1 h and then at room temperature overnight. The reaction mixture was quenched with water (50 mL) and the biphasic mixture was separated. The aqueous layer was neutralized with 10 M NaOH solution and extracted with CH_2Cl_2 (3 X 75 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL), dried over $MgSO_4$, and concentrated under vacuum to give aminophosphine as viscous liquid **(223-225).**

(2S,3S)-2-((tert-butoxycarbonyl)amino)-3-methylpentyl methanesulfonate (217)



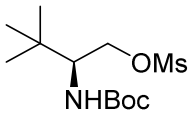
Compound **217** was synthesized according to the **GP9** as a white solid in quantitative yield, R_F = 0.37 (10% EtOAc/Petroleum ether);^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 4.67 (d, *J* = 9.0 Hz, 1H), 4.33 – 4.20 (m, 2H), 3.68 (m, 1H), 3.01 (d, *J* = 1.9 Hz, 3H), 1.65 – 1.47 (m, 2H), 1.43 (s, 9H), 1.22 – 1.09 (m, 1H), 0.96 – 0.86 (m, 6H); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 155.6, 79.8, 69.8, 53.8, 37.4, 35.7, 28.4, 25.3, 15.5, 11.2; HRMS (ESI)**:** Calculated for $C_{12}H_{25}O_5NNaS$ [M+Na^+]: 318.13456, Found: 318.13567.

(S)-2-((tert-butoxycarbonyl)amino)-3-phenylpropyl methanesulfonate (218)



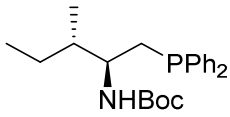
Compound **218** was synthesized according to the **GP9** as a white solid in quantitative yield, R_F = 0.31 (10% EtOAc/Petroleum ether);^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 7.39 – 7.15 (m, 5H), 4.76 (s, 1H), 4.31 – 4.05 (m, 3H), 3.01 (s, 3H), 2.95 – 2.81 (m, 2H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 155.2, 136.7, 129.3, 128.8, 127.0, 80.0, 69.9, 50.9, 37.3, 28.4; HRMS (ESI)**:** Calculated for $C_{15}H_{23}NO_5NaS$ [M+H^+]: 352.11891, Found: 352.11994.

(S)-2-((tert-butoxycarbonyl)amino)-3,3-dimethylbutyl methanesulfonate (219)



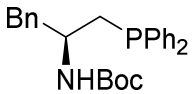
Compound **219** was synthesized according to the **GP9** as a white solid in quantitative yield, R_F = 0.34 (10% EtOAc/Petroleum ether); the spectral data for the obtained compound are in agreement with the data reported. [101] HRMS (ESI)**:** Calculated for $C_{12}H_{25}NO_5NaS$ [M+Na^+]: 318.13456, Found: 318.13533.

Tert-Butyl ((2S,3S)-1-(diphenylphosphanyl)-3-methylpentan-2-yl)carbamate (220)



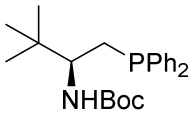
Compound **220** was synthesized according to the **GP10** as a viscous colourless liquid in 58% yield, R_F = 0.41 (10% EtOAc/Petroleum ether); ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 7.48 – 7.41 (m, 4H), 7.37 – 7.29 (m, 6H), 4.45 (d, *J* = 7.8 Hz, 1H), 3.67 (s, 1H), 2.27 (dd, *J* = 13.6, 3.5 Hz, 1H), 2.16 – 2.04 (m, 1H), 1.65 (s, 1H), 1.46 – 1.34 (m, 11H), 1.12 – 0.99 (m, 1H), 0.88 – 0.77 (m, 6H); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 155.3, 138.2 (d, $J_{C\text{-}P}$ = 12.7 Hz), 133.2 (d, $J_{C\text{-}P}$ = 19.4 Hz), 132.7 (d, $J_{C\text{-}P}$ = 18.6 Hz), 130.8 (d, $J_{C\text{-}P}$ = 4.1 Hz), 130.7 (d, $J_{C\text{-}P}$ = 3.9 Hz), 128.9, 128.6 (d, $J_{C\text{-}P}$ = 1.5 Hz), 128.5 (d, $J_{C\text{-}P}$ = 1.0 Hz), 78.9, 52.6 (d, $J_{C\text{-}P}$ = 14.4 Hz), 39.4, 31.3 (d, $J_{C\text{-}P}$ = 12.0 Hz), 28.5, 25.2, 15.0, 11.7; ^{31}P NMR (121 MHz, 25 °C, $CDCl_3$): δ -21.2; HRMS (ESI)**:** Calculated for $C_{23}H_{33}NO_2P$ [M+H^+]: 386.22434, Found: 386.22512.

Tert-butyl (S)-(1-(diphenylphosphanyl)-3-phenylpropan-2-yl)carbamate (221)



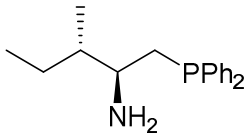
Compound **221** was synthesized according to the **GP10** as a white solid in 51% yield, R_F = 0.45 (10% EtOAc/Petroleum ether); the spectral data for the obtained compound are in agreement with the reported data.[101]; m.p. – 153.8- 154.2 ^{o}C; HRMS (ESI)**:** Calculated for $C_{26}H_{31}NO_2P$ [M+H^+]: 420.20869, Found: 420.20969.

Tert-butyl (S)-(1-(diphenylphosphanyl)-3,3-dimethylbutan-2-yl)carbamate (222)



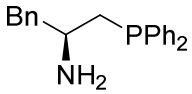
Compound **222** was synthesized according to the **GP10** as a viscous colourless liquid in 52% yield, R_F = 0.43 (10% EtOAc/Petroleum ether); ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 7.49 – 7.42 (m, 4H), 7.37 – 7.29 (m, 6H), 4.37 (d, *J* = 10.4 Hz, 1H), 3.58 – 3.47 (m, 1H), 2.42 – 2.31 (m, 1H), 2.01 – 1.93 (m, 1H), 1.45 (s, 9H), 0.88 (s, 9H); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 155.5, 139.4 (d, J_{C-P} = 12.6 Hz), 138.2 (d, J_{C-P} = 13.9 Hz), 133.3 (d, J_{C-P} = 19.5 Hz), 132.5 (d, J_{C-P} = 18.7 Hz), 128.8, 128.5, 128.4, 128.3, 78.7, 56.3 (d, J_{C-P} = 13.5 Hz), 35.7 (d, J_{C-P} = 6.3 Hz), 31.2 (d, J_{C-P} = 12.4 Hz), 28.5, 26.2; ^{31}P NMR (121 MHz, 25 °C, $CDCl_3$): δ -20.3; HRMS (ESI)**:** Calculated for $C_{23}H_{33}O_2NP$ [M+H$^+$]: 386.22434, Found: 386.22567.

(2S,3S)-1-(diphenylphosphanyl)-3-methylpentan-2-amine (223)



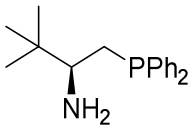
Compound **223** was synthesized according to the **GP11** as a viscous colourless liquid in 85% yield, R_F = 0.38 (10% MeOH/DCM); ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 7.53 – 7.44 (m, 2H), 7.44 – 7.36 (m, 2H), 7.36 – 7.27 (m, 6H), 2.83 – 2.73 (m, 1H), 2.43- 2.23 (m, 3H), 2.03- 1.94 (m, 1H), 1.53 – 1.44 (m, 1H), 1.43 – 1.32 (m, 1H), 1.19 – 1.07 (m, 1H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.80 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 139.3 (d, J_{C-P} = 11.9 Hz), 138.0 (d, J_{C-P} = 13.1 Hz), 133.3 (t, J_{C-P} = 17.5 Hz), 132.4 (d, J_{C-P} = 18.1 Hz), 131.9, 131.1 (d, J_{C-P} = 9.5 Hz), 130.6 (d, J_{C-P} = 9.4 Hz), 129.0, 128.8 (d, J_{C-P} = 11.7 Hz), 128.6 (d, J_{C-P} = 7.1 Hz), 128.5 (d, J_{C-P} = 6.4 Hz), 128.3, 53.0 (d, J_{C-P} = 13.6 Hz), 41.2 (d, J_{C-P} = 7.0 Hz), 33.6 (d, J_{C-P} = 12.0 Hz), 24.9, 14.8, 11.88; ^{31}P NMR (121 MHz, 25 °C, $CDCl_3$): δ -20.3; HRMS (ESI)**:** Calculated for $C_{18}H_{25}NP$ [M+H$^+$]: 286.17191, Found: 286.17255.

(S)-1-(diphenylphosphanyl)-3-phenylpropan-2-amine (224)



Compound **224** was synthesized according to the **GP11** as a viscous colourless liquid in 87% yield, R_F = 0.4 (10% MeOH/DCM); ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 7.27 – 6.94 (m, 15H), 2.98- 2.87 (m, 1H), 2.74 (dd, *J* = 13.3, 5.1 Hz, 1H), 2.47 (dd, *J* = 13.3, 8.1 Hz, 1H), 2.21 – 2.14 (m, 1H), 1.92 (ddd, *J* = 13.7, 8.4, 1.4 Hz, 1H), 1.38 (s, 2H); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 139.1, 139.0 (d, J_{C-P} = 12.1 Hz), 138.0 (d, J_{C-P} = 12.3 Hz), 133.0 (d, J_{C-P} = 19.2 Hz), 132.6 (d, J_{C-P} = 18.6 Hz), 129.4, 128.8, 128.6, 128.5, 128.5, 128.4, 126.3, 50.7 (d, J_{C-P} = 15.1 Hz), 45.8 (d, J_{C-P} = 8.2 Hz), 37.3 (d, J_{C-P} = 12.8 Hz); ^{31}P NMR (121 MHz, 25 °C, $CDCl_3$): δ -21.2; HRMS (ESI): Calculated for $C_{21}H_{23}NP$ [M+H$^+$]: 320.15626, Found: 320.15712.

(S)-1-(diphenylphosphanyl)-3,3-dimethylbutan-2-amine (225)



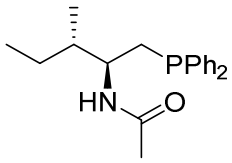
Compound **225** was synthesized according to the **GP11** as a viscous colourless liquid in 83% yield, R_F = 0.37 (10% MeOH/DCM); ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 7.55 – 7.48 (m, 2H), 7.42 – 7.35 (m, 5H), 7.34 – 7.27 (m, 3H), 2.54 – 2.42 (m, 2H), 1.84- 1.75 (m, 1H), 1.44 (bs, 2H), 0.88 (d, *J* = 1.8 Hz, 9H); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 139.9 (d, *J* J_{C-P} = 12.1 Hz), 137.8 (d, J_{C-P} = 13.6 Hz), 133.6 (d, J_{C-P} = 19.7 Hz), 132.3 (d, J_{C-P} = 17.9 Hz), 129.1, 128.5 (d, J_{C-P} = 7.2 Hz), 128.4 (d, J_{C-P} = 6.2 Hz), 128.2, 57.8 (d, J_{C-P} = 12.3 Hz), 35.0 (d, J_{C-P} = 6.5 Hz), 32.7 (d, J_{C-P} = 11.0 Hz), 26.0; ^{31}P NMR (121 MHz, 25 °C, $CDCl_3$): δ -19.6; HRMS (ESI)**:** Calculated for $C_{18}H_{25}NP$ [M+H$^+$]: 286.1719, Found: 286.17248.

General Procedure 12 (GP12) for the preparation of aminophosphines (196, 206, 226-230)

To a solution of aminophosphine (**223- 225**) (0.2 mmol) and triethylamine (0.3 mmol) in CH_2Cl_2 (1.5 ml) at 0 ^{o}C, a solution of acyl chloride (0.3 mmol) in CH_2Cl_2 (1.5 mL) was added dropwise *via* a syringe at 0 ^{o}C and the mixture was then warmed to RT. The reaction was monitored by TLC for completion. On completion the reaction mixture was diluted with

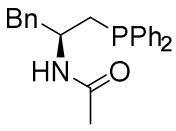
CH_2Cl_2 (20 mL), washed with saturated $NaHCO_3$ (10 mL) and dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel chromatography using petroleum ether and EtOAc as the eluents to afford the desired aminophosphine.

_N_-((2S,3S)-1-(diphenylphosphanyl)-3-methylpentan-2-yl)acetamide (226)



Aminophosphine **223** was treated with acetyl chloride following **GP12** yielding aminophosphine **226** as a white solid in 71% yield, R_F = 0.35 (30% EtOAc/Petroleum ether); m.p. – 154.3– 154.9°C; ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 8.00 (s, 2H , 7.93 (s, 1H), 7.57 – 7.38 (m, 4H), 7.34 – 7.23 (m, 6H), 6.34 (s, 1H), 4.39 – 4.27 (m, 1H), 2.59 – 2.42 (m, 2H), 1.96 – 1.82 (m, 1H), 1.59 – 1.42 (m, 1H), 1.24 – 1.12 (m, 1H), 0.98 (d, J = 6.8 Hz, 3H), 0.89 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): 163.8, 136.6, 133.0 (d, $J_{C\text{-}P}$ = 8.1 Hz), 132.8 (d, $J_{C\text{-}P}$ = 8.1 Hz), 132.0 (q, $J_{C\text{-}F}$ = 33.8 Hz), 129.6 (d, $J_{C\text{-}P}$ = 9.6 Hz), 128.9 (d, $J_{C\text{-}P}$ = 6.4 Hz), 128.9 (d, $J_{C\text{-}P}$ = 6.4 Hz), 127.36 (d, $J_{C\text{-}P}$ = 2.7 Hz), 124.9, 124.4, 121.7, 52.7 (d, $J_{C\text{-}P}$ = 12.0 Hz), 39.4 (d, $J_{C\text{-}P}$ = 8.3 Hz), 29.8 (d, $J_{C\text{-}P}$ = 8.4 Hz), 25.7, 15.0, 11.6; ^{31}P NMR (121 MHz, 25 °C, $CDCl_3$): δ -22.5; HRMS (ESI)**:** Calculated for $C_{27}H_{27}NOF_6P$ [M+H$^+$]: 526.17290, Found: 526.17411.

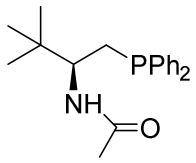
(S)-_N_-(1-(diphenylphosphanyl)-3-phenylpropan-2-yl)acetamide (227)



Aminophosphine **224** was treated with acetyl chloride following **GP12** yielding aminophosphine **227** as a white solid in 68% yield, R_F = 0.38 (30% EtOAc/Petroleum ether); m.p. – 168.3– 168.4°C; ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 7.37 – 7.05 (m, 15H), 5.30 (d, J = 8.0 Hz, 1H), 4.25 – 4.16 (m, 1H), 2.97 – 2.81 (m, 2H), 2.27 (ddd, J = 14.1, 5.5, 1.5 Hz, 1H), 2.14 (dd, J = 14.1, 7.7 Hz, 1H), 1.66 (s, 3H); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 169.4, 138.1 (d, $J_{C\text{-}P}$ = 11.3 Hz), 137.9 (d, $J_{C\text{-}P}$ = 11.6 Hz), 137.7, 132.9 (d, $J_{C\text{-}P}$ = 6.5 Hz), 132.8 (d, $J_{C\text{-}P}$ = 6.3 Hz), 129.6, 128.9 (d, $J_{C\text{-}P}$ = 7.7 Hz), 128.7 (d, $J_{C\text{-}P}$ = 7.0 Hz),

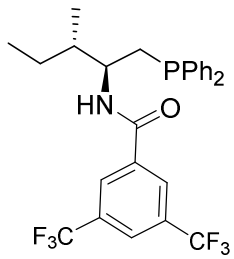
128.5, 126.6, 48.8 (d, J_{C-P} = 14.8 Hz), 41.1 (dd, J_{C-P} = 26.5, 7.8 Hz), 33.0 (d, J_{C-P} = 14.1 Hz), 23.3; ^{31}P NMR (121 MHz, 25 °C, $CDCl_3$): δ -22.7**;** HRMS (ESI)**:** Calculated for $C_{23}H_{25}NOP$ [M+H$^+$]: 362.16683, Found: 362.16813.

(S)-*N*-(1-(diphenylphosphanyl)-3,3-dimethylbutan-2-yl)acetamide (228)



Aminophosphine **225** was treated with acetyl chloride following **GP12** yielding aminophosphine **228** as a white solid in 65% yield; R_F = 0.33 (30% EtOAc/Petroleum ether); m.p. – 208.8 – 209.6^{o}C; ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 7.52 – 7.38 (m, 4H), 7.36 – 7.28 (m, 6H), 5.18 (d, *J* = 10.1 Hz, 1H), 4.04 – 3.88 (m, 1H), 2.41- 2.33 (m, 1H), 2.06-1.97 (m, 1H), 1.77 (s, 3H), 0.88 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.56, 139.0 (d, *J* = 12.8 Hz), 138.2 (d, J_{C-P} = 13.3 Hz), 133.0 (d, J_{C-P} = 15.0 Hz), 132.8 (d, J_{C-P} = 15.3 Hz), 128.8, 128.7, 128.6, 128.6 (d, J_{C-P} = 1.5 Hz), 128.5, 54.9 (d, J_{C-P} = 14.0 Hz), 35.5 (d, J_{C-P} = 6.9 Hz), 30.6 (d, J_{C-P} = 13.0 Hz), 26.3, 23.3; ^{31}P NMR (121 MHz, 25 °C, $CDCl_3$): δ -19.6; HRMS (ESI)**:** Calculated for $C_{20}H_{27}ONP$ [M+H$^+$]: 328.18248, Found: 328.18364.

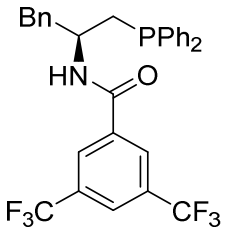
N-((2S,3S)-1-(diphenylphosphanyl)-3-methylpentan-2-yl)-3,5bis(trifluoromethyl)benzamide (206)



Aminophosphine **223** was treated with 3,5-(bistrifloromethyl)benzoyl chloride following **GP12** yielding aminophosphine **206** as a white solid in 60% yield; R_F = 0.41 (5% EtOAc/Petroleum ether); m.p. – 117.9 – 118.4^{o}C; ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 8.00 (s, 2H) , 7.93 (s, 1H), 7.57 – 7.38 (m, 4H), 7.34 – 7.23 (m, 6H), 6.34 (s, 1H), 4.39 – 4.27 (m, 1H), 2.59 – 2.42 (m, 2H), 1.96 – 1.82 (m, 1H), 1.59 – 1.42 (m, 1H), 1.24 – 1.12 (m, 1H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.89 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, 25

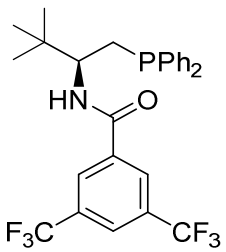
°C, $CDCl_3$): 163.8, 136.6, 133.0 (d, J_{C-P} = 8.1 Hz), 132.8 (d, J_{C-P} = 8.1 Hz), 132.0 (q, J_{C-F} = 33.8 Hz), 129.6 (d, J_{C-P} = 9.6 Hz), 128.97 (d, J_{C-P} = 6.4 Hz), 128.90 (d, J_{C-P} = 6.4 Hz), 127.36 (d, J_{C-P} = 2.7 Hz), 124.9, 124.4, 121.7, 52.7 (d, J_{C-P} = 12.0 Hz), 39.4 (d, J_{C-P} = 8.3 Hz), 29.8 (d, J_{C-P} = 8.4 Hz), 25.7, 15.0, 11.6; ^{31}P NMR (121 MHz, 25 °C, $CDCl_3$): δ -22.5; HRMS (ESI): Calculated for $C_{27}H_{27}NOF_6P$ [M+H$^+$]: 526.17290, Found: 526.17411.

(S)-*N*-(1-(diphenylphosphanyl)-3-phenylpropan-2-yl)-3,5-bis(trifluoromethyl)benzamide (229)



Aminophosphine **224** was treated with 3,5-(bistrifloromethyl)benzoyl chloride following **GP12** yielding aminophosphine **229** as a white solid in 60% yield; R_F = 0.47 (5% EtOAc/Petroleum ether); m.p. – 166.5 – 167.1°C; ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 7.85 (s, 3H), 7.41 – 7.27 (m, 4H), 7.24 – 7.12 (m, 11H), 6.38 (s, 1H), 4.57 – 4.41 (m, 1H), 3.06 (qd, *J* = 13.6, 6.8 Hz, 2H), 2.58 – 2.41 (m, 2H); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 163.9, 137.4, 136.5, 132.9 (d, J_{C-P} = 2.7 Hz), 132.8 (d, J_{C-P} = 2.6 Hz), 132.0 (q, J_{C-F} = 33.9 Hz), 129.6 (d, J_{C-P} = 9.5 Hz), 129.5, 128.9 (t, J_{C-P} = 7.3 Hz), 128.8, 127.3 (d, J_{C-P} = 2.7 Hz), 127.0, 124.9, 124.3, 121.6, 50.1 (d, J_{C-P} = 13.2 Hz), 41.5 (d, J_{C-P} = 9.3 Hz), 32.1 (d, J_{C-P} = 8.7 Hz); ^{31}P NMR (121 MHz, 25 °C, $CDCl_3$): δ -23.7; HRMS (ESI): Calculated for $C_{30}H_{25}NOF_6P$ [M+H$^+$]: 560.15725, Found: 560.15900.

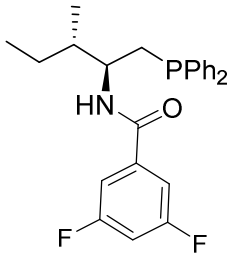
(S)-*N*-(1-(diphenylphosphanyl)-3,3-dimethylbutan-2-yl)-3,5-bis(trifluoromethyl)benzamide (230)



Aminophosphine **225** was treated with 3,5-(bistrifloromethyl)benzoyl chloride following **GP12** yielding aminophosphine **230** as a a white solid in 57% yield; R_F = 0.40 (5%

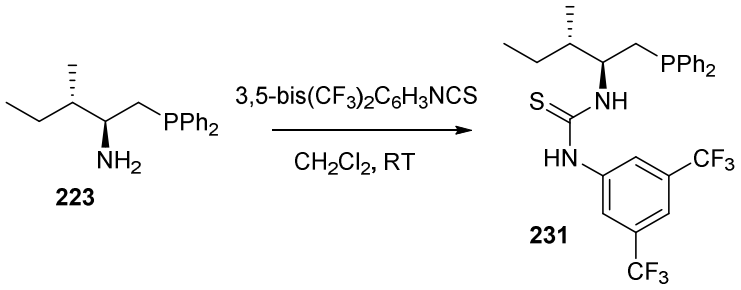
EtOAc/Petroleum ether); m.p. – 172.3 – 173.0°C; ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 8.24 (s, 2H), 7.95 (s, 1H), 7.73- 7.61 (m, 4H), 7.55 – 7.39 (m, 6H), 7.19 (d, J = 9.3 Hz, 1H), 4.43- 4.34 (m, 1H), 2.74 – 2.61 (m, 2H), 0.99 (s, 9H); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 164.2, 136.9, 132.5 (d, J_{C-P} = 2.8 Hz), 132.1 (d, J_{C-P} = 2.7 Hz), 131.9 (q, J_{C-F} = 33.8 Hz), 130.8 (d, J_{C-P} = 9.5 Hz), 130.5 (d, J_{C-P} = 9.5 Hz), 129.0 (d, J_{C-P} = 8.7 Hz), 128.9 (d, J_{C-P} = 8.6 Hz), 127.7 (d, J_{C-P} = 3 Hz), 124.7, 124.54, 121.84, 53.70 (d, J_{C-P} = 6.0 Hz), 36.72 (d, J_{C-P} = 8.4 Hz), 30.29 (d, J_{C-P} = 8.3 Hz), 26.3; ^{31}P NMR (121 MHz, 25 °C, $CDCl_3$): δ -23.5; HRMS (ESI)**:** Calculated for $C_{27}H_{27}ONF_6P$ [M+H$^+$]: 526.17290, Found: 526.17443.

N-((2S,3S)-1-(diphenylphosphanyl)-3-methylpentan-2-yl)-3,5-difluorobenzamide (196)



Aminophosphine **223** was treated with 3,5-diflorobenzoyl chloride following **GP12** yielding aminophosphine **196** as a white solid in 69% yield; R_F = 0.45 (5% EtOAc/ Petroleum ether); m.p. – 118.4 – 118.7°C; ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 7.50 – 7.39 (m, 4H), 7.35 – 7.28 (m, 6H), 6.98 – 6.92 (m, 2H), 6.90 - 6.84 (m, 1H), 5.83 (d, J = 8.7 Hz, 1H), 4.35 – 4.20 (m, 1H), 2.44 – 2.29 (m, 2H), 1.92 - 1.80 (m, 1H), 1.54 - 1.42 (m, 1H), 1.22 – 1.09 (m, 1H), 0.94 (d, J = 6.8 Hz, 3H), 0.89 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 164.2, 164.1, 164.0, 161.6 (d, J_{C-P} = 12.0 Hz), 138.4 (d, J_{C-P} = 12.3 Hz), 138.2 (d, J_{C-P} = 3.7 Hz), 138.1, 138.0, 133.0 (d, J_{C-P} = 19.3 Hz), 132.8 (d, J_{C-P} = 19.2 Hz), 129.0 (d, J_{C-P} = 6.7 Hz), 128.8 (d, J_{C-P} = 5.8 Hz), 128.7 (d, J_{C-P} = 5.9 Hz), 110.1 (d, J_{C-P} = 26.3 Hz), 110.0 (d, J_{C-P} = 11.2 Hz), 106.6 (t, J_{C-F} = 25.3 Hz), 52.6 (d, J_{C-P} = 13.6 Hz), 39.2 (d, J_{C-P} = 8.0 Hz), 30.4 (d, J_{C-P} = 14.7 Hz), 25.6, 14.9, 11.7; ^{31}P NMR (121 MHz, 25 °C, $CDCl_3$): δ -22.2; HRMS (ESI): Calculated for $C_{25}H_{27}NOF_2P$ [M+H$^+$]: 426.17928, Found: 426.18036

Synthetic scheme for the synthesis of 1-(3,5-bis(trifluoromethyl)phenyl)-3-((2S,3S)-1-(diphenylphosphanyl)-3-methylpentan-2-yl)thiourea (231)

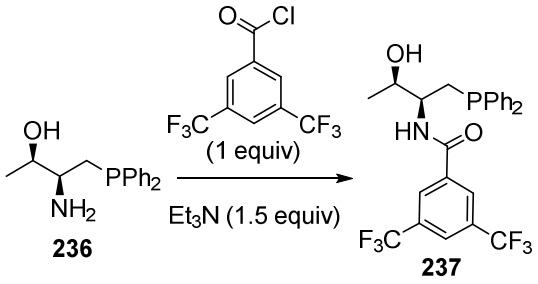


To a solution of aminophosphine **223** (300 mg, 1.05 mmol) in CH_2Cl_2 (10 mL), 3,5-bistrifloromethyl phenyl isothiocyanate (241.68 mg, 1.26 mmol) was added. The reaction mixture was stirred for 4h at RT. The solvent was removed in vacuo and the crude reaction mixture was directly purified by silica gel column chromatography with EtOAc and petroleum ether as eluents yielding the aminophosphine **231** as a white solid in 68% yield; R_F = 0.43 (5% EtOAc/Petroleum ether); m.p. – 167.5- 167.8, ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 8.41 (s, 1H), 7.67 (s, 2H), 7.64 (s, 1H), 7.46 – 7.37 (m, 4H), 7.35 – 7.27 (m, 6H), 6.31 (s, 1H), 4.66 (s, 1H), 2.53 – 2.46 (m, 1H), 2.23- 2.21 (m, 1H), 1.94 (s, 1H), 1.49 – 1.37 (m, 1H), 1.19 – 1.06 (m, 1H), 0.92 (d, J = 6.8 Hz, 3H), 0.86 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 179.8, 138.9, 137.4 (d, J_{C-P} = 11 Hz), 137.0 (d, J_{C-P} = 9 Hz), 133.1 (d, J_{C-P} = 19.3 Hz), 132.7, 132.6 (d, J_{C-P} = 18.7 Hz), 129.4, 129.0, 128.8 (dd, J_{C-P} = 7.0, 3.9 Hz), 122.9 (q, J_{C-F} = 271 Hz), 123.3, 119.0, 57.4 (d, J_{C-P} = 12.3 Hz), 38.6, 29.9, 25.8, 15.0, 11.5; ^{31}P NMR (121 MHz, 25 °C, $CDCl_3$): δ -22.9; HRMS (ESI)**:** Calculated for $C_{27}H_{28}N_2F_6PS$ [M+H$^+$]: 557.16095, Found: 557.16282.

5.3.2 Synthesis of *L*-threonine based aminophosphines

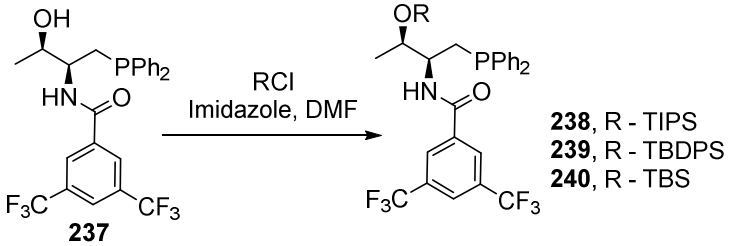
Aminophosphine **236** was synthesized according to literature procedure over 4 synthetic steps [116] as a colourless sticky oil, R_F = 0.35 (10% MeOH/DCM); ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 7.50 – 7.38 (m, 4H), 7.37 – 7.29 (m, 6H), 3.63- 3.55 (m, 1H), 2.74 (s, 3H), 2.67 – 2.57 (m, 1H), 2.43 – 2.36 (m, 1H), 2.1- 2.02 (m, 1H), 1.14 (d, J = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 138.6 (d, J_{C-P} = 11.3 Hz), 137.5 (d, J_{C-P} = 12.3 Hz), 133.2 (d, J_{C-P} = 19.5 Hz), 132.6 (d, J_{C-P} = 18.4 Hz), 129.2, 128.7 (dd, J_{C-P} = 10.7, 6.9 Hz), 70.8 (d, J_{C-P} = 8.4 Hz), 55.0 (d, J_{C-P} = 13.3 Hz), 34.3 (d, J_{C-P} = 12.3 Hz), 20.1; ^{31}P NMR (121 MHz, 25 °C, $CDCl_3$): δ -22.0; HRMS (ESI)**:** Calculated for $C_{16}H_{21}NOP$ [M+H$^+$]: 274.13553, Found: 274.13636.

Procedure for the synthesis of *N*-((2S,3R)-1-(Diphenylphosphino)-3-hydroxybutan-2-yl)-3,5-bis(trifluoromethyl)benzamide (237) .



To a solution of aminophosphine **236** (546 mg, 2 mmol) and Et_3N (417 µl, 3 mmol) in anhydrous CH_2Cl_2 (30 mL) was added dropwise a solution of 3,5-bis(trifluoromethyl)benzoyl chloride (360 µl, 2 mmol) in CH_2Cl_2 (30 mL) at -50^oC over 30 min. The resulting reaction mixture was stirred at the same temperature for 1h and then warmed to room temperature. Water (45 mL) was added to the reaction mixture and the aqueous phase was extracted with CH_2Cl_2 (2 x 15 ml). The combined organic layers were washed with brine (45 ml) and dried over Na_2SO_4. Solvent was removed *in vacuo* and the residue was purified by column chromatography on silica gel with EtOAc and petrolether as eluents to afford the desired aminophosphine **237** as a white solid in 75% yield; R_F = 0.38 (20% EtOAc/Petroleum ether); ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 7.91 (s, 2H), 7.87 (s, 1H), 7.43 – 7.32 (m, 4H), 7.25 – 7.13 (m, 6H), 6.44 (d, *J* = 7.3 Hz, 1H), 4.28 – 4.08 (m, 2H), 2.50 (d, *J* = 6.8 Hz, 3H), 1.14 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 164.5, 136.3, 132.9 (d, J_{C-P} = 8.7 Hz), 132.7 (d, J_{C-P} = 8.6 Hz), 132.0 (q, J_{C-F} = 33.9 Hz), 129.2 (d, J_{C-P} = 2.7 Hz), 128.8 (d, J_{C-P} = 1.4 Hz), 128.7 (d, J_{C-P} = 1.5 Hz), 127.35 (d, J_{C-P} = 2.8 Hz), 125.0, 124.3, 69.6 (d, J_{C-P} = 8.6 Hz), 53.7 (d, J_{C-P} = 14.2 Hz), 31.8 (d, J_{C-P} = 13.9 Hz), 20.8; ^{31}P NMR (121 MHz, 25 °C, $CDCl_3$): δ -22.73; HRMS (ESI): Calculated for $C_{25}H_{23}NO_2PF_6$ [M+H$^+$]: 514.13651, Found: 514.13736.

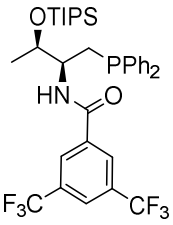
General Procedure 13 (GP13) for the synthesis of *o*-silylated *L*-threonine based aminophosphines (238- 240)



To a solution of aminophosphine **237** (150 mg, 0.29 mmol) in dry DMF (1 ml) was added imidazole (60.41mg, 0.87 mmol) and triisopropylsilyl chloride (77µl, 0.36 mmol) at room

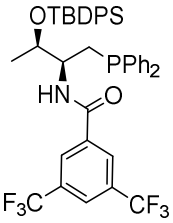
temperature under N_2. The solution was stirred at RT and monitored *via* TLC for completion. The reaction mixture was directly purified by column chromatography on silica gel with EtOAc and petroleum ether as eluents affording the desired aminophopshine **238.**

_N_-((2_S_,3_R_)-1-(Diphenylphosphino)-3-(triisopropylsilyloxy)butan-2-yl)-3,5-bis(trifluoromethyl)benzamide (238)



Aminophosphine **238** was synthesized according to the **GP13** as a white solid in 78% yield, R_F = 0.54 (5% EtOAc/Petroleum ether); m.p. – 122.9 – 123.4^{o}C; ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 8.09 (s, 2H), 7.98 (s, 1H), 7.61- 7.53 (m, 2H), 7.43 – 7.36 (m, 2H), 7.36 – 7.27 (m, 6H), 6.61 (d, *J* = 8.5 Hz, 1H), 4.50 (q, *J* = 6.2 Hz, 1H), 4.20 (dd, *J* = 15.1, 8.0 Hz, 1H), 2.72- 2.62 (m, 1H), 2.45- 2.35 (m, 1H), 1.23 (d, *J* = 6.2 Hz, 3H), 1.14 – 1.10 (m, 21H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.6, 136.6, 133.1 (d, J_{C-P} = 19.6 Hz), 132.6 (d, J_{C-P} = 18 Hz), 132.2 (q, J_{C-F} = 33.9 Hz), 129.1, 128.7 (d, J_{C-P} = 6.9 Hz), 128.6 (d, J_{C-P} = 6.8 Hz), 127.2 (d, *J* J_{C-P} = 2.8 Hz), 124.9, 124.4, 69.8 (d, J_{C-P} = 10.3 Hz), 54.0 (d, J_{C-P} = 16.3 Hz), 32.0 (d, J_{C-P} = 14.1 Hz), 21.4, 18.3 (d, J_{C-P} = 7.7 Hz), 12.8; ^{31}P NMR (121 MHz, 25 °C, $CDCl_3$): δ -22.0; HRMS (ESI): Calculated for $C_{34}H_{43}NO_2F_6PSi$ [M+H$^+$]: 670.26994, Found: 670.27268.

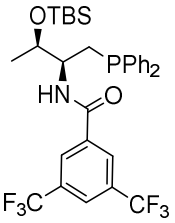
_N_-((2_S_,3_R_)-3-(*tert*-Butyldiphenylsilyloxy)-1-(diphenylphosphino)butan-2-yl)-3,5-bis(trifluoromethyl)benzamide (239)



Aminophosphine **239** was synthesized according to the **GP13** (using *tert*-butyldiphenylsilyl chloride) as a white solid in 73% yield, R_F = 0.58 (5% EtOAc/ Petroleum ether); m.p. – 154.3 – 154.9; ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 8.04 (s, 2H), 7.97 (d, *J* = 7.4 Hz, 1H), 7.73 – 7.67 (m, 2H), 7.66 – 7.60 (m, 2H), 7.49 – 7.33 (m, 8H), 7.30 – 7.22 (m, 8H), 6.49 (d, *J* = 8.8 Hz, 1H), 4.35 – 4.29 (m, 1H), 4.27 – 4.17 (m, 1H), 2.63 – 2.53 (m, 1H),

2.24 (dd, J = 13.9, 5.8 Hz, 1H), 1.11 (s, 9H), 1.08 (d, J = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 163.7, 136.6, 135.9 (d, J_{C-P} = 1.4 Hz), 133.7, 133.2, 133.0 (d, J_{C-P} = 19.6 Hz), 132.6 (d, J_{C-P} = 19 Hz), 132.2 (q, J_{C-F} = 33.8 Hz), 130.1 (d, J_{C-P} = 7.6 Hz), 129.1, 128.7 (d, J_{C-P} = 6.8 Hz), 128.6, 128.6 (d, J_{C-P} = 6.9 Hz), 127.9 (d, J_{C-P} = 16 Hz), 127.2 (d, J_{C-P} = 2.9 Hz), 124.9, 124.4, 71.4 (d, J_{C-P} = 10.4 Hz), 53.8 (d, J_{C-P} = 15.7 Hz), 32.4 (d, J_{C-P} = 13.9 Hz), 27.2, 21.2, 19.5; ^{31}P NMR (121 MHz, 25 °C, $CDCl_3$): δ -21.87; HRMS (ESI): Calculated for $C_{41}H_{41}NO_2F_6PSi$ [M+H$^+$]: 752.25429, Found: 752.25747.

_N_-((2_S_,3_R_)-3-(_tert_-Butyldimethylsilyloxy)-1-(diphenylphosphino)butan-2-yl)-3,5-bis(trifluoromethyl)benzamide (240)

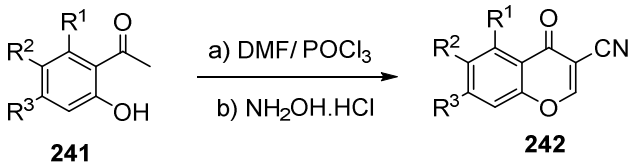


Aminophosphine **240** was synthesized according to the **GP13** (using *tert*-butyldimethylsilyl chloride) as a white solid in 74% yield, R_F = 0.55 (5% EtOAc/ petroleum ether); m.p. – 137.5 – 138^{o}C; ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 8.10 (s, 2H), 7.98 (s, 1H), 7.61 – 7.55 (m, 2H), 7.42 – 7.28 (m, 8H), 6.64 (d, J = 8.5 Hz, 1H), 4.36- 4.30 (m, 1H), 4.21 – 4.10 (m, 1H), 2.69 – 2.60 (m, 1H), 2.31- 2.23 (m, 1H), 1.16 (d, J = 6.2 Hz, 3H), 0.95 (s, 9H), 0.16 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 163.6, 136.6, 133.0 (d, J_{C-P} = 19.4 Hz), 132.7 (d, J_{C-P} = 18.8 Hz), 132.3 (q, J_{C-F} = 33.0 Hz), 129.2, 128.9, 128.8 (d, J_{C-P} = 7.1 Hz), 128.7 (d, J_{C-P} = 6.9 Hz), 127.2 (d, J_{C-P} = 2.7 Hz), 125.0, 124.4, 69.3 (d, J_{C-P} = 10.7 Hz), 53.5 (d, J_{C-P} = 15.9 Hz), 32.2 (d, J_{C-P} = 13.6 Hz), 25.9, 21.4, 18.0; ^{31}P NMR (121 MHz, 25 °C, $CDCl_3$): δ -22.43, HRMS (ESI): Calculated for $C_{31}H_{37}NO_2F_6PSi$ [M+H$^+$]: 628.22299, Found: 628.22483.

5.3.3 General Procedure 14 (GP14) for the synthesis of differently substituted 3-cyano chromones 242

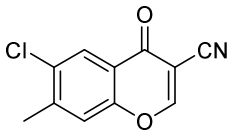
A mixture of dimethylformamide (46.8 mmol, 3.76 mL) and phosphorus oxychloride (23.4 mmol, 2.17 mL) was stirred at 0 ^{o}C for 30 min. To this a solution of the corresponding 2-hydroxyacetophenone **241** (5.86 mmol) was added dropwise at 0 ^{o}C. The reaction mixture was stirred at room temperature for 4 h. After completion of the reaction as indicated by TLC,

the reaction mixture was diluted with dichloromethane (22 mL). The resulting reaction mixture was cooled to 0 ^{o}C followed by addition of hydroxylamine hydrochloride (17.58 mmol, 1.2g) in DMF (6 mL) and the reaction mixture was stirred at room temperature for 3–4 h. After the reaction was complete, as indicated by TLC, it was diluted with cold water (58 mL) and extracted with DCM (2 X 29 mL). The combined organic phases were washed with water (2 X 29 mL), saturated $NaHCO_3$ solution (10 mL) and finally with water (29 mL). The combined organic extracts were dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* and the residual solid was directly crystallized from methanol to give the desired cyano chromone **242**.



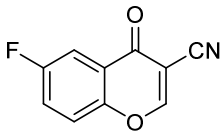
241 **242**

6-Chloro-7-methyl-4-oxo-4H-chromene-3-carbonitrile (243)



Compound **243** was synthesized according to the **GP14** as a yellowish brown solid in 51% yield, R_F = 0.43 (30% EtOAc/Petroleum ether); m.p. – 175.6 – 176.1^{o}C; ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 8.36 (s, 1H), 8.10 – 8.09 (m, 1H), 7.58 (s, 1H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 171.8, 162.0, 154.1, 142.1, 136.4, 127.4, 121.8, 118.9, 112.0, 103.3, 19.9; LCMS (ESI): Calculated for $C_{11}H_6NClO_2$ [M+H^{+}]: 219.00, Found: 220.13.

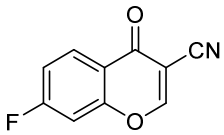
6-Fluoro-4-oxo-4H-chromene-3-carbonitrile (244)



Compound **244** was synthesized according to the **GP14** as a yellowish orange solid in 57% yield, R_F = 0.52 (30% EtOAc/Petroleum ether); m.p. – 173.6 – 174.3^{o}C; ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 8.44 (s, 1H), 7.88 (dd, *J* = 7.8, 3.0 Hz, 1H), 7.59 (dd, *J* = 9.2, 4.1

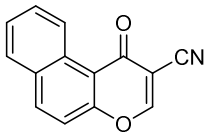
Hz, 1H), 7.54- 7.48 (m, 1H); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 171.8 (d, *J* = 2.4 Hz), 162.2, 160.5 (d, *J* = 250.8 Hz, CF), 152.1 (d, *J* = 2.0 Hz), 124.8 (d, *J* = 7.8 Hz), 123.7 (d, *J* = 25.4 Hz), 121.0 (d, *J* = 8.3 Hz), 112.0, 111.5 (d, *J* = 24.4 Hz), 102.5; HRMS (ESI)**:** Calculated for $C_{10}H_4NFO_2$ [M+H$^+$]: 190.02988, Found: 190.02978.

7-Fluoro-4-oxo-4H-chromene-3-carbonitrile (245)



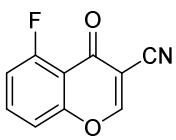
Compound **245** was synthesized according to the **GP14** as a yellowish solid in 55% yield, R_F = 0.53 (30% EtOAc/Petroleum ether); m.p. – 159.9 – 160.3^{o}C; ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 8.40 (s, 1H), 8.31 – 8.26 (m, 1H), 7.29 – 7.22 (m, 2H); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 171.43, 166.48 (d, *J* = 259.1 Hz, CF), 162.27, 156.90 (d, *J* = 13.3 Hz), 129.17 (d, *J* = 10.7 Hz), 120.41 (d, *J* = 2.7 Hz), 116.15 (d, *J* = 22.8 Hz), 111.90, 105.71 (d, *J* = 25.9 Hz), 103.59; HRMS (ESI)**:** Calculated for $C_{10}H_4NFO_2$ [M+H$^+$]: 190.02988, Found: 190.02977.

1-oxo-1H-benzo[f]chromene-2-carbonitrile (246)



Compound **246** was synthesized according to the **GP14** as a pale white solid in 69% yield, R_F = 0.41 (30% EtOAc/Petroleum ether); m.p. – 182.7 – 183.1^{o}C; ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 9.89 (d, *J* = 8.7 Hz, 1H), 8.43 (s, 1H), 8.20 (d, *J* = 9.1 Hz, 1H), 7.95 (d, *J* = 8.1 Hz, 1H), 7.84- 7.79 (m, 1H), 7.72 – 7.66 (m, 1H), 7.55 (d, *J* = 9.1 Hz, 1H); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 173.8, 159.7, 157.3, 137.4, 131.3, 130.4, 129.9, 128.6, 127.9, 127.3, 117.3, 117.0, 112.5, 105.8; HRMS (ESI)**:** Calculated for $C_{14}H_7NO_2$ [M+H$^+$]: 222.05496, Found: 222.05530.

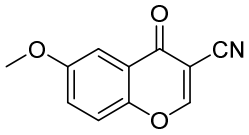
5-Fluoro-4-oxo-4H-chromene-3-carbonitrile (247)



Compound **247** was synthesized according to the **GP14** as a orangish solid in 51% yield, R_F = 0.54 (30% EtOAc/Petroleum ether); m.p. – 164.8 – 165.3^{o}C; ^{1}H NMR (400 MHz, 25 °C,

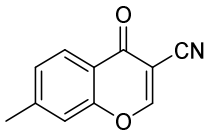
$CDCl_3$): δ 8.36 (s, 1H), 7.74 (td, *J* = 8.4, 5.4 Hz, 1H), 7.39- 7.34 (m, 1H), 7.21- 7.15 (m, 1H); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 170.2 (d, *J* = 1.8 Hz), 161.5, 160.5 (d, *J* = 267 Hz, CF), 156.5 (d, *J* = 3.1 Hz), 135.7 (d, *J* = 10.7 Hz), 114.5 (d, *J* = 4.6 Hz), 114.3 (d, *J* = 20.3 Hz), 114.0 (d, *J* = 10.6 Hz), 111.8, 104.2; HRMS (ESI)**:** Calculated for $C_{10}H_4NFO_2$ [$M+H^+$]: 190.02988, Found: 190.02980.

6-Methoxy-4-oxo-4H-chromene-3-carbonitrile (248)



Compound **248** was synthesized according to the **GP14** as a yellowish solid in 50% yield, R_F = 0.54 (30 % EtOAc/Petroleum ether); m.p. – 188.0 – 188.4°C; ^1H NMR (400 MHz, 25 °C, $CDCl_3$): δ 8.39 (s, 1H), 7.57 (d, *J* = 3.1 Hz, 1H), 7.48 (d, *J* = 9.2 Hz, 1H), 7.34 (dd, *J* = 9.2, 3.1 Hz, 1H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 172.5, 161.7, 158.3, 150.7, 125.2, 124.3, 120.1, 112.5, 105.5, 102.2, 56.2; HRMS (ESI)**:** Calculated for $C_{11}H_7NO_3$ [$M+H^+$]: 202.05017, Found: 202.04987.

7-Methyl-4-oxo-4H-chromene-3-carbonitrile (249)



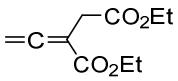
Compound **249** was synthesized according to the **GP14** as a pale yellow solid in 50% yield, R_F = 0.38 (30 % EtOAc/Petroleum ether); m.p. – 189.8 – 190.3°C; ^1H NMR (400 MHz, 25 °C, $CDCl_3$): δ 8.36 (d, *J* = 0.8 Hz, 1H), 8.15 – 8.10 (m, 1H), 7.37 – 7.30 (m, 2H), 2.52 (s, 3H); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 172.3, 161.9, 156.0, 147.3, 128.7, 126.1, 121.2, 118.3, 112.4, 103.1, 22.1; HRMS (ESI)**:** Calculated for $C_{11}H_7NO_2$ [$M+H^+$]: 186.05496, Found: 186.05474.

5.3.4 General Procedure 15 (GP15) for the synthesis of α-substituted allenes 253.

To a stirred solution of (ethoxycarbonylmethylene)triphenylphosphorane (5g, 14.36mmol) in chloroform (40 mL) was added 1.3 equivalents of the ethyl bromoacetate at room temperature. The reaction mixture was refluxed and monitored *via* TLC for completion and then

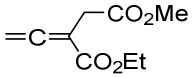
concentrated to give the phosphonium bromide as a brown solid. To the resulting phosphonium salt was added dichloromethane (50 mL) and 2.2 equivalents of triethylamine (4.4 mL) and the mixture was stirred for 2 h. Acetyl chloride (1.1 equivalents, 1.1 mL) in dichloromethane (5 mL) was added dropwise over 1 h and the reaction mixture was stirred overnight. The resulting reaction mixture was poured into a buchner funnel that was packed with silica gel and was washed with dichloromethane for several times. The combined filtrate was concentrated and the residue was subjected to flash column chromatography with ethyl acetate and petroleum ether as eluents.

Diethyl 2-vinylidenesuccinate (175a)



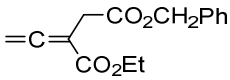
Compound **175a** was synthesized according to the **GP15** as a colourless oil in 70% yield, R_F = 0.47 (10% EtOAc/Petroleum ether); ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 5.21 (t, *J* = 2.2 Hz, 2H), 4.24 – 4.13 (m, 4H), 3.25 (t, *J* = 2.2 Hz, 2H), 1.29 – 1.23 (m, 6H); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 214.6, 170.6, 166.4, 94.8, 79.6, 61.4, 61.0, 34.9, 14.3, 14.3; HRMS (ESI): Calculated for $C_{10}H_{14}O_4Na$ [M+Na^+]: 221.07843, Found: 221.07915.

1-Ethyl 4-methyl 2-vinylidenesuccinate (254)



Compound **254** was synthesized according to the **GP15** (14.36 mmol scale using 1.3 equiv of methyl bromoacetate) as a colourless oil in 69% yield, R_F = 0.44 (10% EtOAc/Petroleum ether); ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 5.23 – 5.20 (m, 2H), 4.25- 4.17 (m, 2H), 3.70 (d, *J* = 1.1 Hz, 3H), 3.28- 3.26 (m, 2H), 1.27 (td, *J* = 7.1, 1.1 Hz, 3H); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 214.6, 171.0, 166.4, 94.6, 79.6, 61.5, 52.2, 34.7, 14.3; GC-MS (m/z) : Calculated for $C_9H_{12}O_4$ - 184.07, Found: 184.0.

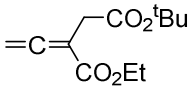
4-Benzyl 1-ethyl 2-vinylidenesuccinate (255)



Compound **255** was synthesized according to the **GP15** (14.36 mmol scale using 1.3 equiv of benzyl bromoacetate) as a colourless oil in 65% yield, R_F = 0.44 (10% EtOAc/Petroleum

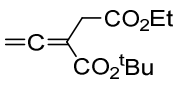
ether); ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 7.39 – 7.30 (m, 5H), 5.20 (t, *J* = 2.2 Hz, 2H), 5.15 (s, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.33 (t, *J* = 2.2 Hz, 2H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 214.6, 170.4, 166.3, 135.9, 128.6, 128.3, 94.6, 79.7, 66.8, 61.5, 34.9, 14.3; HRMS (ESI)**:** Calculated for $C_{15}H_{16}O_4Na$ [M+Na^+]: 283.09408, Found: 283.09439.

4-(*tert*-Butyl) 1-ethyl 2-vinylidenesuccinate (256)



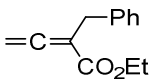
Compound **256** was synthesized according to the **GP15** (14.36 mmol scale using 1.3 equiv of *t*-butyl bromoacetate) as a colourless oil in 60% yield, R_F = 0.51 (10% EtOAc/Petroleum ether); ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 5.20 (td, *J* = 2.2, 0.6 Hz, 2H), 4.24- 4.17 (m, 2H), 3.17 (td, *J* = 2.2, 0.7 Hz, 2H), 1.45 (d, *J* = 0.7 Hz, 9H), 1.30 – 1.24 (m, 3H); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 214.6, 169.8, 166.5, 95.2, 81.2, 79.4, 61.4, 36.0, 28.1, 14.3; HRMS (ESI)**:** Calculated for $C_{12}H_{18}O_4Na$ [M+Na^+]: 249.10973, Found: 249.10995.

1-(*tert*-Butyl) 4-ethyl 2-vinylidenesuccinate (257)



Compound **257** was synthesized according to the **GP15** (using 14.36 mmol of (*tert*-butoxycarbonylmethylene)triphenylphosphorane and 1.3 equiv of ethyl bromoacetate) as a colourless oil in 59% yield, R_F = 0.49 (10% EtOAc/Petroleum ether); ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 5.16 (td, *J* = 2.2, 1.0 Hz, 2H), 4.19 – 4.10 (m, 2H), 3.21 (td, *J* = 2.2, 1.0 Hz, 2H), 1.46 (d, *J* = 1.1 Hz, 9H), 1.28 – 1.23 (m, 3H); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 214.6, 170.6, 166.4, 94.8, 79.6, 61.4, 61.0, 34.9, 14.3, 14.3; HRMS (ESI)**:** Calculated for $C_{12}H_{18}O_4Na$ [M+Na^+]: 249.10973, Found: 249.10987

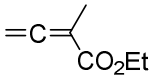
Ethyl 2-benzylbuta-2,3-dienoate (258)



Compound **258** was synthesized according to the **GP15** (14.36 mmol scale using 1.3 equiv of benzyl bromide) as a pale yellow oil in 54% yield, R_F = 0.45 (5% EtOAc/Petroleum ether); ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 7.31 – 7.17 (m, 5H), 5.09 (t, *J* = 2.6 Hz, 2H), 4.23 – 4.15 (m, 2H), 3.57 (t, *J* = 2.6 Hz, 2H), 1.28 – 1.24 (m, 3H); ^{13}C NMR (100 MHz, 25 °C,

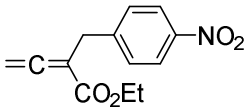
$CDCl_3$): δ 214.5, 166.9, 139.2, 129.00, 128.3, 126.4, 100.4, 79.3, 61.2, 35.0, 14.3; GC-MS (m/z) : Calculated for $C_{13}H_{14}O_2$ - 202.09, Found: 202.1.

Ethyl 2-methylbuta-2,3-dienoate (259)



Compound **259** was synthesized according to the **GP15** (14.36 mmol scale using 1.3 equiv of methyl iodide) as a yellow oil in 47% yield, R_F = 0.5 (5% EtOAc/Petroleum ether); ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 5.06 (q, *J* = 3.2 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 1H), 1.87 (td, *J* = 3.2, 0.7 Hz, 1H), 1.30 – 1.25 (m, 1H); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 214.1, 167.7, 95.6, 77.9, 61.1, 14.8, 14.4; GC-MS (m/z) : Calculated for $C_7H_{10}O_2$ - 126.06, Found: 126.0.

Ethyl 2-(4-nitrobenzyl)buta-2,3-dienoate (260)



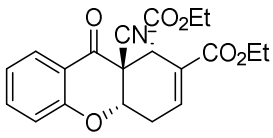
Compound **260** was synthesized according to the **GP15** (14.36 mmol scale using 1.3 equiv of *p*-nitro benzyl bromide) as a colourless oil in 63% yield, R_F = 0.48 (10% EtOAc/Petroleum ether); ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 8.10 (d, *J* = 8.2 Hz, 2H), 7.37 (d, *J* = 8.2 Hz, 2H), 5.13 (s, 2H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.63 (s, 2H), 1.22 (dd, *J* = 7.1, 6.6 Hz, 3H); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 214.3, 166.3, 146.9, 146.7, 129.7, 123.5, 99.1, 79.7, 61.3, 34.8, 14.1; GC-MS (m/z) : Calculated for $C_{13}H_{13}NO_4$ - 247.08, Found: 247.0.

5.3.5 General Procedure 16 (GP16) for the asymmetric [4+2] annulation reaction between differently substituted 3-cyano chromones (261) and α-substituted allenes (253).

To a mixture of 3-cyano chromone or analogs **261** (0.175 mmol, 1 equiv), 3Å powdered molecular sieves (30mg) and aminophosphine catalyst **238** (0.01 equiv, 11.75 mg) dissolved in anhydrous 1,4-dioxane (1.75 mL) in a well dried schlenk flask charged with argon was added the α-substituted allene **253** in one portion *via* a microsyringe. The resulting reaction mixture was vigorously stirred at RT for 24h. The reaction mixture was then directly purified by column chromatography with EtOAc and petroleum ether as eluents to yield the desired [4+2] adduct. The diastereoselectivity of the reaction was determined *via* analysis of the

proton NMR spectrum of the crude reaction mixture. The enantioselectivity for the major diastereomer was determined *via* chiral HPLC.

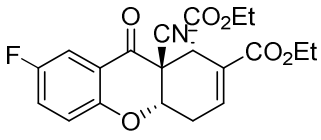
Compound 213



Compound **213** was synthesized according to the **GP 16**(using commerially available 3-cyano chromone and allenoate **175a**) as a colourless thick oil in 93% yield (both the diastereomers together) with **dr** = 8 : 92 and **ee** = 96% (for the major diastereomer), R_F = 0.42 (25 % EtOAc/ petroleum ether, minor diastereomer), R_F = 0.40 (25% EtOAc/Petroleum ether, major diastereomer),

Major Diastereomer = ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 8.00 - 7.96 (m, 1H), 7.56 – 7.50 (m, 1H), 7.32 – 7.27 (m, 1H), 7.17 – 7.11 (m, 1H), 6.99 - 6-95 (m, 1H), 4.88 – 4.79 (m, 1H), 4.30 – 4.16 (m, 3H), 3.68 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.14 (dq, *J* = 10.8, 7.2 Hz, 1H), 3.07 – 2.91 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.89 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 183.5, 167.0, 164.6, 160.3, 137.1, 136.0, 128.1, 126.2, 123.2, 119.2, 118.2, 116.0, 74.3, 62.0, 61.4, 49.4, 43.4, 29.6, 14.2, 13.4; HRMS (ESI)**:** Calculated for $C_{20}H_{19}NO_6$ [M+H$^+$]: 370.13034, Found: 370.12851; $[\alpha]^{20}_D$ = -312 ($CHCl_3$, *c* = 1); HPLC conditions: CHIRAPAK IC column, ethanol/ iso-hexane = 20/100, flow rate = 1 ml min^{-1}, major enantiomer: t_R = 21.0 min; minor enantiomer: t_R = 17.2 min.

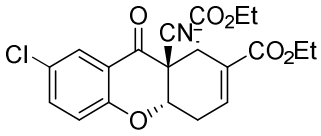
Compound 263



Compound **263** was synthesized according to the **GP16** (using commerially available 6- floro 3-cyano chromone and allenoate **175a**) as a colourless thick oil in 91% yield (both the diastereomers together) with **dr** = 10 : 90 and **ee** = 95% (for the major diastereomer), the diastereomers are separated by reverse phase HPLC (using the C18 column with a gradient of 20/100 AcN / (Water/TFA = 1000/1) to 100% AcN over a period of 30mins) they are inseparable *via* column chromatography.

Major Diastereomer = ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 7.63 (dd, *J* = 7.9, 3.2 Hz, 1H), 7.30 – 7.22 (m, 2H), 6.98 (dd, *J* = 9.1, 4.1 Hz, 1H), 4.83 (dd, *J* = 4.0, 0.8 Hz, 1H), 4.28 – 4.17 (m, 3H), 3.73 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.29 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.11 – 2.92 (m, 2H), 1.31- 1.25 (m, 3H), 0.98- 0.90 (m, 3H); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 183.0 (d, *J* = 2.0 Hz), 165.7 (d, *J* = 243.9 Hz), 159.3, 156.9, 156.54 (d, *J* = 1.8 Hz), 135.8, 126.1, 124.6 (d, *J* = 24.6 Hz), 120.0 (dd, *J* = 7.2, 4.4 Hz), 115.8, 113.0 (d, *J* = 24.0 Hz), 74.6, 62.1, 61.4, 49.2, 43.3, 29.5, 14.2, 13.5; HRMS (ESI)**:** Calculated for $C_{20}H_{18}NFO_6$ [M+H$^+$]: 388.11909, Found: 388.12066; $[\alpha]^{20}_D$ = -300 ($CHCl_3$, *c* = 1.1); HPLC conditions: CHIRAPAK IC column, *iso*-propanol / iso-hexane = 20/100, flow rate = 1 mL min^{-1}, major enantiomer: t_R = 25.3 min; minor enantiomer: t_R = 22.2 min.

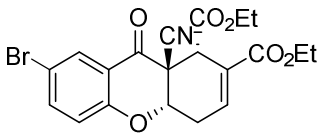
Compound 264



Compound **264** was synthesized according to the **GP16** (using commerially available 6-chloro 3-cyano chromone and allenoate **175a**) as a colourless thick oil in 91% yield (both the diastereomers together) with **dr** = 9 : 91 and **ee** = 96% (for the major diastereomer), the diastereomers are separated by reverse phase HPLC (using the C18 column with a gradient of 20/100 AcN / (Water/TFA = 1000/1) to 100% AcN over a period of 30mins) they are inseparable *via* column chromatography.

Major Diastereomer = ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$) : δ 7.93 (d, *J* = 2.6 Hz, 1H), 7.47 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.28 (t, *J* = 3.8 Hz, 1H), 6.94 (d, *J* = 8.8 Hz, 1H), 4.85 - 4.80 (m, 1H), 4.27 – 4.18 (m, 3H), 3.73 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.28 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.14 – 2.92 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 3H), 0.94 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 182.8, 167.0, 164.5, 158.7, 136.9, 135.8, 129.0, 127.3, 126.2, 120.3, 119.9, 115.8, 74.6, 62.3, 61.6, 49.3, 43.4, 29.6, 14.3, 13.5 ppm; HRMS (ESI)**:** Calculated for $C_{20}H_{18}NClO_6$ [M+H$^+$]: 404.08954, Found: 404.09108; $[\alpha]^{20}_D$ = -316.2 ($CHCl_3$, *c* = 1.06); HPLC conditions: CHIRAPAK IC column, EtOH / iso-hexane = 20/100, flow rate = 1 mL min^{-1}, major enantiomer: t_R = 46.6 min; minor enantiomer: t_R = 42.4 min.

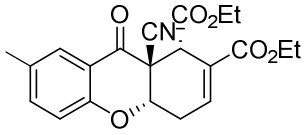
Compound 265



Compound **265** was synthesized according to the **GP16** (using commerially available 6-bromo 3-cyano chromone and allenoate **175a**) as a colourless thick oil in 92% yield (both the diastereomers together) with **dr** = 9 : 91 and **ee** = 96% (for the major diastereomer), the diastereomers are separated by reverse phase HPLC (using the C18 column with a gradient of 20/100 AcN / (Water/TFA = 1000/1) to 100% AcN over a period of 30mins) they are inseparable *via* column chromatography.

Major Diastereomer = ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 8.14 – 8.01 (m, 1H), 7.60 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.29- 7.25 (m, 1H), 6.93 – 6.83 (m, 1H), 4.85 – 4.75 (m, 1H), 4.32 – 4.17 (m, 3H), 3.72 (dq, *J* = 10.8, 7.2 Hz, 1H), 3.27 (dq, *J* = 10.2, 6.9 Hz, 1H), 3.12 – 2.90 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 3H), 0.94 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 182.5, 166.9, 164.5, 159.1, 139.6, 135.7, 130.4, 126.1, 120.6, 120.1, 116.0, 115.6, 74.5, 62.2, 61.5, 49.1, 43.39, 29.53, 14.2, 13.4; HRMS (ESI): Calculated for $C_{20}H_{18}NBrO_6$ [M+H$^+$]: 448.03903, Found: 448.04035; $[\alpha]^{20}_D$ = -278.4 ($CHCl_3$, *c* = 1.13); HPLC conditions: CHIRAPAK IC column, EtOH / iso-hexane = 20/100, flow rate = 1 mL min^{-1}, major enantiomer: t_R = 29.9 min; minor enantiomer: t_R = 32.0 min.

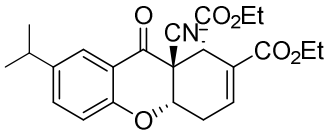
Compound 266



Compound **266** was synthesized according to the **GP16** (using commerially available 6-methyl 3-cyano chromone and allenoate **175a**) as a colourless thick oil in 81% yield (both the diastereomers together) with **dr** = 20 : 80 and **ee** = 93% (for the major diastereomer), R_F = 0.46 (25% EtOAc/ Petroleum ether, minor diastereomer), R_F = 0.43 (25% EtOAc/Petroleum ether, major diastereomer)

Major Diastereomer = ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 7.78 – 7.74 (m, 1H), 7.35 – 7.31 (m, 1H), 7.28 (t, *J* = 3.8 Hz, 1H), 6.86 (d, *J* = 8.5 Hz, 1H), 4.79 (dd, *J* = 4.5, 0.9 Hz, 1H), 4.28 – 4.17 (m, 3H), 3.69 (dq, *J* = 10.8, 7.2 Hz, 1H), 3.19 (dq, *J* = 10.8, 7.2 Hz, 1H), 3.08 – 2.92 (m, 2H), 2.33 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.90 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 183.7, 167.1, 164.6, 158.4, 138.1, 136.0, 133.0, 127.6, 126.2, 118.9, 117.9, 116.2, 74.3, 62.0, 61.4, 49.5, 43.4, 29.7, 20.6, 14.2, 13.4; HRMS (ESI)**:** Calculated for $C_{21}H_{21}NO_6$ [M+H$^+$]: 384.14416, Found: 384.14606; $[\alpha]^{20}_D$ = -292.33 ($CHCl_3$, *c* = 0.72); HPLC conditions: CHIRAPAK IC column, EtOH / iso-hexane = 20/100, flow rate = 1 mL min^{-1}, major enantiomer: t_R = 46.6 min; minor enantiomer: t_R = 42.5 min.

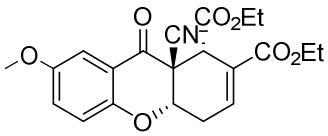
Compound 267



Compound **267** was synthesized according to the **GP16** (using commerially available 6-isopropyl 3-cyano chromone and allenoate **175a**) as a colourless thick oil in 80% yield (both the diastereomers together) with **dr** = 25 : 75 and **ee** = 86% (for the major diastereomer), R_F = 0.45 (25 % EtOAc/ petroleum ether, minor diastereomer), R_F = 0.43 (25% EtOAc/Petroleum ether, major diastereomer)

Major Diastereomer = ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 7.81 (d, *J* = 2.0 Hz, 1H), 7.40 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.30 (t, *J* = 3.8 Hz, 1H), 6.90 (d, *J* = 8.5 Hz, 1H), 4.81 (dd, *J* = 2.5, 2.0 Hz, 1H), 4.33 – 4.11 (m, 3H), 3.68 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.11 – 2.97 (m, 3H), 2.90 (dq, *J* = 13.6, 6.9 Hz, 1H), 1.32 – 1.18 (m, 9H), 0.88 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 183.7, 167.1, 164.6, 158.5, 144.0, 136.2, 136.0, 126.2, 124.9, 118.7, 118.1, 116.2, 74.2 (d, *J* = 2.1 Hz), 61.96, 61.4, 49.5, 43.3, 33.5, 29.6, 23.9, 23.8, 14.2, 13.4; HRMS (ESI)**:** Calculated for $C_{23}H_{25}NO_6$ [M+H$^+$]: 412.17546, Found: 412.17727; $[\alpha]^{20}_D$ = -282.1 ($CHCl_3$, *c* = 0-92); HPLC conditions: CHIRAPAK IC column, *iso*-propanol / iso-hexane = 30/100, flow rate = 1 mL min^{-1}, major enantiomer: t_R = 30.7 min; minor enantiomer: t_R = 19.3 min.

Compound 268

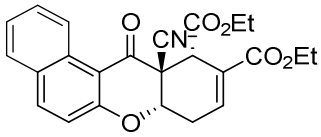


Compound **268** was synthesized according to the **GP16** (using 3-cyano chromone **248** and allenoate **175a** and 20mol% of the catalyst **238** for 48 h) as a colourless thick oil in 60% yield (both the diastereomers together) with **dr** = 20 : 80 and **ee** = 96% (for the major diastereomer), the diastereomers are separated by reverse phase HPLC (using the C18 column with a gradient of 20/100 AcN / (Water/TFA = 1000/1) to 100% AcN over a period of 30mins) they are inseparable *via* column chromatography.

Major Diastereomer = ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 7.36 (d, *J* = 3.1 Hz, 1H), 7.30- 7.26 (m, 1H), 7.12 (dd, *J* = 9.1, 3.2 Hz, 1H), 6.90 (d, *J* = 9.1 Hz, 1H), 4.82 – 4.75 (m, 1H), 4.28 – 4.17 (m, 3H), 3.82 (s, 3H), 3.72 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.24 (dq, *J* = 10.8, 7.2 Hz, 1H), 3.09 – 2.91 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H), 0.92 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 183.7, 167.0, 164.6, 155.3, 154.9, 136.0, 126.3,

126.2, 119.5, 119.3, 116.2, 108.0, 74.5, 62.0, 61.4, 56.0, 49.4, 43.4, 29.7, 14.2, 13.5; HRMS (ESI): Calculated for $C_{21}H_{21}O_7NNa$ [M+H$^+$]: 422.12102, Found: 422.12241; $[\alpha]^{20}_D$ = -357.8 ($CHCl_3$, *c* = 1.13); HPLC conditions: CHIRAPAK IC column, *iso*-propanol / iso-hexane = 30/100, flow rate = 1 mL min^{-1}, major enantiomer: t_R = 43.9 min; minor enantiomer: t_R = 28.6 min.

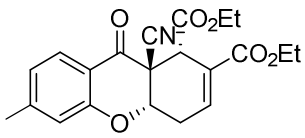
Compound 269



Compound **269** was synthesized according to the **GP16** (using 3-cyano chromone **246**, allenoate **175a** and 15mol% of the catalyst **238** for 48 h) as a colourless thick oil in 81% yield (both the diastereomers together) with **dr** = 16 : 84 and **ee** = 91% (for the major diastereomer), R_F = 0.40 (25% EtOAc/Petroleum ether, minor diastereomer), R_F = 0.37 (25% EtOAc/Petroleum ether, major diastereomer)

Major Diastereomer = ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 9.45 (d, *J* = 8.7 Hz, 1H), 7.97 (d, *J* = 9.0 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.74 – 7.69 (m, 1H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.33 (t, *J* = 3.7 Hz, 1H), 7.06 (d, *J* = 9.0 Hz, 1H), 5.05 – 4.96 (m, 1H), 4.31 – 4.11 (m, 3H), 3.50- 3.40 (m, 1H), 3.15 – 2.97 (m, 2H), 2.66 (dq, *J* = 10.8, 7.2 Hz, 1H), 1.26 (q, *J* = 6.9 Hz, 3H), 0.53 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 184.0, 167.4, 164.6, 162.6, 139.0, 136.0, 131.1, 130.7, 129.7, 128.9, 126.4, 126.0, 125.8, 118.1, 116.5, 110.5, 73.8 (d, *J* = 3.5 Hz) , 61.9, 61.4, 50.3, 43.7, 29.56, 14.22, 12.9; HRMS (ESI): Calculated for $C_{24}H_{21}NO_6$ [M+H$^+$]: 420.14416, Found: 420.14594; $[\alpha]^{20}_D$ = -379.6 ($CHCl_3$, *c* = 1); HPLC conditions: CHIRAPAK IA column, *iso*-propanol / iso-hexane = 20/100, flow rate = 1 mL min^{-1}, major enantiomer: t_R = 14.1 min; minor enantiomer: t_R = 16.1 min.

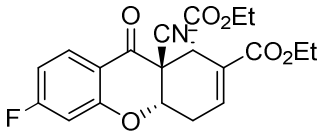
Compound 270



Compound **270** was synthesized according to the **GP16** (using 3-cyano chromone **249** and allenoate **175a**) as a colourless thick oil in 83% yield (both the diastereomers together) with **dr** = 16 : 84 and **ee** = 91% (for the major diastereomer), R_F = 0.43 (20% EtOAc/Petroleum ether, minor diastereomer), R_F = 0.40 (25% EtOAc/Petroleum ether, major diastereomer)

Major Diastereomer = ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 7.85 (d, *J* = 8.1 Hz, 1H), 7.30 – 7.27 (m, 1H), 6.96- 6.92 (m, 1H), 6.80 – 6.73 (m, 1H), 4.85 – 4.76 (m, 1H), 4.28 – 4.17 (m, 3H), 3.69 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.16 (dq, *J* = 10.7, 7.2 Hz, 1H), 3.08 – 2.91 (m, 2H), 2.35 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.91 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 183.1, 167.1, 164.6, 160.3, 149.1, 136.1, 127.9, 126.2, 124.6, 118.1, 116.8, 116.2, 74.2, 62.0, 61.4, 49.3, 43.4, 29.6, 22.1, 14.2, 13.4; HRMS (ESI)**:** Calculated for $C_{21}H_{21}NO_6$ [M+H$^+$]: 384.14416, Found: 384.14606; $[\alpha]^{20}_D$ = -292.1 ($CHCl_3$, *c* = 1.72); HPLC conditions: CHIRAPAK IA column, *iso*-propanol / iso-hexane = 20/100, flow rate = 1 mL min^{-1}, major enantiomer: t_R = 11.1 min; minor enantiomer: t_R = 27.6 min.

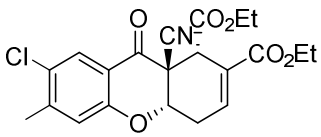
Compound 271



Compound **271** was synthesized according to the **GP16** (using 3-cyano chromone **245** and allenoate **175a**) as a colourless thick oil in 89% yield (both the diastereomers together) with **dr** = 16 : 84 and **ee** = 96% (for the major diastereomer), R_F = 0.46 (20% EtOAc/Petroleum ether, minor diastereomer), R_F = 0.43 (25% EtOAc/Petroleum ether, major diastereomer)

Major Diastereomer = ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 8.00 (dd, *J* = 8.9, 6.3 Hz, 1H), 7.29 – 7.25 (m, 1H), 6.88- 6.82 (m, 1H), 6.66 (dd, *J* = 9.3, 2.4 Hz, 1H), 4.89 – 4.84 (m, 1H), 4.29 – 4.16 (m, 3H), 3.72 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.27 (dq, *J* = 10.8, 7.2 Hz, 1H), 3.09 – 2.93 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.94 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 182.2, 167.7 (d, *J* = 256 Hz, CF), 166.9, 164.5, 162.0 (*J* = 3.7 Hz), 135.7, 130.7 (d, *J* =11.3 Hz), 126.1, 116.1 (d, *J* = 2.6 Hz), 115.8, 111.9 (d, *J* = 24.7 Hz), 105.2 (d, *J* = 24.7 Hz), 74.7, 62.1, 61.5, 49.1, 43.4, 29.4, 14.2, 13.5; HRMS (ESI)**:** Calculated for $C_{20}H_{18}NFO_6$ [M+H$^+$]: 388.11909, Found: 388.12036; $[\alpha]^{20}_D$ = -295.4 ($CHCl_3$, *c* = 1.1); HPLC conditions: CHIRAPAK IC column, *iso*-propanol / iso-hexane = 30/100, flow rate = 1 mL min^{-1}, major enantiomer: t_R = 36.3 min; minor enantiomer: t_R = 19.5 min.

Compound 272

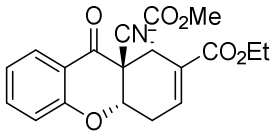


Compound **272** was synthesized according to the **GP16** (using 3-cyano chromone **243** and allenoate **175a**) as a colourless thick oil in 89% yield (both the diastereomers together) with

dr = 16 : 84 and **ee** = 95% (for the major diastereomer), R_F = 0.46 (25% EtOAc/Petroleum ether, minor diastereomer), R_F = 0.43 (25 % EtOAc/Petroleum ether, major diastereomer)

Major Diastereomer = ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 7.82 (d, *J* = 0.5 Hz, 1H), 7.30 – 7.22 (m, 1H), 7.00 (s, 1H), 4.85 – 4.76 (m, 1H), 4.83 – 4.77 (m, 1H), 4.28 – 4.18 (m, 3H), 3.73 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.32 (dq, *J* = 10.8, 7.2 Hz, 1H), 3.09 – 2.90 (m, 2H), 2.37 – 2.32 (m, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.94 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$): δ 182.9, 167.0, 164.5, 158.5, 143.4, 135.7, 131.8, 129.2, 126.1, 118.5, 117.9, 115.94, 74.7, 62.1, 61.5, 49.3, 43.4, 29.5, 19.3, 14.2, 13.4; HRMS (ESI): Calculated for $C_{21}H_{20}NClO_6$ [M+H$^+$]: 418.10519 , Found: 418.10688; $[\alpha]^{20}_D$ = -283 ($CHCl_3$, *c* = 1.53); HPLC conditions: CHIRAPAK IA column, ethanol / iso-hexane = 30/100, flow rate = 1 mL min^{-1}, major enantiomer: t_R = 16.5 min; minor enantiomer: t_R = 30.0 min.

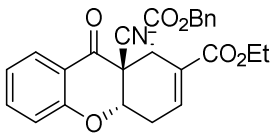
Compound 274



Compound **274** was synthesized according to the **GP16** (using commerially available 3-cyano chromone and allenoate **254**) as a colourless thick oil in 88% yield (both the diastereomers together) with **dr** = 10 : 90 and **ee** = 96% (for the major diastereomer), R_F = 0.45 (25% EtOAc/Petroleum ether, minor diastereomer), R_F = 0.42 (25% EtOAc/Petroleum ether, major diastereomer).

Major Diastereomer = ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$) δ 7.97 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.56- 7.50 (m, 1H), 7.30 (dd, *J* = 4.3, 3.4 Hz, 1H), 7.17 – 7.11 (m, 1H), 7.00 – 6.95 (m, 1H), 4.84 (dd, *J* = 4.4, 1.7 Hz, 1H), 4.29 – 4.17 (m, 3H), 3.11 – 2.94 (m, 5H), 1.27 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$) δ 183.5, 167.4, 164.5, 160.0, 137.1, 136.2, 128.0, 126.0, 123.3, 119.0, 118.1, 115.9, 74.1, 61.4, 52.3, 49.4, 43.3, 29.6, 14.2; $[\alpha]^{20}_D$ = -320.3 ($CHCl_3$, *c* = 1.13); HRMS (ESI)**:** Calculated for $C_{19}H_{17}NO_6$ [M+H$^+$]: 356.11286, Found: 356.11425; HPLC conditions: CHIRAPAK IA column, *iso*-propanol / iso-hexane = 30/100, flow rate = 1 mL min^{-1}, major enantiomer: t_R = 17.4 min; minor enantiomer: t_R = 28.2 min.

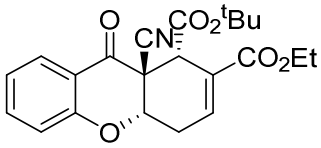
Compound 275



Compound **275** was synthesized according to the **GP16** (using commerially available 3-cyano chromone and allenoate **255**) as a colourless thick oil in 91% yield (both the diastereomers together) with **dr** = 14 : 86 and **ee** = 97% (for the major diastereomer), R_F = 0.47 (25% EtOAc/Petroleum ether, minor diastereomer), R_F = 0.44 (25% EtOAc/Petroleum ether, major diastereomer).

Major Diastereomer = ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ 7.86 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.55 – 7.49 (m, 1H), 7.34 – 7.27 (m, 4H), 7.12 – 7.03 (m, 3H), 6.98 – 6.91 (m, 1H), 4.86 (dd, *J* = 4.5, 1.8 Hz, 1H), 4.68 (d, *J* = 12.6 Hz, 1H), 4.32 (d, *J* = 0.8 Hz, 1H), 4.19 – 4.11 (m, 2H), 4.08 (d, *J* = 12.6 Hz, 1H), 3.15 – 2.95 (m, 2H), 1.19 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$) δ 183.5, 166.9, 164.4, 160.1, 137.1, 136.2, 134.4, 128.5, 128.3, 128.1, 127.8, 126.0, 123.2, 119.0, 118.08, 116.01, 74.1, 67.4, 61.4, 49.4, 43.5, 29.6, 14.1; HRMS (ESI)**:** Calculated for $C_{25}H_{21}NO_6$ [M+H$^+$]: 432.14416, Found: 432.14632; $[\alpha]^{20}_D$ = -249.2 ($CHCl_3$, *c* = 1.26); HPLC conditions: CHIRAPAK IA column, *iso*-propanol / iso-hexane = 30/100, flow rate = 1 mL min^{-1}, major enantiomer: t_R = 10.7 min; minor enantiomer: t_R = 16.9 min.

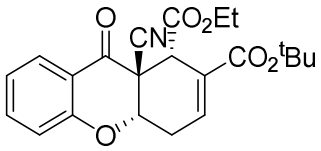
Compound 276



Compound **276** was synthesized according to the **GP16** (using commerially available 3-cyano chromone and allenoate **256**) as a colourless thick oil in 89% yield (both the diastereomers together) with **dr** = 14 : 86 and **ee** = 96% (for the major diastereomer), R_F = 0.42 (20% EtOAc/Petroleum ether, minor diastereomer), R_F = 0.39 (20% EtOAc/Petroleum ether, major diastereomer).

Major Diastereomer = ^{1}H NMR (400 MHz, 25 °C, CD_2Cl_2): δ 7.99 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.58- 7.51 (m, 1H), 7.23 – 7.15 (m, 2H), 7.01 – 6.97 (m, 1H), 4.85 – 4.81 (m, 1H), 4.24 – 4.16 (m, 3H), 3.08- 2.99 (m, 1H), 2.98- 2.90 (m, 1H), 1.31 – 1.26 (m, 3H), 0.97 (s, 9H); ^{13}C NMR (100 MHz, 25 °C, CD_2Cl_2): δ 184.3, 166.0, 165.0, 161.1, 137.2, 135.4, 128.4, 127.0, 123.7, 120.5, 118.7, 116.7, 83.3, 75.2, 61.6, 50.0, 44.6, 29.9, 27.1, 14.3; HRMS (ESI): Calculated for $C_{22}H_{23}O_6NNa$ [M+Na$^+$]: 420.14176, Found: 420.14299; $[\alpha]^{20}_D$ = -277.6 ($CHCl_3$, *c* = 1.03); HPLC conditions: CHIRAPAK IC column, *iso*-propanol / iso-hexane = 20/100, flow rate = 1 mL min^{-1}, major enantiomer: t_R = 25.3 min; minor enantiomer: t_R = 22.3 min.

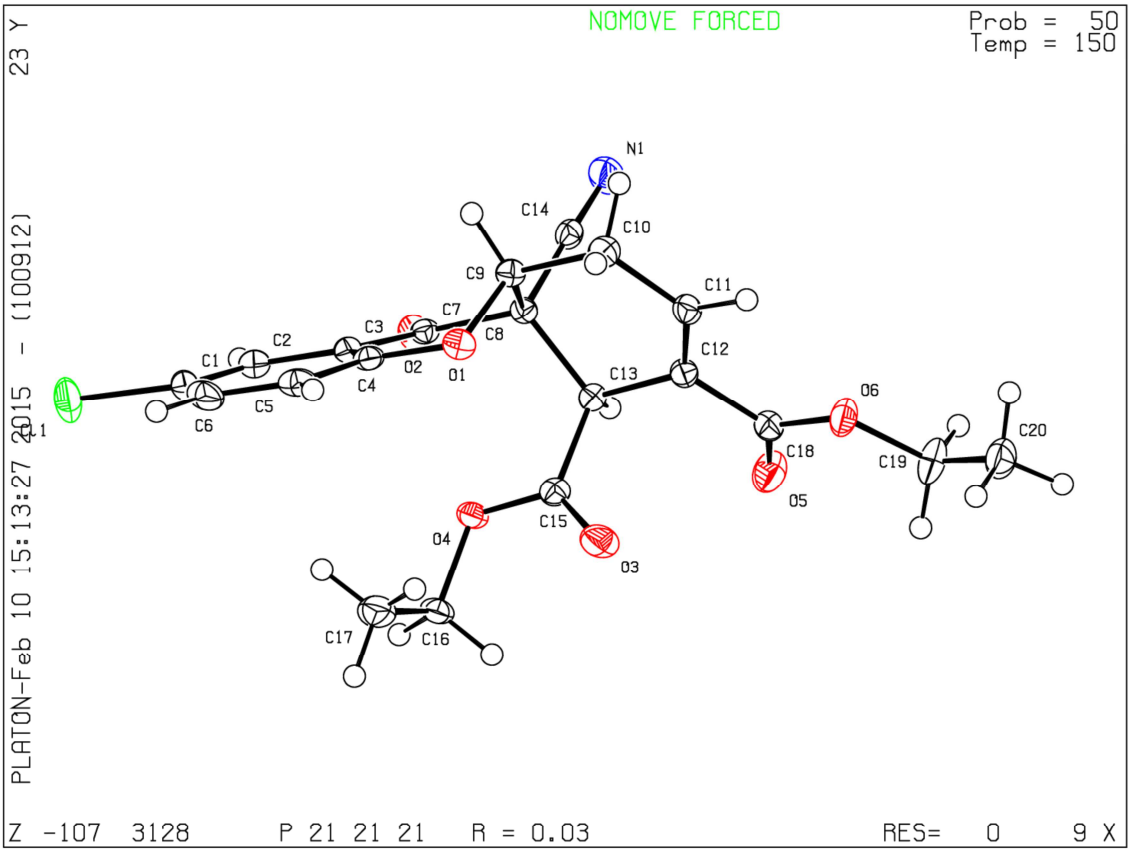
Compound 277



Compound **277** was synthesized according to the **GP16** (using commerially available 3-cyano chromone and allenoate **257**) as a colourless thick oil in 85% yield (both the diastereomers together) with **dr** = 16 : 84 and **ee** = 94% (for the major diastereomer), R_F = 0.38 (20% EtOAc/Petroleum ether, minor diastereomer), R_F = 0.35 (20% EtOAc/Petroleum ether, major diastereomer).

Major Diastereomer = ^{1}H NMR (400 MHz, 25 °C, CD_2Cl_2): δ 7.94 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.58 – 7.52 (m, 1H), 7.20 – 7.12 (m, 2H), 6.99 – 6.95 (m, 1H), 4.90 – 4.80 (m, 1H), 4.14 (d, *J* = 0.9 Hz, 1H), 3.60 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.16 (dq, *J* = 10.8, 7.2 Hz, 1H), 3.07 – 2.88 (m, 2H), 1.45 (s, 9H), 0.91 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, 25 °C, CD_2Cl_2): δ 184.0, 167.3, 163.6, 160.4, 137.2, 135.1, 128.0, 127.4, 123.2, 119.1, 118.2, 116.3, 81.9, 74.3, 62.0, 49.5, 43.8, 29.6, 27.8, 13.4; HRMS (ESI)**:** Calculated for $C_{22}H_{23}O_6NNa$ [M+Na^+]: 420.14176, Found: 420.14251; $[\alpha]^{20}_D$ = -208.3 ($CHCl_3$, *c* = 0.92); HPLC conditions: CHIRAPAK IC column, *iso*-propanol / iso-hexane = 30/100, flow rate = 1 mL min^{-1}, major enantiomer: t_R = 15.4 min; minor enantiomer: t_R = 12.0 min.

5.4 Absolute configuration of the [4+2] annulation product 264 (major diastereomer): Crystal Structure data



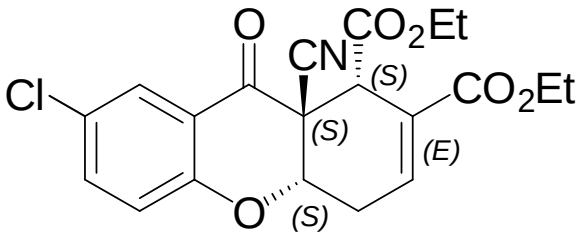


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Table 1 Crystal data and structure refinement for 3128.

Identification code	3128
Empirical formula	$C_{20}H_{18}ClNO_6$
Formula weight	403.80
Temperature/K	150(2)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	7.4088(2)
b/Å	12.5634(3)
c/Å	20.4594(7)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1904.36(10)
Z	4
ρ_{calc}g/cm^3	1.408
μ/mm^{-1}	0.238
F(000)	840.0
Crystal size/mm^3	? × ? × ?
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	5.136 to 56
Index ranges	$-9 \le h \le 9$, $-16 \le k \le 16$, $-26 \le l \le 26$
Reflections collected	38821
Independent reflections	4580 [R_{int} = 0.0411, R_{sigma} = 0.0266]
Data/restraints/parameters	4580/0/255
Goodness-of-fit on F^2	1.045
Final R indexes [I>=2σ (I)]	R_1 = 0.0331, wR_2 = 0.0720
Final R indexes [all data]	R_1 = 0.0388, wR_2 = 0.0741
Largest diff. peak/hole / e Å^{-3}	0.23/-0.25
Flack parameter	-0.030(17)

Table 2 Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for 3128. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	***x***	***y***	***z***	**U(eq)**
Cl1	6009.5(9)	11431.8(4)	6137.0(4)	41.13(17)
O1	5953.1(19)	6857.7(11)	6724.5(6)	18.4(3)
O2	4242(2)	7771.8(11)	4923.1(6)	22.1(3)
O3	1459(2)	5962.3(12)	6840.4(7)	29.6(4)
O4	1841.3(18)	7413.9(11)	6216.7(6)	18.6(3)
O5	651(2)	4195.3(12)	5676.0(8)	30.4(4)

O6	2158(2)	3044.0(11)	6320.3(7)	25.4(3)
N1	6116(3)	5253.4(15)	4615.7(9)	28.5(4)
C1	5953(3)	10073.1(15)	6308.1(11)	25.2(5)
C2	5462(3)	9375.6(16)	5819(1)	21.0(4)
C3	5459(2)	8284.7(15)	5952.3(9)	16.4(4)
C4	5933(3)	7923.4(15)	6575.4(9)	17.0(4)
C5	6374(3)	8641.4(18)	7067.1(10)	23.3(4)
C6	6390(3)	9719.1(18)	6931.8(11)	27.4(5)
C7	4850(3)	7520.3(15)	5448.5(9)	15.0(4)
C8	5035(3)	6328.5(15)	5640.0(9)	14.7(4)
C9	6489(2)	6207.2(15)	6175.3(9)	16.4(4)
C10	6731(3)	5066.0(15)	6402.5(10)	21.4(4)
C11	5098(3)	4375.1(16)	6333.8(10)	19.4(4)
C12	3534(3)	4686.2(15)	6083.3(9)	17.3(4)
C13	3212(3)	5815.9(15)	5855.3(9)	15.2(4)
C14	5649(3)	5737.2(15)	5052.2(9)	17.7(4)
C15	2109(3)	6402.3(16)	6375.9(9)	17.2(4)
C16	582(3)	8006.1(16)	6631.6(10)	20.7(4)
C17	1537(3)	8513(2)	7200.1(12)	30.6(5)
C18	1959(3)	3967.0(16)	5999.1(10)	19.8(4)
C19	734(3)	2256.6(17)	6221.5(12)	34.0(5)
C20	1034(3)	1379.0(17)	6701.8(11)	31.5(5)

Table 3 Anisotropic Displacement Parameters ($Å^2×10^3$) for 3128. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Cl1	37.9(3)	16.0(2)	69.4(4)	-7.7(3)	-0.7(3)	-3.4(2)
O1	20.3(7)	22.0(6)	12.7(6)	-0.3(5)	-0.4(5)	1.3(6)
O2	29.6(8)	21.5(7)	15.4(7)	2.6(5)	-1.6(6)	2.1(6)
O3	36.4(9)	25.8(8)	26.5(8)	7.7(6)	14.7(7)	7.5(7)
O4	18.3(7)	17.9(6)	19.6(7)	1.5(5)	4.3(6)	4.5(5)
O5	25.4(8)	26.7(8)	39.0(9)	6.3(7)	-6.7(7)	-5.6(7)
O6	25.6(8)	17.7(7)	33.0(8)	3.6(6)	-1.4(6)	-6.2(6)
N1	35.3(11)	26.3(9)	23.9(9)	-5.9(8)	5.6(8)	-0.2(8)
C1	17.2(10)	15.8(9)	42.6(13)	-5.2(9)	3.0(9)	-0.8(8)
C2	16.3(9)	20.2(9)	26.4(11)	-0.7(8)	2.8(8)	0.7(8)
C3	12.8(9)	16.5(9)	19.8(9)	-1.8(7)	1.6(7)	-0.8(7)
C4	11.9(8)	20.7(9)	18.3(9)	-1.9(7)	2.3(7)	-0.1(8)
C5	15.3(10)	33.8(11)	20.7(10)	-7.8(9)	0.1(8)	0.2(8)
C6	18.1(11)	30.4(11)	33.9(12)	-18.1(10)	-0.7(9)	0.0(9)

C7	13.9(9)	16.5(9)	14.6(8)	1.8(7)	2.3(7)	1.0(7)
C8	15.8(9)	15.2(9)	13.0(8)	-0.3(7)	0.3(7)	0.3(7)
C9	16.1(9)	17.8(9)	15.3(9)	0.8(7)	0.3(7)	1.0(7)
C10	18.4(9)	20.1(10)	25.6(10)	5.2(8)	-1.0(8)	2.1(8)
C11	23.2(10)	15.3(9)	19.6(10)	3.0(8)	3.7(8)	1.4(8)
C12	20(1)	15.5(8)	16.3(9)	0.2(7)	3.4(7)	0.0(7)
C13	14.9(8)	15.8(9)	15.0(9)	1.2(7)	-0.8(7)	-0.4(7)
C14	18.9(9)	16.1(8)	18.1(9)	2.9(8)	1.0(8)	-1.7(8)
C15	14.1(9)	19.2(9)	18.4(9)	1.4(8)	-2.6(7)	1.2(7)
C16	17.9(10)	20.3(10)	23.8(10)	0.3(8)	4.7(8)	6.2(8)
C17	23.8(11)	33.0(11)	35.0(12)	-13.1(10)	6.0(9)	-1.7(9)
C18	21.6(10)	17.5(9)	20.4(10)	-2.2(8)	3.2(8)	-0.3(8)
C19	35.8(13)	23.7(11)	42.6(14)	2.2(10)	-1.6(11)	-14.9(10)
C20	39.4(13)	22.4(10)	32.7(12)	-0.5(9)	10.2(10)	-8.6(10)

Table 4 Bond Lengths for 3128.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
Cl1	C1	1.743(2)	C3	C7	1.479(3)
O1	C4	1.373(2)	C4	C5	1.390(3)
O1	C9	1.445(2)	C5	C6	1.382(3)
O2	C7	1.208(2)	C7	C8	1.554(3)
O3	C15	1.200(2)	C8	C14	1.485(3)
O4	C15	1.327(2)	C8	C9	1.543(3)
O4	C16	1.464(2)	C8	C13	1.560(3)
O5	C18	1.207(3)	C9	C10	1.518(3)
O6	C18	1.341(2)	C10	C11	1.495(3)
O6	C19	1.461(3)	C11	C12	1.326(3)
N1	C14	1.134(3)	C12	C18	1.486(3)
C1	C2	1.379(3)	C12	C13	1.513(3)
C1	C6	1.390(3)	C13	C15	1.531(3)
C2	C3	1.397(3)	C16	C17	1.503(3)
C3	C4	1.398(3)	C19	C20	1.494(3)

Table 5 Bond Angles for 3128.

Atom	Atom	Atom	Angle/˚	Atom	Atom	Atom	Angle/˚
C4	O1	C9	112.43(14)	C9	C8	C13	111.30(15)
C15	O4	C16	116.07(15)	C7	C8	C13	113.10(15)
C18	O6	C19	115.99(16)	O1	C9	C10	109.17(15)
C2	C1	C6	121.63(19)	O1	C9	C8	107.72(14)

C2	C1	Cl1	118.89(18)	C10	C9	C8	113.14(15)
C6	C1	Cl1	119.48(16)	C11	C10	C9	115.09(17)
C1	C2	C3	118.83(19)	C12	C11	C10	124.90(18)
C2	C3	C4	119.74(18)	C11	C12	C18	123.50(18)
C2	C3	C7	120.09(18)	C11	C12	C13	122.24(18)
C4	C3	C7	120.08(17)	C18	C12	C13	114.26(16)
O1	C4	C5	117.98(18)	C12	C13	C15	108.72(15)
O1	C4	C3	121.47(17)	C12	C13	C8	109.74(15)
C5	C4	C3	120.54(18)	C15	C13	C8	117.38(15)
C6	C5	C4	119.5(2)	N1	C14	C8	177.6(2)
C5	C6	C1	119.69(19)	O3	C15	O4	125.13(18)
O2	C7	C3	124.34(18)	O3	C15	C13	122.91(18)
O2	C7	C8	120.64(17)	O4	C15	C13	111.70(15)
C3	C7	C8	115.02(16)	O4	C16	C17	111.34(17)
C14	C8	C9	108.15(15)	O5	C18	O6	124.21(19)
C14	C8	C7	107.75(15)	O5	C18	C12	123.31(18)
C9	C8	C7	109.62(15)	O6	C18	C12	112.48(17)
C14	C8	C13	106.71(15)	O6	C19	C20	107.53(19)

Table 6 Torsion Angles for 3128.

A	B	C	D	Angle/˚	A	B	C	D	Angle/˚
C6	C1	C2	C3	-1.9(3)	C7	C8	C9	C10	178.77(16)
Cl1	C1	C2	C3	178.51(15)	C13	C8	C9	C10	52.9(2)
C1	C2	C3	C4	0.6(3)	O1	C9	C10	C11	92.7(2)
C1	C2	C3	C7	176.88(18)	C8	C9	C10	C11	-27.3(2)
C9	O1	C4	C5	-147.21(17)	C9	C10	C11	C12	1.5(3)
C9	O1	C4	C3	33.7(2)	C10	C11	C12	C18	177.60(18)
C2	C3	C4	O1	-179.71(17)	C10	C11	C12	C13	-2.2(3)
C7	C3	C4	O1	4.0(3)	C11	C12	C13	C15	-102.1(2)
C2	C3	C4	C5	1.3(3)	C18	C12	C13	C15	78.1(2)
C7	C3	C4	C5	-175.05(17)	C11	C12	C13	C8	27.5(3)
O1	C4	C5	C6	179.13(18)	C18	C12	C13	C8	-152.28(16)
C3	C4	C5	C6	-1.8(3)	C14	C8	C13	C12	66.12(19)
C4	C5	C6	C1	0.5(3)	C9	C8	C13	C12	-51.7(2)
C2	C1	C6	C5	1.3(3)	C7	C8	C13	C12	-175.58(14)
Cl1	C1	C6	C5	-179.04(16)	C14	C8	C13	C15	-169.14(16)
C2	C3	C7	O2	-4.3(3)	C9	C8	C13	C15	73.1(2)
C4	C3	C7	O2	172.04(19)	C7	C8	C13	C15	-50.8(2)
C2	C3	C7	C8	175.96(17)	C16	O4	C15	O3	-3.0(3)
C4	C3	C7	C8	-7.7(3)	C16	O4	C15	C13	171.33(15)

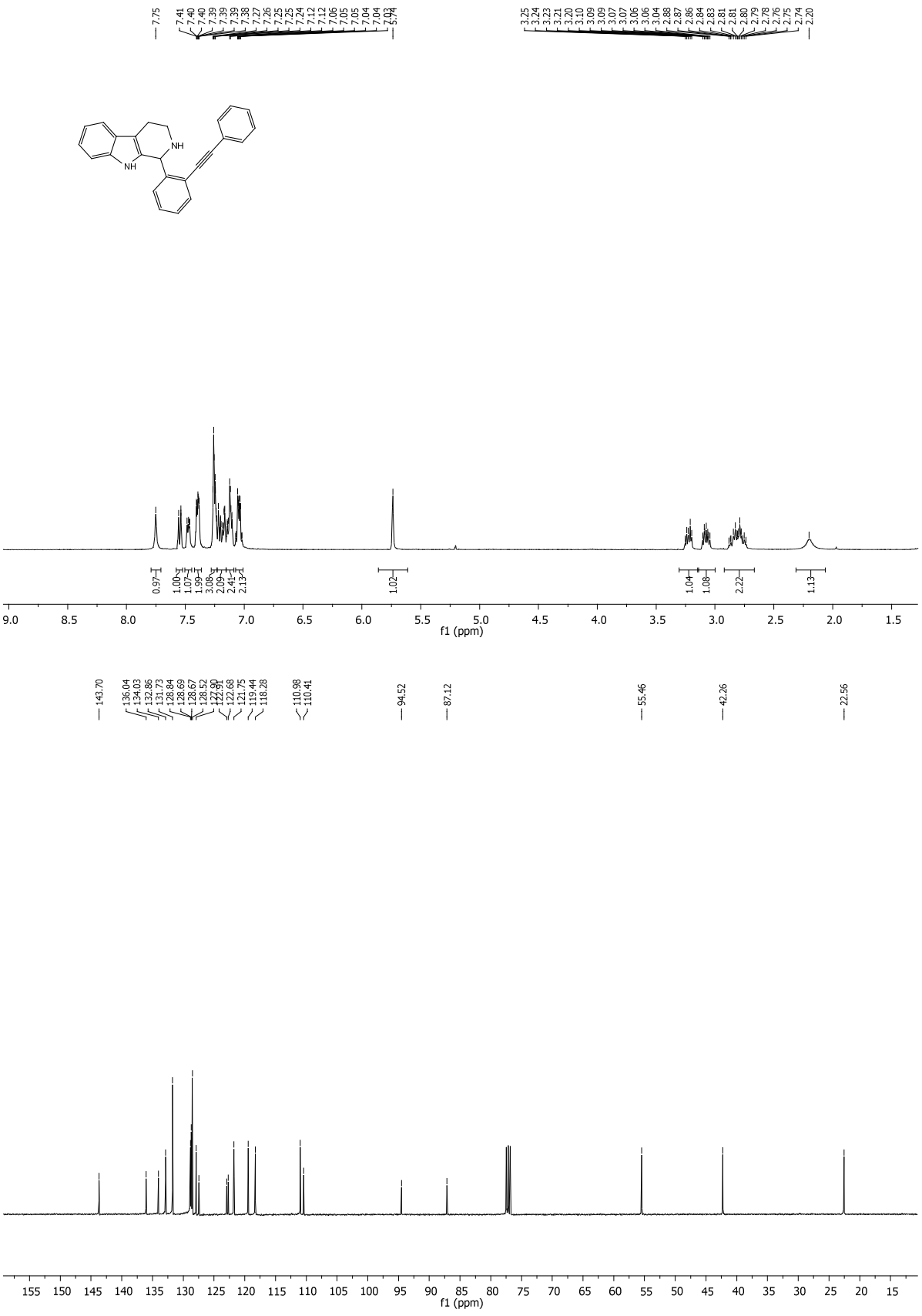
O2	C7	C8	C14	39.6(2)	C12	C13	C15	O3	-8.0(3)
C3	C7	C8	C14	-140.58(17)	C8	C13	C15	O3	-133.3(2)
O2	C7	C8	C9	157.10(17)	C12	C13	C15	O4	177.48(15)
C3	C7	C8	C9	-23.1(2)	C8	C13	C15	O4	52.2(2)
O2	C7	C8	C13	-78.1(2)	C15	O4	C16	C17	89.0(2)
C3	C7	C8	C13	101.73(19)	C19	O6	C18	O5	4.6(3)
C4	O1	C9	C10	172.18(16)	C19	O6	C18	C12	-175.32(17)
C4	O1	C9	C8	-64.60(19)	C11	C12	C18	O5	-167.3(2)
C14	C8	C9	O1	175.24(15)	C13	C12	C18	O5	12.5(3)
C7	C8	C9	O1	58.01(18)	C11	C12	C18	O6	12.7(3)
C13	C8	C9	O1	-67.86(18)	C13	C12	C18	O6	-167.54(16)
C14	C8	C9	C10	-64.0(2)	C18	O6	C19	C20	-170.41(18)

Table 7 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for 3128.

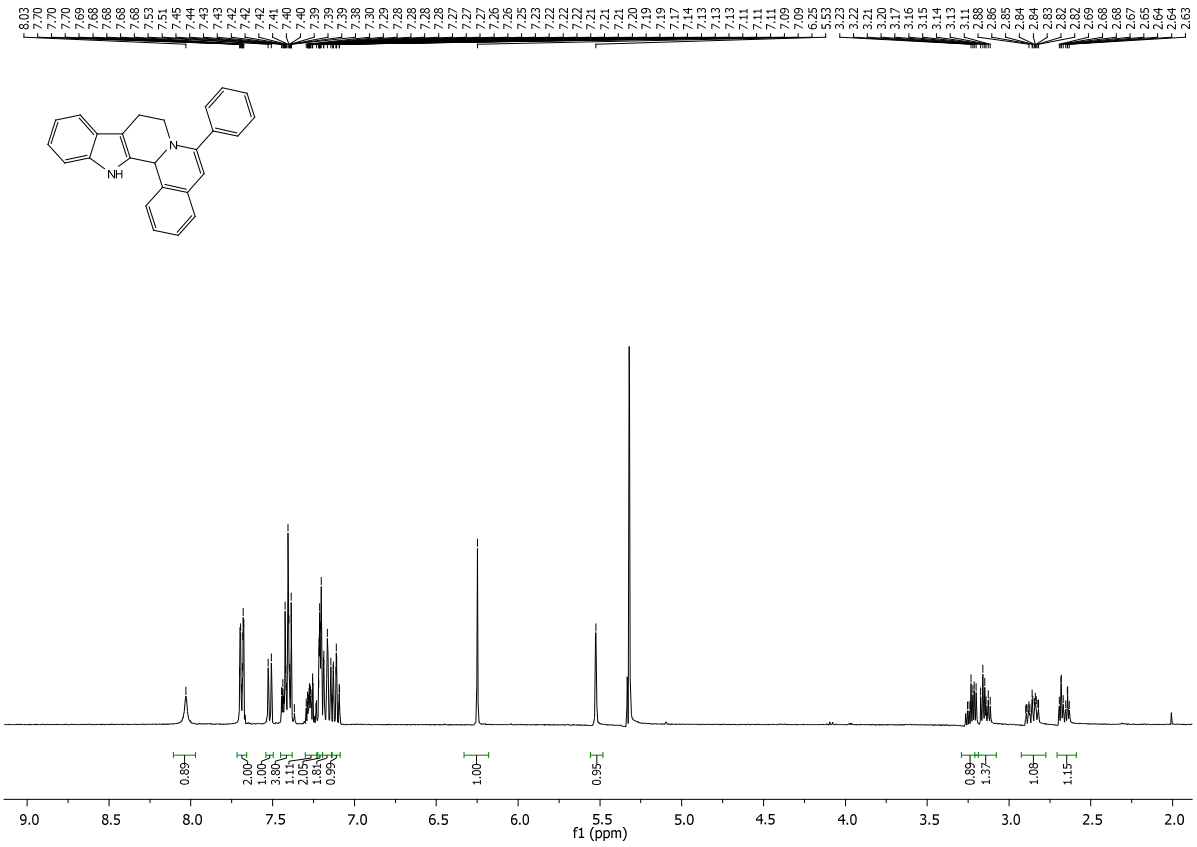
Atom	***x***	***y***	***z***	**U(eq)**
H2	5133	9632	5399	25
H5	6661	8393	7493	28
H6	6700	10216	7264	33
H9	7666	6476	6002	20
H10A	7730	4742	6150	26
H10B	7096	5074	6868	26
H11	5188	3660	6481	23
H13	2438	5771	5456	18
H16A	-361	7516	6797	25
H16B	-19	8565	6369	25
H17A	2119	7961	7464	46
H17B	662	8901	7469	46
H17C	2454	9010	7038	46
H19A	781	1975	5770	41
H19B	-465	2585	6292	41
H20A	2248	1084	6642	47
H20B	135	818	6632	47
H20C	917	1659	7147	47

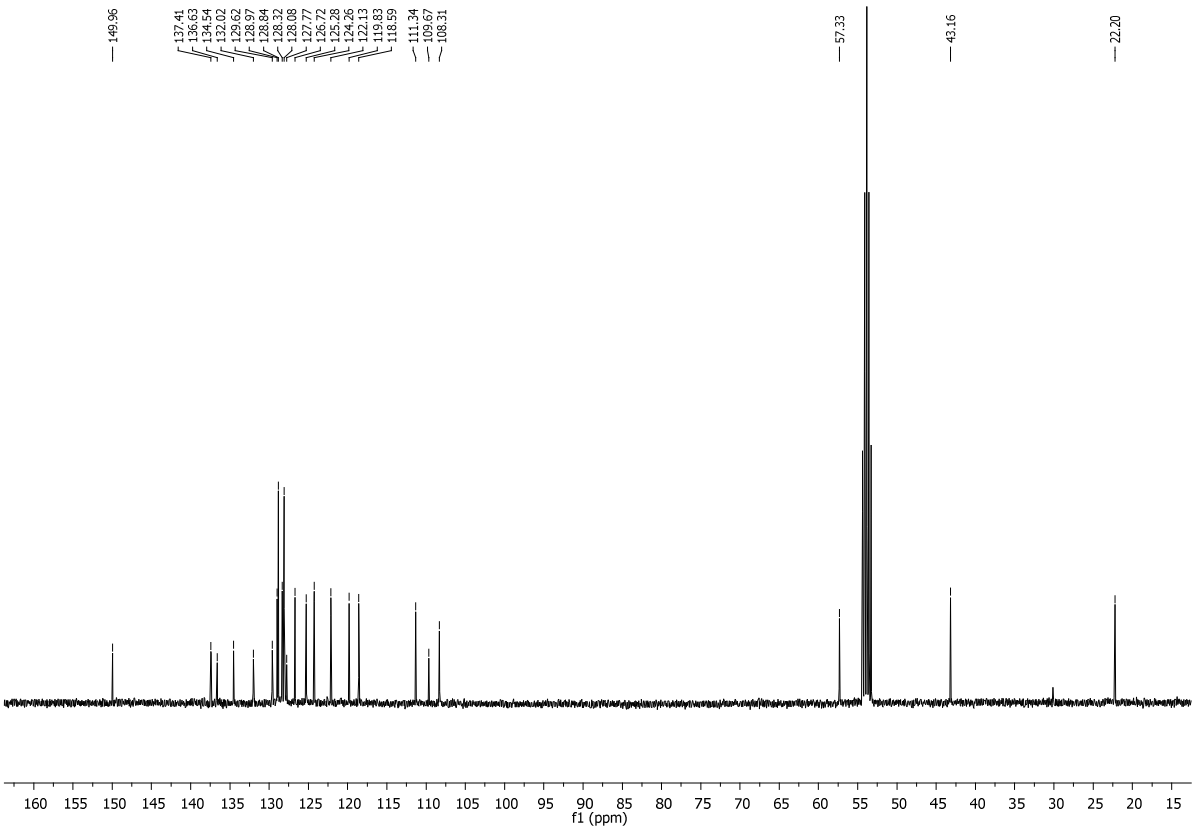
5.5 Representative NMRs

NMR of compound **77** measured in $CDCl_3$ as solvent, 400MHz

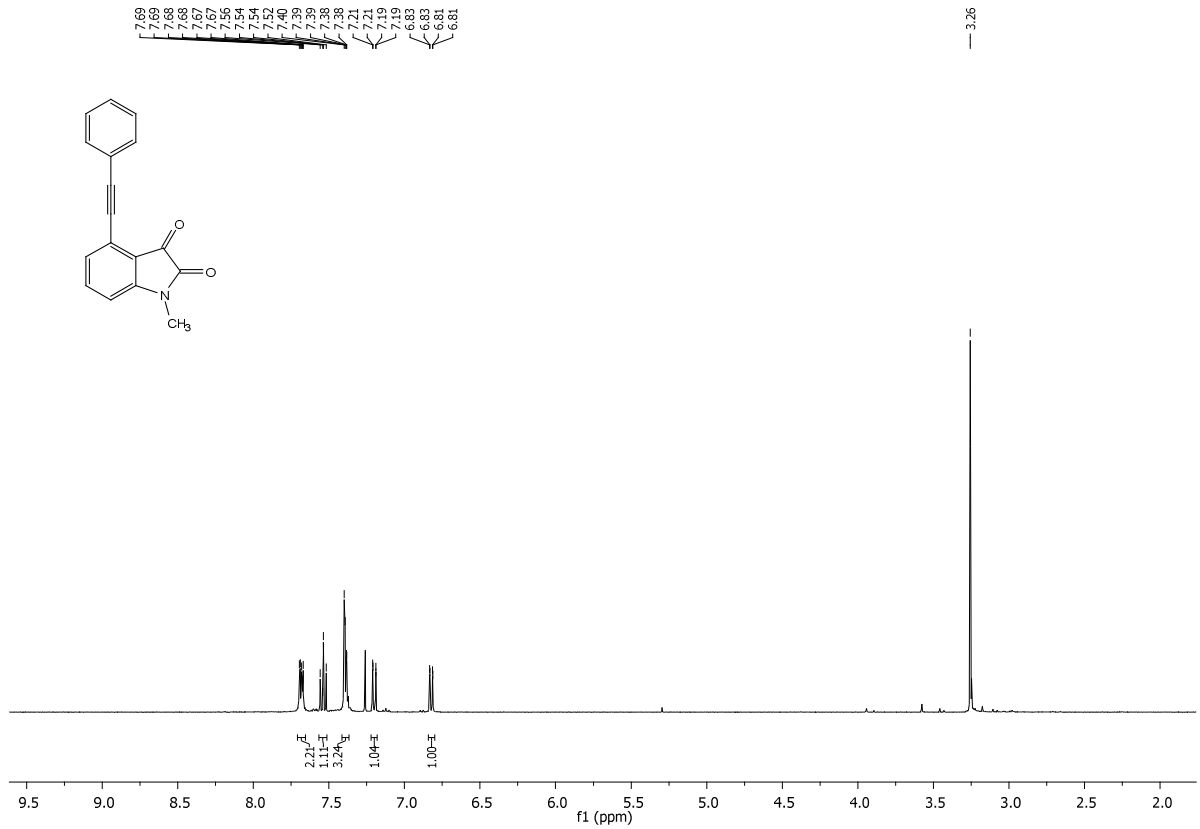


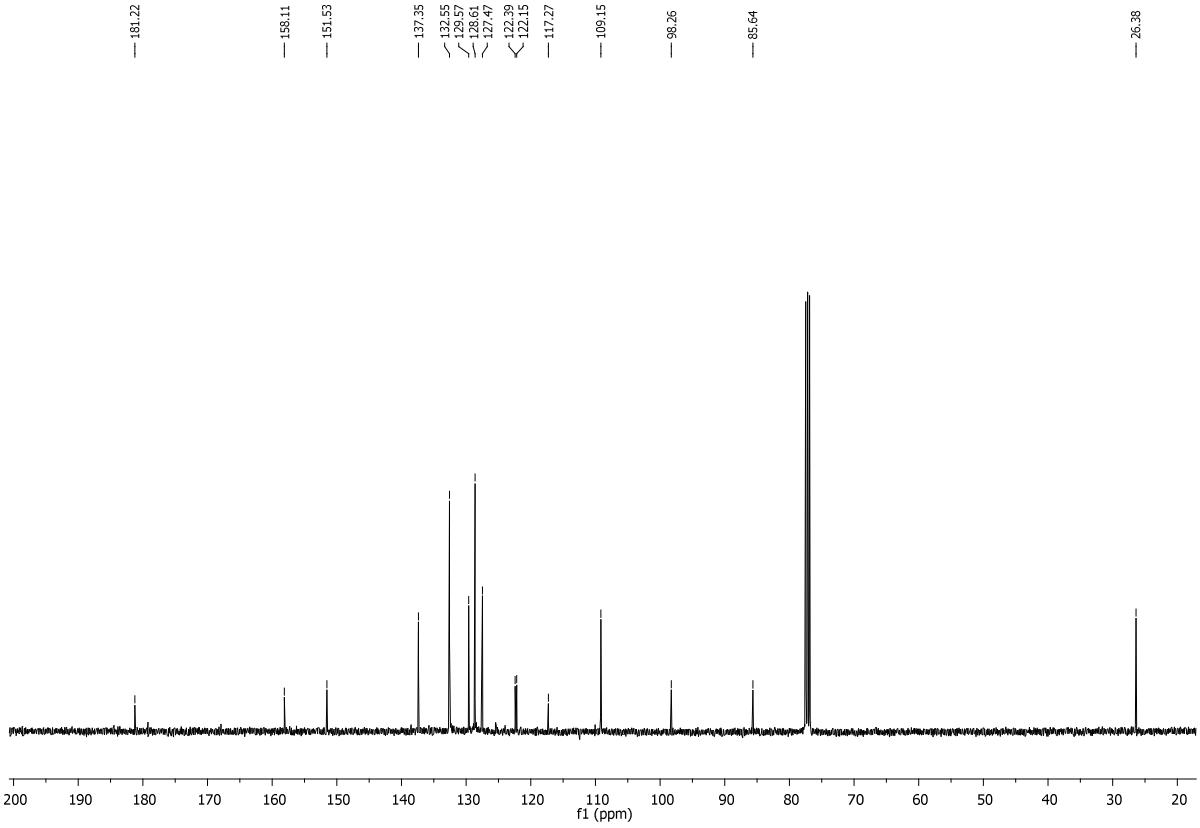
NMR of compound **81** measured in DCM as solvent, 400MHz



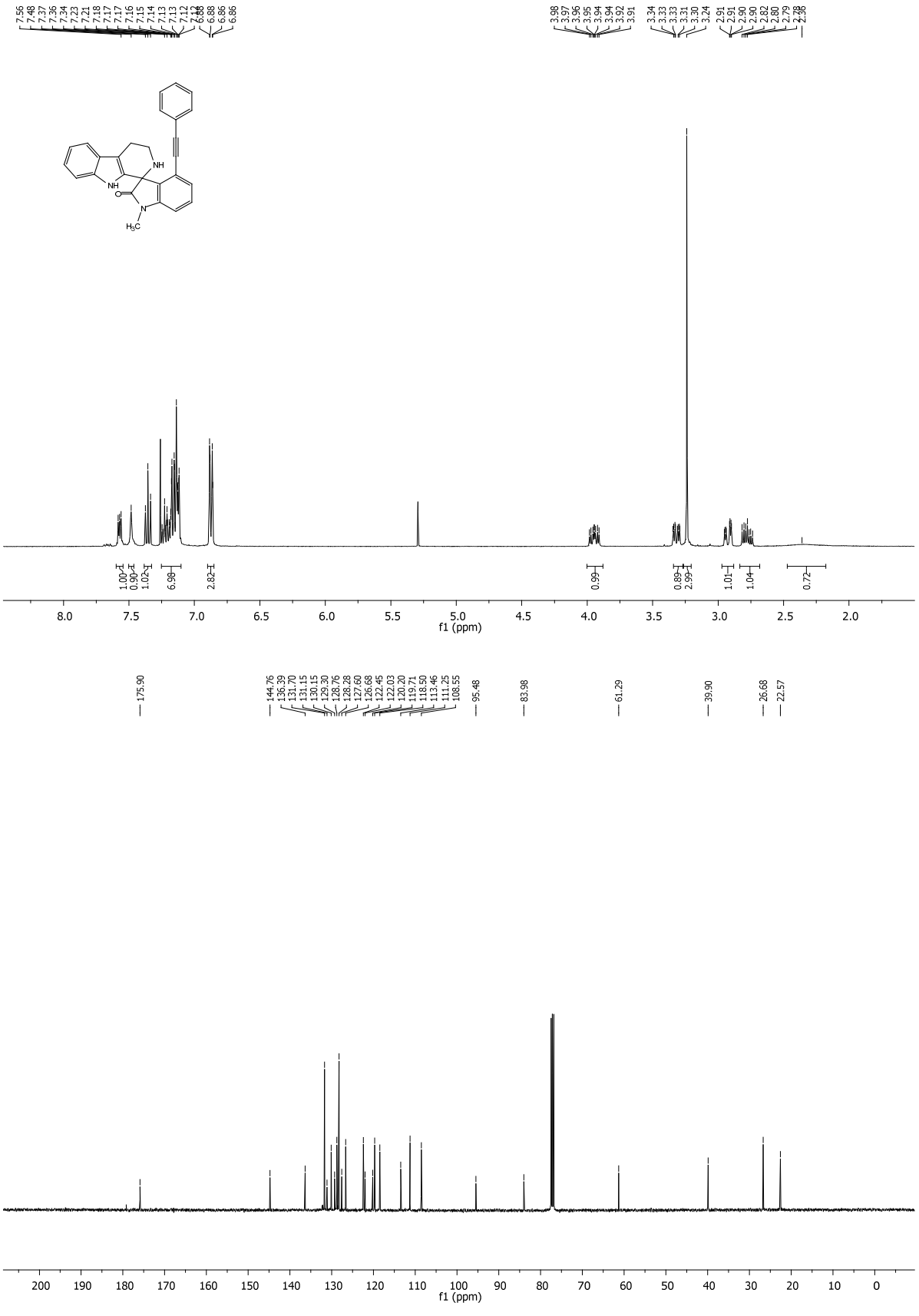


NMR of compound **103** measured in $CDCl_3$ as solvent, 400MHz

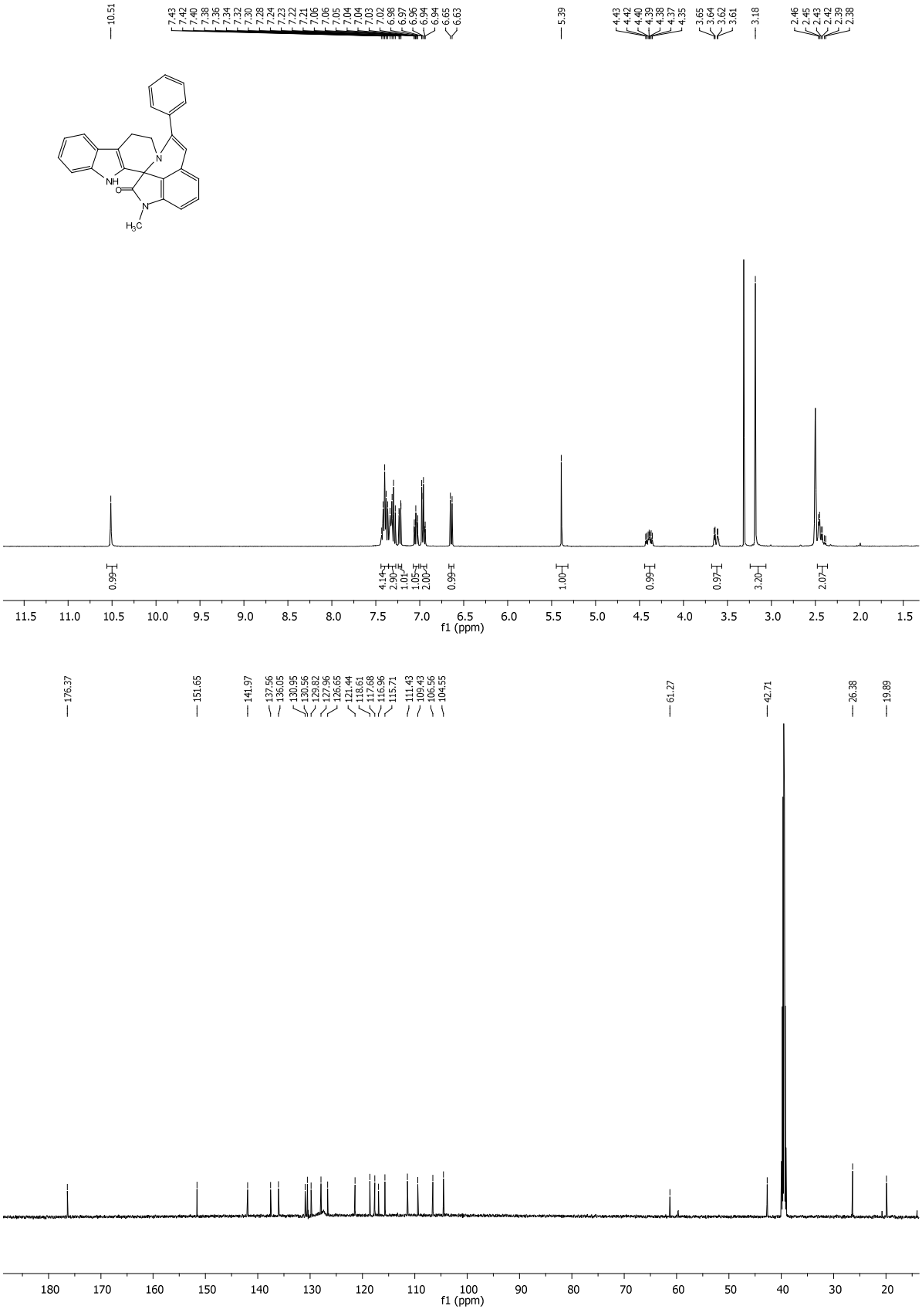




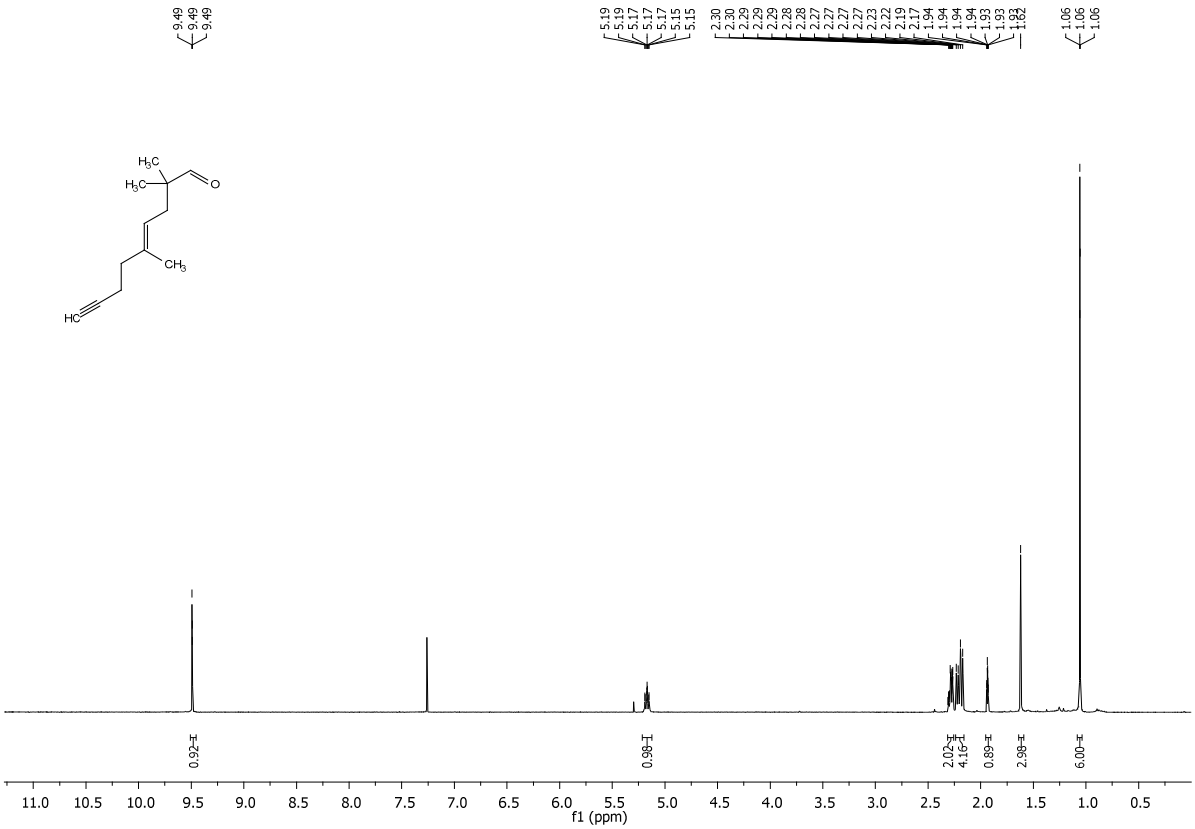
NMR of compound **104** measured in $CDCl_3$ as solvent, 400MHz

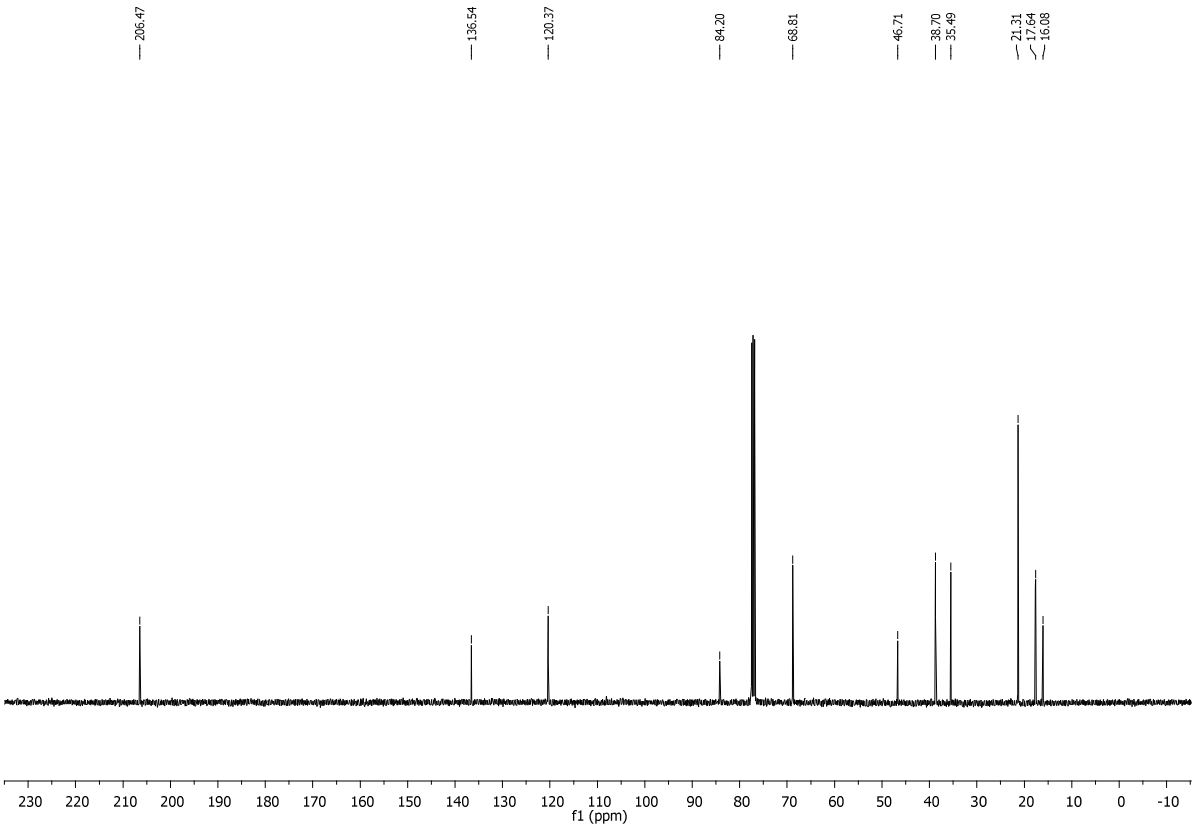


NMR of compound **105** measured in DMSO as solvent 400MHz (^{1}H) and 600MHz (^{13}C).

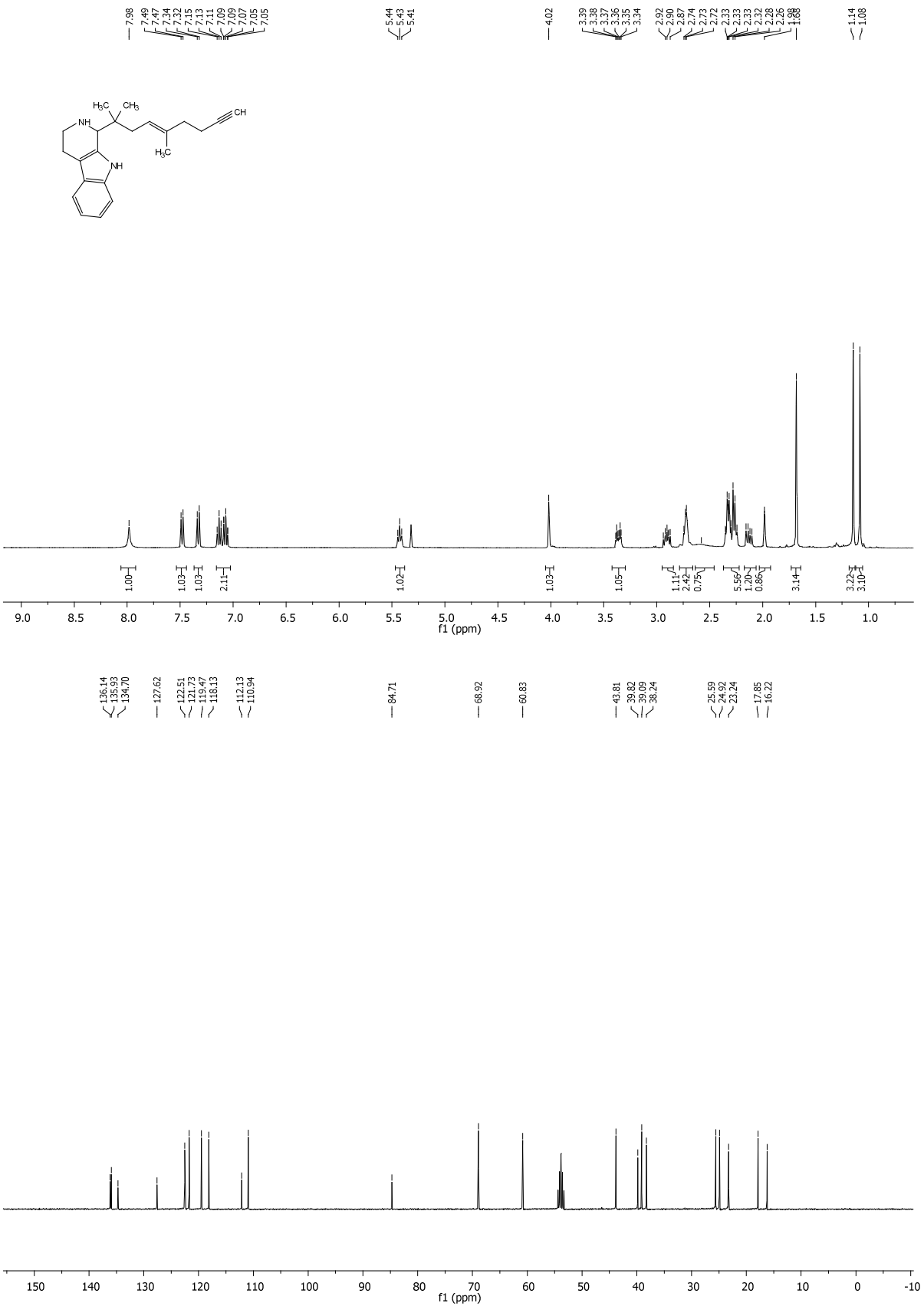


NMR of compound **131** measured in $CDCl_3$ as solvent, 400MHz



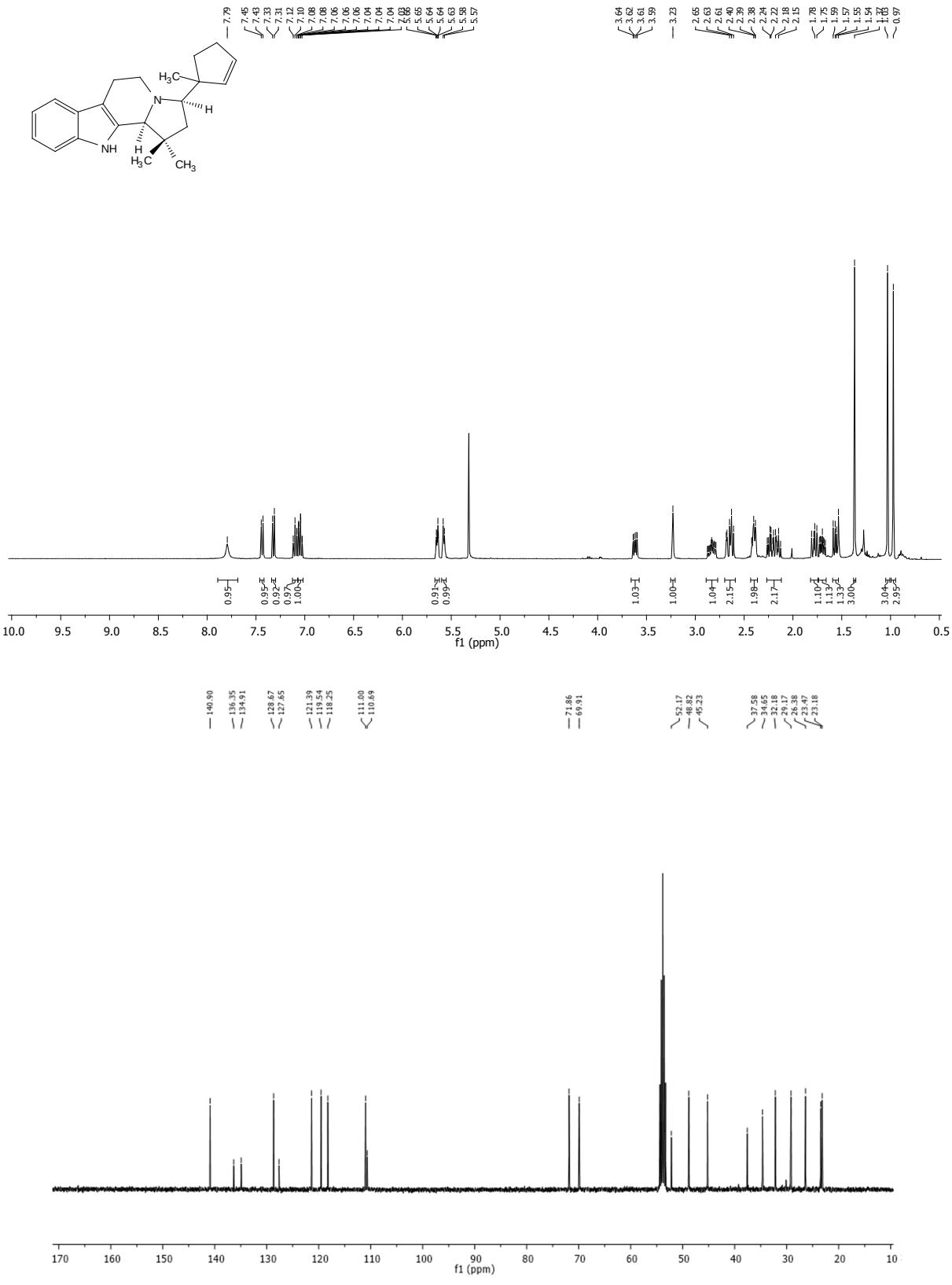


NMR of compound **137** measured in DCM as solvent, 400MHz

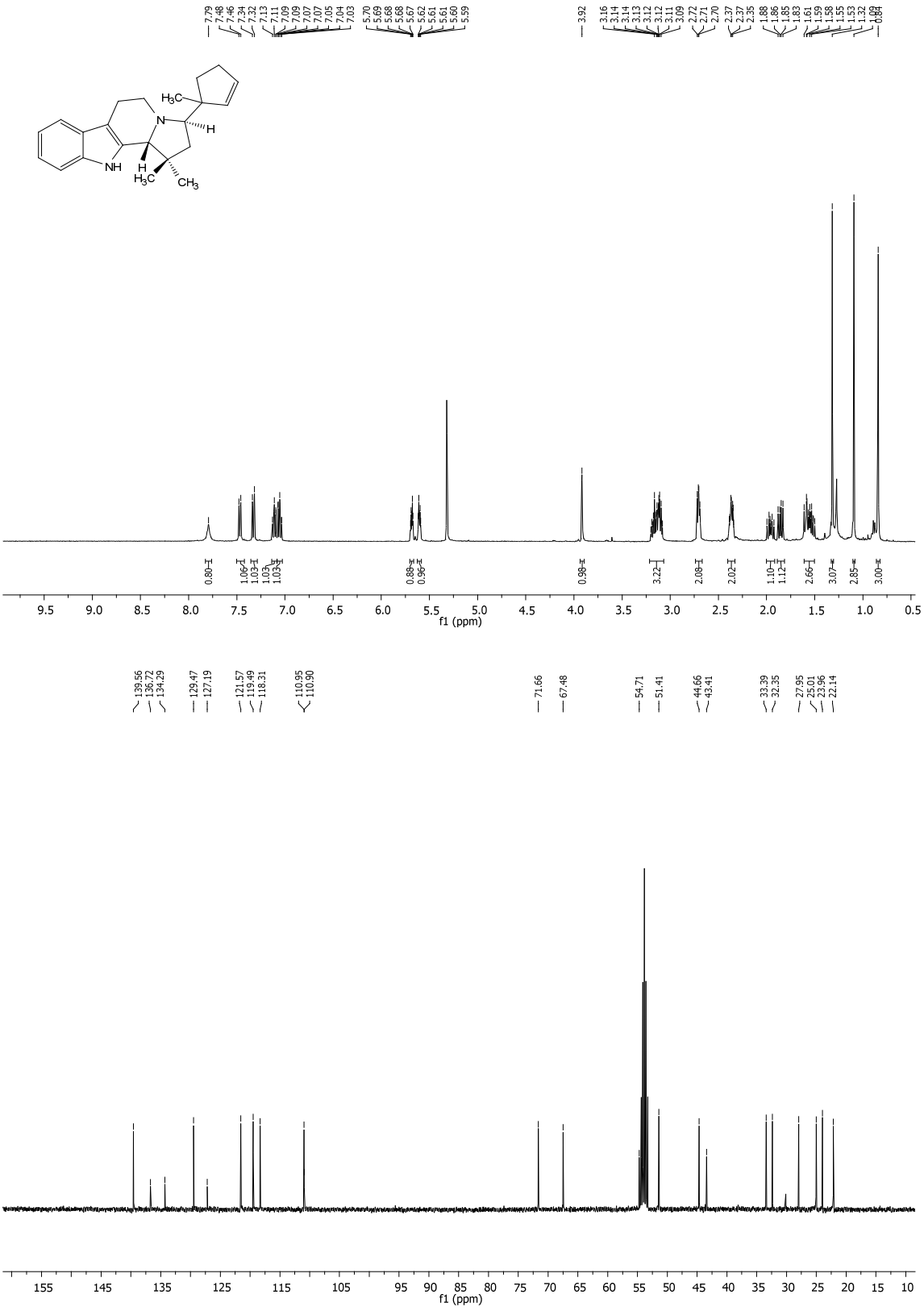


NMR of compound **139**

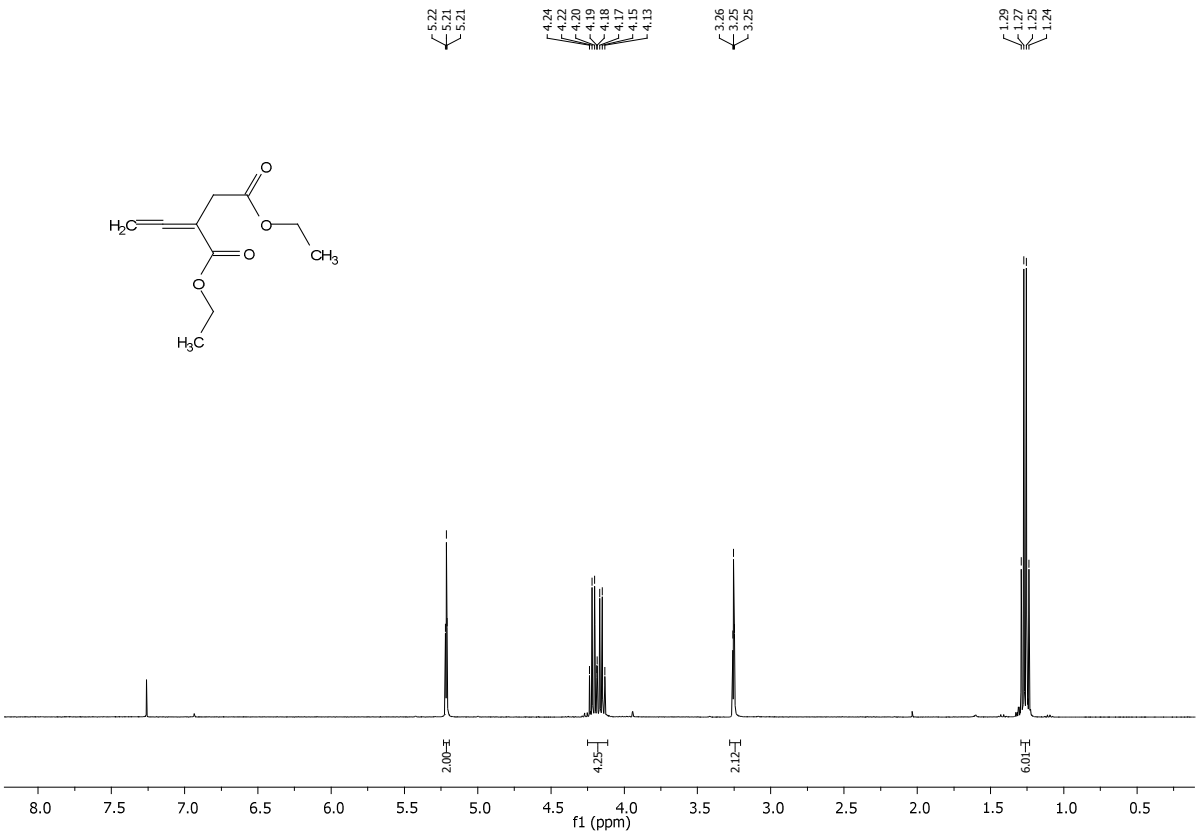
(Minor Diastereomer), NMRs measured in CD_2Cl_2 as solvent, 400 MHz

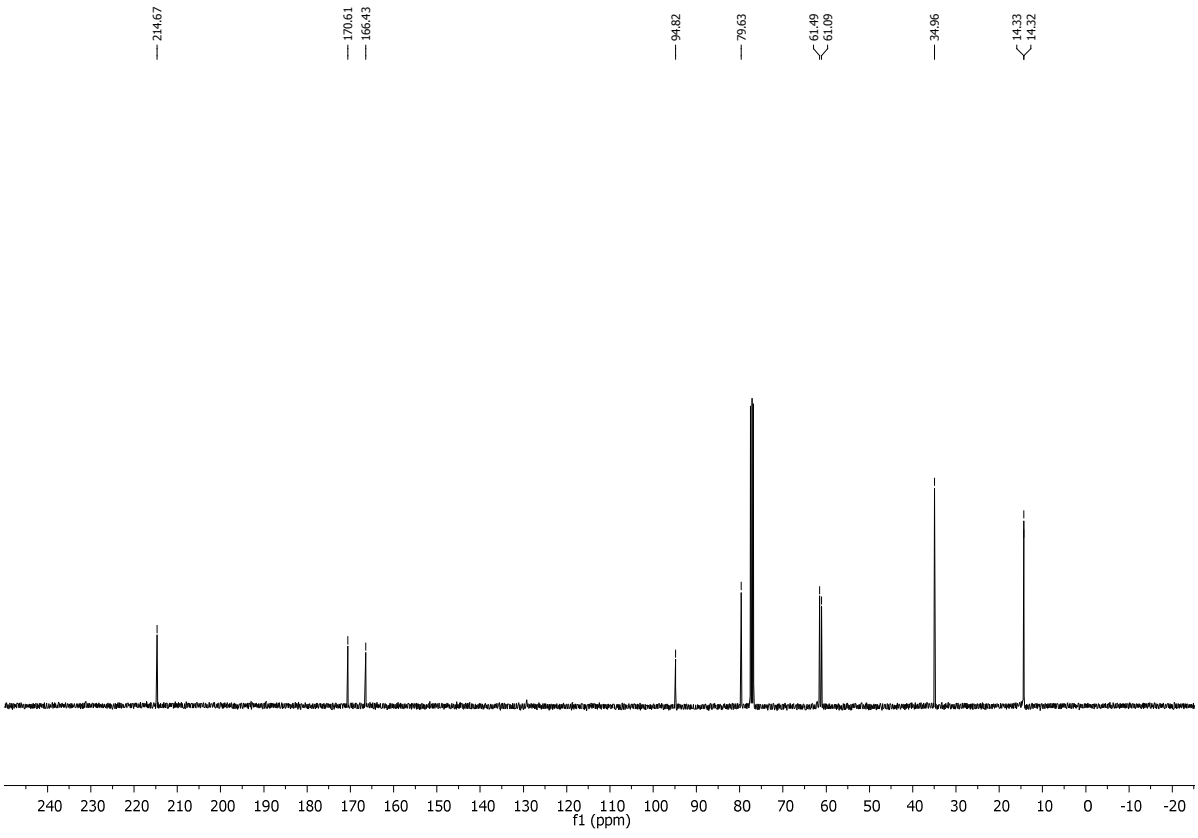


(Major Diastereomer), NMRs measured in CD_2Cl_2 as solvent, 400 MHz

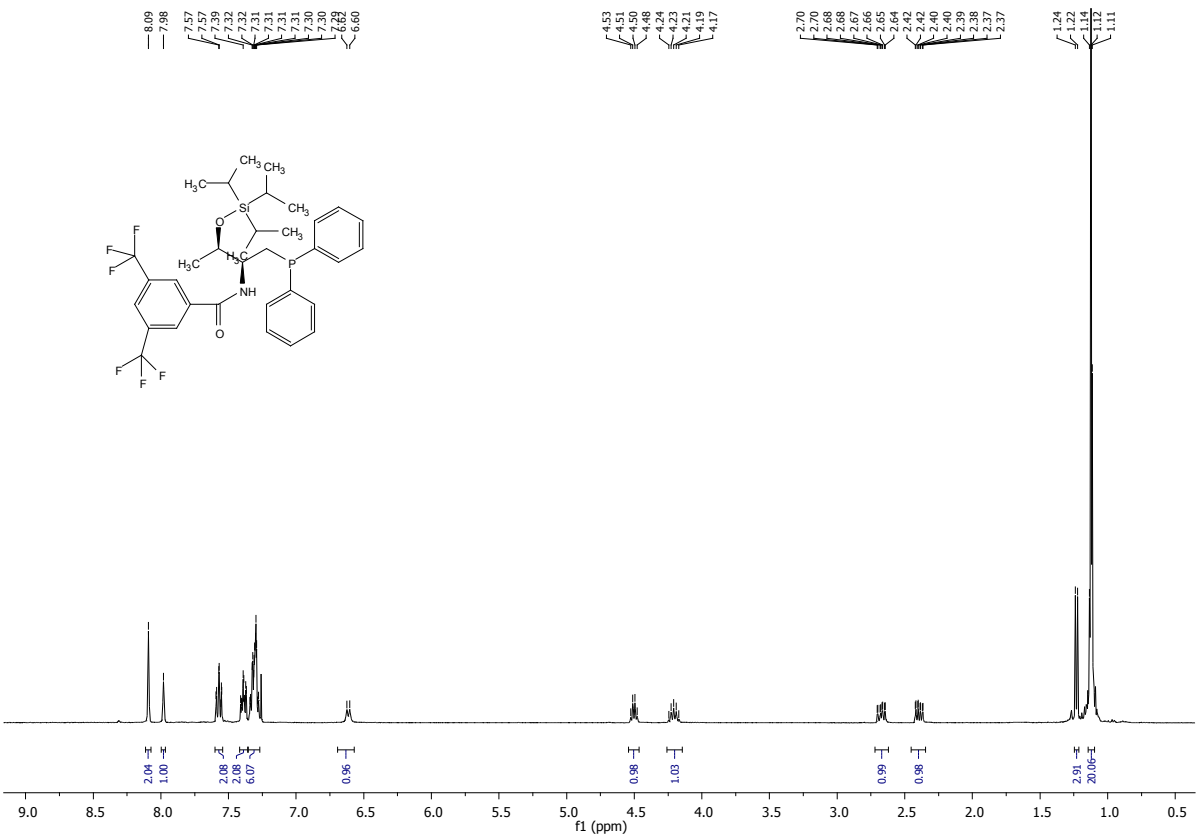


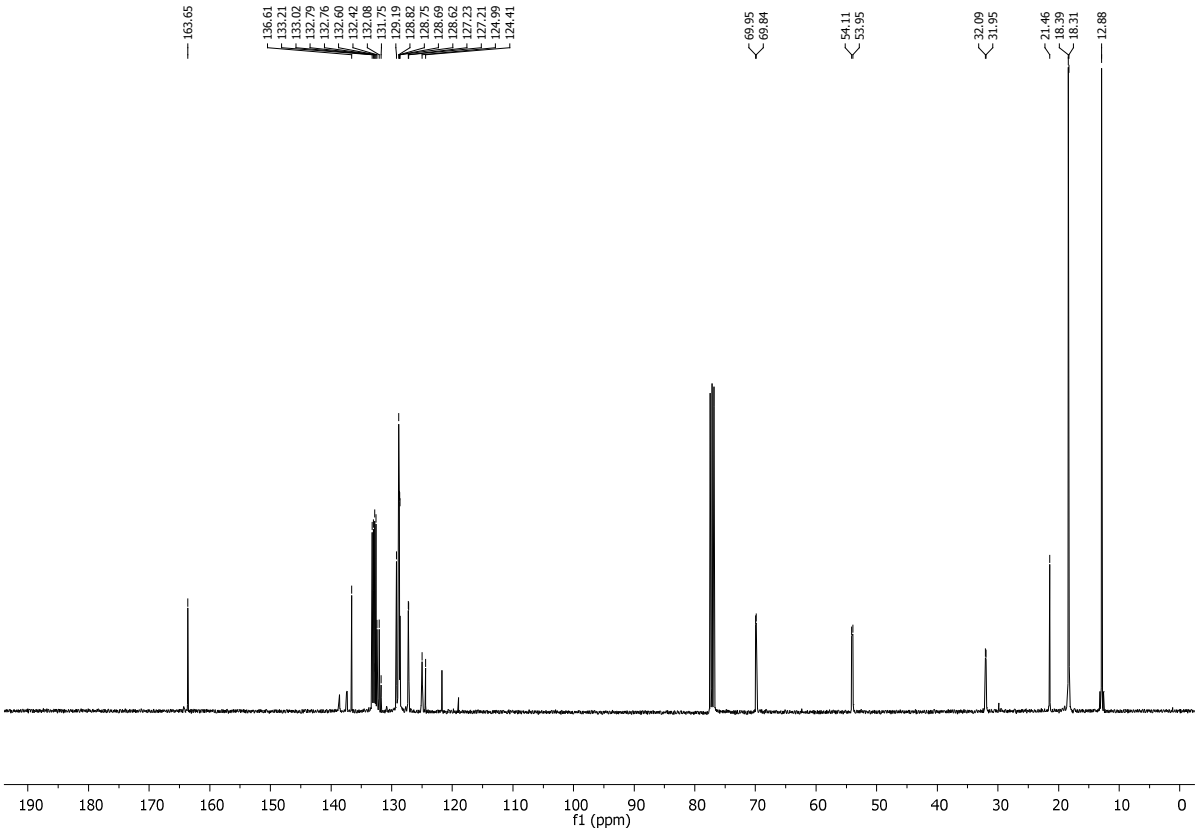
NMR of compound **175a** measured in $CDCl_3$ as solvent, 400MHz



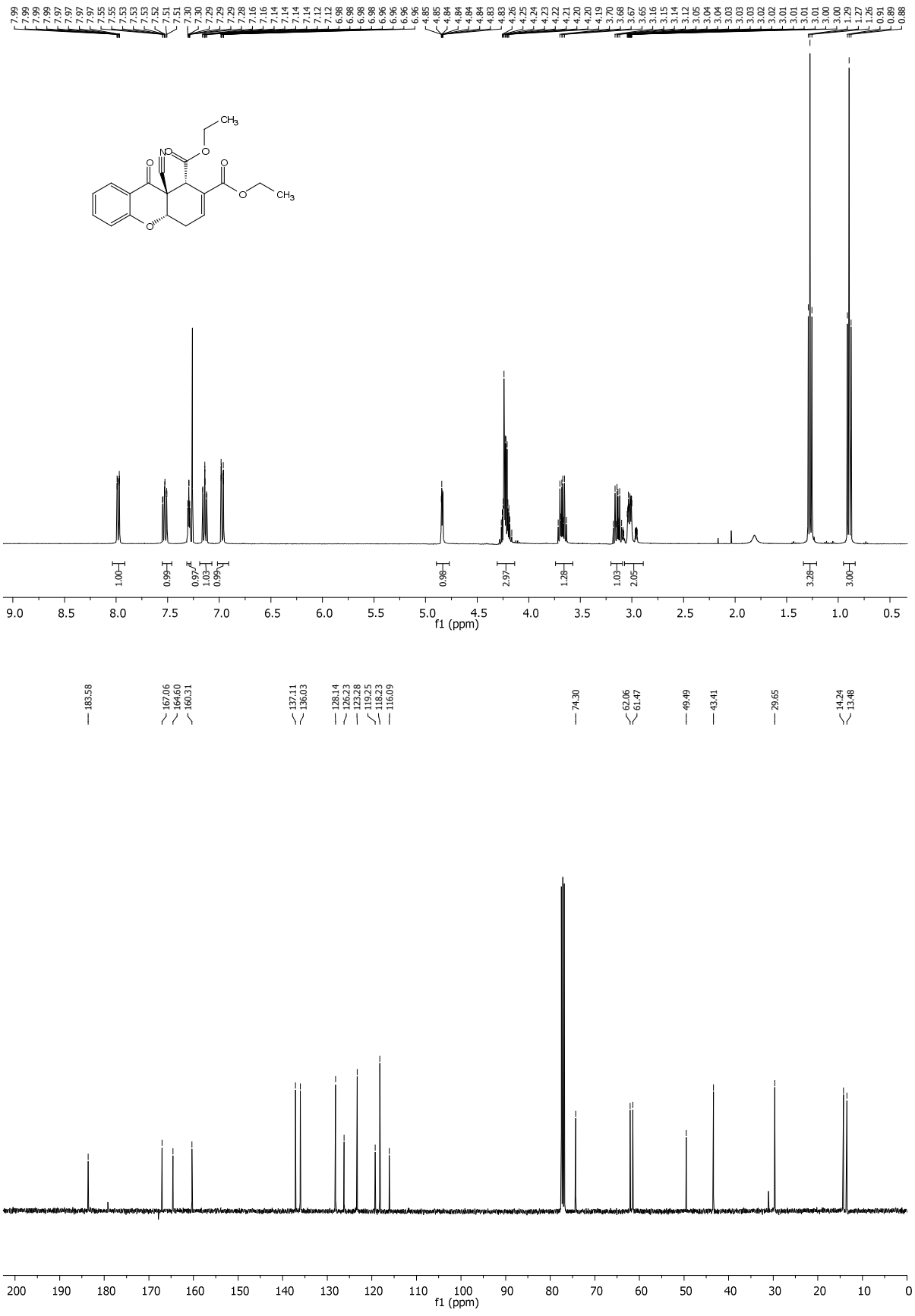


NMR of aminophosphine **238** measured in $CDCl_3$ as solvent, 400MHz





NMR of compound **213** (major diastereomer) measured in $CDCl_3$ as solvent, 400MHz



I List of Abbreviations

Ac	Acyl
Au (I)	Au in oxidation state I
Au (III)	Au in oxidation stat III
Boc	*tert*-butoxycarbonyl
Bn	Benzyl
$CDCl_3$	Deuterated chloroform
$CHCl_3$	Chloroform
CSA	Camphor sulphonic acid
DCM	Dichloromethane
DCE	Dichloroethane
DMF	Dimethyl formamide
DMSO	Dimethyl sulfoxide
E	*E* isomer
ee	Enantiomeric excess
ESI	Electron spray inonisation
Et	Ethyl
Et_2O	Diethylether
Equiv	Equivalent
GC-MS	Gas chromatography mass spectrometry
*g*COSY	Gradient enhanced correlation spectroscopy
gHMBC	Gradient enhanced hetronuclear multiple bond correlation
HPLC	High performance liquid chromatography

HR-MS	High resolution mass spectroscopy
*i*Pr	isopropyl
IL	Ionic liquid
J	Coupling constant
L	Ligand
LAH	Lithium Aluminium Hydride
M	Metal
mCPBA	*meta* chloro perbenzoic acid
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
M*Hz*	Megahertz
Ms	Mesyl
MW	Microwave
NCS	*N*-chloro succinimde
NMR	Nuclear manetic resonance
NOE	Nucler overhauser effect
NR	No reaction
Nu	Nuclophile
Ph	Phenyl
PS	Pictet-Spengler
R_F	Retention factor
RT	Room temperature
T	Temperature

TBDPS	*tert*-butyldiphenylsilyl chloride
TBSCl	*tert*-butyl dimethylsilyl chloride
^{t}Bu	*tert*-butyl
THF	Tetrahydrofuran
TIPSCl	Triisopropylsilyl chloride
TLC	Thin Layer Chromatography
Ts	Tosyl group
THF	Tetrahydrofuran
UV	Ultaviolet
W	Watt
Z	Z- Isomer

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