The 3-Oxidopyridinium [5+2] Cycloaddition in the Total Synthesis of Alkaloids and Development of a Diazo Insertion based Strategy for the Formation of Hexahydrocyclohepta[*b*]indoles

Von der Naturwissenschaftlichen Fakultät der

Gottfried Wilhelm Leibniz Universität Hannover

zur Erlangung des Grades

Doktor der Naturwissenschaften (Dr. rer. nat.)

genehmigte Dissertation

von

M. Sc. Sebastian Krüger

geboren am 26.12.1985 in Schongau

[2016]

Referentin: Prof. Dr. rer. nat. Tanja Gaich

Korreferent: Prof. Dr. rer. nat. Markus Kalesse

Tag der Promotion: 29.02.2016

Scientific contributions from 03/2013 to 11/2015

Publications

S. Krüger, T. Gaich, "Enantioselective, Protecting-Group-Free Total Synthesis of *Sarpagine* Alkaloids—A Generalized Approach", *Angew. Chem. Int. Ed.* **2014,** *54* (1), 315–317. Mentioned in *Synfacts*: "Synthesis of *Sarpagine* Alkaloids", *Synfacts* **2015,** *11* (1), 7.

S. Krüger, T. Gaich, "Recent applications of the divinylcyclopropane–cycloheptadiene rearrangement in organic synthesis", *Beilstein J. Org. Chem.* **2014**, *10*, 163–193.

Posters & Talks

NOS-Meeting 2015, 02.07.2015, University of Maryland, MA, USA,
Poster: "A Unified, Protecting Group Free Enantioselective Access to the *Sarpagine* Alkaloids"

Winterfeldt Preis 2015, 26.06.2015, Leibniz Universität Hannover
Talk: "The 3-Oxidopyridinium [5+2] Cycloaddition in Total Synthesis – Access to Several *Sarpagine* Alkaloids and Parvineostemonine –"

MINAS Kolleg 2014, 19.06.2014, Burg Warberg, Warberg
Talk: "Synthetic Access to the *Sarpagine* Alkaloids – Enantioselective Total Synthesis of Vellosimine –"

Leibniz Symposium 2014, 14.02.2014, Leibnizhaus, Hannover
Poster: "Enantioselective, Protecting Group Free Total Synthesis of *Sarpagine* Alkaloids."

“I am Sebastian, or Sebastian is I, or perhaps we both are someone whom neither of us knows.”

V. Nabokov

Abstract

I The enantioselective, protecting group free total syntheses of the *sarpagine* alkaloids vellosimine, *N*-methylvellosimine and 10-methoxyvellosimine were achieved *via* a joint synthetic sequence. Furthermore, the flexibility of the synthetic route was showcased by the formal synthesis of 16-epinormacusine B, thereby expanding the synthetic access to both the 16-regular and the 16-epi subgroup of *sarpagine* alkaloids. The key steps include a 3-oxidopyridinium [5+2] cycloaddition, a diazo-mediated ring expansion and a late stage product differentiation using the Fischer indole synthesis.

II The enantiodivergent, protecting group free total synthesis of the *stemona* alkaloid parvineostemonine was achieved. Our synthetic strategy includes a 3-oxidopyridinium [5+2] cycloaddition and differentiation of the obtained regioisomers into both antipodes of the natural product. Both enantiomers of the natural product can be obtained in only nine steps from literature known starting materials.

III A new methodology for the construction of hexahydrocyclohepta[*b*]indoles has been established. This methodology relies on the diazo insertion of 1-(diazomethyl)-2-nitrobenzene with cyclic, six-membered ketones mediated by trimethylaluminium and subsequent reduction. To demonstrate the synthetic potential of this methodology, the formal synthesis of an A-FABP (adipocyte fatty acid binding protein) inhibitor was concluded.

keywords: total synthesis, alkaloid, cycloaddition.

Kurzzusammenfassung

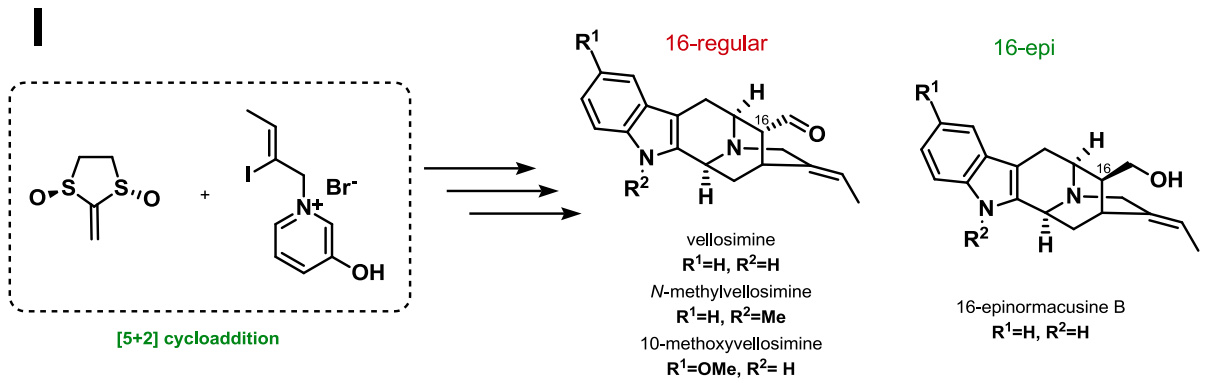
I Die enantioselektive, schutzgruppenfreie Totalsynthese der *Sarpagine* Alkaloide Vellosimine, *N*-Methylvellosimine und 10-Methoxyvellosimine wurde erreicht. Des Weiteren wurde die Flexibilität der Syntheseroute durch die zusätzliche Formalsynthese von 16-Epinormacusine B unterstrichen. Somit konnte der synthetische Zugang von der 16-regular-Untergruppe der *Sarpagine* Alkaloide auch auf die 16-epi-Untergruppe der *Sarpagine* Alkaloide ausgeweitet werden. Als Schlüsselschritte wurden eine 3-Oxidopyridinium [5+2] Cycloaddition und eine Ringerweiterung verwendet. Mittels einer abschließenden Fischer Indole Synthese konnten die verschiedenen Naturstoffe erhalten werden.

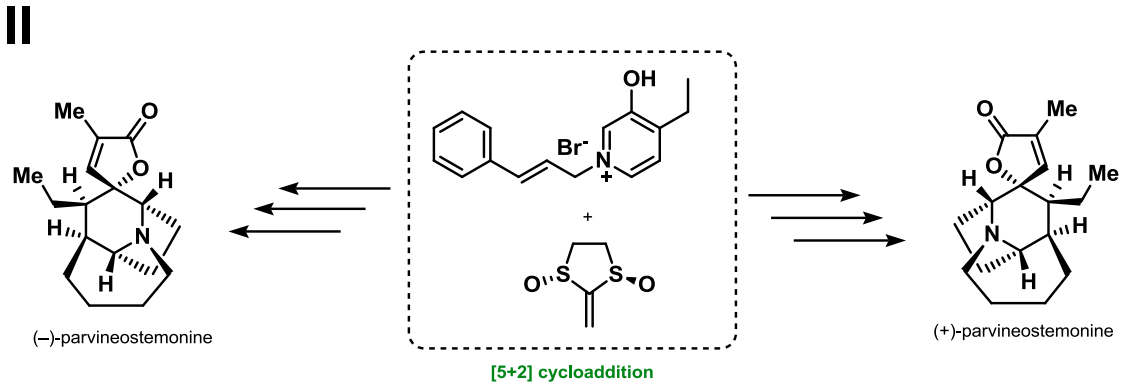
II Die enantiodivergente, schutzgruppenfreie Totalsynthese des *Stemona* Alkaloids Parvineostemonine wurde durchgeführt. Beide Enantiomere des Naturstoffes können in nur neun Stufen von bekannten synthetischen Zwischenstufen ausgehend hergestellt werden. Als Schlüsselschritt diente hier ebenfalls die 3-Oxidopyridinium [5+2] Cycloaddition.

III Eine neue Methode zur Synthese von Hexahydrocyclohepta[*b*]indolen wurde gefunden. Grundlage dieser Methode ist die Insertion von 1-(Diazomethyl)-2-nitrobenzol in sechsgliedrige, zyklische Ketone unter Einwirkung von Trimethylaluminium und anschließender Reduktion. Zudem wurde die Formalsynthese eines A FABP (adipocyte fatty acid binding protein) Hemmstoffes abgeschlossen.

Schlagwörter: Totalsynthese, Alkaloid, Cycloaddition.

Graphical Abstract





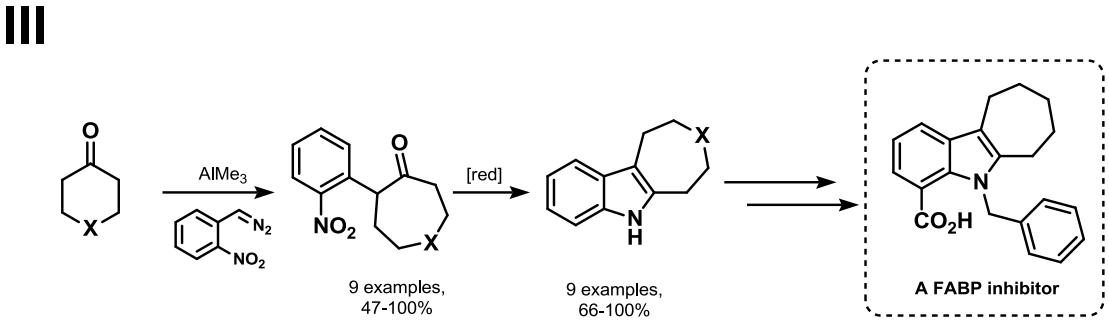


Table of Contents

1 Introduction

“The only real number is one, the rest are mere repetition”

V. Nabokov

1.1 Introduction with Graphs

Alkaloids have been extensively used by mankind throughout the past thousands of years, due to their unique effects on the human body. Early stimulants including coffee and tea rely on alkaloids to stimulate the heart rate, most illegal drugs are based on alkaloids due to their severe interaction with the human body.[1.1] A lot of commercially available drugs against various diseases have been developed from isolated natural products. Newman and Cragg[1.1] state that about a third of all small molecule new chemical entities from 1981-2006 are either natural products or derived from natural products in 2007 (see figure 1, graph 1). According to Cordell and co-workers[1.2] in 2001 roughly 50% of the natural product derived drugs were based on alkaloids (graph 2), much in contrast to the low percentage of known alkaloids compared to the overall known natural products (graph 3). Further astonishing is the percentage of alkaloids that have never been subject to any bioactivity studies, roughly three quarters of every alkaloid ever isolated (graph 4). In fact only about two percent of all alkaloids have been seriously evaluated, and have contributed largely to the list of new chemical entities.

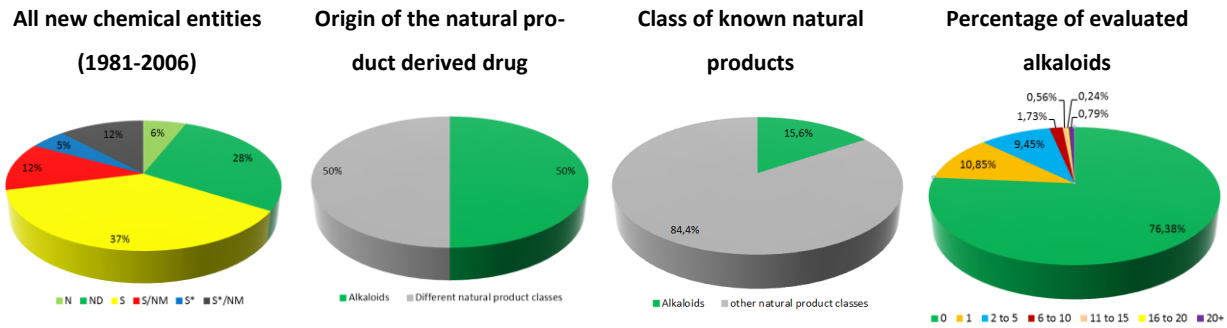


Figure 1: Facts about small chemical entities, natural products and alkaloids as graphs. Graph 1: Small molecule new chemical entities, N=974. Explanation: N=natural products, ND=natural product derived, S=totally synthetic, S/NM=synthetic/natural product mimic, S*=synthetic with a pharmacophore from a natural product, S*/NM= synthetic with a pharmacophore from a natural product/natural product mimetic. Graph 2: Source of a pharmaceutical or biological significant natural product. Graph 3: Known natural products and their classification. Graph 4: Percentage of the bioassay evaluation of alkaloids, N=21120. The numbers indicate the amount of bioassays performed for the percentage of alkaloids.

It can therefore be surmised, that alkaloids have contributed in the most significant way to the development of new drugs, and have thereby greatly improved human life. Alkaloids seem to be the ideal starting point concerning bioactive molecules, and with a large variety of unevaluated alkaloid natural products there is a huge chance of finding interesting properties in any targeted molecule. Within the natural product classes (*sarpagine* and *stemona* alkaloids), which will be part of the following chapters, bioactive molecules against leukemia

cells and human KB (cancer-)cells[1.3] have been found. As all molecules that will be discussed are obtained from trees or bushes, the vast majority of bioactivities is focused on the defense against herbivores. Several molecules have been isolated that fend of worms, insects[1.4] or rats.[1.3] The alkaloid-containing extracts of those trees can furthermore be used as an effective anticough treatment.[1.4]

This work is focused on the development of a unified synthetic strategy towards several alkaloids of different biosynthetic origin (different trees or bushes), from different alkaloid families, isolated in a large variety of countries on several continents. The aim is to pave the way to the evaluation of several very different natural products, which most likely will have interesting biological properties. Independent of any possible findings regarding the bioactivity of the synthesized molecules (which is not part of this work) there is a variety of synthetic knowledge that is readily obtained by working in the field of alkaloid total synthesis.

1.2 A Synthetic Introduction

As a total synthetic chemist there is an incredible pool of natural products awaiting a synthetic access. There is also a very limited time frame. In order to achieve a maximum of successfull syntheses in as short a period of time as possible, there is no way but to display a very high synthetic efficiency. In other words, the quest is to achieve as much as possible with the minimal amount of effort necessary. An efficient, up to date total synthesis needs to fullfill several aspects:

- short (below 20 steps)
- protecting group free (reduces the step count)
- asymmetric
- targets multiple natural products
- convergent synthesis of several building blocks.

The concept of an ideal synthesis has been addressed by Hendrickson[1.5] in 1975 (and later by Baran and co-worker[1.6]) and resulted in the following guideline:

“Ideally, the [ideal] synthesis would start from available small molecules so functionalized as to allow constructions linking them together directly, in a sequence only of successive construction reactions involving no intermediary refunctionalizations, and leading directly to the

structure of the target, not only its skeleton but also its correctly placed functionality. If available, such a synthesis would be the most economical, and it would contain only construction reactions."

Fourty years later, we intended to stretch this description of a total synthesis further towards a common intermediate based synthetic acces towards several alkaloids from different families (see figure 2). Instead of the classical concept of total synthesis, which converts a massive amount of starting material to a barely existing amount of one single natural product in a very long linear synthesis, we intended to prepare a common intermediate (**?**) in a convergent fashion. From this intermediate we will be able to access different natural products of different biosynthetic origins. The mutual building block (**?**) should be placed roughly in the middle of the synthesis. This would allow a significant amount of chemical complexity of the common intermediate, while being still shapable enough to access very different alkaloids. The steps from the starting materials to the privileged intermediate (**?**) will not have to optimized for the second total synthesis *via* the synthetic route.

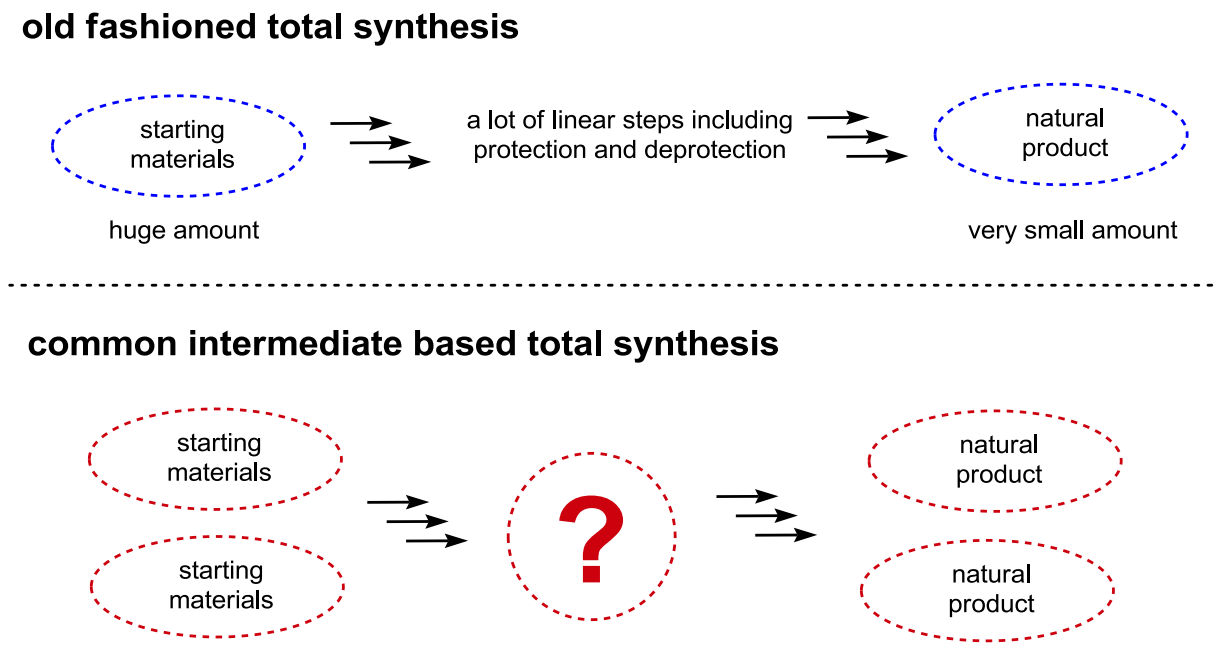


Figure 2: Two concepts of total synthesis.

This synthetic concept is demonstrated with the alkaloids that we intended to target in figure 3. The three alkaloids vellosimine (**1**, a *sarpagine* alkaloid), parvineostemonine (**2**, isolated from a *stemona* species) and alstonerine (**3**, an *alstonia* alkaloid)[1.7] should be traced back to an unknown, common intermediate (**?**).

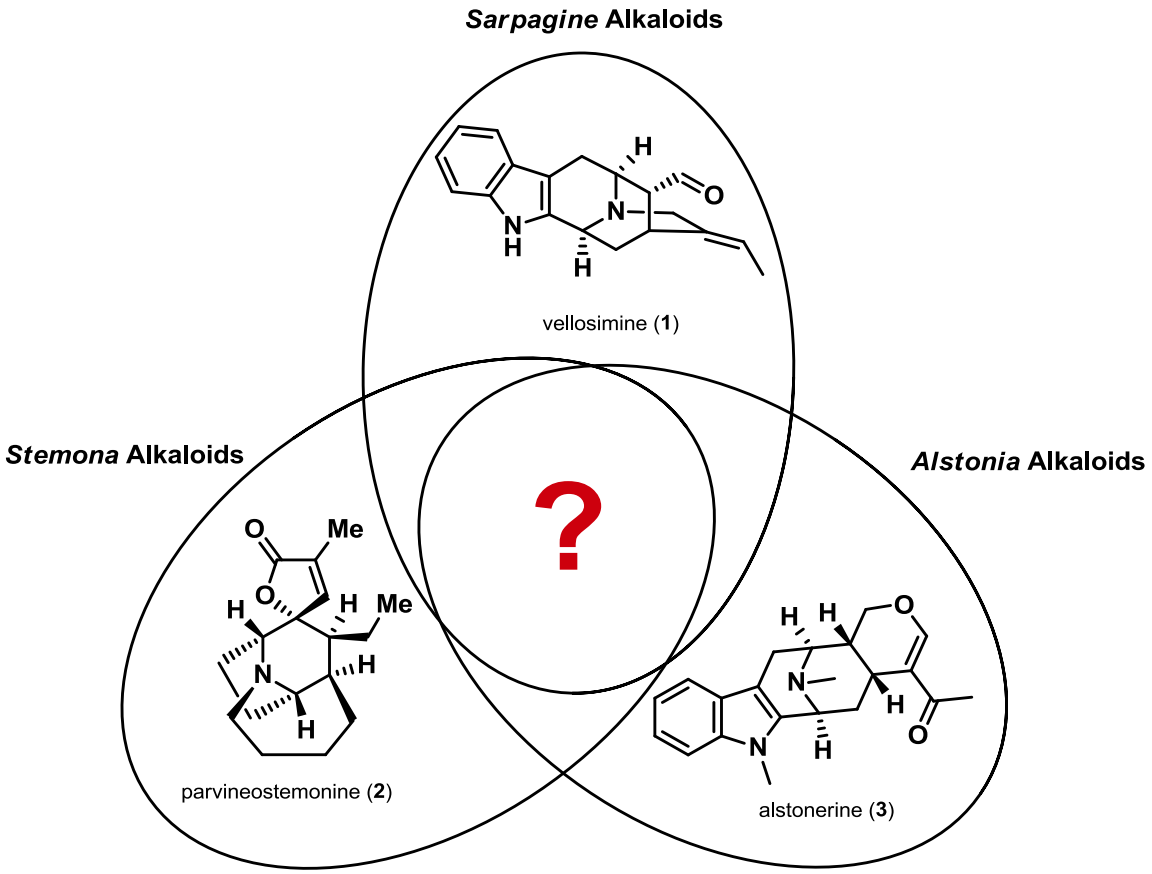


Figure 3: The quest for a common synthetic precursor.

In order to decipher the identity of this mutual building block, a common structural motive has to be found. In all the natural products from figure 3 (note that the other enantiomer of parvineostemonine **2** is used for simplicity in figure 4) the piperidine moiety (highlighted in red) is the most obvious common feature. All of those piperidine units differ in the substitution at the nitrogen atom. They also have an all-carbon bridge (from position (ps) 2 to ps 6) in common, as well as substitution (albeit very different substitution) on the positions 3 and 4. The postion 5 is unsubstituted in compound **1** and compound **3**, but is part of another four carbon atom-containing bridge in compound **2**. Redrawn without any distracting moieties (compounds **4** to **6**) a much more unperturbed picture emerges, ultimately resulting in the recognition of compound **7** as the ultimate mutual precursor.

All those very different substitutions can be implemented using a dihydropyridinone core (ketone moiety at ps3, double bond ps 4-5, different nitrogen-substitution at ps 1). A further requirement is a bride from ps 2 to ps 6, which will be containing two carbon atoms. To successfully synthesize compounds **1**–**3** this bridge will be subject to a C1-homologation.

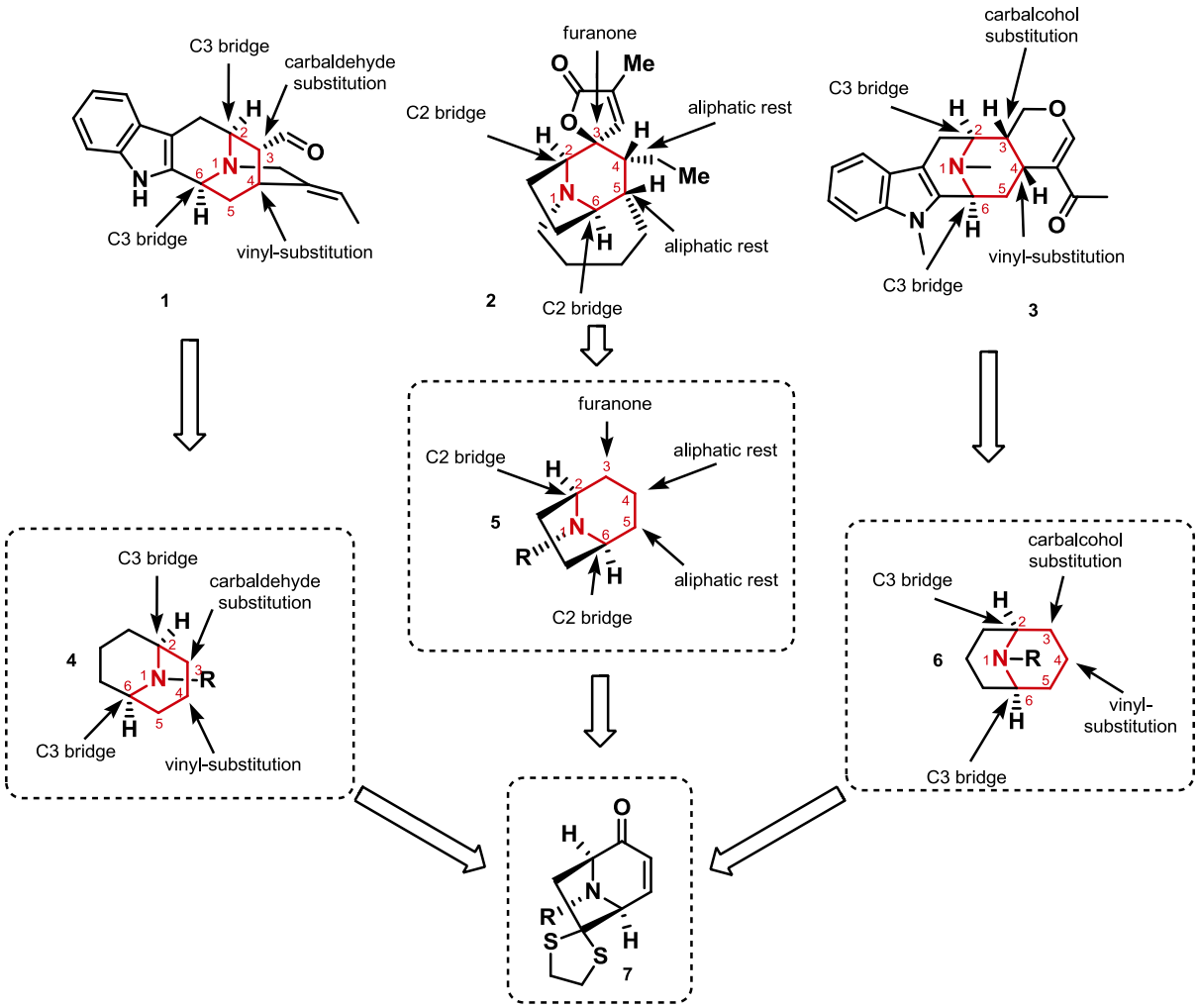


Figure 4: Comparison of the substitution pattern of the central piperidine core and explanation of the thought progress behind a common intermediate based synthetic strategy. Note that parvineostemonine (**2**) is displayed in this figure alone as the opposing antipode due to simplicity.

We furthermore aim to develop a rapid, enantioselective, protecting group free synthetic access to a vast variety of alkaloids, which are isolated from a variety of different plants in various countries. These plants and the resulting alkaloids do not need to share the same biosynthetic origin, but are synthesized based on the same chemistry. The establishment of a common intermediate with late stage product differentiation will enable us to produce large quantities of a variety of natural occurring and unnatural alkaloids for biological evaluation. Figure 5 highlightes the overall synthetic concept in a colourfull and easily remembered way. The total synthesis of parvineostemonine (**2**) should be carried out in an enantiodivergent fashion. For this synthetic concept see chapter 3. For an introduction to the methodology part of this thesis see chapter 4.

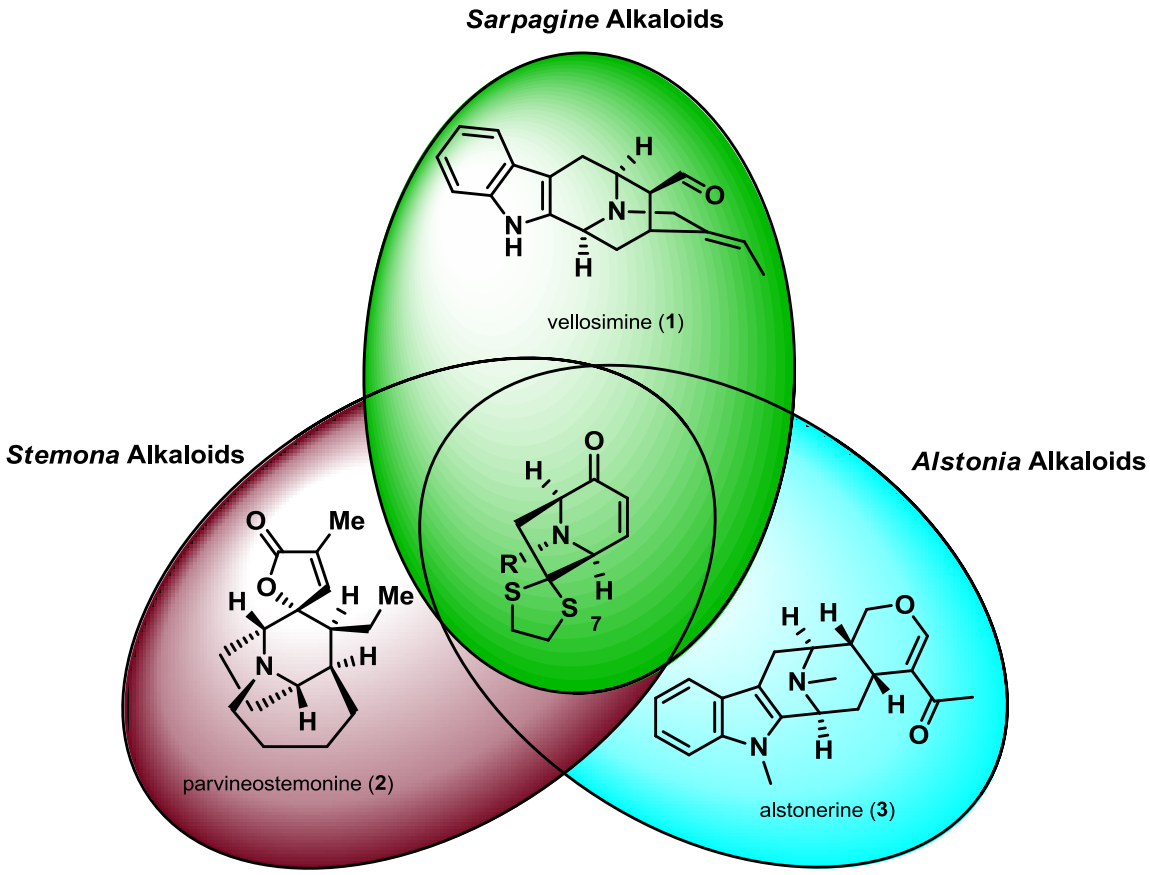


Figure 5: Synthetic concept (with colours) and the common intermediate.

1.3 References

[1.1] D. J. Newmann, G. M. Cragg, *J. Nat. Prod.* **2007**, *70*, 461–477.

[1.2] G. A. Cordell, M. L. Quinn-Beattie, N. R. Farnsworth, *Phytother. Res.* **2001**, *15*, 183–205.

[1.3] for a closer look on the bioactivities of the *sarpagine* alkaloids see chapter 2.5.

[1.4] for a closer look on the bioactivities of the *stemona* alkaloids see chapter 3.5.

[1.5] J. B. Hendrickson, *J. Am. Chem. Soc*. **1975**, *97*, 5784–5800.

[1.6] T. Gaich, P. S. Baran, *J. Org. Chem*. **2010**, *75*, 4657–4673.

[1.5] for the isolation of alstononerine see: J. M. Cook, P.W. LeQuesne, *Chem. Commun.* **1969**, 1306–1307.

2 The Sarpagine Project

This chapter covers the occurance and biosynthesis of the *sarpagine* alkaloids, the already accomplished synthetic approaches, our synthetic concept and its results. Large parts of this chapter have been published previously.

2.1 Occurence

The *sarpagine* family of alkaloids has mostly been isolated from a variety of *Apocynaceae* genera. Due to the sheer amount of plants and locations, from which *sarpagine* alkaloids have been isolated, this discussion is limited to the occurance of the synthesized molecules. Vellosimine (**1**) was isolated from:

- *Alstonia yunnanensis (Apocycnaceae)* found on the West Mountain of Kunming, Yunnan Province, China in 1983. 3.95 kg of roots led to the isolation of 350 mg vellosimine (**1**).[2.1]
- *Cabucala erythrocarpa* var. *erythrocarpa* found in Madagascar in 1974. One kilogram of leaves yielded 15 mg of vellosimine (**1**).[2.2]
- *Geissospermum velosii* found in brazil in 1958. 6.87 kg of bark yielded about 900 mg of vellosimine (**1**).[2.3]
- *Rauvolfia caffra* found in Pretoria, South Africa in 1977. 6 kg of stem bark yielded 20 mg of vellosimine (**1**).[2.4]
- *Rauvolfia macrophylla* found in Ibadan, Nigeria in 1974. 2.1 kg stem bark yielded 10 mg of vellosimine (**1**).[2.5]
- *Rauvolfia nitida* found in Jamaica in 1960. 2 kg of roots gave rise to 10 mg of vellosimine (**1**).[2.6]
- *Rauvolfia salicifolia* found in Rio Maravi, Cuba. Vellosimine (**1**) was isolated from the stem bark extracts, but not from the leaf or root extracts.[2.7]
- *Rauvolfia cubana*, found in the province of la Habana, Cuba in 1978. Vellosimine (**1**) was isolated from the leaves of this tree, but not from the roots.[2.8]
- *Rauvolfia verticillata* found in Hong Kong.[2.9]
- *Vinca difformis*.[2.10]
- *Rauvolfia reflexa*, *Rauvolfia vomitoria*, *Rauvolfia yunnanensis*, *Strychnos divaricans* (*Loganiaceae*).[2.11]

N-Methylvellosimine (**8**) was isolated from:

- *Rauvolfia nitida* found in Jamaica in 1960. 2 kg of roots yielded 15 mg of *N*-methylvellosimine (**8**).[2.6]

10-Methoxyvellosimine (**9**) was isolated from:

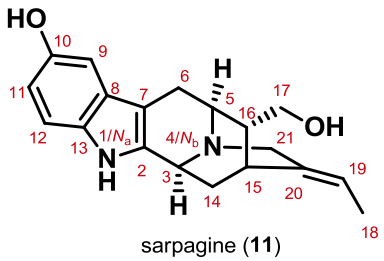
- *Vinca major* found in the department of Gers in the south of France.[2.11] 280 g of roots provided 57 mg of 10-methoxyvellosimine (**9**).

16-Epinormacusine (**10**) was isolated from:

- *Ervatamia hirta* found in Malaysia in 1984. 3.3 kg of root bark yielded 188 mg of 16-epinormacusine B (**10**).[2.12]

2.2 Structures

The *sarpagine* class of alkaloids consists of over one hundred members. 89 have been summarized previously.[2.11] A corrected version of this collection of molecules and newly isolated members starting from 1999 can be found on the following pages. For a detailed understanding see the carbon-atom numbering in figure 6.



sarpagine (**11**)

Figure 6: Carbon atom numbering for the parent compound sarpagine.

For a comprehensive overview of the *sarpagine* alkaloids, all known structures are listed in the following figures. For compounds **1, 16**-**89** (figures 7-10) see reference 2.11 and the references cited therein. Three dihydydroperaksine congeners (**96**-**98**, figure 10) have been isolated by Stöckigt and coworkers.[2.13] Rauvotetraphyllines B&C (**99-100**) have been isolated by the Liu group.[2.14] *Z*-Affinisine (**101**) has been isolated by the group of Kam.[2.15] A methylated talpinine derivative (**102**) has been isolated by Kinghorn and coworkers.[2.16] The group of Takayama isolated an oxidated koumidine derivative (**103**).[2.17] Both double bond

isomers of the alkaloid 16-epivoacarpine (**104**&**105**) have been isolated by Takayama.[2.18] The group of Kam isolated two more sarpagine-macroline dimers called lumitinine C&D (**106**&**107**).[2.19] The group of Kam isolated the first eburnane-sarpagine bisindole alkaloid leuconoline (**108**).[2.20] Gelsochalotine (**109**) was suggested to be a *sarpagine* decomposition product.[2.21] Gardquinolone (**110**) was suggested to be derived from gardnerine.[2.22]

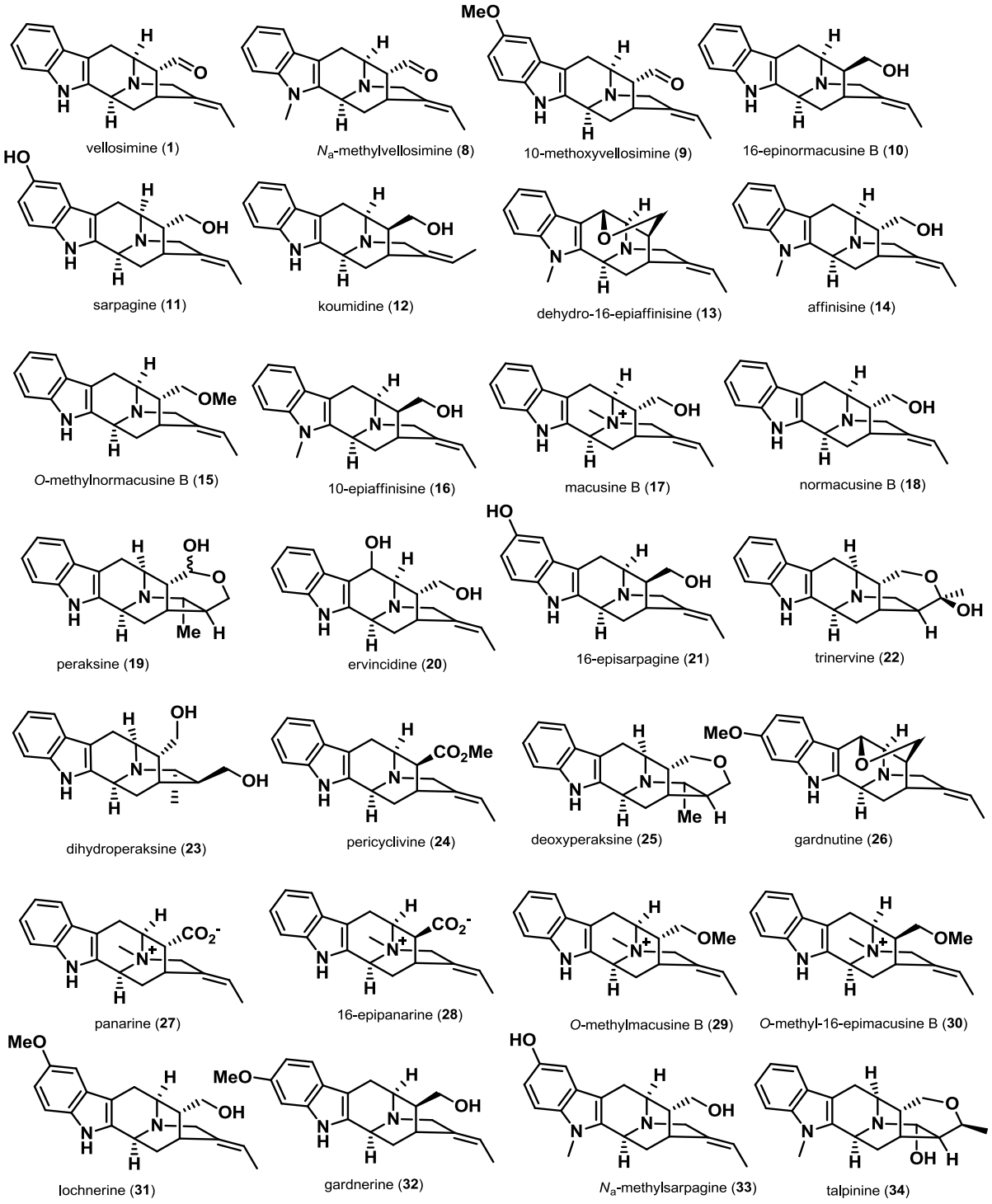


Figure 7: Isolated *sarpagine* alkaloids, part 1.

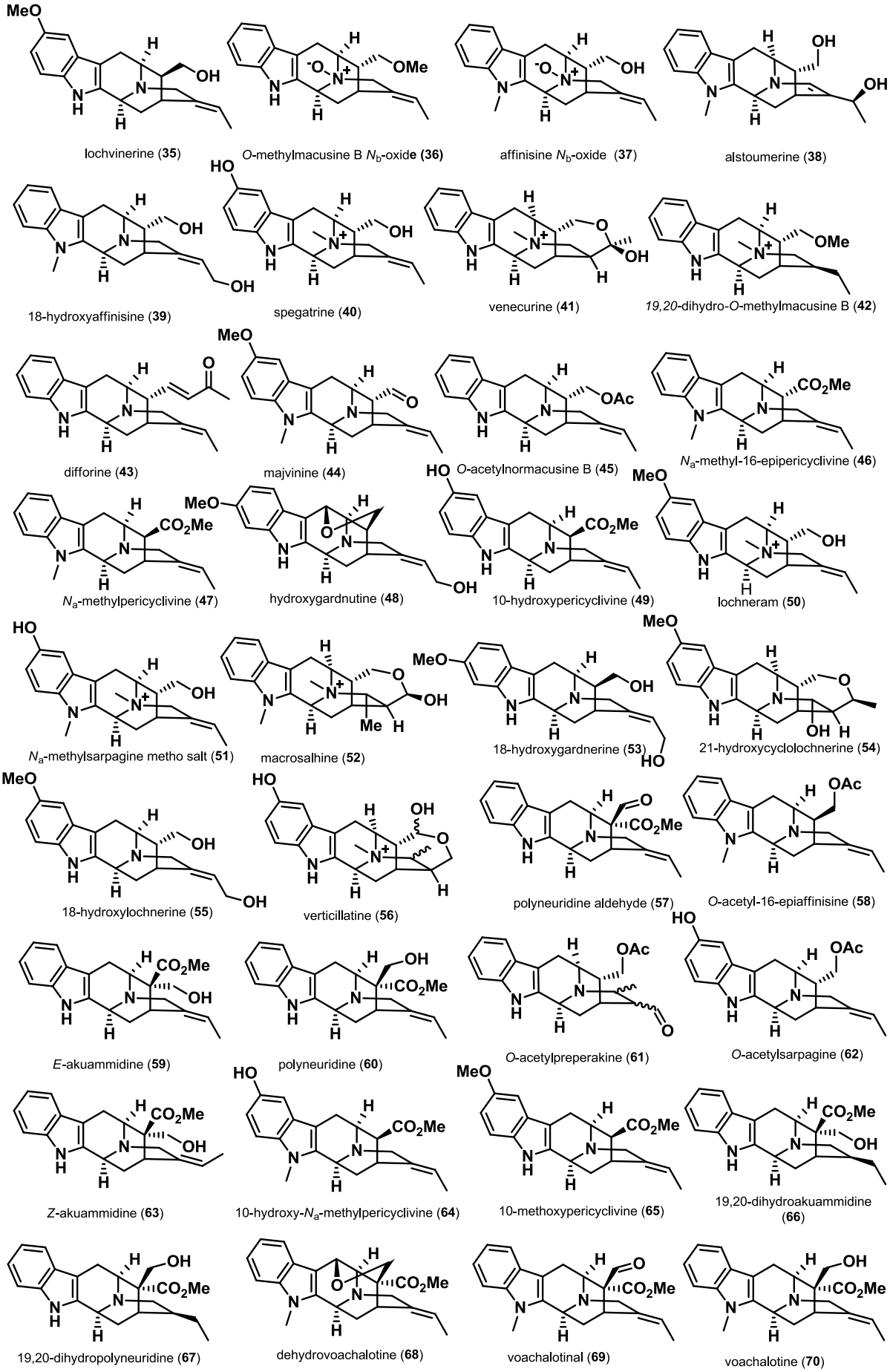


Figure 8: Isolated *sarpagine* alkaloids, part 2.

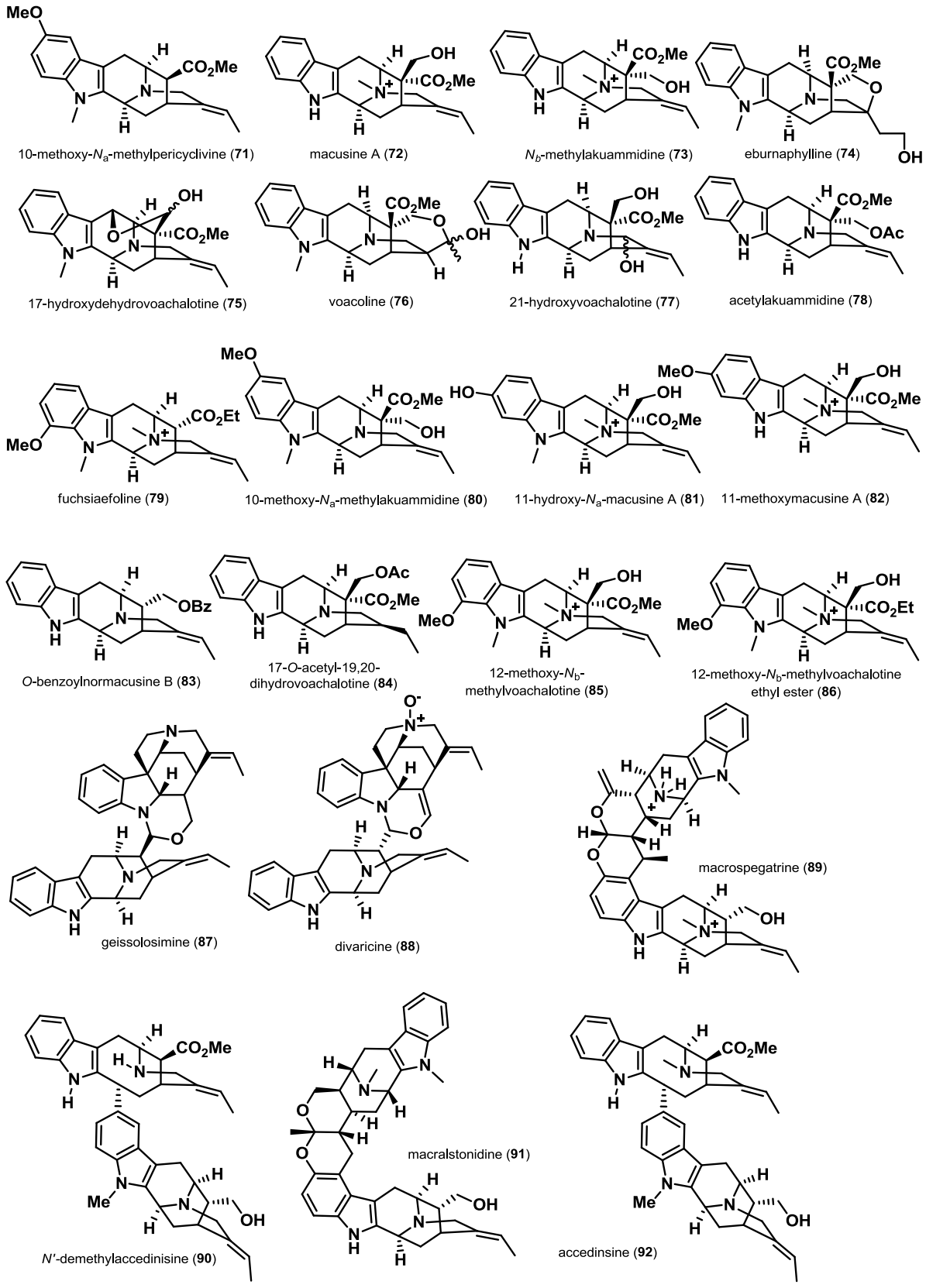


Figure 9: Isolated *sarpagine* alkaloids, part 3.

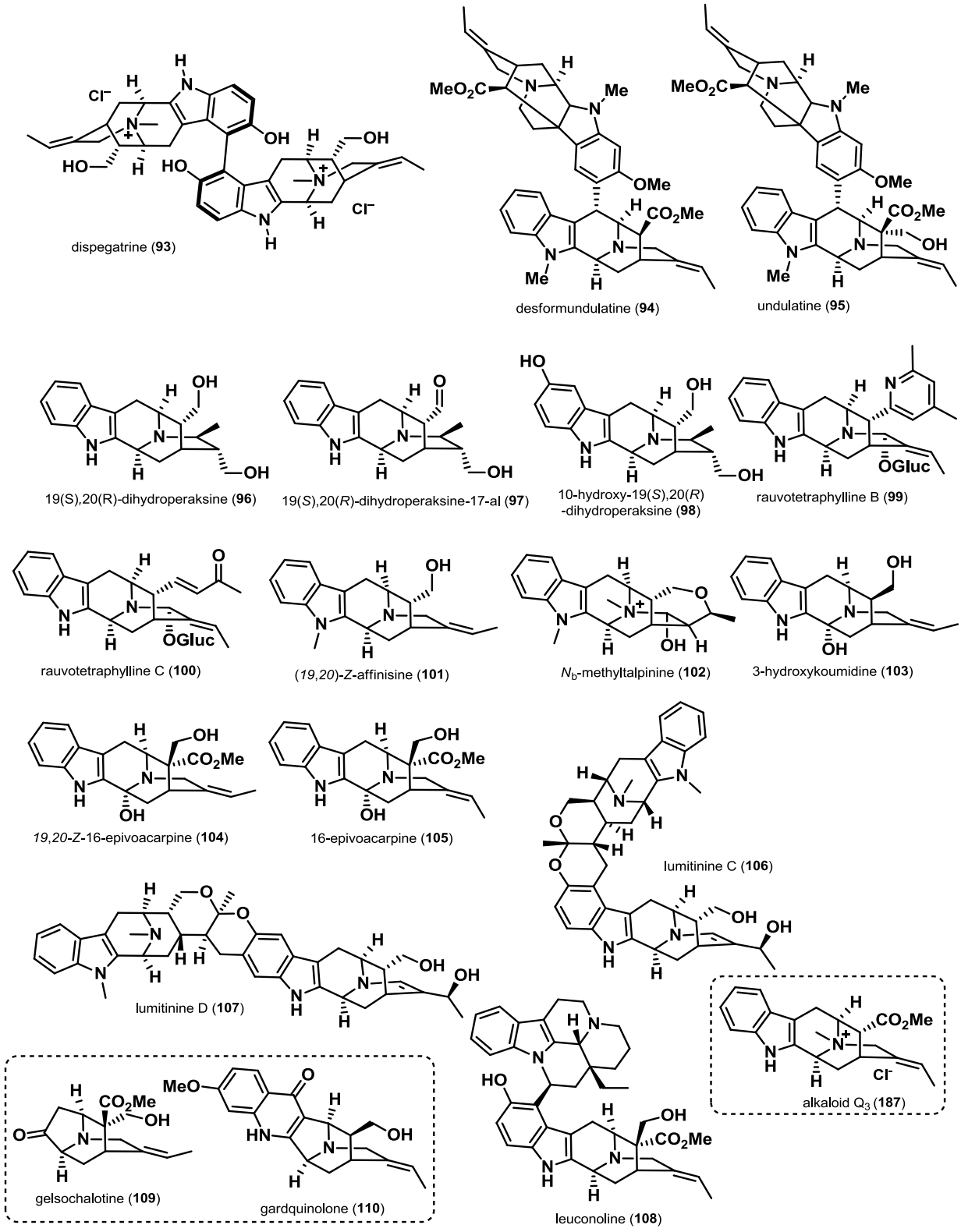
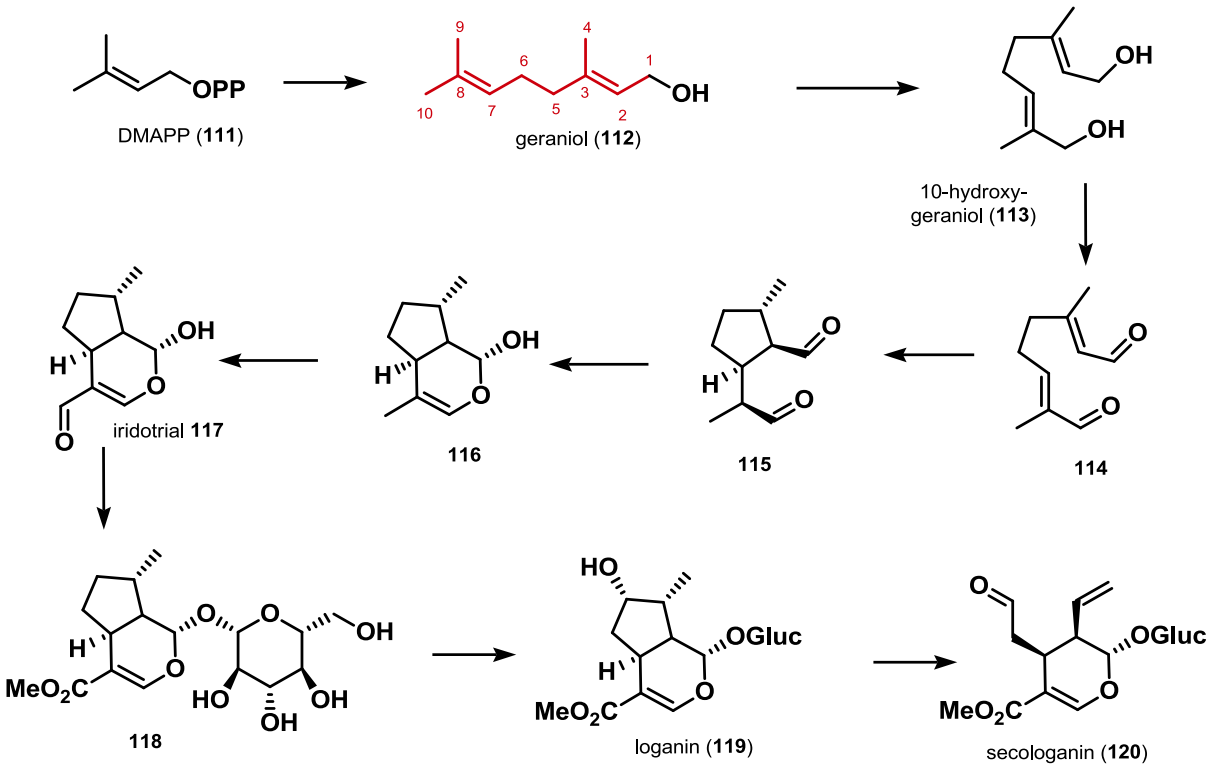


Figure 10: Isolated *sarpagine* alkaloids, part 4.

For information on alkaloid Q_3 (**187**) see page 33.

2.3 Biosynthesis

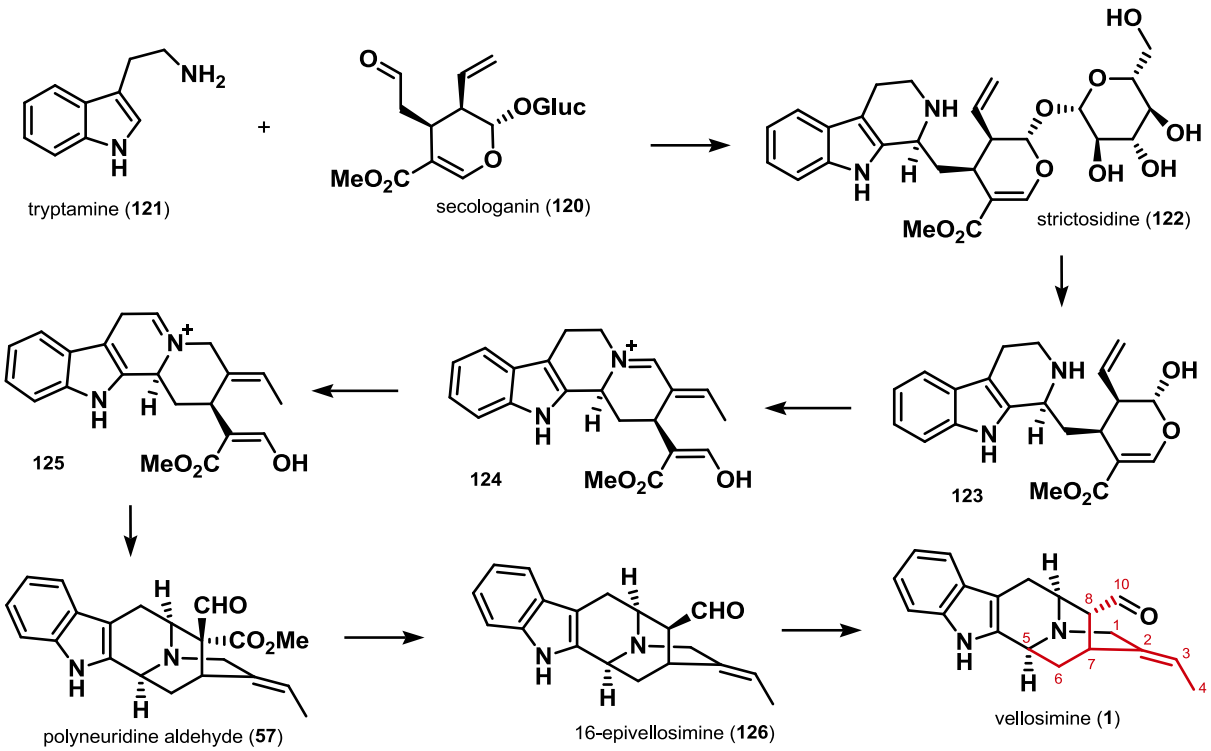
Sarpagine alkaloids are built up from two main building blocks, secologanin **120** and tryptophane. The biosynthesis of secologanin (**120**, see scheme 1) starts with head-to-tail connection of two molecules of dimethylallyl pyrophosphate (DMAPP, **111**) to form geraniol (**112**) after dephosphorylation. Subsequent oxidation at the 10-position furnishes **113** and further oxidation leads to bisaldehyde **114**, which undergoes ring closure to give **115**. Tautomerism and cyclization leads to enolhemiacetal **116**. Another oxidation occurs to yield iridotrial **117**. Further oxidation and esterification furnished the ester moiety of **118**, the remaining alcohol of iridotrial is then subject to glycosylation to give **118**. Hydroxylation occurs to give loganin **119**, which is then transformed to secologanin (**120**) *via* the secologanin synthase.[2.23]



Scheme 1: Biosynthesis of secologanin starting from DMAPP.

In the next step, secologanin **120** and tryptamine **121** (see scheme 2, from decarboxylated tryptophane) are joined in a Pictet-Spengler reaction catalyzed by the strictosidine synthase to yield strictosidine **122**. Next, deglucosidation occurs to give hemiacetal **123**, which in turn undergoes acetal cleavage, imminium ion formation and double bond shift to furnish tetracycle **124**. After translocalization of the imminium ion (see **125**) attack from the β-carboxyester sets up the cage structure of polyneuridine aldehyde **57**. Decarboxylation

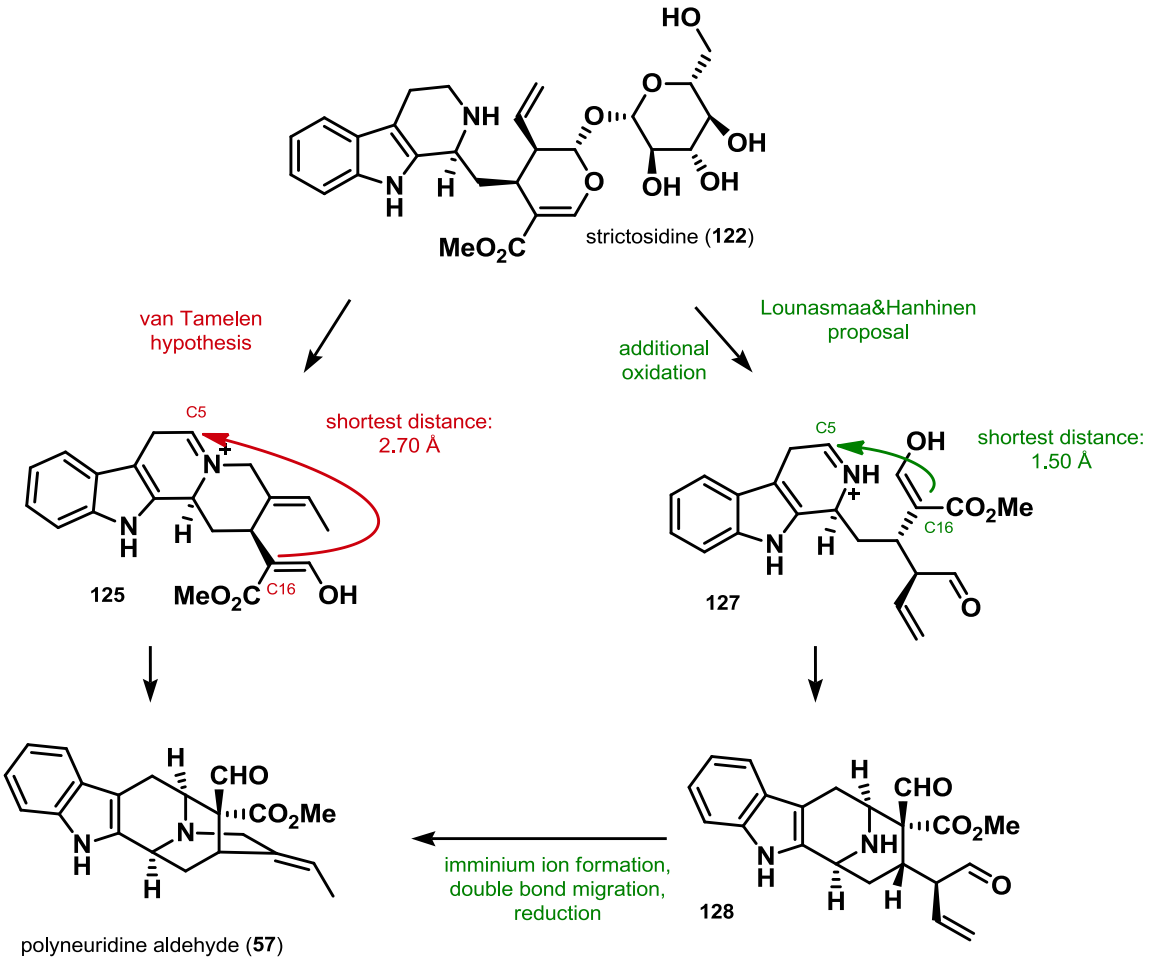
gives rise to 16-epivellosimine (**126**, not isolated as a natural product), which tautomerizes to the thermodynamically more stable natural product vellosimine **1**.[2.24-2.27] The identification of the diterpene unit in the cage structure of vellosmine (**1**, highlighted in red in scheme 2, compare to geraniol (**112**) in scheme 1) is not easily accomplished, as the C3-C5 carbon bond has been cleaved by the secologanin synthase, and C10 has been subject to decarboxylation.



Scheme 2: Biosynthesis of vellosimine (**1**) from secologanin **120** and tryptamine **121**. The carbon atoms stemming from the diterpene moiety are highlighted in red for vellosimine. For the numbering see scheme 1.

The cyclization event from strictosidine **122** to polyneuridine aldehyde **57** has been subject to different hypothesis. The initial hypothesis from van Tamelen[2.28-2.31] suggests the cage structure formation from immium ion **125** to polyneuridine aldehyde **57** (see scheme 3). Lounasmaa and Hanhinen argued that the shortest bond-forming distance in this cyclization would be 2.70 Å, which is no reasonable range for C-C bond formation. Instead they put forward an opposing proposal, in which the bond-forming step between C5 and C16 takes place directly after fragmentation of strictosidine **122**.[2.11,2.32] The bond forming distance between C5 and C16 for compound **127** is approximately 1.50 Å, which is much better suited for C-C-bond formation. Tetracycle **128** is then transformed to polyneuridine aldehyde **57** in 3 steps. Nevertheless, this proposal adds one oxidation step in the beginning and one reduction step

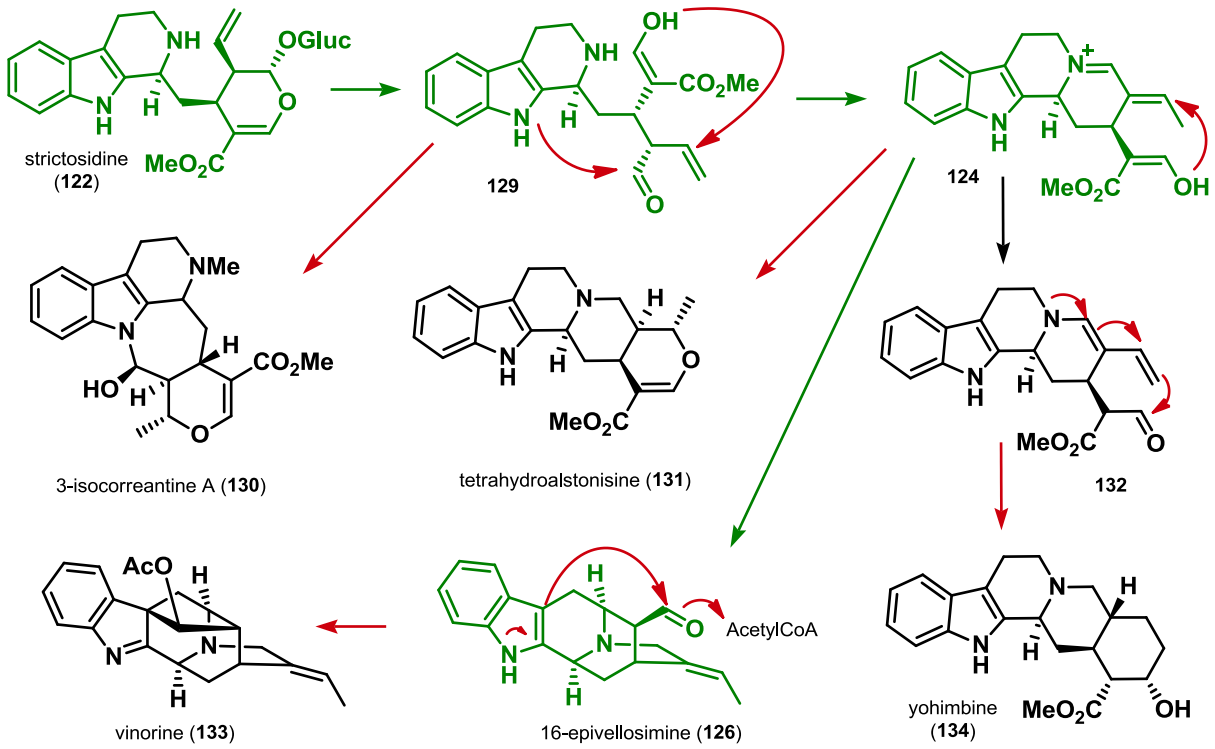
in the end of the cage structure formation, whereas the van Tamelen hypothesis proceeds redoxneutral. So far, no experimental evidence has been provided for either hypothesis.



Scheme 3: Comparison of the van Tamelen ring-closing hypothesis and the Lounasmaa and Hanhinen proposal.

A variety of natural products are closely related to intermediates in the vellosimine biosynthesis. After the fragmentation of strictosidine (**122**, see scheme 4) to give aldehyde **129** 3-isocorreantine A (**130**) can be obtained by conjugation of the skipped vinylogous aldehyde and subsequent nucleophilic attack of the enolate-oxygen, followed by attack of the indole nitrogen onto the aldehyde moiety (see red arrows).

Tetrahydroalstoninine **131** is derived from conjugated imminium ion **124** and attack of the enolate oxygen onto the vinylogous imminium ion. Yohimbine **134** is obtained after the formation of vinylogous enamine **132** and its attack onto the aldehyde. 16-Epivellosimine **126** can be transformed into vinorine (**133**) by attack of the indole onto the nearby aldehyde followed by acetalization of the resulting alcohol.[2.23]



Scheme 4: Major compounds (highlighted in green) in the biosynthesis of *sarpagine* alkaloids and related natural prdoucts.

Apart from different natural products from various alkaloid families which arise from different reactions with *sarpagine* biosynthetis intermediates (like in scheme 4), the late stage modification of polyneuridine aldehyde **57** forms about one hundred congeners (see figures 7-10 for details) of the *sarpagine* alkaloid family. A simple classification can be achieved by dividing these alkaloids in two major subgroups (see figure 11), depending on a possible decarboxylation at the C16 β-carboxyester. If this decarboxylation took place, the corresponding alkaloid is part of the "decarboxylation" subgroup, which comprises 71 congeners. If this decarboxylation event has not occurred, the alkaloid is part of the "no decarboxylation" subgroup, which consists of 28 members.

Each major subgroup can be devided further, depending on the orientation of the highest oxidated substituent R at C16. If this moiety is pointing up, the alkaloid is part of the "C16-epi" class, if it is pointing down, the alkaloid can be assigned to the "C16-regular" group. For both major subgroups, the "C16-regular" subgroup comprises approximately twice the number of congeners as the "C-16-epi" subgroup. Each subgroup can now be further devided according to the late stage additional cyclization events ("additional rings" or "no additional rings") or if dimerization has occurred.

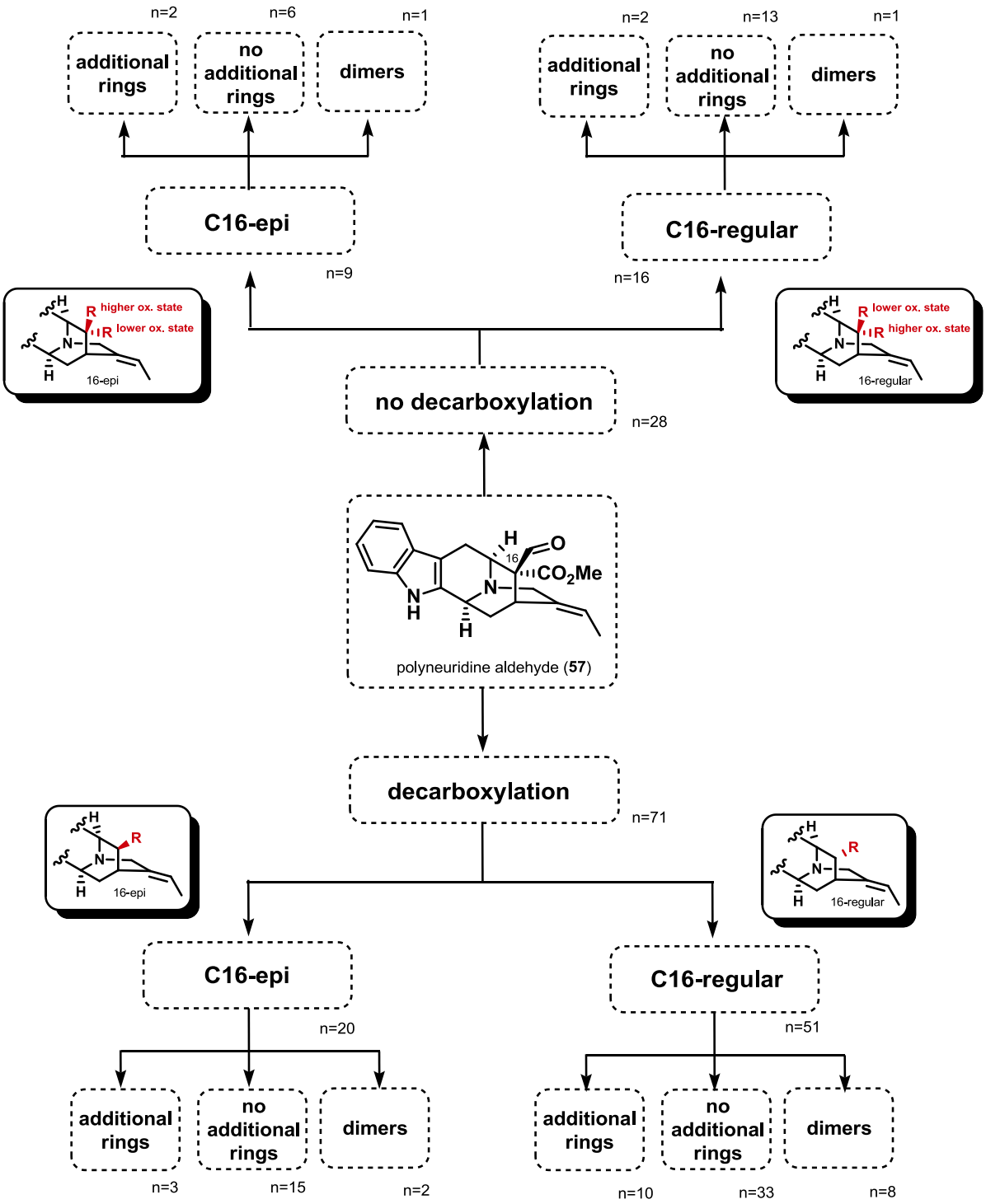


Figure 11: Classification of *sarpagine* alkaloids. n=number of natural products.

The alkaloids gelsochaltoine **109** and gardquinolone **110** are not part of this summary, as they are decomposition products of already known alkaloids. Note that rauvotetraphylline B (**99**) is the only alkaloid with a pyridine as the additional ring.

Additional Rings For the C16-Epi alkaloids the only known additional ring-formation has been observed *via* oxidative ring closure of the C16-epi-carbalcohol into the 6-position. This ring-forming event has been observed for the compounds below, for both the "decarboxylated" or the "no decarboxylation" subgroup (see figure 12).

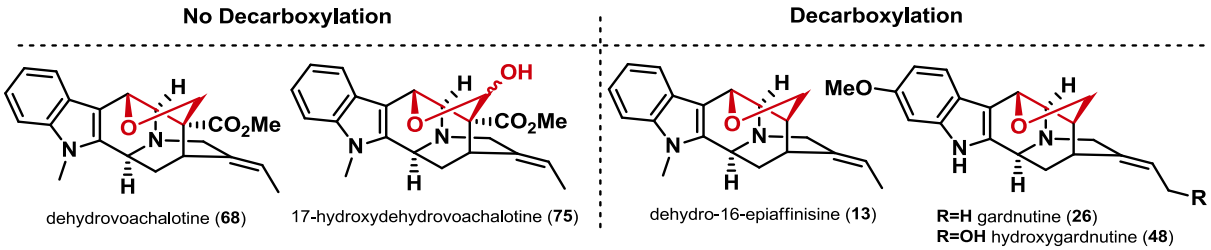


Figure 12: *Sarpagine* alkaloids with an additional ring in the C16-epi series.

For the decarboxylated C16-regular congeners the formation of a tetrahydropyrane ring is observed, as the oxidative cyclization into the 6-position is impossible. Two different compound classes can be observed, either possessing a methyl group at the piperidine moiety, or a methyl group at the tetrahydropyrane moiety (see figure 13).

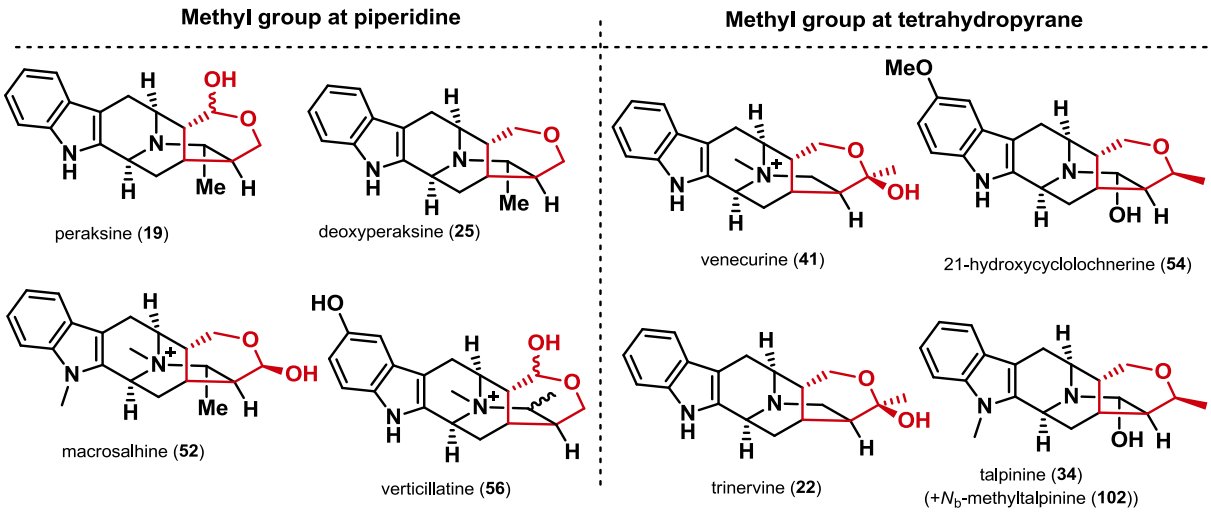
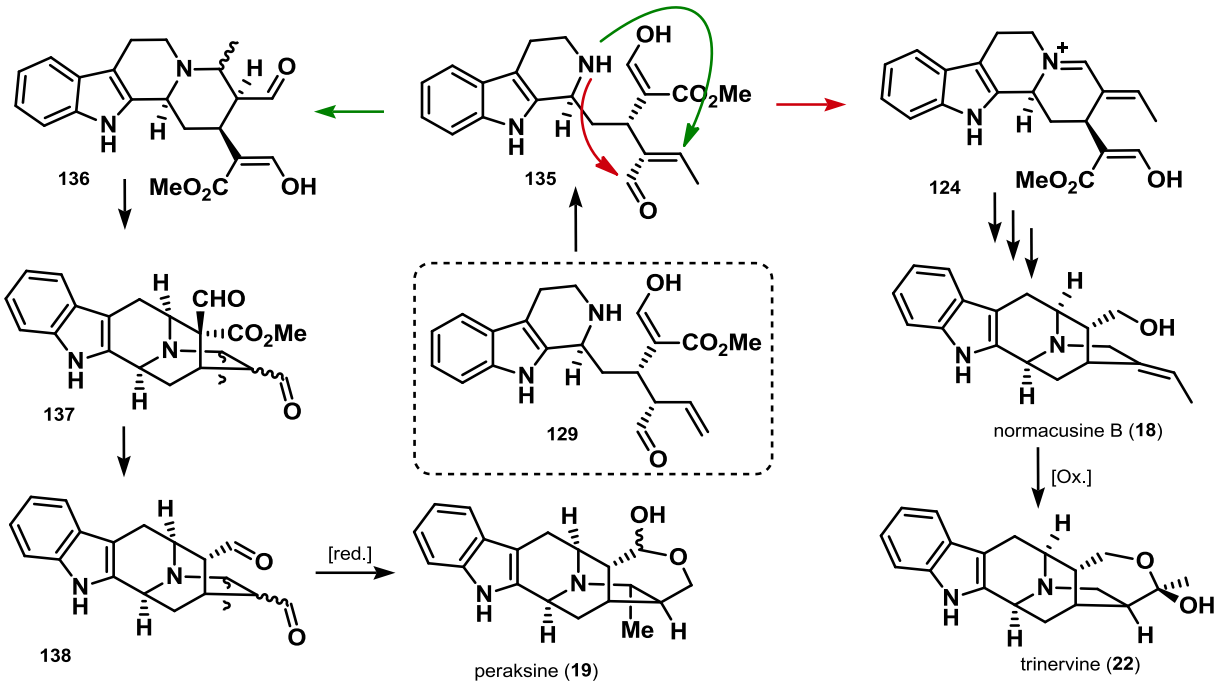


Figure 13: Alkaloids with additional ring systems in the decarboxylated C16-regular series.

An explanation for the different position of the methyl group can be found within the biosynthesis of the sarpagine alkaloids (see scheme 5). The skipped unsaturated aldehyde **129** is converted to the more stable conjugated aldehyde **135**, followed by the attack of the secondary amine either onto the aldehyde (red arrows) or in a conjugated fashion (green arrows). Following the red arrows, imminium ion **124** is formed, and in the known fashion

normacusine B (**18**). Trinervine (**22**) can then be obtained after oxidative tetrahydropyrane formation. Follwing the green arrows, aldehyde **136** is formed first, followed by oxidative cyclization to give intermediate **137**. Decarboxylation and epimerization at C16 leads to bisaldehyde **138**, which then forms peraksine (**19**) in a reductice cyclization.



Scheme 5: Plausible biosynthesis of additional ring systems in the *sarpagine* biosynthesis.

For the compounds without decarboxylation, two different ring formation events can be observed. Voacoline (**76**, see figure 14) is formed in a similar fashion as trinervine (**22**) *via* a late stage oxidative cyclization. Eburnaphylline (**74**) is most likely derived from a C18-oxidized polyneuridine aldehyde derivative, which then forms a tetrahydrofurane ring upon addition of the alcohol onto the former double bond.

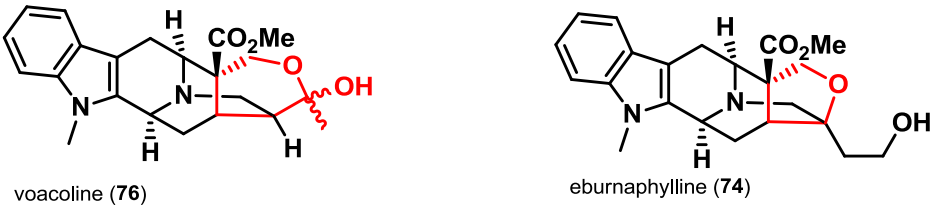
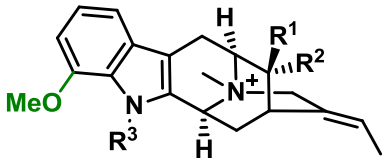


Figure 14: Non Decarboxylated alkaloids with an additional ring formation

Rauvotetraphylline (**99**, figure 9) is the only compound with an additional pyridine moiety as an additional ring, its formation is unknown.

Aromatic Substitution Heteroatomsubstitution is limited to three positions on the indole core and two different substituents, methoxy and hydroxy. *N*-Methylation at the indole-nitrogen (N_a) is frequently observed. Some dimers form an additional carbon-carbon bond at C9, C10 or C11.

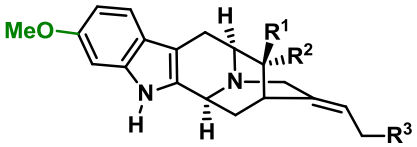
Substitution on the C12 is rarely observed, and has been reported only with a methoxy substituent. All alkaloids bearing this substitution pattern have been N_a-methylated as well (see figure 15).



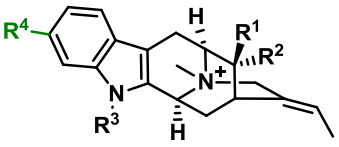
R^1=CH_2OH **R**^{2}=CO_2Et **R**^{3}=Me
12-methoxy-N_b-methylvoachalotine ethyl ester (**86**)
R^1=CH_2OH **R**^{2}=CO_2Me **R**^{3}=Me
12-methoxy-N_b-methylvoachalotine (**85**)
R^1=H **R**^{2}=CO_2Et **R**^{3}=Me
fuchsiaefoline (**79**)

Figure 15: Aromatic substitution at C12 within the *sarpagine* alkaloids.

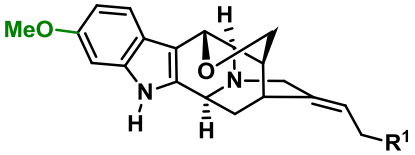
C11 is more prone to oxidative substitution. Both possible substituents (methoxy, hydroxy) are encountered. Further oxidation processes are encountered within these alkaloids, as 18-hydroxygardnerine is further oxidized at the allylic position, and gardnutine has been subject to oxidative ring formation with C6 (see figure 16).



R^1=CH_2OH **R**^{2}=H **R**^{3}=H
gardnerine (**32**)
R^1=CH_2OH **R**^{2}=H **R**^{3}=OH
18-hydroxygardnerine (**53**)



R^1=CH_2OH **R**^{2}=CO_2Me **R**^{3}=H **R**^{4}=OMe
11-methoxymacusine A (**82**)
R^1=CH_2OH **R**^{2}=CO_2Me **R**^{3}=Me **R**^{4}=OH
11-hydroxy-N_a-methylmacusine A (**81**)



R^1=H
gardnutine (**26**)
R^1=OH
18-hydroxygardnutine (**48**)

Figure 16: Aromatic substitution at C11 within the *sarpagine* alkaloids.

Substitution at C10 is observed most often. Both possible substituents are encountered, as well as methylation at the indole nitrogen N_a. Further oxidation at the allylic position has been observed as well in the case of 18-hydroxylochnerine (see figure 17).

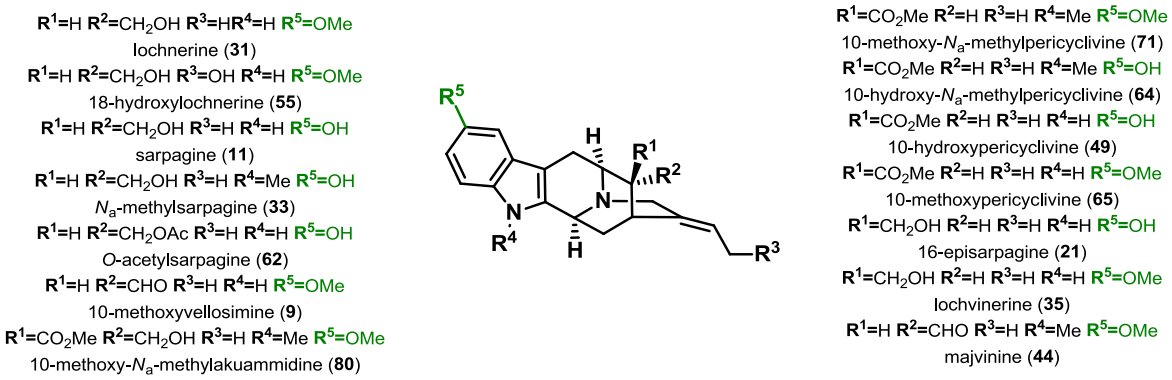


Figure 17: Aromatic substitution at C10 within the *sarpagine* alkaloids.

Further alkaloids have been isolated with substitution at C10. All of those compounds have been subject to N_b-methylation, in most cases without N_a-methylation. For two compounds additional oxidative ring formation is observed (see scheme 18). A peraksine congener (**98**) was isolated with hydroxy substituent at C10.

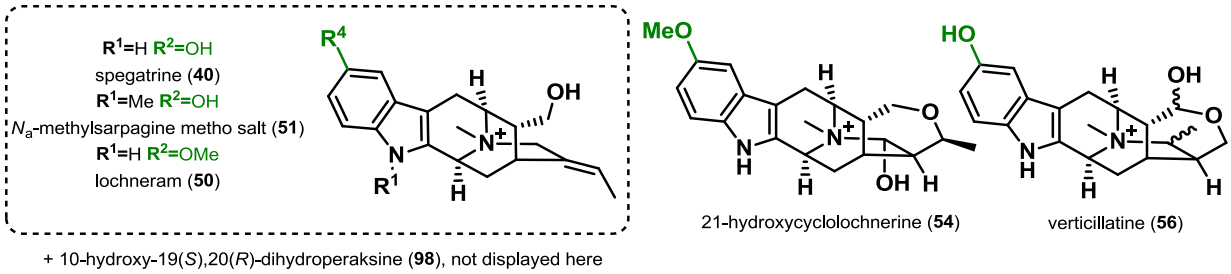


Figure 18: Aromatic substitution at C10 within the *sarpagine* alkaloids, metho salts and additional rings.

Variation at the quinuclidine core Variation at the quinuclidine core is frequently observed and occurs both reductively and oxidativly. For four examples reduction of the double bond has been observed, leading to an ethyl group with defined stereochemistry (see figure 19).

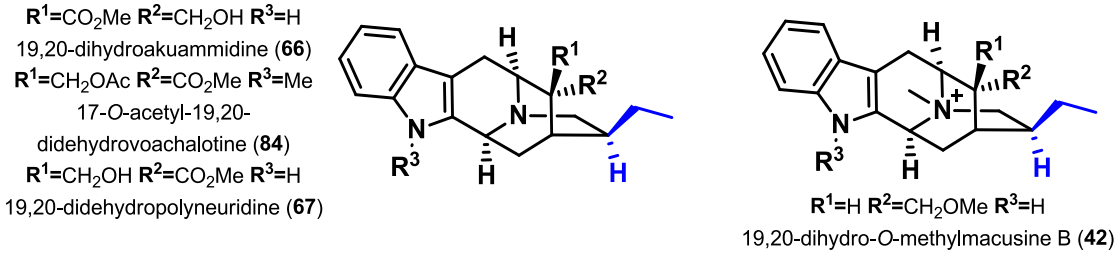


Figure 19: Reduction of the double bond within the *sarpagine* alkaloids.

A rather uncommon variation at the quinuclidine core is the observation of a *Z*-configured double bond. Five examples of this variation have been isolated (see figure 20). Gelsochalotine (**109**) has been suggested to arrive from *Z*-akkuamidine and bears the *Z*-configured double bond as well. Oxidation in the allylic position leading to 18-hydroxy-affinisine, -lochnerine, -gardnerine and -gardnutine can be observed in four cases.

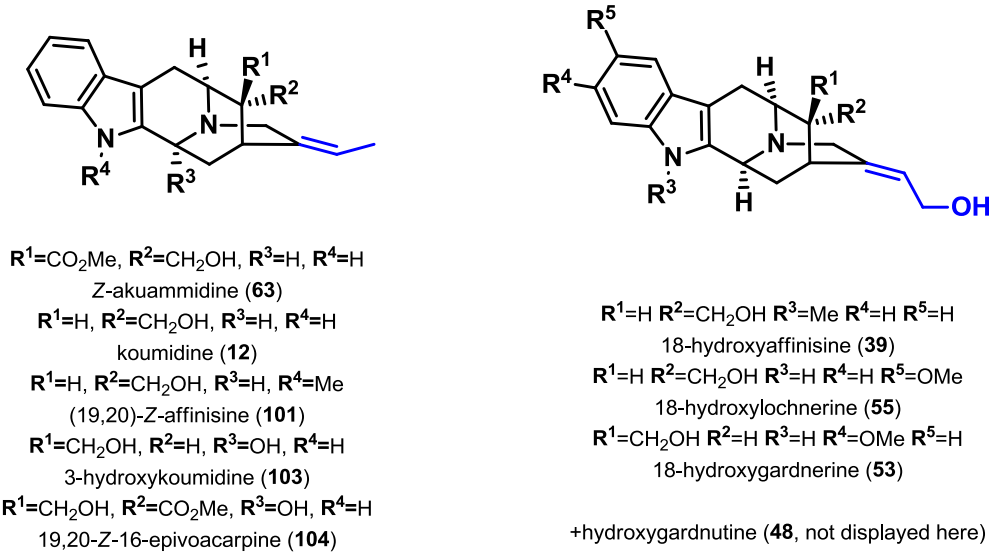


Figure 20: Variation in the double bond configuration and allylic oxidation within the *sarpagine* alkaloids.

Furthermore, N_b-oxidation has been reported twice, forming affinisine derivative **37** and normacusine congener **36** (see figure 21). Alstoumerine (**38**) displays a double bond within the quinuclidine core (part of an allyl alcohol), probably due to conjugate addition of water to the vinylogous imminium ion **124** (see scheme 2). The alstoumerine core is also found in two dimers, lumitinine C (**106**) and lumitinine D (**107**). Oxidation in the pseudo-benzylic indole position (C6) forming an alcohol has been observed in the case of ervincidine (**20**). This type of oxidation is more frequently observed within the 16-epi series to oxidativley form a five-membered ring (see figure 11). Oxidation next to the N_b-nitrogen (or addition of water to an intermediate imminium ion) leads to the formation of 21-hydroxyvoachalotine (**77**). Two similar analogues were isolated (rauvotetraphylline B (**99**) and rauvotetraphylline C (**100**)), which are unique concerning the glucosidated hydroxy-group at C21. They furthermore contain two unique moieties at C16, which are stated to be artefacts from the isolation process.[2.14] Within the *sarpagine* alkaloids emerges a certain different subgroup after the isolation of compounds **96**-**98**.[2.13] The peraksine skeleton (for the biosynthesis see scheme 5) displays a characteristic methyl substituent at C21, resulting from a deviation in

the sarpagine biosynthesis. This subgroup contains nine members, including compounds **23**, **51**, **96**-**98** and four oxidized congeners (see figure 12).

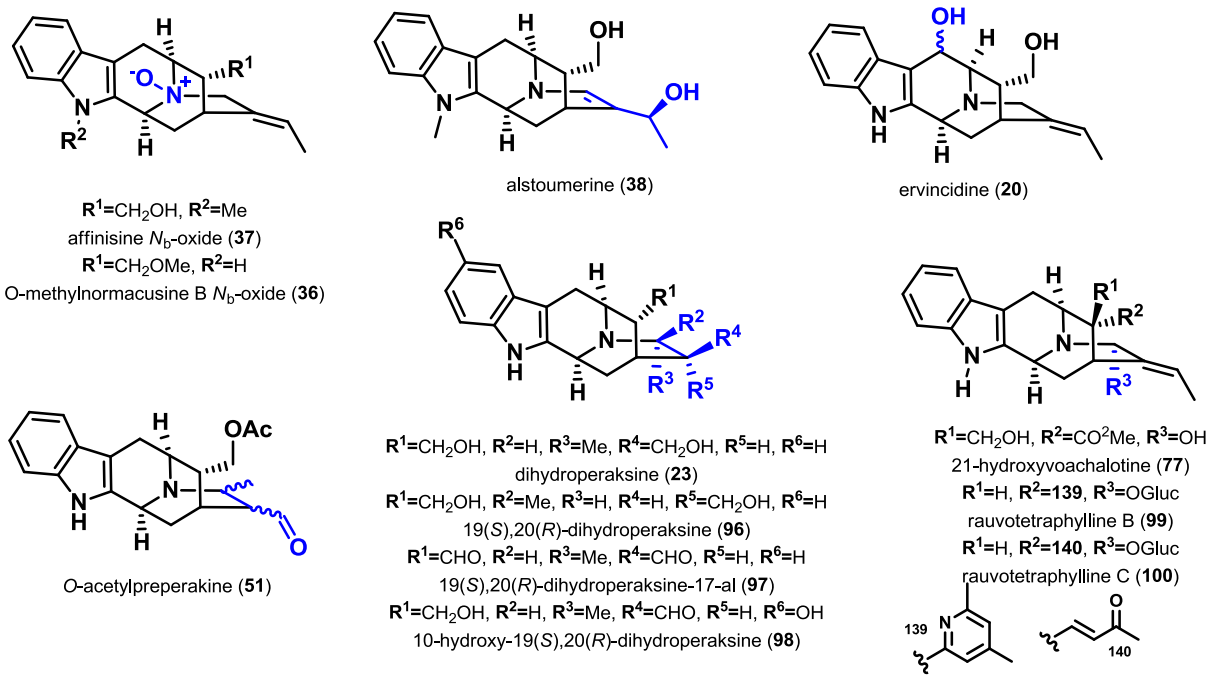
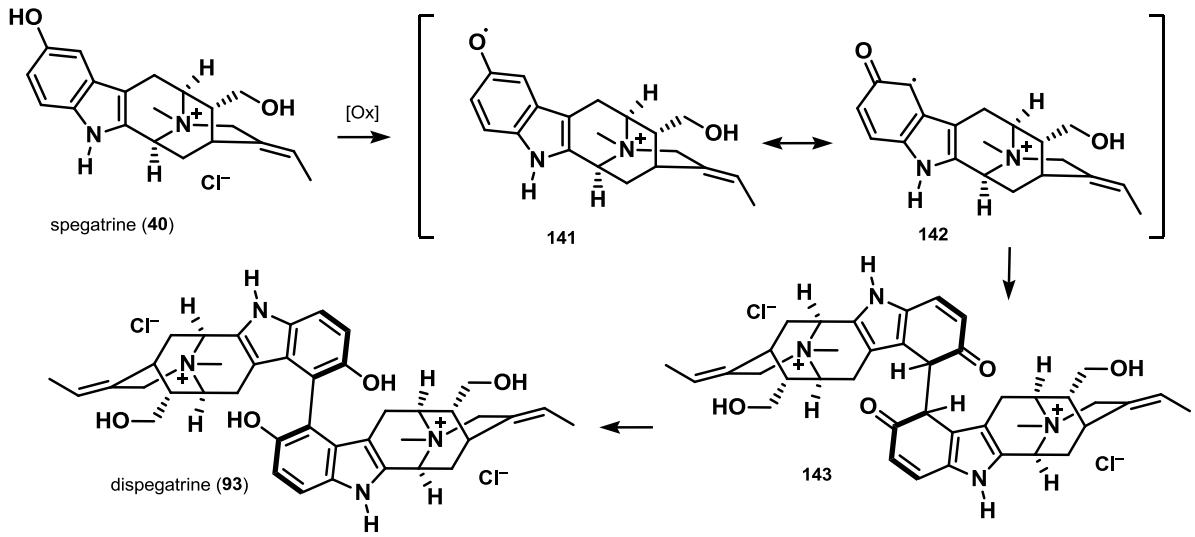


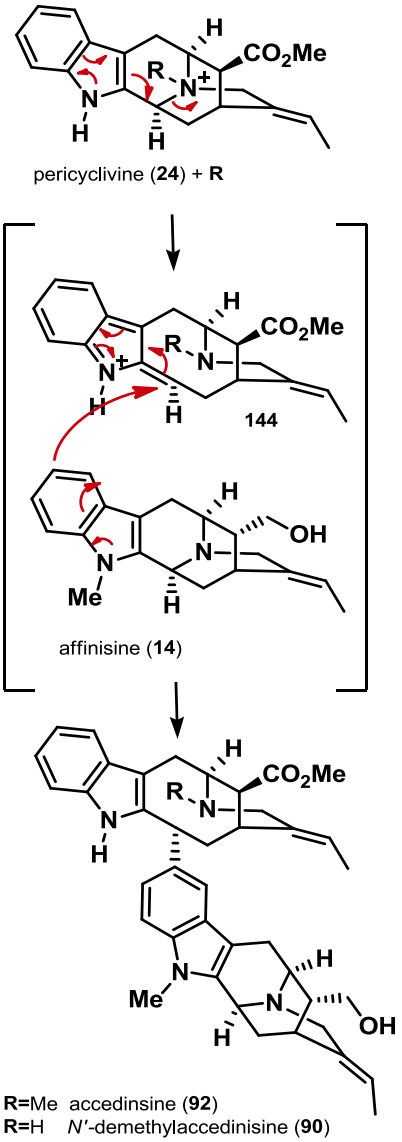
Figure 21: Various other oxidations and rearranged *sarpagine* alkaloids of the peraksine subgroup.

Dimerization Within the family of dimeric sarpagine alkaloids exist both homo- and hetero-dimers. The most understandable dimer dispegatrine (**93**) is furnished *via* oxidative phenol coupling of spegatrine (**40**, see scheme 6). The phenolic hydroxygroup is oxidized to phenoxyradical **141**, which is in conjugation with α-keto radical **142**. This radical can now undergo dimerization to give dimer **143**, which can tautomerize to dispegatrine **93**.



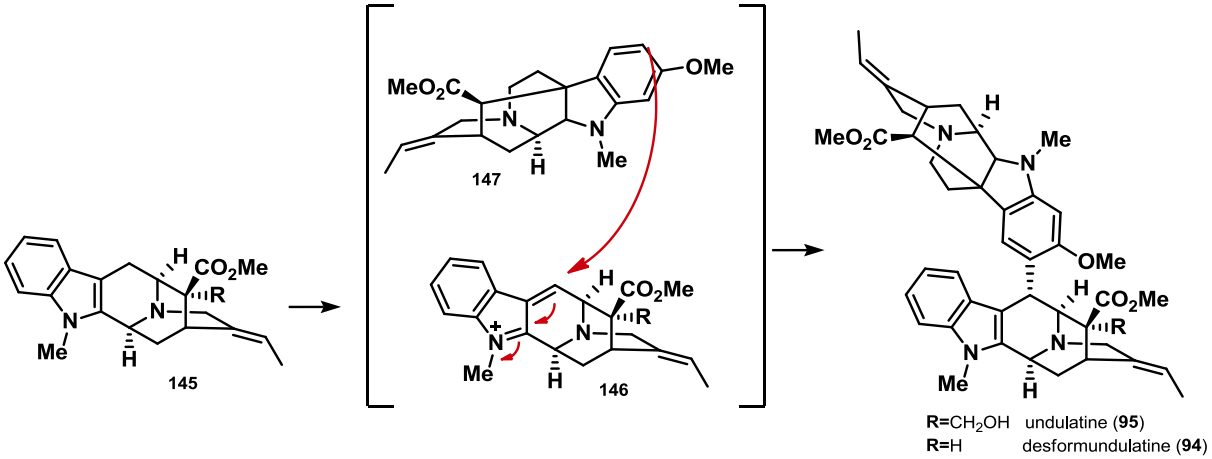
Scheme 6: Oxidative phenol couling in the formation of dispegatrine **93**.

Accedinsine **92** and its nor-methyl equivalent *N'*-demethylaccedinsine **90** (see scheme 7) are assembled from two different sarpagine alkaloids, affinisine (**14**) and pericyclivine (**24**). In the first biosynthetic step, N_b-quaternization occurs, followed by ring opening assisted by the indole core to give intermediate **144**. The indole core of affininsine **14** attacks at C3, resulting in rearomatization of the former pericyclivine moiety. Rearomatization of the affinisine part leads to accedinsine **92** and its nor-methyl equivalent *N'*-demethylaccedinsine **90**.



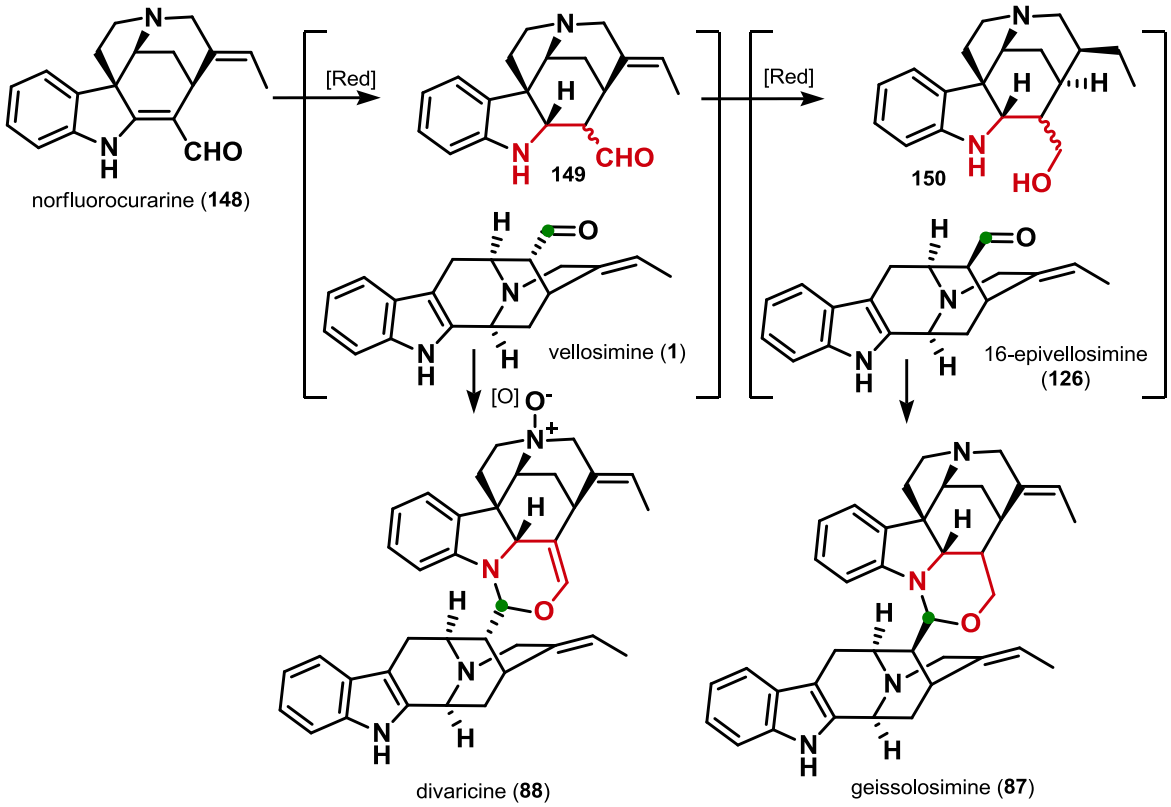
Scheme 7: Dimerization of accedisine **92** and its nor-methyl equivalent *N'*-demethylaccedinsine **90**.

A similar dimerization can be stated for the formation of undulatine **95** and desformundulatine **94** (see scheme 8). Oxidation of compound **145** leads to the formation of delocalized imminium ion **146**, which is attacked by the indole core of the ajmaline type compound **147**. Rearomatization leads to the two discussed dimers.



Scheme 8: Formation of undulatine **95** and its congener **94**.

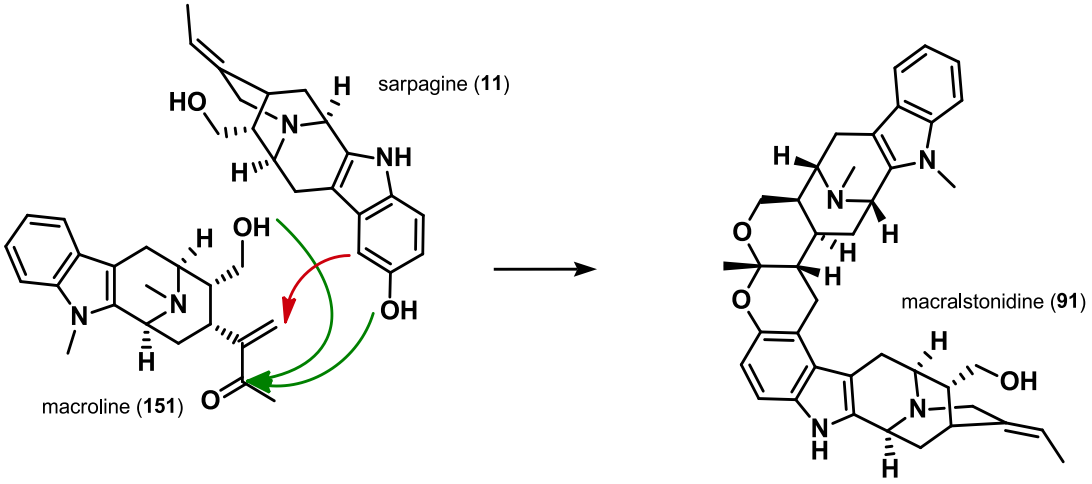
The two dimeric compounds divaricine **88** and geissolosimine **87** (see scheme 9) stem from two different alkaloid families. The northern part of both molecules originates from the strychnine biosynthesis.[2.33] Norfluorocurarine **148** is reduced to to either aldehyde **149** or alcohol **150**. These two compounds undergo condensation with either vellosimine **1** or 16-epivellosimine **126** to give divaricine **88** or geissolosimine **87**.



Scheme 9: Biosynthesis of divaricine **88** and geissolosimine **87**.

The hetereodimer macralstonidine **91** (see scheme 10) is formed from the addition of sarpagine (**11**) onto macroline **151**. The activated C9 of the indole nucleus of sarpagine (**11**)

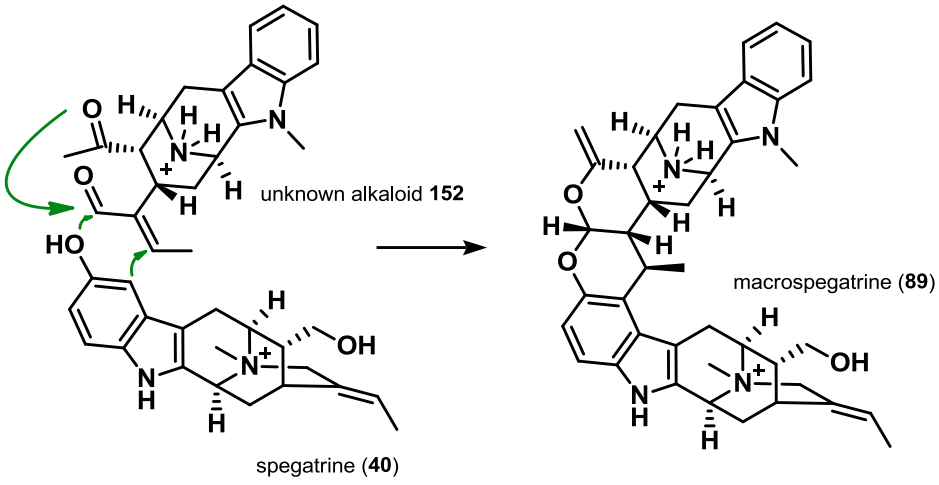
attacks macroline's Michael acceptor in a conjugated fashion. Next in line follows the condensation of the phenolic C10-hydroxy group of sarpagine (**11**) and the primary alcohol of macroline (**151**) onto macroline's ketone under the loss of water.



Scheme 10: Formation of macralstonidine **91**.

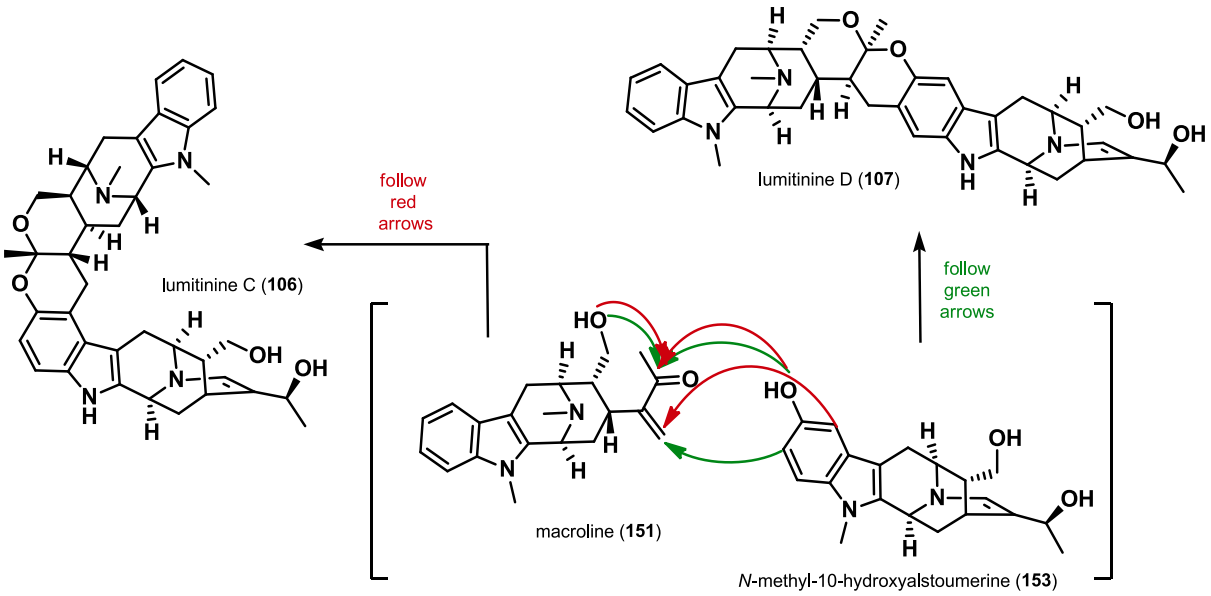
Another dimerization product of spegatrine **40** was isolated and called macrospegatrine (**89**, see scheme 11). Interestingly, the second alkaloid in this heterodimer is the unkown macroline type compound **152**.

This compound bears an unusual ketone functionality. The activated C9 of the indole nucleus of spegatrine (**40**) attacks the Michael acceptor in a conjugated fashion. Next in line follows the condensation of the phenolic C10-hydroxy group of spegatrine (**40**) and the enolate form of the ketone from **152** onto the aldehyde of former spegatrine (**40**) under the loss of water to form macrospegtarine **89**.



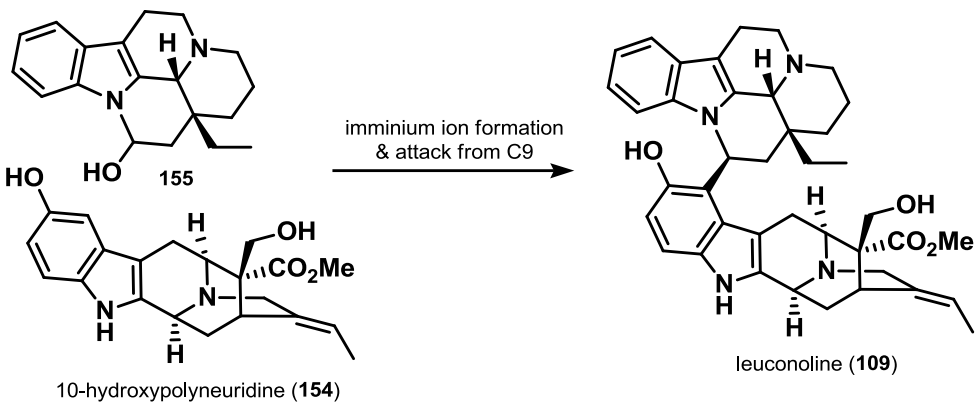
Scheme 11: Formation of macrospegatrine **89**.

The two heterodimers lumitinine C (**106**) and lumitinine D (**107**, see scheme 12) are formed *via* two different modes of attack of the unisolated *N*-methyl-10-hydroxyalstoumerine (**153**) and known macroline **151**. If the C9-position of **153** attacks the Michael acceptor, and subsequent condensation occurs with the phenolic C10-hydroxy group and the carbalcohol of macroline **151**, lumitinine C (**106**) is formed. If the initial attack occurs from the 11-position of **152** and subsequent condensation is carried out in a similar fashion, lumitinine D (**107**) is formed.



Scheme 12: Hetereodimerization yielding lumitinine C **106** and lumitinine D **107**.

Finally, leuconoline (**108**, see scheme 13) is formed by condensation of unknown 10-hydroxypolyneuridine **154** and polycyclic compound **155** *via* the formation of a very reactive imminium ion (dearomatization because of the participation of the N_a-lone pair) and subsequent nucleophilic attack of the activated C9-position of 10-hydroxypolyneuridine **154**.

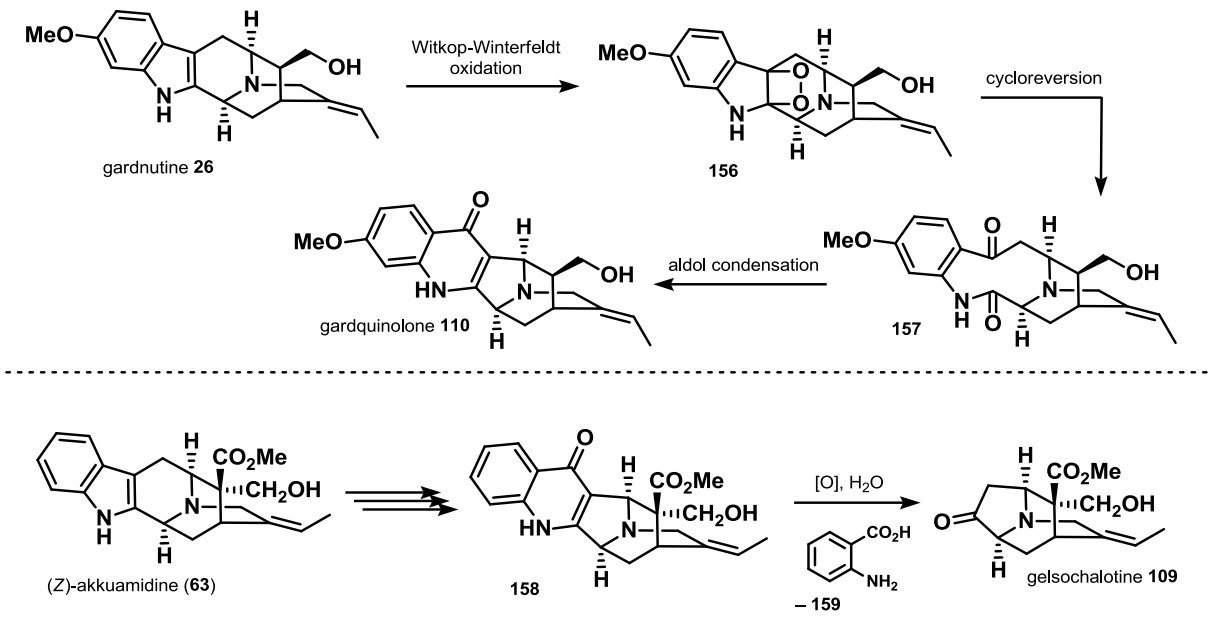


Scheme 13: Formation of leuconoline **109**.

Degradation Two degradation products have been isolated, both resulting from oxidation of the indole core. Gardquinolone **110**[2.22] has been suggested to arise from gardnerine **26**, probably *via* Witkop-Winterfeldt oxidation of the indole moiety to give peroxy-intermediate **156**, which collapses to form **157**. This 10-membered macrocycle is then converted to the quinolone core of gardquinolone **110** *via* intramolecular aldol condensation This kind of oxidative rearrangement has been experimentally observed on similar systems.[2.34,2.35]

Gelsochalotine **109** has been coisolated with 19-(*Z*)-akuammidine **63** (see scheme 14). It has been suggested that gelsochalotine arises from this compound, but the authors provide a rather sluggish biosynthetic pathway.[2.21] Instead it is more likely, that (*Z*)-akkuamidine **63** is oxidized in the same fashion as gardnutine, leading to the similar quinolone derivative **158**. Final epoxidation of the quinolone double bond, followed by Meinwald-like rearrangement leads to gelsochalotine **109** under the netto loss of 2-aminobenzoic acid **159**.

It seems likely, that the authors did isolate either gardnutine **26** or 19-(*Z*)-akuammidine **63**, and the obtained degradation products formed during the isolation process.

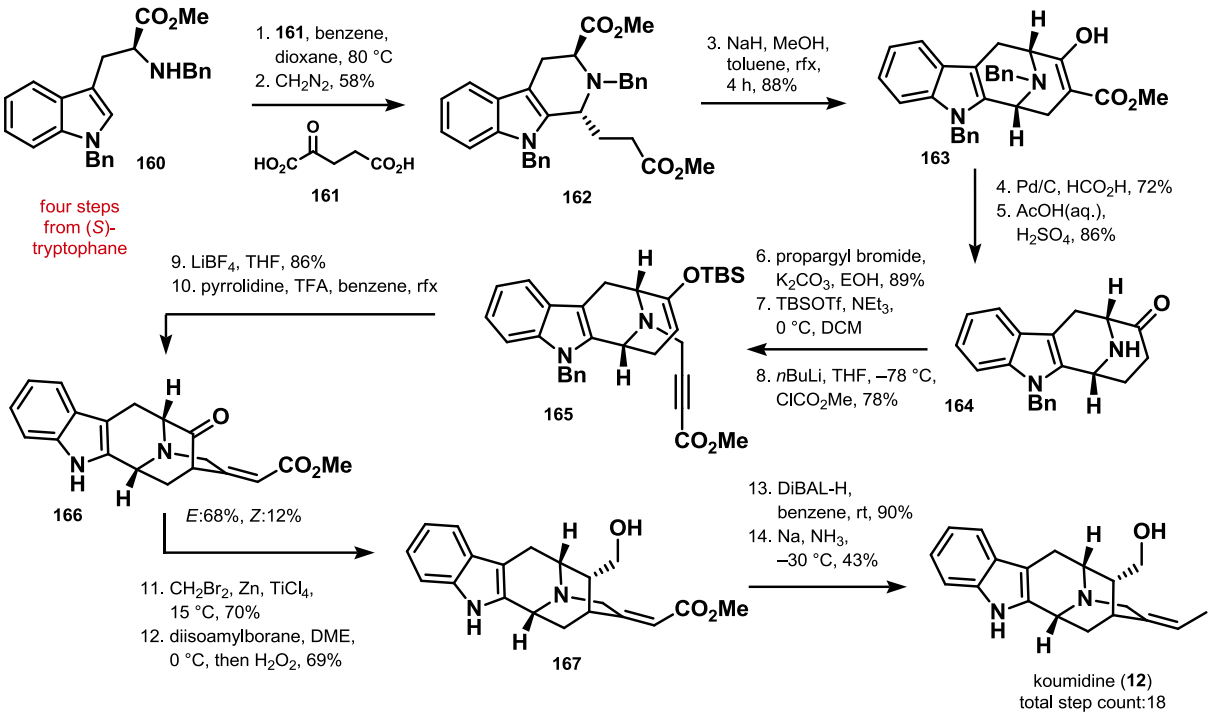


Scheme 14: Degradadtion of *sarpagine* alkaloids, leading to gardquinolone **110** and gelsochalotine **109**.

2.4 Synthetic Efforts

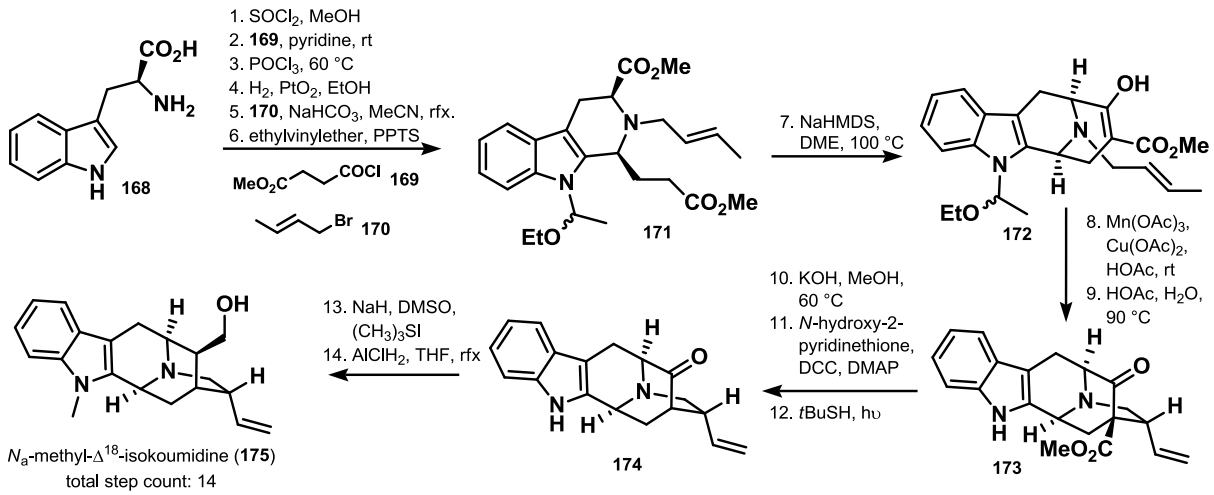
For a comprehensive and complete summary of the synthetic efforts on *sarpagine* synthesis see the review from Lewis.[2.36]

The group of Magnus has pioneered in the synthesis of *sarpagine* alkaloids by assembling *E*-koumidine (**12**, see scheme 15).[2.37] Starting from tryptophane derivative **160** (obtained in four steps from (*S*)-tryptophane) they were able to obtain tricycle **162** after reductive Pictet-Spengler reaction using acid **161** and subsequent esterification using diazomethane. Subjection to basic conditions led to the formation of β-ketoester **163**. Selective N_b-debenzylation followed by acid-catalyzed decarboxylation yielded ketone **164**. Propargylation was achieved next, followed by silyl-enol ether formation and attachment of an ester moiety to the propargylic position, yielding ester **165**. Next followed deprotection of the ketone by $LiBF_4$, which set the stage for the pyrrolidine catalyzed ring closure to obtain compound **166**. Both double bond isomers were obtained, heavily favouring the undesired *E*-isomer. *Exo*-methylene formation was achieved next, followed by hydroboration/oxidation yielding alcohol **167**. The redundant ester moiety was then removed using a two step reduction protocol. This synthesis is able to form the antipode of koumidine **12** in 18 steps total.



Scheme 15: Magnus total synthesis of koumidine **12**.

The group of Liu has accomplished a synthesis of the *sarpagine* alkaloid derivative N_a-methyl-Δ^{18}-isokoumidine (**175**, see scheme 16).[2.38] They started from *L*-tryptophane **168**, which was transformed into its methyl ester derivative, followed by the formation of the corresponding amide using acid chloride **169**. Generation of the chloroiminium ion led to a Pictet-Spengler reaction, the resulting imine was reduced to the corresponding amine using H_2/PtO_2. Next in line was alkylation and protection of the indole nitrogen to yield tricycle **171**. This compound was then subjected to basic conditions at elevated temperatures, which led to the formation of tetracycle **172**. Radical cyclization was initiated using $Mn(OAc)_3$, which led to the formation of the quinuclidine core. The indole protecting group was cleaved under acidic conditions to give **173**. The surplus ester moiety was saponificated and decarboxylated using Barton conditions, furnishing ketone **174**. Finally the remaining C1-homoloagtion was achieved *via* Corey-Tschaikowsky epoxidation (with concomitant N_a-methylation). The resulting epoxide was then opened under reducing conditions using Lewis-acidic $AlClH_2$ to give **175**. The Liu group was able to generate a non-natural *sarpagine* alkaloid in 14 steps.

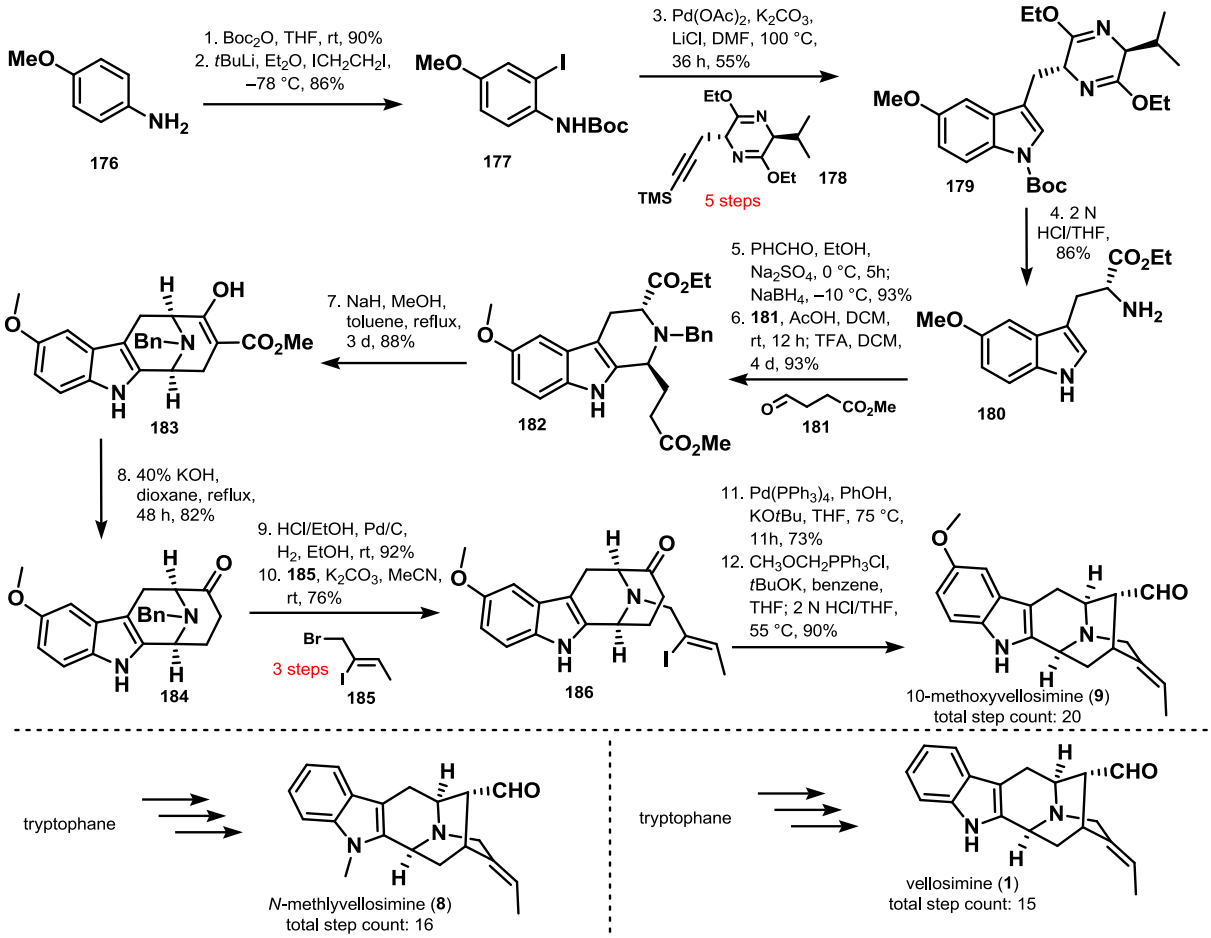


Scheme 16: Liu's total synthesis of N_a-methyl-Δ^{18}-isokoumidine **175**.

The group of James Cook accomplished numerous total syntheses of *sarpagine* congeners. Their syntheses are short and straight forward, as long as the starting carboxylic acid is commercially available. For substituted indole cores a large number of additional steps has to be added.

The Cook total synthesis of 10-methoxyvellosimine (**9**, see scheme 17)[2.39] starts with paramethoxyaniline **176**, which is Boc-protected and iodinated using *ortho*-lithiation to yield

aniline **177**. Larock indole synthesis with Schöllkopf-auxilliary **178** (obtained in 5 steps from valine) furnished Boc-protected indole **179**. Both the Schöllkopf auxiliary and the Boc-protecting group are removed to obtain tryptophane derivative **180**. Reductive amination followed by Pictet-Spengler cyclization with aldehyde **181** yields tricycle **182**. Treatment with basic conditions furnished β-ketoester **183**, which can be decarboxylated to give ketone **184**. Removal of the benzyl protecting group followed by allylation using **185** yields vinyliodide **186**. This compound is then submitted to the α-vinylation conditions developed by the Bonjoch group, followed by MOM-Wittig elongation and enol ether equilibration to the thermodynamically more stable aldehyde of 10-methoxyvellosimine (**9**). The total step count for this total synthesis is 20 steps, including the steps that are necessary to obtain the Schöllkopf-auxilliary and the vinyliodide. For *N*-methylvellosimine (**10**) the synthesis can be carried out in almost the same manner, but requiring only 16 steps for completion, starting from the commercially available amino acid tryptophane. Vellosimine (**1**) can be obtained by similar chemistry in 15 steps, also starting from tryptophane.



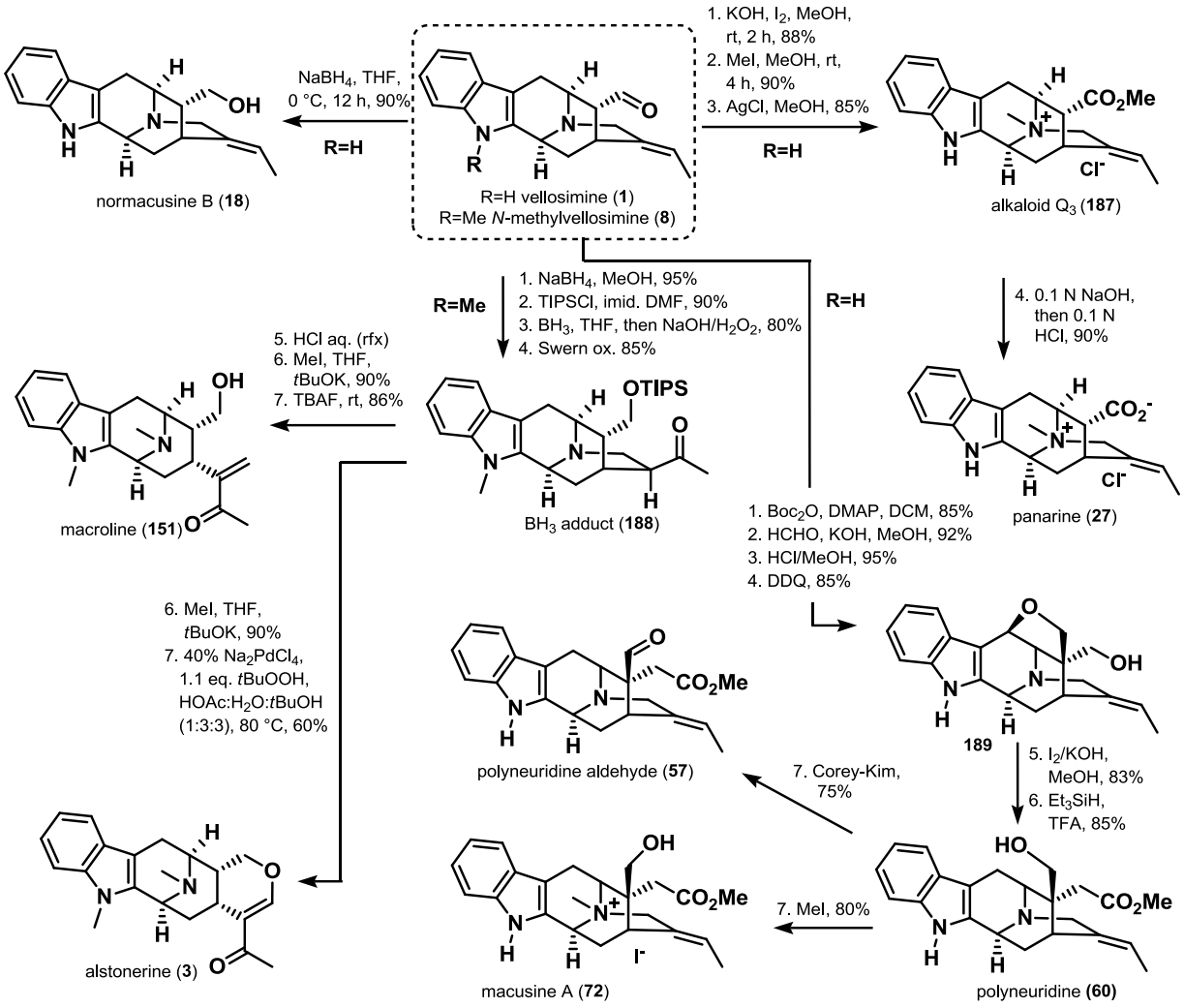
Scheme 17: Cook's synthesis of 10-methoxyvellosimine (**9**), *N*-methylvellosimine (**8**) and vellosimine (**1**).

Vellosimine (**1**, R=H) was used as a platform for the Cook group to access several different *sarpagine* alkaloids *via* further chemistry (see scheme 18).[2.40a] Reduction of vellosimine (**1**) with sodium borohydride yields normacusine B (**18**) in good yield. Oxidation followed by methylation and anion exchange leads to the formation of alkaloid Q_3 (**187**), which can be transformed into panarine (**27**) by saponification. Note that alkaloid Q_3 (**187**) was not considered to be a *sarpagine* alkaloid by Lounasmaa&Hanhinen[2.11] due to the lack of rigorous proof. As it has been prepared by Cook and coworkers,[2.40a] and matches the previously sluggish data,[2.40b] it can now be considered to be part of the *sarpagine* alkaloids.

Access to the non decarboxylated subclass of sarpagine alkaloids can be obtained *via* quarternization of C16.[2.41] Boc-protection of the indole-nitrogen of vellosimine (**1**) is followed by the addition of formaldehyde. Next in line is deprotection under acidic conditions and oxidation at C6 (*sarpagine* numbering) using DDQ to differentiate both alcohols and obtain compound **189**. Esterification of the free alcohol followed by reduction opening of the hydrofurane moiety yields polyneuridine **60**. Macusine A (**72**) can be accessed from this compound *via* N_b-methylation. Polyneuridine aldehyde **57** can be obtained after Corey-Kim oxidation of the free alcohol of compound **60**.

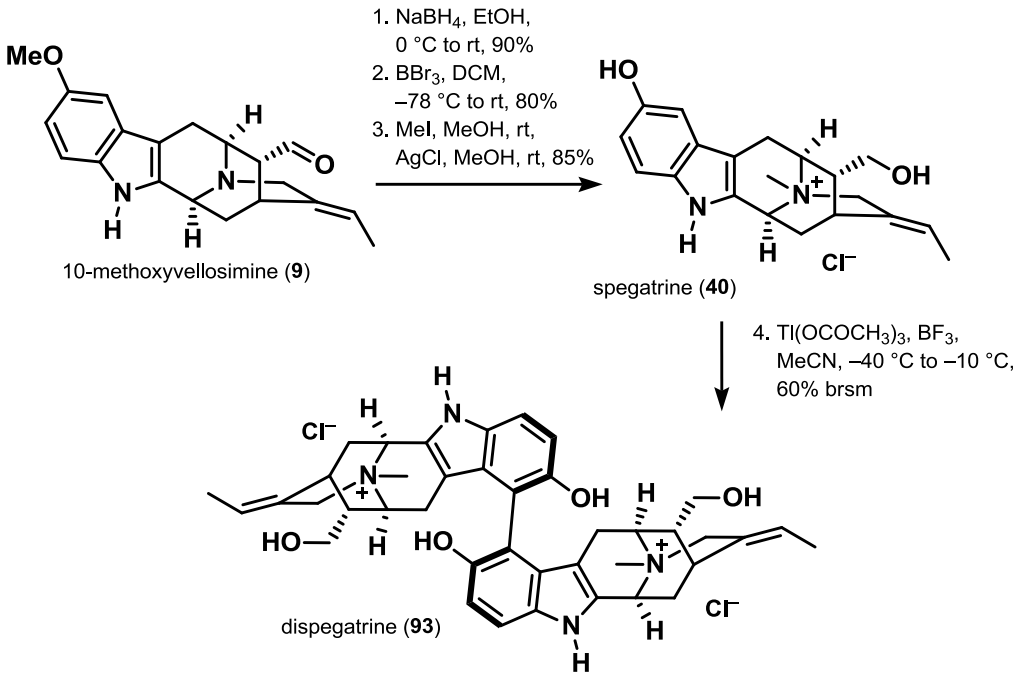
They were further able to demonstrate that *N*-methylvellosimine (**8**) could be converted to macroline (**151**)[2.42] and alstonerine (**3**) (two alkaloids which are not part of the *sarpagine* alkaloids).[2.43] This reaction sequence commenced with reduction of the aldehyde moiety of *N*-methylvellosimine (**9**) and subsequent protection of the free alcohol to give an intermediate silyl enol ether. Next followed the hydroboration/oxidation of the double bond to the corresponding alcohol, which was obtained as the *tert*. amine/BH_3 adduct. The alcohol was oxidized using Swern conditions to obtain ketone **188** still as the BH_3-adduct. Acidic cleavage of the amine/borane adduct under reflux conditions followed next. Macroline **151** could readily be obtained *via* Hoffmann-elimination and deprotection of the alcohol.

Alstonerine (**3**) can be obtained *via* the same Hoffmann-elimination process. After the formation of an intermediate enone the alcohol is deprotected under acidic conditions, resulting in its conjugated attack onto the enone. Final oxidation under palladium catalysis yields alstonerine (**3**).[2.43]



Scheme 18: Accessing different alkaloids from vellosimine (**1**) or *N*-methylvellosimine (**9**), according to J. M. Cook.

They were furthermore able to convert 10-methoxyvellosimine (**9**) to spegatrine (**40**) in three steps (see scheme 19). Reduction of the aldehyde using sodium borohydride was followed by demethylation with tribromoborane, liberating the phenolic hydroxygroup. N_b-methylation occurred next using methyliodide, followed by ion exchange with silver(I) chloride to obtain the desired chloride counter ion of spegatrine (**40**). After considerable experimentation they were able to achieve the desired homodimerization to yield dispegatrine **93** using thallium(III) catalysis in the presence of the Lewis acid boron trifluoride.[2.44] The overall conversation starting from 10-methoxyvellosimine (**9**) proceeds in overall good yield. The yield for the homodimerization to give dispegatrine **93** is impressive.



Scheme 19: Cook's total synthesis of dispegatrine **93**.

2.5 Bioactivities

Only a few bioactivity studies have been conducted in case of the *sarpagine* alkaloids, despite the fact that *sarpagine* alkaloids have been supposed to be the active ingredients in chinese traditional medicine. Of the few tested examples, pericyclivine (**24**, see figure 22) exhibits moderate activity against the P388 leukemia cell line.[2.45] 11-Methoxymacusine (**82**) has shown to posses muscle relaxant effects in rats,[2.46] whereas gardnerine (**32**) displayed the best inhibition in ganglionic transmission from six different gardneria alkaloids.[2.47] Leuconoline (**108**, see figure 9) displays weak cyctotoxyity against human KB cells.[2.20]

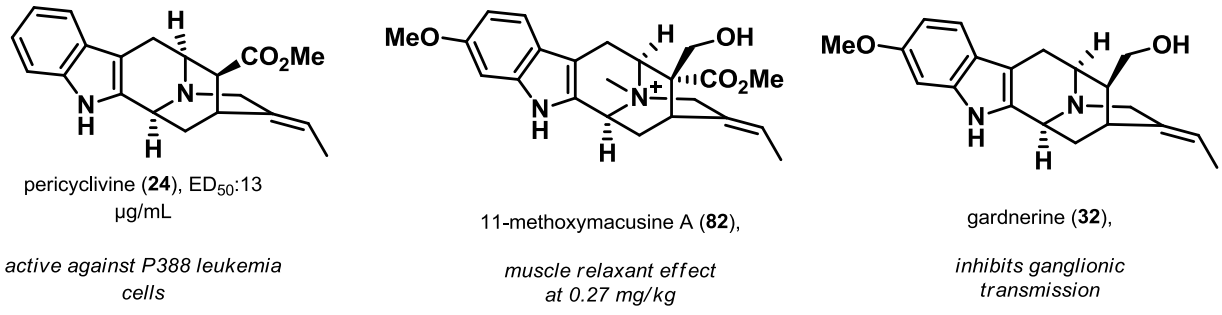
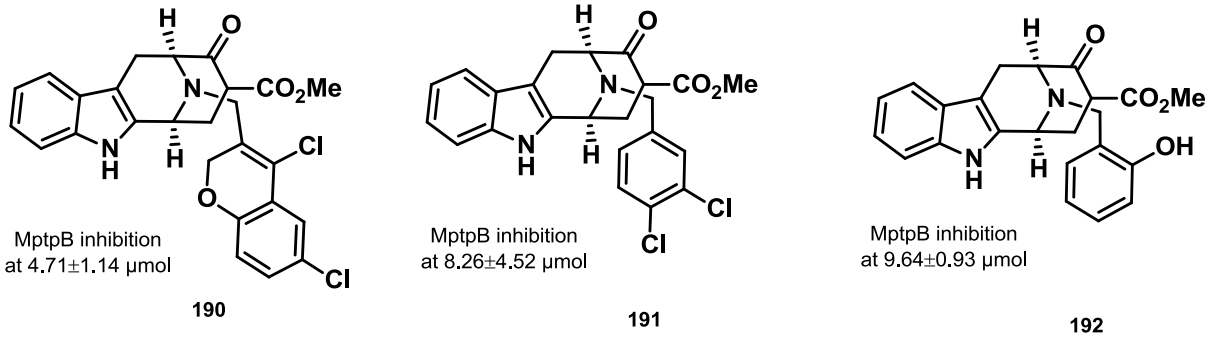


Figure 22: Three *sarpagine* alkaloids and their bioactivities.

Waldmann and coworkers investigated the use of *sarpagine* substructures as protein tyrosine phosphatase B inhibitors.[2.48] These phospotases are used by *mycobacterium tuberculo-*

sis to render the host's defense mechanism ineffective. As inhibition of these enzymes might hinder the bacterial growth, this compound class has gained attention due to the development of antibiotic resistant strains. After the formation of a solid-phase based compound-library, thex were able to identify compounds **190**-**192** (see figure 23) as very potent MptpB inhibitors, which selectively only inhibit the desired phosphatase.



190 **191** **192**

Figure 23: Waldmann's protein tyrosine phosphatase B inhibitors **190**-**192**..

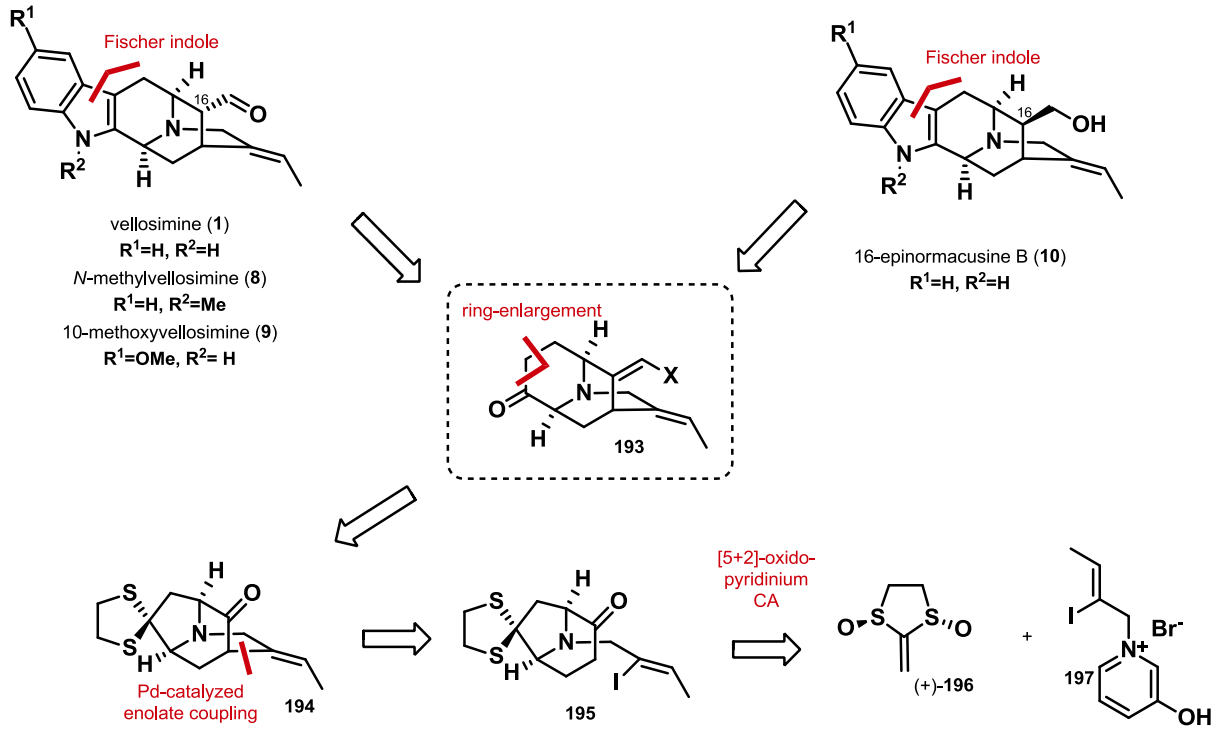
2.6 Synthetic Planning

We started our synthetic planning by detailed analysis of the isolated *sarpagine* congeners. As the most *sarpagine* congeners are part of the "decarboxylated" subclass of *sarpagine* alkaloids (see figure 11), we decided to start our synthetic studies targeting this subclass exclusively. As within this subgroups most alkaloids do not have additional ring systems and have not suffered from dimerization, we aimed for a unified total synthetic access towards these two subclasses (16-epi & 16-regular of the "decarboxylated" *sarpagine* alkaloids), comprising a total of 48 alkaloids out of 99 alkaloids isolated (including alkaloid Q_3).

As the alkaloids we are targeting (vellosimine (**1**), *N*-methylvellosimine (**8**), 10-methoxyvellosmine (**9**) and 16-epinormacusine B (**10**)) mostly defer in the substitution pattern at the indole core, we decided that a unified, late stage diversification strategy could be best carried out by late stage indolization (see scheme 20). Keeping this strategy in mind, we aimed for a late stage Fischer indolization, as a large number of the necessary phenylhydrazines would be commercially available. In this manner, we would even be able to obtain a vast library of unnatural vellosimine analogues. As we were targeting both the 16-epi and the 16-regular group, we traced those alkaloids back to intermediate **193**. If we are targeting a 16-epi alkaloid, the X-group is a simple proton, as late stage hydroboration/oxidation will

install the desired stereochemistry. If we intend to access a 16-regular compound, we need a methoxygroup for last stage thermodynamically favoured liberation of the desired aldehyde.

The late stage mutual precursor **193** should be build up *via* C1-homologation from dithiolane **194** after liberation of the masked ketone. The cage structure of compound **194** is obtained after palladium-catalyzed enolate coupling of vinyliodide **195** according to the Bonjoch protocol.[2.49,2.50] Compound **195** is the reduced version of the common intermediate that has been introduced in the introduction (compound 7, figure 5). Tricycle **195** should be readily obtained from a [5+2] oxidopyridinium cycloaddition with Aggarwal's chiral ketene equivalent (+)-**196** and 3-hydroxypyridinium salt **197**.[2.51] In order to establish a modern, state of the art synthetic approach we focused on a low step count (maximum 15 steps as in the Cook benchmark synthesis), a late stage diversification strategy targeting a variety of *sarpagine* alkaloids and a complete dismissal of protecting groups. If we could demonstrate the access to both the 16-epi and the 16-regular subgroup, we will have access to a large part of all *sarpagine* alkaloids that have been isolated.



Scheme 20: Retrosynthetic analysis for the desired alkaloids.

The following section briefly summarizes the occurrence of the key step (the [5+2] oxidopyridinium cycloaddition) in total synthesis.

2.7 The 3-Oxidopyridnium [5+2] Cyloaddition

Although the 3-oxidopyridinium [5+2] cycloaddition allows rapid access to the tropane skeleton, it has only been used scarcely in the total synthesis of complex natural products.[2.52,2.53] Jung, Longmei and co-workers achieved the total synthesis of racemic Bao Gong Teng A (**198**, see figure 24) *via* the cycloaddition between pyridinium salt **199a** and acrylonitrile **200a**.[2.54a] The same compound **198** was synthesized by Liebeskind and co-worker using a molybdenum-mediated [5+2] cycloaddition between organometallic chiron **199b** and methylvinyl ketone **200b**.[2.54b] The intramolecular cycloaddition of oxidoisoquinoline betaine (**202**) has been published by Gin and co-worker in their synthesis of nominine (**201**).[2.55] Stoltz and co-workers[2.56] have used oxidopyrazinium betaine **204** and chiral Michael acceptor **205** in their total synthesis of lemonomycin (**203**). Kozikowski and coworkers utilized the tropane skeleton arising from the 3-oxidopyridinium [5+2] cycloaddition for the investigation of cocaine congeners.[2.57,2.58] Cha *et al.* synthesized the tricyclic core of sarain A using a 3-oxidopyridinium betaine cycloaddition approach.[2.59]

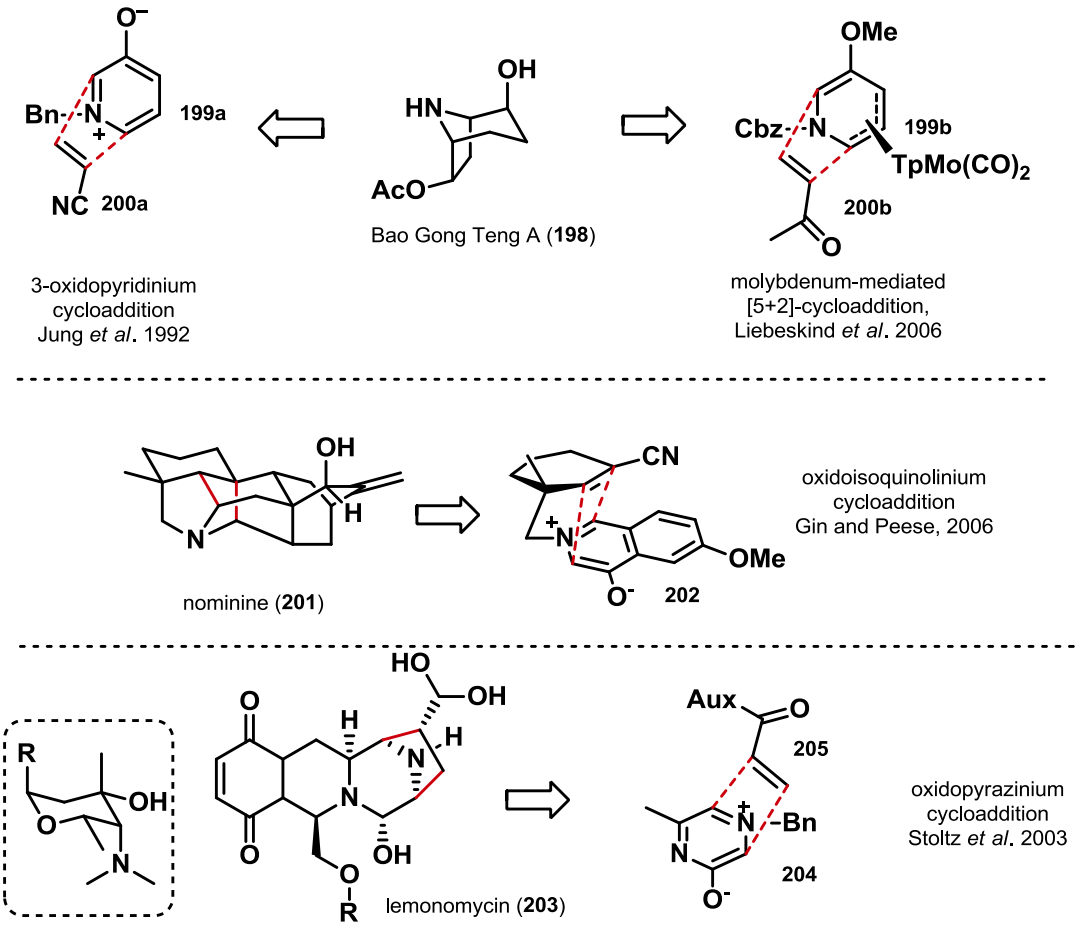
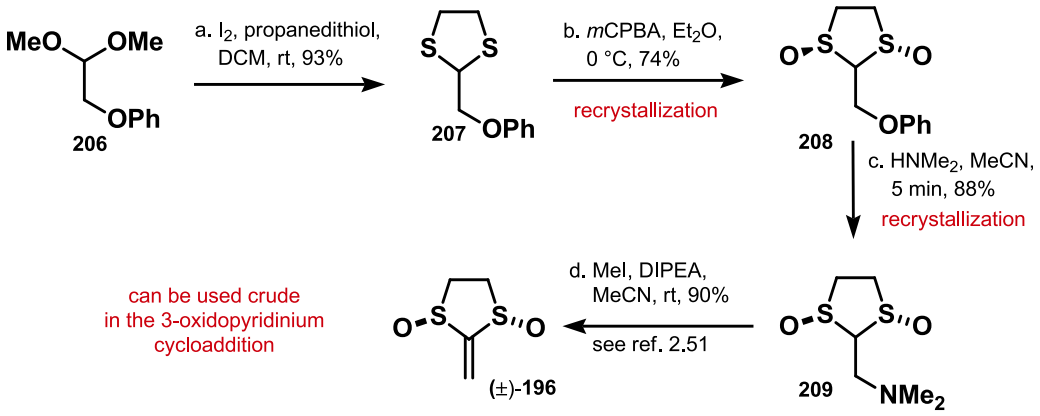


Figure 24: Application of the 3-oxidopyridinium [5+2] cycloaddition in total synthesis. Tp=hydridotris(pyrazolyl)borate

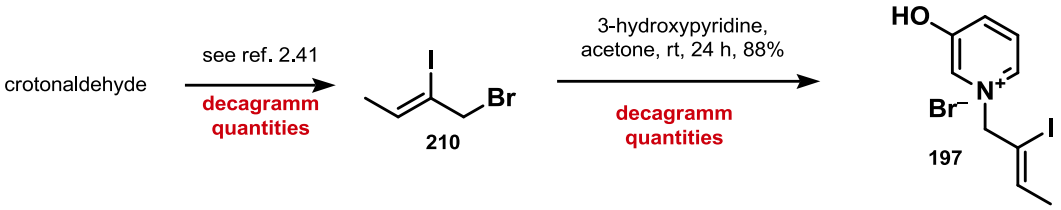
2.8 Results

Bissulfoxide 196 The synthetic work on the *sarpagine* alkaloids started with the quest for a fast and feasible access to Aggarwal's chiral ketene equivalent (±)-**196**[2.51] in a racemic fashion (see scheme 21). In contrast to the originally published procedure, iodine was employed in the generation of dithiolane **207** from commercially available dimethylacetal **206**. *m*CPBA can then be used to generate bissulfoxide **207** in a racemic fashion. Subjection of bissulfoxide **207** to dimethylamine leads to the formation of amine **208** in a very rapid fashion (less then five minutes reaction time). Aggarwal's ketene equivalent **196** can then be obtained by treating amine **208** with methyl iodide under basic conditions. In order to carry out the 3-oxidopyridnium [5+2] cyloaddition on large scale, the access to compound (±)-**196** needs to be as easy as possible. Therefore, the purification of intermediates is mostly carried out *via* crystallization. The final vinyl bissulfoxide can be used crude in the cycloaddition, cutting the amount of purifications *via* column chromatograhpy down to a single one at the very beginning of the synthesis.



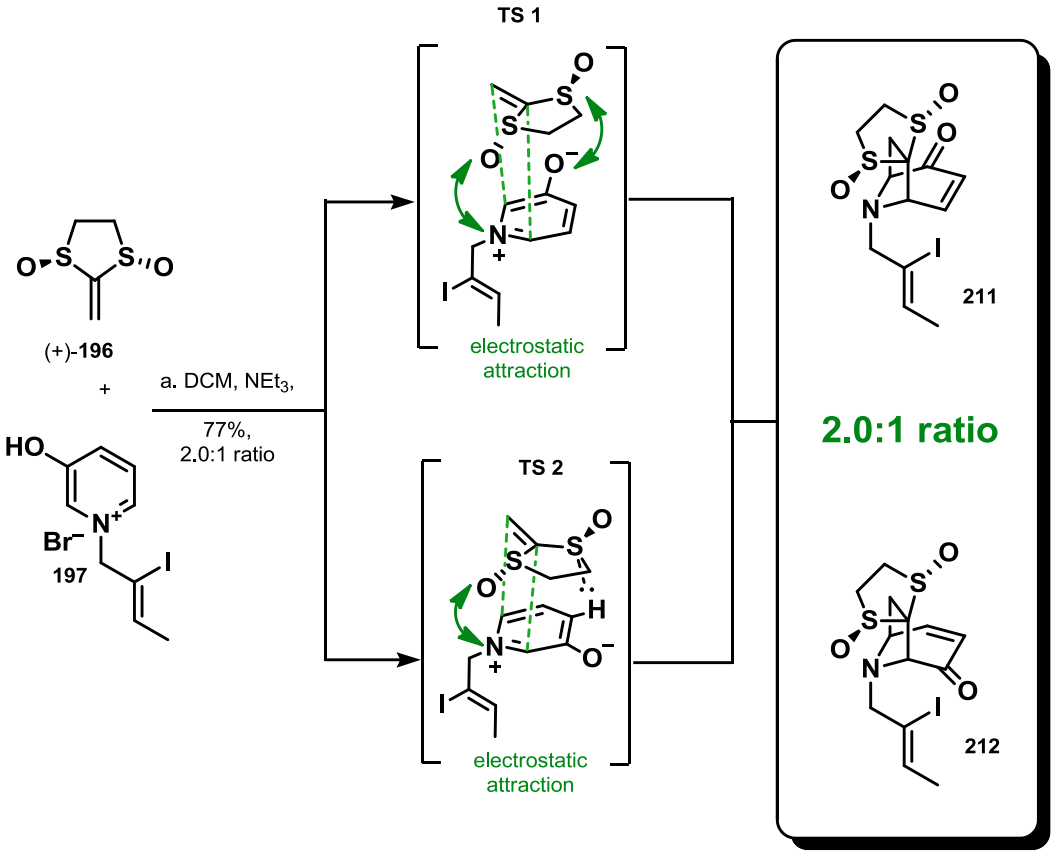
Scheme 21: Synthesis of racemic vinylbissulfoxide **196**.

Pyridinium salt 197 The necessary vinyliodide **210** (see scheme 22) can be easily obtained in decagramm quantities from crotonaldehyde according to literature procedures.[2.41] Pyridinium salt **197** can be obtained in good yield and can be purified *via* crystallization.



Scheme 22: Access to pyridinium salt **197**.

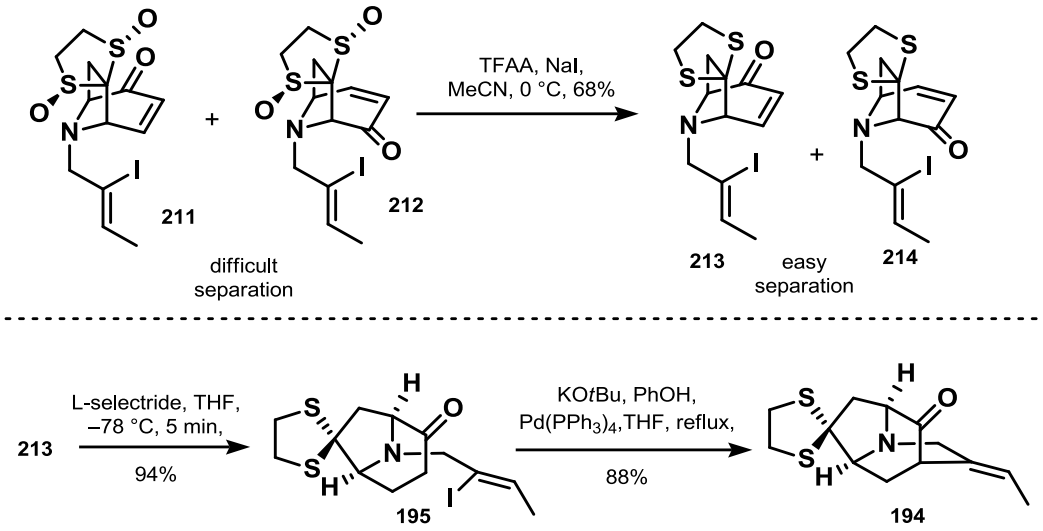
[5+2] Cycloaddition Carrying out the desired 3-oxidopyridnium [5+2] cyloaddition with pyridinium salt **197** and vinyl bissulfoxide (+)-**196** leads to a regioisomeric mixture of compounds **211** and **212** (see scheme 23). Those two regioisomers arise from the the two possible transition states **TS 1** and **TS 2**, with **TS 1** being the more stabilized early transition state. The larger amount of matched charge interactions leads to a higher amount of the desired regioisomer.[2.51b] The less favoured trasition state **TS 2** is not as well stabilized as **TS 1**, thererfore a lesser amount of regioisomer **212** is formed. Note that the interaction between the pyridnium oxygen and the positively charge sulfur in **TS 2** does occur as well, but results in the steric clash of the *S*-lone pair and the indicated proton. The stereoinduction of the chiral sulfoxides is considered to be complete.[2.51b]



Scheme 23: The 3-oxidopyridinium [5+2] cyloaddition and its transition state.

Towards the quinuclidine core As the two regioisomers (**211**/**212**, see scheme 24) that are obtained after the cycloaddition are difficult to separate they are processed as a mixture to the next step. Deoxygenation is achieved next using a mixture of TFAA/NaI.[2.51b] Attempts to use tribromophosphine remained unsuccessfull. After the separation of the regioisomers **213** and **214**, only the desired isomer **213** is carried on through the synthesis, as separation

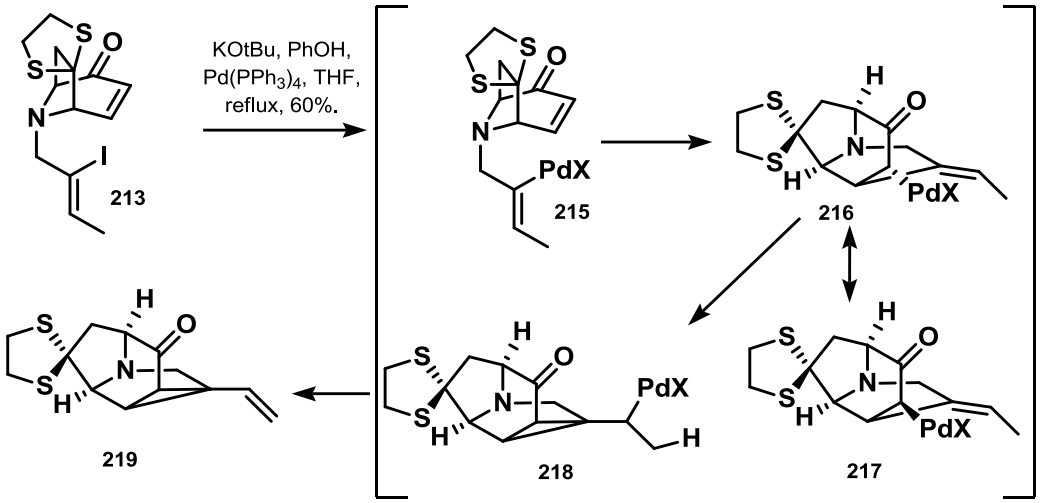
can now be easily achieved. Next in line is the conjugate reduction of enone **213** using L-selectride. This reaction is highly dependent on the amount of equivalents of added L-selectride, as overreduction easily occurs. Using a diluted (0.1 M) and cooled (–78 °C) solution of L-selectride for a short time (about 5 minutes) gives the best yields of ketone **195**. Palladium catalyzed enolate coupling between the vinyl iodide moiety of **195** and the enolate resulting from high temperature deprotonation with the *in situ* formed very weak base PhOK can be achieved in the next steps using the conditions developed by the Bonjoch group[2.49,2.50] and gives compound **194**. No decomposition of the vinyliodie moiety to either an alkyne or an allene has been observed. As enone **213** and ketone **195** cannot be separated *via* chromatography, the complete conjugate reduction of enone **213** has to be ensured, as remaining **213** lowers the reaction rate with which **194** is formed.



Scheme 24: Deoxygenation, conjugate reduction and enolate coupling.

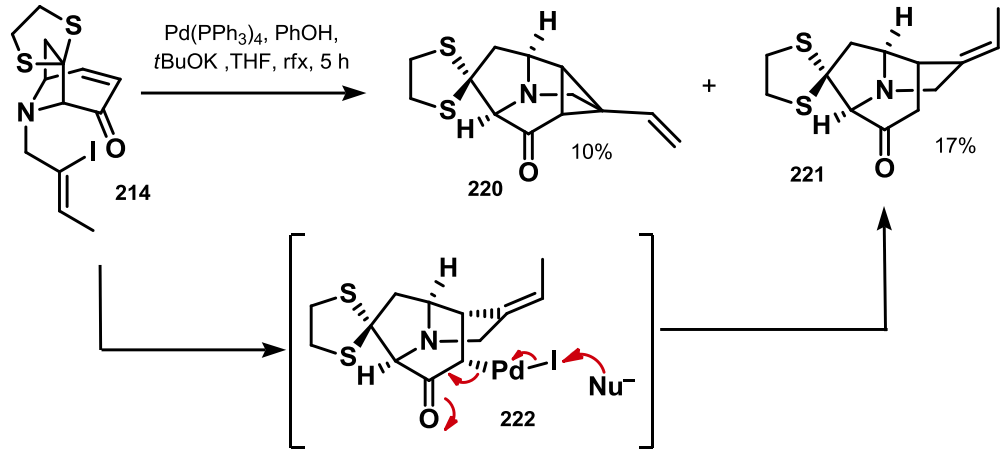
This result can be explained by the formation of byproduct **219** (see scheme 25), which can be obtained by treating enone **213** with the enolate coupling conditions employed earlier. After initial oxidative insertion yielding **215** compound **216** is formed after carbo-palladation. The α-palladium species **216** then undergoes another carbo-palladation, furnishing cyclopropane **218**, as the other possible α-palladium species **217** cannot undergo β-hydride elimination. Final β-hydride elimination of **218** results in the observed vinylcyclopropane moitey of compound **219**. Similar cyclizations have rarely been observed.[2.60-2.62] As the formation of the cyclopropane moiety is accompanied by a penalty in formation energy, the overall reac-

tion rate is slowed down. Furthermore the palladium catalyst decomposes faster due to the longer residence in less stable stages of the catalytic cycle.



Scheme 25: Pd-catalyzed vinylcyclopropane formation.

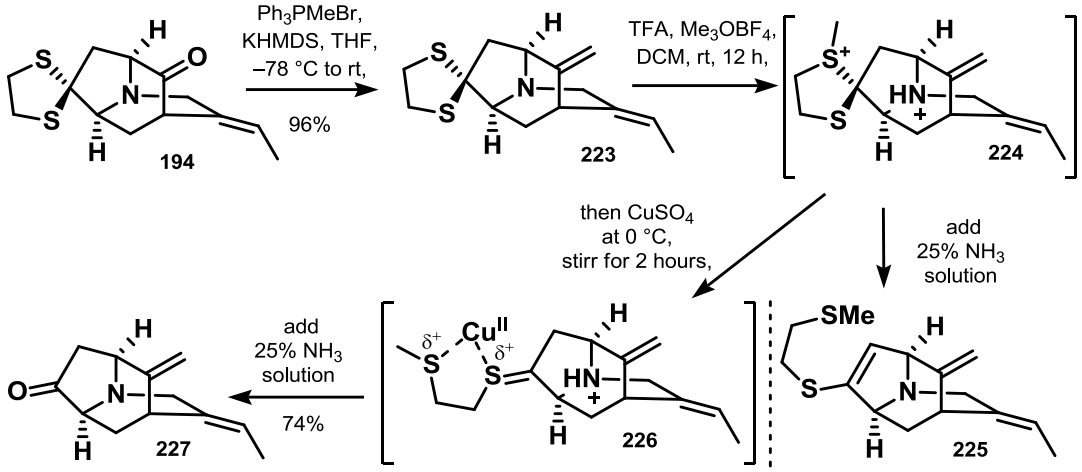
If the other regioisomer **214** (see scheme 26) is used for the same reaction, a much diminished yield (10%) of the desired vinylcyclopropane **220** is obtained. Instead, the competitive formation of five membered cyclic **221** can be observed. The occurrence of compound **221** can be explained by a reductive depalladation from **222** under the formation of iodine.



Scheme 26: Heck cascade and reductive cyclization using enone **214**.

Differentiation In order to gain access to both the 16-epi and the 16-regular subgroup of sarpagine alkaloids, the synthetic route had to differ at some point. With the introduction of different substituents at the position of the ketone moiety a point of differentiation was installed, leading to a first late stage intermediate in the synthesis of *sarpagine* alkaloids (see scheme 20, cp. **193**). The synthetic access to the 16-epi group of *sarpagine* alkaloid is discussed first.

16-epi With racemic compound **194** in hands (see scheme 27) we carried out a Wittig olefination of the ketone functional group, which proceeded smoothly using KHMDS as base to deliver olefin **223** in good yields. Next, the liberation of the masked ketone in **223** proved to be troublesome due to the high basicity of the conformationally fixed nitrogen lone pair. After extensive screening of methods for dithiolane removal,[2.63-2.66] which only resulted in decomposition of starting material **223,** we came across the methodology developed by Oi-shi *et al*.[2.67,2.68] This constitutes an alkylation of sulfur in the presence of acid to prevent *N*-alkylation. The combination of TFA/Meerwein's salt led exclusively to *S*-alkylation, yielding intermediate **224**. Direct treatment of this species with base resulted in the formation of vinyl sulfide **225**. Addition of $CuSO_4$-solution to compound **224** instead formed copper-complex **226**. In this complex the positive charge is delocalized over both sulfur atoms and the copper atom, resulting in an overall decreased acidity of the α-sulfenic proton of **226** compared to the α-sulfenic proton of **224**. Using this procedure, ketone **227** can be obtained in high yield after the addition of ammonia solution.

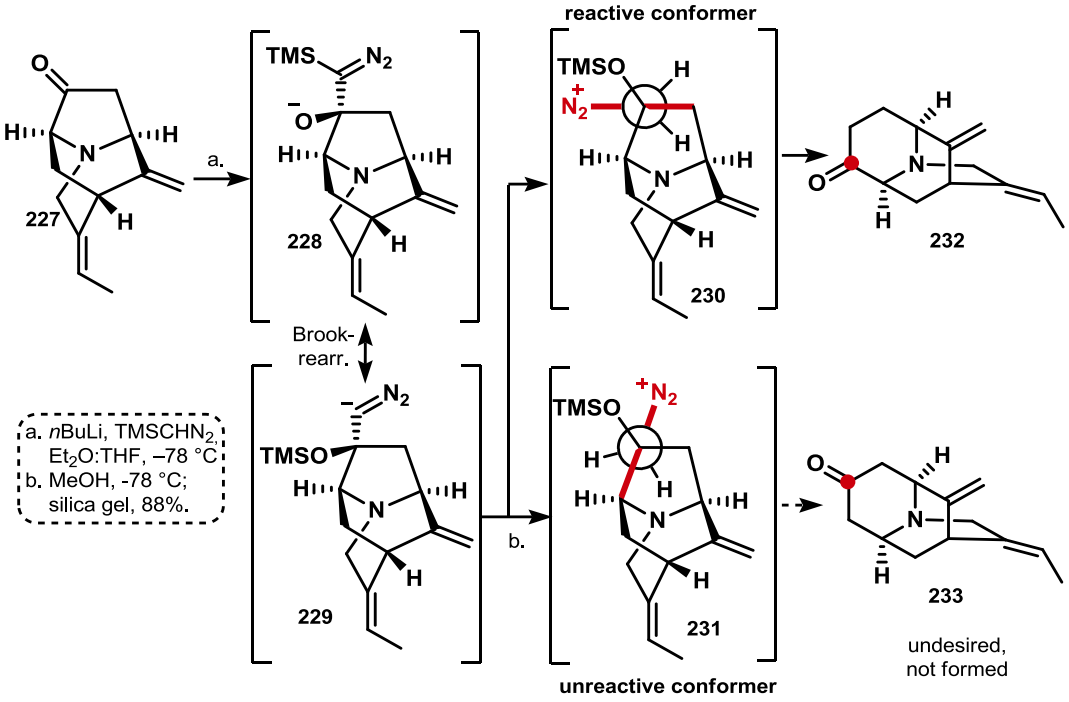


Scheme 27: Wittig olefination and ketone liberation.

We then turned our attention towards the homologation of ketone **227** (scheme 28). Thereby we faced the challenge of regioselectivity in the course of the ring enlargement process. In principle the two regioisomers **232** and **233** can be formed. The protocol from the Lee group[2.69] proved to be applicable to our system, and cleanly afforded homologated ketone **232** as a single regioisomer. This reaction proceeds *via* nucleophilic attack of TMS-diazomethane to ketone **227** to give alkoxy species **228** and silyl enol ether **229** *via* Brook rearrangement. The reaction mixture was then quenched with methanol at –78 °C to ensure

selective *C*-protonation. At this stage ring enlargement took place after diazo-decomposition induced by the addition of silica. The regioselectivity can be explained by conformations **230** and **231**. The highlighted bond in each conformer will undergo the enlargement, since it is antiperiplanar to the diazo-group and thus two regioisomers **232** and **233** can in principle be formed.

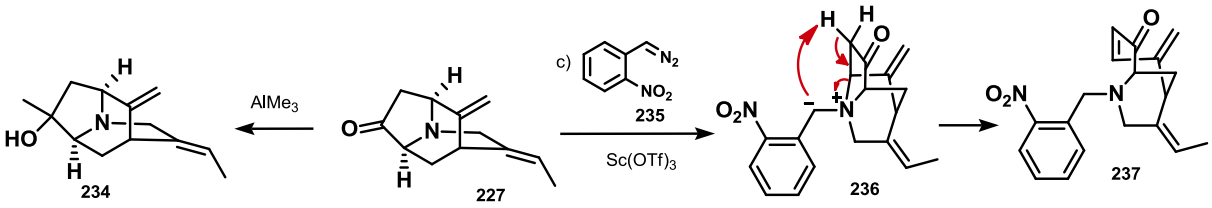
Fortunately, we exclusively observed the formation of desired compound **232** and surmise, that conformation **230** is the reactive conformation due to improved molecular overlap caused by higher flexibility (scheme 30). The transient silyl enol ether that is formed during the reaction is cleaved during the acidic workup.



Scheme 28: Ring enlargement and possible side reactions.

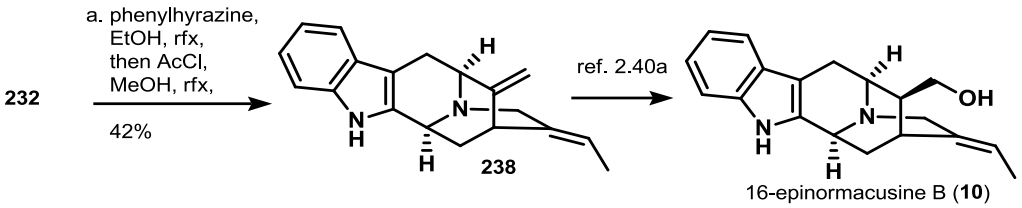
While screening for the desired ring expansion, two side reactions could be identified and the reason for failed reactivity was detected (see scheme 29). In most cases the Lewis acid was complexed between the oxygen of the ketone and the nitrogen lone pair, thus blocking the more accessible face of the ketone and preventing the desired reaction.

Using trimethylaluminium as Lewis acid led to methylation of the ketone yielding alcohol **234**, whereas $Sc(OTf)_3$ in combination with **235**[2.70] led to fragmentation *via* betaine **236** to give enone **237**.[2.71]



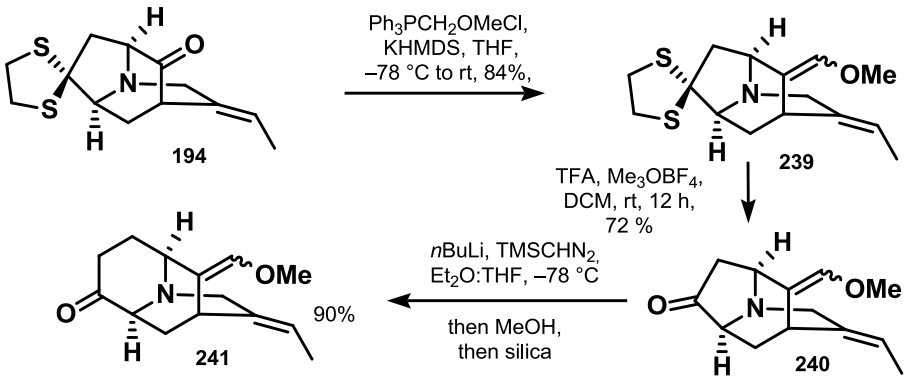
Scheme 29: Side reactions during the investigation of the necessary ring enlargement.

With the desired ketone **232** in hands, we performed the final Fischer indole synthesis. After considerable experimentation we found that conditions similar to those published by the Bonjoch group (scheme 30) led to the desired product **4238** in moderate yields.[2.72] This synthetic intermediate **238** was used by Cook *et al.* in a hydroboration reaction to conclude the total synthesis of 16-epinormacusine B (**1**).[2.40a] We have thus established a protecting group free access to 16-epinormacusine B (**1**) *via* the 3-oxidopyridinium [5+2] cycloaddition.



Scheme 30: Formal synthesis of 16-epinormacusine B (**10**).

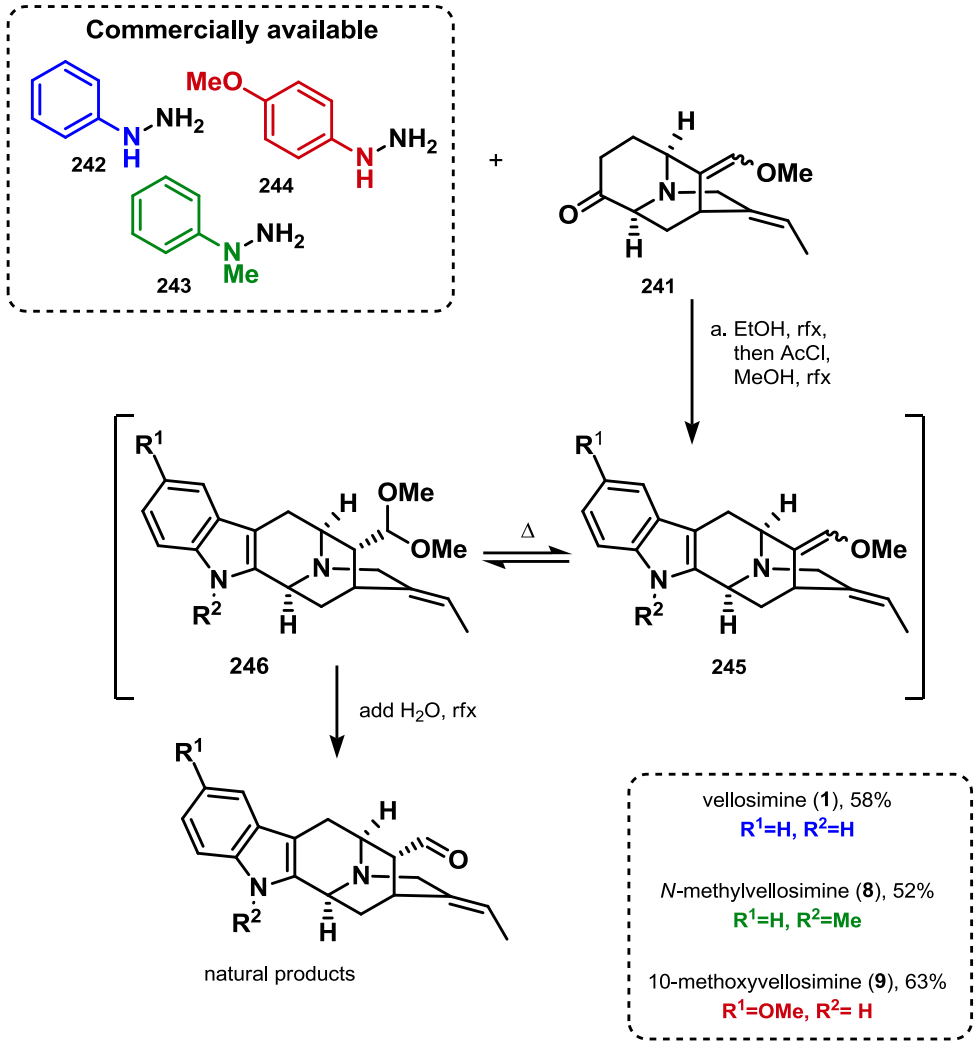
In order to gain enantioselective access to the 16-regular group members of the *sarpagine* alakaloids we then set out to investigate the synthetic strategy mentioned earlier starting from enantioselective ketone **194**. Subjection of compound **194** to MOM-Wittig conditions led to a regioisomeric mixture of enol ethers **240** (see scheme 31). The same conditions for unmasking the ketone moiety (sees scheme 27) and ring enlargement (see scheme 28) were then applied. Much to our enlightenment, the enol ether moiety remained untouched under these reaction conditions, yielding ketones **240** and **241**.



Scheme 31: Ketone liberation, MOM-Wittig and ring enlargement.

To finally showcase the versatility of our synthetic route, we decided to prepare three different members of the 16-regular group of the sarpagine alkaloids. Condensation of commercially available phenylhadryzines **242**-**244** with mutual precursor **241** in EtOH led to hydrazone formation, subjection of the evaporated hydrazones to AcCl in MeOH led to Fischer-indole formation to afford indoles **245** (see scheme 32).

The enol ether moiety was shown to equilibrate to acetal **246**, which can be converted to the desired natural products vellosimine (**1**, 58%), *N*-methylvellosimine (**8**, 52%) and 10-methoxyvellosmine (**9**, 62%) after the addition of water and prolonged heating.[2.73]



Scheme 32: Access to vellosimine **1**, *N*-methylvellosimine **8** and 10-methoxyvellosimine **9**.

2.9 Summary and Outlook

With a synthetic access to several natural products from the 16-epi group of *sarpagine* alkaloids and the 16-regular subgroup, a unified strategy towards these alkaloids has been achieved. As most *sarpagine* alkaloids differ by the substitution pattern on the indole core, which can be most conveniently installed at the end of the presented synthesis, our strategy is able to furnish a vast variety of *sarpagine* alkaloids on demand.

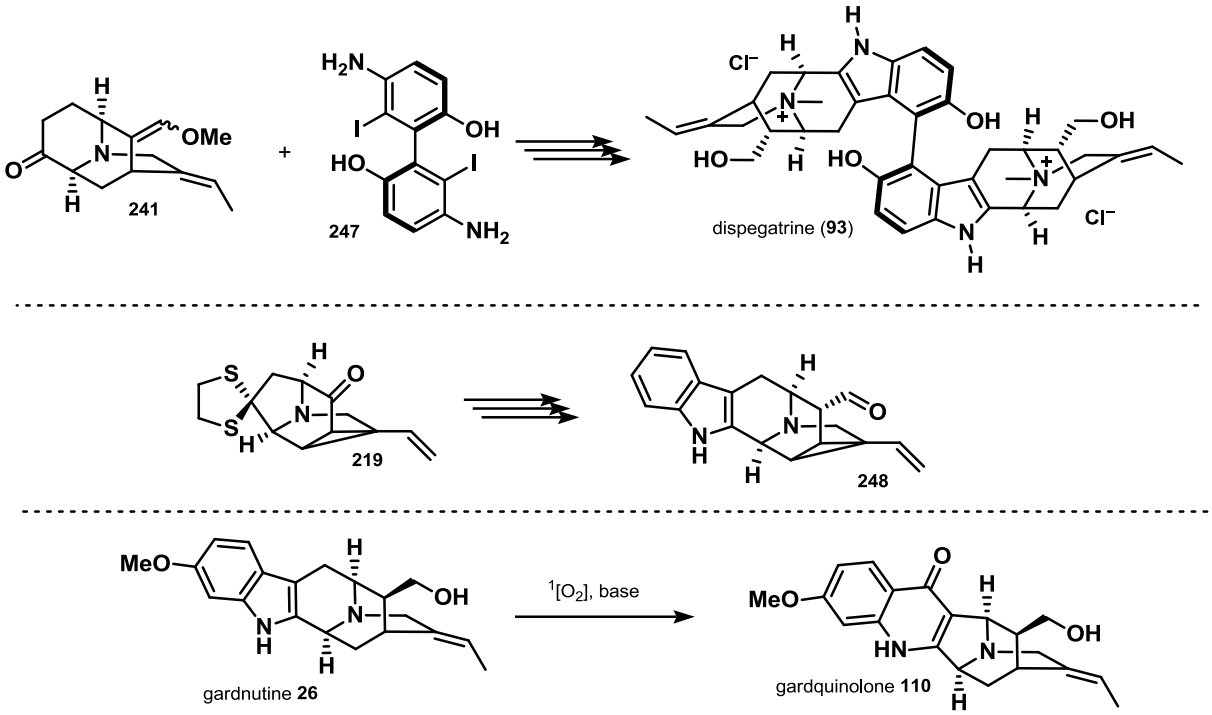
With the possibility to attach indole derivatives with unnatural substituents, we are able to finetune natural product derived compounds in any desired way. The presented synthetic access provides an ideal scaffold for a total synthesis derived screening of a great number of individually substituted alkaloids *via* late stage differentiation.

From a synthetic point of view, we have achieved a concise, protecting group free access to several alkaloids. Regarding the stepcount, our synthetic route matches the traditional synthesis for sarpagine alkaloids with an unsubstituted indole moiety (for vellosimine **1**: nine steps from known compounds, 16 steps total, for 16-epinormacusine B: ten steps from known compounds, 17 steps total). In regard of sarpagine alkaloids with substitution at the indole core (for both *N*-methylvellosimine (**8**) and 10-methoxyvellosmine (**9**): nine steps from known compounds, 16 steps total) our access is superior to all other synthesis.

Future work will be focused on accessing further *sarpagine* alkaloids, such as homo- and heterodimers, members of the peraksine subgroup or alkaloids wich have not been subject to decarboxylation at C16. Nevertheless, we have by now established a rapid access to the two biggest subgroups known.

Current synthetic investigations are focused on the synthesis of dispegatrine **93** from ketone **241** and bisaryl compound **247** (see scheme 33). Interesting future studies can be aimed at the incorperation of compound **219** into the sarpagine skeleton, and biological evaluation of the vinylcycolopropane derived *sarpagine* alkaloids like **248**.

A biosynthetic investigation for the formations of gardquinolone **110** from gardnutine **26** (which is within reach) can be carried out as well.



Scheme 33: Possible future synthetic work on the *sarpagine* alkaloids.

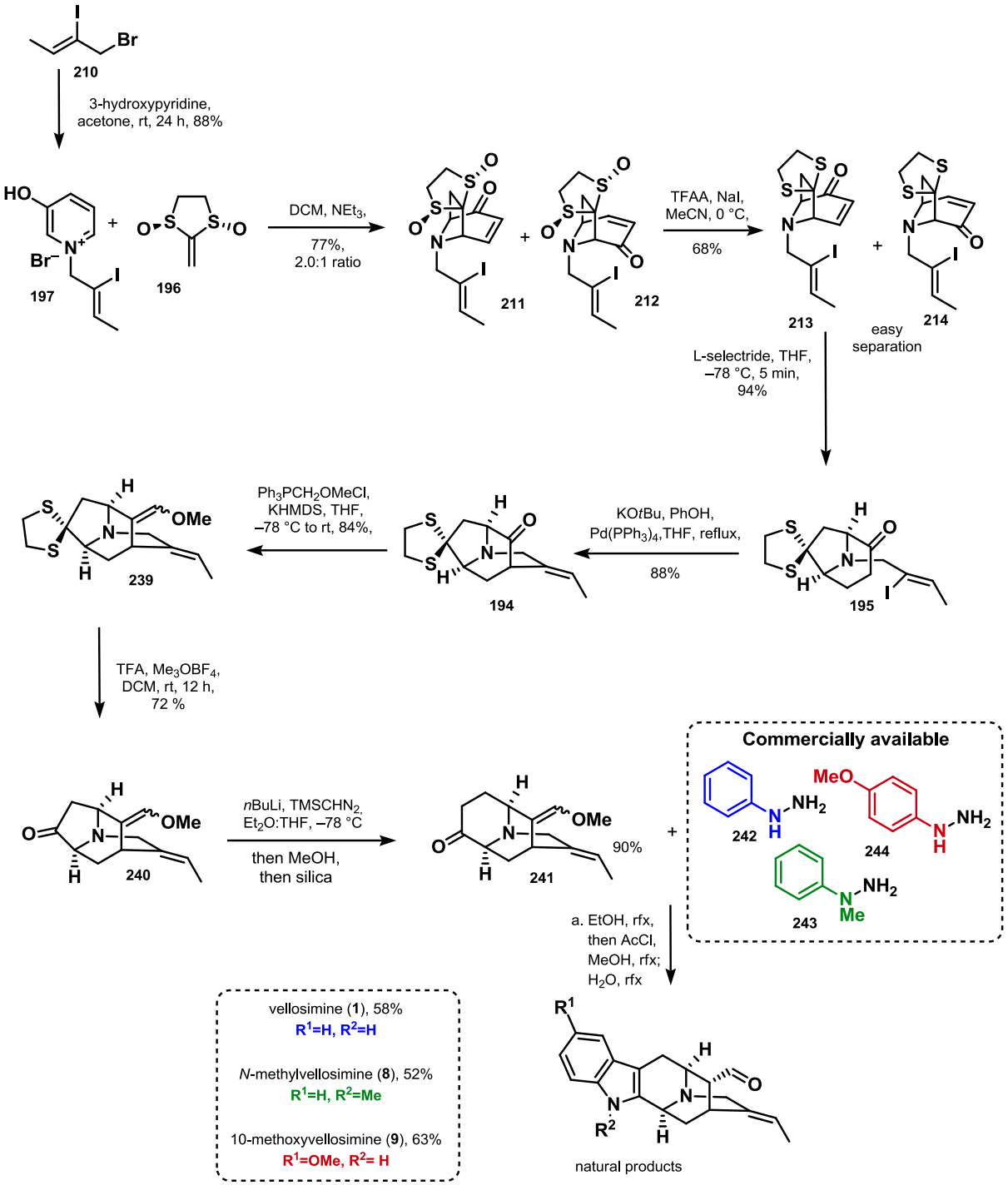
2.10 Experimentals

The following experimental data are from: S. Krüger, T. Gaich, *Angew. Chem. Int. Ed.* **2014,** *54* (1), 315–317.

General

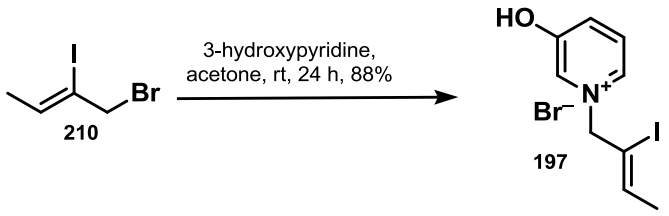
All reactions were performed under an inert atmosphere using Argon as the inert gas, using oven-dried glassware unless stated otherwise. Chemicals were used as bought from chemical suppliers. Solvents were used as bought from chemical suppliers or obtained from a dispensory system. THF was used dry after being distilled from Na/benzophenone or as bought from Acros Organics, 99,5 % over molsieves, stabilized. DCM was used after distillation over CaH_2 or as bought from chemical suppliers. Acetonitrile was used as bought from Acros Organics 99.9% over molsieves. Acetone was used as bought from Acetone: VMR, technical grade. NEt_3 was used after distillation over CaH_2 or as bought from chemical suppliers. No difference in reactivities/yields was observed using different solvent sources. THF for Pd-catalyzed enolate coupling was used after sparging the solvent with argon for 30 minutes under ultrasonication. TLC was carried out using Macherey-Nagel, ALUGRAM Xtra SIL G/UV_{254}, Aluminium plates, silica 60. Silica gel-chromatography was carried out using Macherey-Nagel, Silica 60M, 0.04-0.083 mm mesh. Preparative thin layer chromatography was carried out using Macherey-Nagel, ADAMANT UV_{254}, Glass plates, silica 60. NMR-measurements were carried out using Bruker DPX 200 MHz, Bruker AV 400 MHz, Bruker DPX 400 MHz and Bruker DRX 500 MHz. All NMR-spectra are referenced to 7.26 ppm ($CDCl_3$, ^1H) and 77.16 ppm ($CDCl_3$, ^{13}C), 3.31 ppm (methanol-d_4, ^1H) and 49.00 ppm (methanol-d_4, ^{13}C) or 2.50 ppm (DMSO-d_6, ^1H) and 39.52 (DMSO-d_6, ^{13}C). IR measurements were carried out using Bruker Vector 22 or Shimadzu IRAffinity-1S. UPLC-MS Spectra were recorded using Waters QTOF-Premier (Waters Aquity Ultra Performance, electron spray ionization). HR-EI-MS were obtained using Micromass GCT. Optical rotations were measured using Perkin Elmer Polarimeter 341.

Graphical Overview I



Procedures

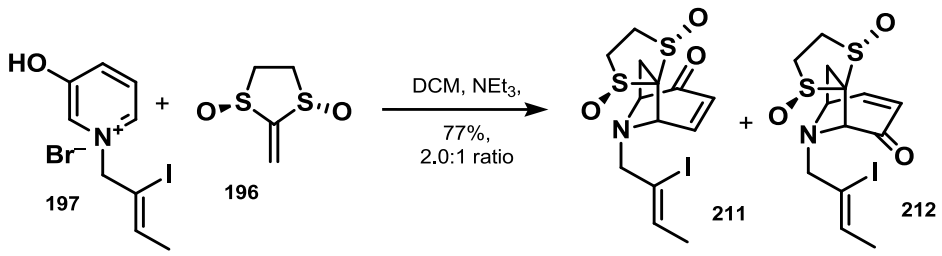
(*Z*)-3-hydroxy-1-(2-iodobut-2-en-1-yl)pyridin-1-ium **197**



(*Z*)-1-bromo-2-iodobut-2-ene **210** (14.91 g, 57.15 mmol, 1.2 eq.) was dissolved in acetone (108 mL, 0.5 M) and hydroxypyridine (5.18 g, 54.43 mmol, 1.0 eq.) was added at rt. The reaction mixture was stirred at ambient temperature for 24 hours. After one hour a white precipitate formed. This precipitate was filtered off after 24 hours, and was washed with PE to yield 15.1 g (78%) of the desired compound. The solvent of the mother lye was removed under reduced pressure, and the resulting crude mixture was recrystallized from acetone to yield further 2.40 g (12%) of the pyridinium salt **197**.

^{1}H-NMR (400 MHz, methanol-d$_4$): δ = 8.50–8.45 (m, 2H), 8.05–7.94 (m, 2H), 6.59 (q, *J*=6.5 Hz, 1H), 5.53 (s, 2H), 1.89 (d, *J*=6.1 Hz) ppm. **^{13}C-NMR (100 MHz, methanol-d$_4$):** δ = 159.2, 143.1, 137.0, 133.9, 133.6, 129.9, 99.0, 72.7, 22.3 ppm. **IR (neat sample):** 3035, 2851, 2734, 2629, 2510, 1634, 1578, 1486, 1434, 1298, 1251, 1139, 1029, 997, 908, 861, 814 cm^{-1}. **MS:** calc. for $C_9H_{11}INO^+$: 275.9880, found, 275.9881, **MP:** 180-185 °C.

(1*S*,5*S*)-8-((*Z*)-2-iodobut-2-en-1-yl)-8-azaspiro[bicyclo[3.2.1]oct[3]ene-6,-(*1S,*3*R)-2'*-[1,3]dithiolane-1,3-dioxide]-2-one **211** and **212**



(+)-Bissulfoxide **196** (410 mg, 2.74 mmol, 0.9 eq.) was dispersed in DCM (6.0 mL) under an inert atmosphere, followed by the addition of solid pyridinium salt **197** (1.08 g, 3.04 mmol, 1.0 eq.) and NEt_3 (0.42 mL, 3.04 mmol, 1.0 eq.). The pyridinium salt dissolved during the addition of the base. The reaction vessel was wrapped in aluminium foil and the reaction mixture was stirred at rt for 36 hours. The remaining solvent was then removed under reduced pressure and the crude remains were loaded onto a silica gel column eluting with acetone to yield 900 mg (77%) of regioisomeric tricycles **211** and **212** as a yellow solid. The mixture of regioisomers was used directly in the next step without separation. Analytically pure samples of both regioisomers can be prepared using multiple column chromatograph or multiple preparative thin layer chromatography (4% MeOH-DCM).

Desired regioisomer 211

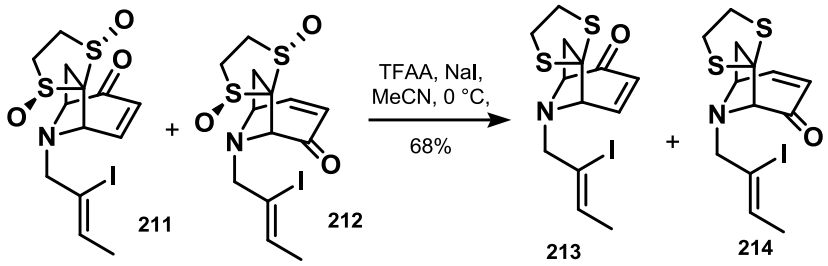
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.03 (dd, *J*=9.9, 5.1 Hz, 1H), 6.33 (dd, *J*=9.9, 1.2 Hz, 1H), 5.84 (q, *J*=4.8 Hz, 1H), 4.29 (d, *J*=5.0 Hz, 1H), 4.01 (td, *J*=14.0, 4.4 Hz, 1H), 3.80 (d, *J*=7.5 Hz, 1H) 3.63–3.57 (m, 2H), 3.56-3.37 (m, 3H), 2.59 (d, *J*=15.7 Hz, 1H), 2.24 (dd, *J*=15.4, 7.9 Hz, 1H), 1.78 (d, *J*=6.5 Hz, 3H) ppm. **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 196.1, 143.8, 134.1, 131.0, 105.0, 99.9, 66.7, 59.4, 56.4, 52.2, 48.4, 26.7, 21.9 ppm. **IR (neat sample):** 2920, 2850, 1687, 1648, 1443, 1398, 1370, 1337, 1306, 1235, 1143, 1094, 1063, 1039, 999, 952, 911, 850, 803 cm^{-1}. **$[\alpha]_D^{20}$**: +27 (c= 0.2;$CHCl_3$).

Undesired regioisomer 212

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.14 (dd, *J*=9.7, 5.0 Hz, 1H), 6.22 (dd, *J*=9.7, 1.2 Hz, 1H), 5.87 (q, *J*=6.5 Hz, 1H), 4.11 (br.s, 1H), 4.04 (t, *J*=5.8 Hz, 1H), 3.87–3.78 (m, 1H), 3.64–3.55 (m, 2H), 3.53–3.45 (m, 3H), 2.73 (d, *J*=14.3 Hz, 1H), 2.38 (dd, *J*=14.0, 6.5 Hz, 1H), 1.79 (d, *J*=6.1, 3H) ppm. **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 193.6, 150.1, 133.9, 128.8, 105.4, 94.2, 68.3, 60.0, 57.5, 52.5, 49.7, 31.9, 21.9 ppm. **IR (neat sample):** 2970, 2920, 1682, 1441, 1397, 1374, 1340, 1305, 1230, 1146, 1094, 1041, 911, 853 cm^{-1}. **MS:** (mixture of regioisomers) calc. for [$C_{13}H_{16}INO_3S_2$+Na]: 447.9514, found: 447.9511.

R_f: undesired regioisomer 0.70 (acetone), 0.56 (4% MeOH-DCM), desired regioisomer 0.64 (acetone), 0.51 (4% MeOH-DCM).

(1*S*,5*S*)-8-((*Z*)-2-iodobut-2-en-1-yl)-8-azaspiro[bicyclo[3.2.1]oct[3]ene-6,2'-[1,3]dithiolan]-2-one **213** and **214**



Regiosiomeric mixture of bissulfoxides **211**/**212** (2:1 mixture of desired/undesired by NMR, 900 mg, 2.11 mmol, 1.0 eq.) was dissolved in actetonitrile (42 mL) and the solution was cooled to 0 °C. NaI (951 mg, 6.35 mmol, 3.0 eq.) was added in one portion, followed by the dropwise addition of TFAA (0.89 mL, 6.35 mmol, 3.0 eq.). The reaction mixture was stirred at 0 °C for 2 hours before the addition of sat. $Na_2S_2O_3$ solution followed by the addition of 2 M NaOH solution quenched the reaction. The mixture was diluted with DCM and transferred to a separation funnel. The phases were separated, and the aqueous layer was extracted two more times with DCM. The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude mixture was purified *via* silica gel chromatography using 6:1 (PE:EtOAc) as eluent to give 563 mg (68%, 2.1:1 ratio of regioisomers **213**/**214**) as a yellow oil.

Desired regioisomer **213**

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.93 (dd, *J*=9.7, 5.0 Hz, 1H), 6.06 (dd, *J*=9.9, 1.7 Hz, 1H), 5.89–5.82 (m, 1H), 3.76 (d, *J*=4.8 Hz, 1H), 3.53 (d, *J*=7.9 Hz, 1 H), 3.50–3.40 (m, 2H), 3.40–3.31 (m, 2H, 3.28–3.17 (m, 2H), 3.10 (dd, *J*=14.7, 8.2 Hz, 1H), 2.36–2.30 (m, 1H), 1.75–1.71 (m, 3H) ppm. **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 198.1, 147.6, 132.6, 127.5, 106.1, 70.8, 69.1, 67.3, 60.2, 45.4, 40.6, 40.3, 21.8 ppm. **IR (neat sample):** 2919, 2821, 1684, 1440, 1370, 1331, 1303, 1278, 1251, 1140, 1102, 1051, 976, 957, 908, 846, 804 cm^{-1}. **$[\alpha]_D^{20}$**: +51 (c= 0.16; $CHCl_3$).

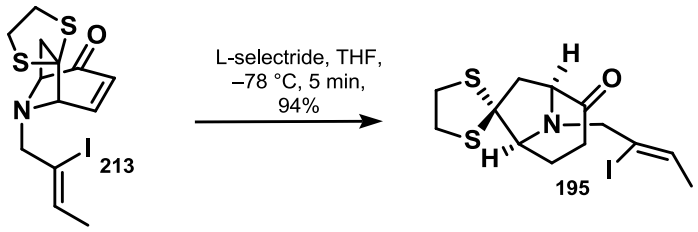
Undesired regioisomer **214**

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.93 (dd, *J*=9.7, 5.0 Hz, 1H), 6.00 (dd, *J*=9.7, 1.5 Hz, 1H), 5.90–5.82 (m, 1H), 3.78 (t, *J*=5.8 Hz, 1H), 3.64–3.60 (m, 1H), 3.53–3.46 (m, 2H), 3.44–3.32 (m, 2H), 3.29–3.20 (m, 1H), 3.17–3.09 (m, 1H), 2.93 (dd, *J*=13.7, 6.5 Hz, 1H), 2.42 (d, *J*=13.3 Hz, 1H),

1.76 (dt, *J*=6.3, 1.3 Hz, 3H) ppm. **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 195.3, 149.0, 132.9, 127.8, 106.4, 83.3, 65.5, 60.8, 57.9, 46.1, 41.1, 39.0, 21.8 ppm. **IR (neat sample):** 2924, 2822, 1682, 13438, 1373, 1337, 1304, 1242, 1145, 1050, 1019, 970, 913, 882, 855 cm^{-1}.

MS: (mixture of regioisomers) calc. for [$C_{13}H_{16}INOS_2$+H]: 393.9796, found: 393.9796, **R_f:** desired: 0.52, undesired: 0.41 (both 4:1 PE/EtOAc).

(1*S*,5*S*)-8-((*Z*)-2-iodobut-2-en-1-yl)-8-azaspiro[bicyclo[3.2.1]octane-6,2'-[1,3]dithiolan]-2-one **195**

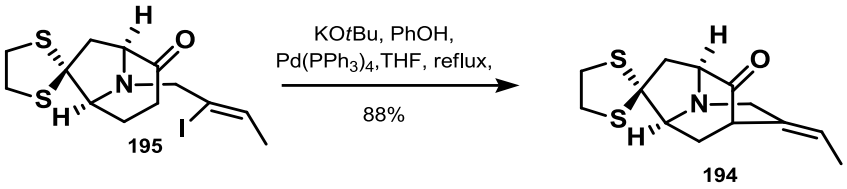


Unsaturated ketone **213** (430 mg, 1.09 mmol, 1.0 eq.) was dissolved in THF (12 mL) and the solution was cooled to –78 °C. L-selectride (1.09 mL of a 1 M solution in THF, 1.09 mmol, 1.0 eq.) was diluted to a 0.1 M solution in THF, which was then cooled to –78 °C. The diluted solution was then added slowly along the inner flask walls to the cooled unsaturated ketone *via* syringe. Immediately after the addition of the reducing agent the reaction mixture was quenched by the addition of 2M NaOH solution at –78 °C. The resulting mixture was diluted with EtOAc and was then allowed to warm to room temperature. The mixture was transferred to a separation funnel, followed by the addition of solid NaCl. The phases were separated and the aqueous phase was extracted two more times with EtOAc. The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude mixture was purified *via* silica gel chromatography using 6:1 (PE:EtOAc) as eluent to yield 405 mg (94%) of desired ketone **195** as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.00–5.88 (m, 1H), 3.56–3.49 (m, 2H), 3.47–3.34 (m, 4H), 3.33–3.20 (m, 2H), 3.07 (dd, *J*=15.2, 8.0 Hz, 1H), 2.66–2.46 (m, 2H), 2.42 (d, *J*=15.0 Hz, 1H), 2.31–2.12 (m, 2H), 1.79 (dt, *J*=6.5, 1.2 Hz, 3H) ppm. **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 210.0, 132.8, 106.6, 70.1, 67.7, 60.8, 47.7, 40.5, 40.4, 33.5, 26.6, 21.9 ppm. **IR (neat sample):** 2939, 2870, 2817, 1716, 1647, 1444, 1420, 1363, 1306, 1276, 1258, 1235, 1198, 1143, 1064, 1010,

975, 919, 881, 852, 816 cm^{-1}. **MS:** calc. for [$C_{13}H_{18}INOS_2$+H]: 395.9953, found: 395.9951, **[α]$_D^{20}$**: +79 (c= 0.18; $CHCl_3$), **R_f:** 0.47 (5:1 PE/EtOAc).

(3*S*,8a*S*,*E*)-6-ethylidenehexahydro-2*H*-spiro[3,7-methanoindolizine-1,2'-[1,3]dithiolan]-9-one **194**

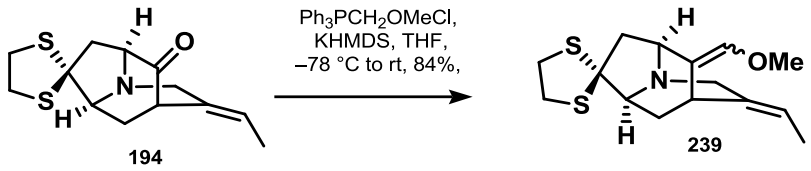


Vinyliodide **195** (405 mg, 1.03 mmol, 1.0 eq.) was dissolved in degassed THF (40 mL, overall concentration 0.05) followed by the addition of $Pd(PPh_3)_4$ (88.0 mg, 77.0 µmol, 7.5 mol%) in THF (5 mL) and a mixture of KO*t*Bu (172 mg, 1.54 mmol, 1.5 eq.) and PhOH (193 mg, 2.05 mmol, 2.0 eq.) in THF (5 mL). The resulting mixture was heated to reflux for 6 hours, before being cooled down to ambient temperature. The cold mixture was diluted with ice-water and EtOAc as well as solid NaCl and 2 M NaOH solution. The phases were separated and the aqueous phase was extracted two more times with EtOAc. The solvent was removed under reduced pressure, and the remains were redissolved in EtOAc (20 mL). The organic layer was extracted three times with 1 M HCl solution (25 mL total). The organic phase containing the non-aminic remains was then discarded. The aqueous acidic phase was then adjusted to basic pH with 2 M NaOH solution (40 mL) and solid NaCl was added. The now basic phase was extracted three times with EtOAc (250 mL total). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure to yield 240 mg (88%) of α-vinylated ketone **194** as a clear oil without significant impurities by ^{1}H-NMR. An analytically pure sample can be obtained using preparative thin-layer chromatography using 3:1 PE:EtOAc as eluent.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.46–5.34 (m, 1H), 3.77–3.58 (m, 2H), 3.52 (d, *J*=9.2 Hz, 1H), 3.44–3.31 (m, 4H), 3.26–3.17 (m, 2H), 3.08–2.97 (m, 1H), 2.38–2.25 (m, 2H), 2.09 (ddd, *J*=14.6, 9.6, 2.1 Hz, 1H), 1.63 (dt, *J*=6.9, 2.2 Hz, 3H) ppm. **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 216.1, 134.6, 120.1, 72.1, 68.3, 67.3, 49.2, 45.9, 44.1, 40.2, 40.1, 28.1, 12.7 ppm. **IR (neat sample):** 2971, 2923, 1734, 1440, 1368, 1279, 1216, 1122, 1001, 940, 888, 818 cm^{-1}. **MS:**

calc. for [$C_{13}H_{17}NOS_2$+H]: 268.0830, found: 268.0827, **$[\alpha]_D^{20}$**: +5 (c= 1.2; $CHCl_3$), **R_f:** 0.31 (3:1 PE:EtOAc).

(3*S*,6*E*,8a*S*)-6-ethylidene-9-(methoxymethylene)hexahydro-2*H*-spiro[3,7-methanoindolizine-1,2'-[1,3]dithiolane] **239**



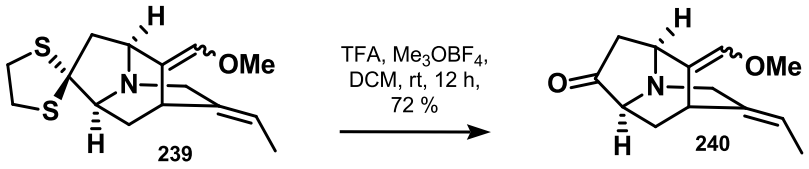
(Methoxymethyl)triphenylphosphonium chloride (1.09 g, 5.54 mmol, 3.5 eq) was dispensed in THF (15.0 mL, 0.3 M) under an inert atmosphere, and the mixture was cooled to –78 °C. KHMDS (7.92 mL of a 0.7 M solution in toluene, 570 mmol, 3.5 eq.) was then added, and the mixture was warmed to 0 °C for 40 minutes. The dark red solution was then cooled back to –78 °C, followed by the addition of ketone **194** (423 mg, 1.58 mmol, 1.0 eq.) in THF (5.0 mL, 3 M). The reaction mixture was allowed to warm to ambient temperature and was stirred at that temperature for 5 hours. The reaction mixture was then diluted with 2 M NaOH solution and EtOAc. The mixture was transferred to a separation funnel, and water and solid NaCl was added. The phases were separated, and the aqueous layer was extracted two more times with EtOAc. The combined organic layers were dried over $MgSO_4$, the solvent was removed under reduced pressure. The crude product was purified *via* column chromatography using 5:1 PE:EtOAc as eluent to yield 364 mg (78%) of the corresponding enol ether **239** as a white solid. An analytically pure sample of the major double bond isomer was prepared *via* multiple column chromatography. Both isomers were used as a mixture in the following reactions.

Major DB-regioisomer

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 5.75 (d, *J*=1.8 Hz, 1H), 5.06–5.00 (m, 1H), 3.97 (d, *J*=7.5 Hz, 1H), 3.64–3.54 (m, 2H), 3.52 (s, 3H), 3.37–3.28 (m, 2H), 3.23–3.11 (m, 3H), 3.05–2.99 (m, 2H), 2.27–2.21 (m, 1H), 2.08 (dt, *J*=13.5, 3.5 Hz, 1H), 1.87–1.85 (m, 1H), 1.57 (dt, *J*=6.8, 2.0, 3H) ppm. **^{13}C-NMR (125 MHz, $CDCl_3$):** δ = 140.5, 138.9, 123.5, 111.3, 72.9, 69.0, 59.7, 57.4, 50.8, 50.0, 39.98, 39.95, 33.5, 30.2, 12.4 ppm. **IR (neat sample):** 2922, 2835, 1688, 1446, 1277,

1231, 1192, 1123, 982, 952, 882, 809 cm^{-1}. **MS:** calc. for [$C_{15}H_{21}NOS_2$+H]: 296.1143, found: 296.1140, **$[\alpha]_D^{20}$**: -52 (c= 0.8; $CHCl_3$), **R_f:** 0.28 (5:1 PE:EtOAc).

(3*S*,6*E*,8a*S*)-6-ethylidene-9-(methoxymethylene)hexahydro-3,7-methanoindolizin-1(5*H*)-one **240**

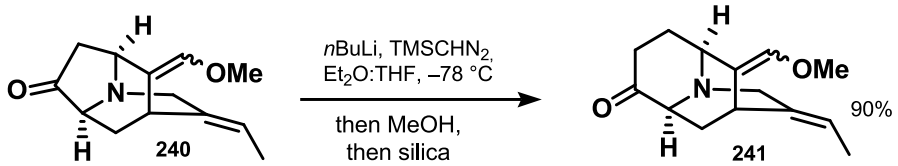


Meerwein salt (147.9 mg, 2.94 mmol, 4.0 eq.) was weighed out in a glovebox. Dithiolane **239** (217 mg, 735 µmol, 1.0 eq) was dissolved in a solution of TFA in DCM (7.4 mL of a solution of 0.23 mL TFA in 15 mL DCM, 1.0 eq.). The protonated amine solution was then added to the neat Meerwein salt, and the reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was then cooled to 0 °C, before 3% $CuSO_4$ solution was added. The reaction mixture was stirred at 0 °C for 30 minutes and was then allowed to warm to room temperature. A yellow-green precipitate formed upon warming to room temperature. After 3 hours at ambient temperature 25% ammonia solution was added, causing a deep blue color and leading to dissolving of the precipitate. The reaction mixture was then transferred to a separation funnel and was diluted with EtOAc. 2 M NaOH solution was added, as well as solid NaCl. The phases weres separated, and the aqueous layers was extracted two more times with EtOAc. The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified *via* column chromatography using 2:1 PE:EtOAc to yield 119 mg (74%) of ketone **240** as a colorless oil.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 5.86 (d, *J*=2.1 Hz, 1H), 5.08 (qt, *J*=6.7, 1.8 Hz, 1H), 4.16 (d, *J*=6.5 Hz, 1H), 3.74–3.56 (m, 2H), 3.55 (s, 3H), 3.37–3.35 (m, 1H), 3.09 (d, *J*=2.9 Hz, 1H), 2.62 (dd, *J*=17.5, 6.6 Hz, 1H), 2.33 (d, *J*=17.5 Hz, 1H), 2.02–1.95 (m, 1H), 1.80–1.75 (m, 1H), 1.57 (dt, *J*=6.9, 2.1 Hz, 3H) ppm. **^{13}C-NMR (125 MHz, $CDCl_3$):** δ = 217.8, 140.8, 139.1, 120.1, 112.3, 62.2, 59.8, 57.5, 49.7, 44.0, 33.0, 30.8, 12.3 ppm. **IR (neat sample):** 2928, 1752, 1681, 1453,

1288, 1229, 1185, 1120, 1074, 1054, 982, 940, 876, 838 cm^{-1}. **MS:** calc. for [$C_{13}H_{17}NO_2$+H]: 220.1338, found: 220.1340, **$[\alpha]_D^{20}$**: -103 (c= 0.4; $CHCl_3$), **R_f:** 0.23 (2:1 PE:EtOAc).

(3*E*,6*S*,9a*S*)-3-ethylidene-1-(methoxymethylene)hexahydro-1*H*-2,6-methanoquinolizin-7(2*H*)-one **241**

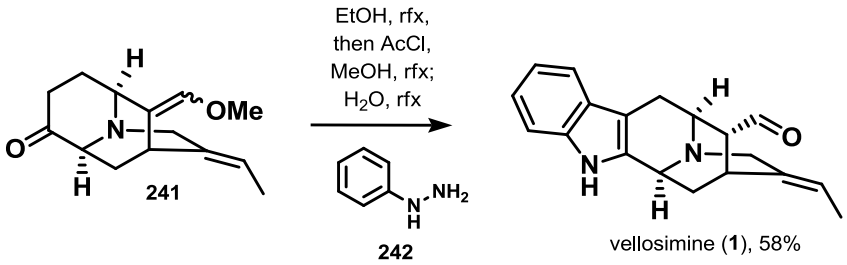


*n*BuLi (67.0 µL mL of a 2.5 M solution in hexanes, 168 µmol, 1.5 eq.) was added to Et_2O (2 mL) at –78 °C, followed by the addition of $TMSCHN_2$ (84.0 µL of a 2.0 M solution in hexanes, 168 µmol, 1.5 eq.) . The mixture was stirred for 15 minutes, before ketone **240** (26.0 mg, 112 µmol, 1.0 eq.) was added in THF (4.0 mL). The reaction mixture was stirred for 45 minutes at –78 °C, before the addition of MeOH (1 mL MeOH in 1 mL THF) at –78 °C quenched the reaction by *C*-protonation. The reaction mixture was diluted with EtOAc and 1 M NaOH. The layers were separated, and the aqueous layer was extracted two more times with EtOAc. The combined organic layers were dried over $MgSO_4$ and silica gel (2.0 g) was added to the solution. The mixture was stirred for 30 minutes, leading to homologation and resulting in a mixture of homologated ketone **10** and its enol-ether derivative. The solvent was removed under reduced pressure. The remains were redissolved in EtOAc (20 mL). The organic layer was extracted three times with 1 M HCl solution (25 mL total). The organic phase containing the non-aminic remains was then discarded. The acidic phase was then adjusted to basic pH with 2 M NaOH solution (40 mL) and solid NaCl was added. The now basic phase was extracted three times with EtOAc (250 mL total). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified *via* column chromatography using 1:1 PE:EtOAc to yield 21.0 mg (80%) of ketone **241** as a crystalline white solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 5.94 (d, *J*=2.6 Hz, 1H), 5.16–5.10 (m, 1H), 3.79–3.75 (m, 1H), 3.58 (s, 3H), 3.56–3.50 (m, 1H), 3.45–3.39 (m, 2H), 3.16 (t, *J*=2.8 Hz, 1H), 2.67 (ddd, *J*=15.8, 13.1, 7.3 Hz, 1H), 2.55–2.49 (m, 1H), 2.23 (dd, *J*=15.8, 5.3 Hz, 1H), 2.02–1.94 (m, 2H), 1.60 (m, 4H) ppm. **^{13}C-NMR (125 MHz, $CDCl_3$):** δ = 209.5, 140.4, 138.7, 117.8, 113.4, 63.9, 59.9, 55.8,

54.3, 32.1, 31.5, 30.9, 26.3, 12.5 ppm. **IR (neat sample):** 3035, 1722, 1643, 1420,, 1229, 1171, 1120, 987, 940, 838 cm^{-1}. **MS:** calc. for [$C_{14}H_{19}NO_2$+H]: 233.1416, found: 233.1420. **$[\alpha]_D^{20}$**: -55 (c= 0.64; $CHCl_3$), **R_f:** 0.15 (1:1 PE:EtOAc).

(+)-Vellosimine **1**

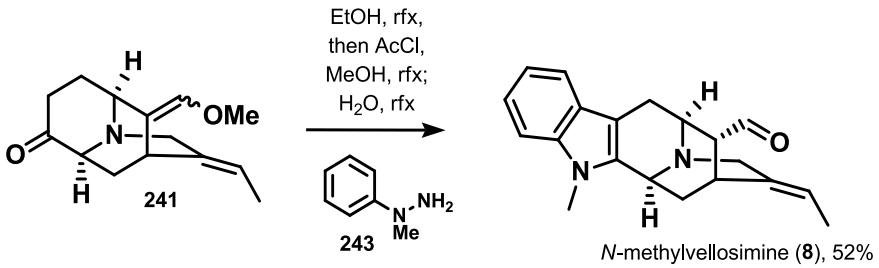


Ketone **241** (4.0 mg, 17.0 µmol, 1.0 eq.) was dissolved in EtOH (1 mL) under an inert atmosphere, and 44 µL of a 0.5 M solution of phenylhydrazine (**242**) in EtOH (24.0 mg, 22 µmol, 1.3 eq.) was added. The reaction mixture was heated to reflux for two hours, before the solvent was removed under reduced pressure. The crude remains were redissolved in 1.2 mL of a 2.5 M solution of HCl in MeOH (0.17 mL AcCl in 2.5 mL MeOH), and the reaction mixture was heated to reflux for six hours. The mixture was then concentrated under reduced pressure and the remains were redissolved in THF. 1 mL of a 2 M solution of HCl in water was then added and the mixture was refluxed for another three hours. The reaction was then cooled to ambient temperature and was diluted with 2 M HCl and was extracted with Et_2O. The protonated amine in the aqueous phase was then liberated by basifying with 2.0 M NaOH, addition of solid NaCl and extraction with EtOAc. The combined EtOAc layers were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was purified *via* column chromatography using 9:1 EtOAc:*i*PrOH with 1% triethylamine as solvent system to yield 2.9 mg (58%) of (+)-vellosimine **1** as a white crystalline solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 9.64 (d, *J*=0.7 Hz, 1H), 7.91 (br.s, 1H), 7.46 (d, *J*=7.7 Hz, 1H), 7.32 (d, *J*=8.0 Hz, 1H), 7.18–7.13 (m, 1H), 7.12–7.07 (m, 1H), 5.34 (q, *J*=6.7 Hz, 1H), 4.20 (d, *J*=9.5 Hz, 1H), 3.66 (t, *J*=6.4 Hz, 1H), 3.57 (d, *J*=16.7 Hz, 2H), 3.22–3.20 (m, 1H), 3.17 (dd, *J*=15.5, 5.0 Hz, 1H), 2.61 (d, *J*=15.5 Hz, 1H), 2.53 (d, *J*=7.4 Hz, 1H), 2.08–2.01 (m, 1H), 1.83 (ddd, *J*=12.9, 3.3, 3.0 Hz, 1H), 1.60 (dt, *J*=6.7, 1.8 Hz, 3H) ppm. **^{13}C-NMR (125 MHz, $CDCl_3$):**

δ = 202.5, 137.5, 136.5, 133.7, 127.6, 121.9, 119.8, 118.4, 117.5, 111.2, 104.4, 55.9, 55.0, 50.7, 50.6, 33.0, 27.2, 26.9, 12.8 ppm. **IR (neat sample):** 3056, 2920, 2361, 2169, 2063, 2022, 1715, 1449, 1348, 1230, 1167, 1081, 847, 807 cm^{-1}. **MS:** calc. for $[C_{19}H_{20}N_2O+H]$: 293.1654, found: 293.1650. **$[\alpha]_D^{20}$**: +41 (c= 0.04; MeOH), **R_f:** 0.15 (1:9 *i*PrOH:EtOAc, 1%NEt_3).

(+)-*N*-Methylvellosimine **8**

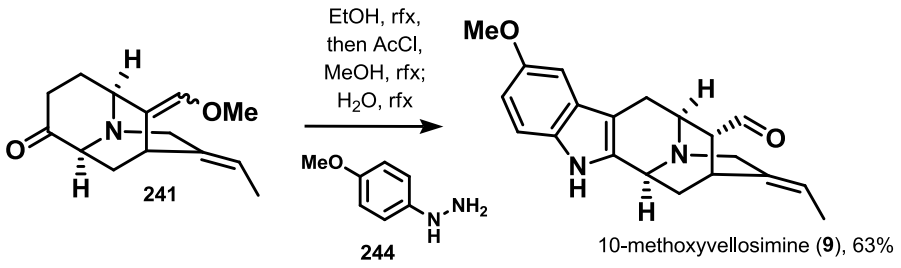


Ketone **241** (10 mg, 43.0 µmol, 1.0 eq.) was dissolved in EtOH (0.5 mL) under an inert atmosphere, and *N*-methyl-phenylhydrazine **243** in EtOH (6 mg, 51 µmol, 1.2 eq.) was added. The reaction mixture was heated to reflux for two hours, before the solvent was removed under reduced pressure. The crude remains were redissolved in 3.0 mL of a 2.5 M solution of HCl in MeOH (0.34 mL AcCl in 5.0 mL MeOH), and the reaction mixture was heated to reflux for four hours. The mixture was then concentrated under reduced pressure and the remains were redissolved in THF (1 mL). 1 mL of a 2 M solution of HCl in water was then added and the mixture was refluxed for another three hours. The reaction was then cooled to ambient temperature and was diluted with 2 M HCl and was extracted with Et_2O. The protonated amine in the aqueous phase was then liberated by basifying with 2.0 M NaOH, addition of solid NaCl and extraction with EtOAc. The combined EtOAc layers were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was purified *via* column chromatography using 9:1 EtOAc:*i*PrOH with 1% triethylamine as solvent system to yield 6.0 mg (52%) of (+)-*N*-methylvellosimine **8** as a white amorphous solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 9.64 (s, 1H), 7.47 (d, *J*=7.7 Hz, 1H), 7.29 (d, *J*=8.0 Hz, 1H), 7.20 (ddd, *J*=7.9, 7.4, 0.6 Hz, 1H), 7.09 (ddd, *J*=7.7, 7.2, 0.6 Hz, 1H), 5.37 (q, *J*=7.4 Hz, 1H), 4.30 (d, *J*=8.2 Hz, 1H), 3.68–3.61 (m, 3H), 3.65 (s, 3H), 3.22–3.20 (m, 1H), 3.17 (dd, *J*=15.5, 5.2 Hz,

1H), 2.62 (dd, *J*=15.5, 0.8 Hz, 1H), 2.50 (d, *J*=7.5 Hz, 1H), 2.14 (ddd, *J*=11.3, 10.1, 1.9 Hz, 1H), 1.78 (ddd, *J*=12.6, 3.6, 2.8 Hz, 1H), 1.62 (d, *J*=6.7 Hz, 3H) ppm. **^{13}C-NMR (125 MHz, $CDCl_3$):** δ = 202.7, 139.1, 137.5, 134.2, 127.3, 121.3, 119.2, 118.4, 117.4, 109.0, 103.3, 56.3, 55.0, 50.8, 49.6, 32.5, 29.6, 27.3, 26.7, 12.8 ppm. **IR (neat sample):** 3056, 2920, 2361, 2169, 2034, 1727, 1147, 847 cm^{-1}. **MS:** calc. for [$C_{20}H_{22}N_2O$+H]: 307.4015, found: 307.1935, **$[\alpha]_D^{20}$**: +78 (c= 0.12; $CHCl_3$), **R_f:** 0.15 (1:9 *i*PrOH:EtOAc, 1%NEt_3).

(+)-10-Methoxyvellosimine **9**

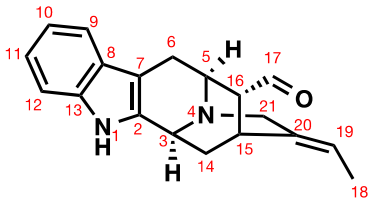


Ketone **241** (10 mg, 43.0 µmol, 1.0 eq.) was dissolved in EtOH (0.5 mL) under an inert atmosphere, and 4-methoxyphenylhydrazine **244** in EtOH (7 mg, 51 µmol, 1.2 eq.) was added. The reaction mixture was heated to reflux for one hour, before the solvent was removed under reduced pressure. The crude remains were redissolved in 3.0 mL of a 2.5 M solution of HCl in MeOH (0.34 mL AcCl in 5.0 mL MeOH), and the reaction mixture was heated to reflux for three hours. The mixture was then concentrated under reduced pressure and the remains were redissolved in THF (1 mL). 1 mL of a 2 M solution of HCl in water was then added and the mixture was refluxed for another 90 minutes. The reaction was then cooled to ambient temperature and was diluted with 2 M HCl and was extracted with Et_2O. The protonated amine in the aqueous phase was then liberated by basifying with 2.0 M NaOH, addition of solid NaCl and extraction with EtOAc. The combined EtOAc layers were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was purified *via* column chromatography using 9:1 EtOAc:*i*PrOH with 1% triethylamine as solvent system to yield 8.0 mg (63%) of (+)-10-methoxyvellosimine **9** as a white amorphous solid.

^{1}H-NMR (500 MHz, DMSO-d_6): δ = 10.60 (br.s., 1H), 9.57 (s, 1H), 7.18 (d, *J*=8.7 Hz, 1H), 6.88 (d, *J*=2.3 Hz, 1H), 6.68 (dd, *J*=8.8, 2.6 Hz, 1H), 5.28 (q, *J*=6.8 Hz, 1H), 4.18 (br.s., 1H), 3.74 (s,

3H), 3.60–3.46 (m, 3H), 3.23 (br. s., 1H), 2.92 (dd, *J*=15.2, 4.6 Hz, 1H), 2.52 (d, *J*=4.2 Hz, 1H), 2.47 (bs, 1H), 2.01 (dd, *J*=11.0 Hz, 1H), 1.74 (d, *J*=12.8, 1H), 1.57 (dt, *J*=7.0, 1.3 Hz, 3H) ppm. **^{13}C-NMR (125 MHz, DMSO-d_6):** δ = 203.5, 153.1, 140.8, 135.6, 131.2, 127.3, 111.7, 110.4, 102.1, 99.9, 55.3, 55.0, 54.2, 50.0, 49.8, 32.6, 26.7, 26.2, 12.4 ppm. **(neat sample):** 3056, 2920, 1731, 1147, 847 cm^{-1}. **MS:** calc. for [$C_{20}H_{22}N_2O_2$+H]: 323.1760, found: 323.1765, **$[\alpha]_D^{20}$**: +64 (c= 0.16; $CHCl_3$), **R_f:** 0.15 (1:9 *i*PrOH:EtOAc, 1%NEt_3).

(+)-vellosimine 1



^{1}H-NMR-data

Nr.	**Isolation** material[1,2] [ppm] (500 MHz, $CDCl_3$)	**Literature:** Synthetic material[3] [ppm] (300 MHz, $CDCl_3$)	**This work:** Synthetic material Gaich [ppm] (500 MHz, $CDCl_3$)
17	9.67 (d, J= ≤ 1Hz, 1H)	9.56 (s, 1H)	9.64 (d, *J*= 0.7 Hz, 1H)
1	7.81 (bs, 1H)	9.16 (bs, 1H)	7.91 (bs, 1H)
12	7.48 (d, J= 7 Hz, 1H)	7.41 (d, *J*= 7.7 Hz, 1H)	7.46 (d, *J*= 7.7 Hz, 1 H)
9	7.35 (d, J= 7 Hz, 1H)	7.35 (d, *J*= 7.8 Hz, 1H)	7.32 (d, *J*= 8.0 Hz, 1H)
11	7.19 (t, J= 7 Hz, 1H)	7.16-7.04 (m, 2H)	7.18-7.13 (m, 1H)
10	7.11 (t, J= 7 Hz, 1H)		7.12-7.07 (m, 1H)
19	5.38 (q, J= 7 Hz, ≈ 1Hz, 1H)	5.25 (q, *J*= 6.9 Hz, 1H)	5.34 (q, *J*= 6.7 Hz, 1H)
3	4.22 (dd, J= 10 Hz, 2 Hz, 1H)	4.44 (d, *J*= 9.4 Hz, 1H)	4.20 (d, *J*= 9.5, 1H)
5	nr[a]	3.80 (t, *J*= 6.0 Hz, 1H)	3.66 (t, *J*= 6.4 Hz, 1H)
21ab	nr	3.58 (d, *J*= 16.5 Hz, 1H)	3.57 (d, *J*= 16.7 Hz, 2H)
15	nr	3.36-3.25 (m, 1H)	3.22-3.20 (m, 1H)
6a	nr	3.22 (s, 1H)	3.17 (dd, *J*= 15.5, 5.0 Hz, 1H)
6b	nr	2.63 (d, *J*= 9.2 Hz, 2H)	2.61 (d, *J*= 15.5 Hz, 1H)
16	nr	2.59 (s, 1H)	2.53 (d, *J*= 7.4 Hz, 1H)
14a	nr	2.16 (t, *J*= 10.4 Hz, 1H)	2.08-2.01 (m, 1H)
14b	nr	1.93 (d, *J*= 13.3 Hz, 1H)	1.83 (ddd, *J*= 12.9, 3.3, 3.0 Hz, 1H)
18	1.65 (dt, J= 7 Hz, 2Hz, 3H)	1.56 (d, *J*=6.8 Hz, 3H)	1.60 (dt, J= 6.7, 1.8 Hz, 3H)

^{13}C-NMR-data:

Nr.	**Isolation** material[1,2] [ppm] (100MHz, $CDCl_3$)	**Literature:** Synthetic material[3] [ppm] (75 MHz, $CDCl_3$)	**This work:** Synthetic material Gaich [ppm] (125 MHz, $CDCl_3$)
17	200.0	201.34	202.54
13	136.0	136.46	137.46
2	135.2	136.15	136.55
20	130.2	131.05	133.71
8	126.4	127.10	127.58
11	121.6	121.97	121.93
10	119.2	119.65	119.76
19	118.2	118.20	118.37
9	117.6	118.15	117.50
12	110.9	111.26	111.18
7	102.9	103.69	104.36
21	54.7	55.38	55.86
3	53.8	54.50	54.96
5	50.5	50.85	50.72
16	50.3	50.69	50.55
14	31.9	32.59	32.97
15	26.0	26.71	27.21
6	25.9	26.49	26.86
18	12.1	12.65	12.80

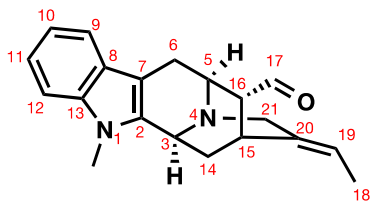
[a] nr = not reported

[1] A. Pfitzner, J. Stöckigt, *Planta Medica*, **1983**, *48*, 221-227.

[2] J. Banerji, B. Das, R. Chakrabarti, J. N. Shoolery, *Indian J. Chem.* **26B**, *709*, 1987.

[3] J. Yu, T. Wang, X. Liu, J. Deschamps, J. Flippen-Anderson, X. Liao, J. M. Cook, *JOC*, **2003**, *68*, 7565-7581.

(+)-*N*-Methylvellosimine 8:



^{1}H-NMR-data

Nr	**Literature:** Synthetic material[4] [ppm] (60 MHz, DMSO-d_6)	**Literature:** Synthetic material[5] [ppm] (500 MHz, $CDCl_3$)	**This work:** Synthetic material Gaich [ppm] (500 MHz, $CDCl_3$)
17	9.52 (s, 1H)	9.64 (d, *J*= 1 Hz, 1H)	9.64 (s, 1H)
12	7.65-7.01 (m, 4H)	7.47 (ddd, *J*=7.7, 1.0, 1.0, Hz, 1H	7.47 (d, *J*= 7.7 Hz, 1H)
9		7.30 (d, *J*= 8.0 Hz, 1H)	7.29 (d, *J*= 8.0 Hz, 1H)
11		7.21 (ddd, *J*= 8.0, 7.0, 1.0 Hz, 1H)	7.20 (ddd, *J*= 7.9, 7.4, 0.6 Hz, 1H)
10		7.09 (ddd, *J*= 7.5, 7.0, 1 Hz, 1H)	7.09 (ddd, *J*=7.7, 7.2, 0.6 Hz, 1H)
19	5.45 (q, 1H)	5.37 (q, *J*=7.0 Hz, 1H)	5.37 (q, *J*= 7.4 Hz, 1H)
3	nr	4.27 (dd, *J*= 10.0, 2.5 Hz, 1H)	4.30 (d, *J*= 8.2 Hz, 1H)
21;5	nr	3.67-3.60 (m, 3H)	3.68-3.61 (m, 3H)
N-Me	3.52 (s, 3H)	3.65 (s, 3H)	3.65 (s, 3H)
15	nr	3.21-3.19 (m, 1H)	3.22-3.20 (m, 1H)
6b	nr	3.14 (dd, *J*=15.5, 5.0 Hz, 1H)	3.17 (dd, *J*= 15.5, 5.2 Hz, 1H)
6a	nr	2.62 (dd, *J*= 15.5, 1.5 Hz, 1H)	2.62 (dd, *J*=15.5, 0.8 Hz, 1H)
16	nr	2.49 (d, *J*= 7.5 Hz, 1H)	2.50 (d, *J*= 7.5 Hz, 1H)
14a	nr	2.13 (ddd, *J*= 12.5, 9.5, 2.0 Hz, 1H)	2.14 (ddd, *J*= 11.3, 10.1, 1.9 Hz, 1H)
14b	nr	1.77 (ddd, *J*= 12.5 4.0, 2.5 Hz, 1H)	1.78 (ddd, *J*= 12.6,3.6, 2.8 Hz, 1H)
18	1.65 (d, 3H)	1.62 (dt, *J*=7.0, 2.0 Hz, 3H)	1.62 (d, *J*= 6.7 Hz, 3H)

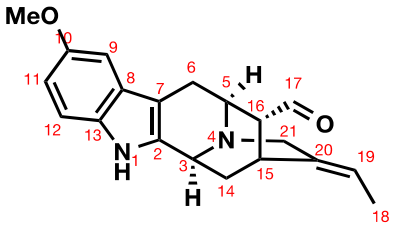
^{13}C-NMR-data:

Nr.	**Isolation** material[4] [ppm] (60 MHz, $CDCl_3$)	**Literature:** Synthetic material[5] [ppm] (125 MHz, $CDCl_3$)	**This work:** Synthetic material Gaich [ppm] (125 MHz, $CDCl_3$)
17	200.0	202.8	202.73
2	136.0	139.2	139.07
13	135.2	137.4	137.55
20	130.2	134.4	134.17
8	126.4	127.2	127.30
11	121.6	121.1	121.35
10	119.2	119.0	119.23
12	118.2	118.2	118.41
19	117.6	117.0	117.41
9	110.9	108.8	108.98
7	102.9	103.1	103.30
21	54.7	56.2	56.27
16	53.8	54.9	54.97
5	50.5	50.6	50.77
3	50.3	49.4	49.61
14	31.9	32.4	32.48
N-Me	26.0	29.4	29.57
6	25.9	27.3	27.34
15	12.1	26.6	26.70
18		12.6	12.84

[4] M. A. Amer, W. E. Court, *Phytochemistry, 1980*, *20*, 2569-2573.

[5] D. Alexander, C. Kevin, E. C. Todd, S. F. Martin, *J. Am. Chem. Soc.,* **2003**, *125, 15,* 4541-4550.

(+)-10-Methoxyvellosimine 9:



^{1}H-NMR-data

Nr	**Isolation** material[6] [ppm][a]	**Literature:** Synthetic material[7] [ppm] (300 MHz, DMSO-d_6)	**This work:** Synthetic material Gaich [ppm] (500 MHz, DMSO-d_6)
17	nr[b]	10.66 (s, 1H)	10.60 (bs, 1H)
	9.00 (s, 1H)	9.57 (s, 1H)	9.57 (s, 1H)
19	nr	7.17 (d, *J*= 8.7 Hz, 1H)	7.18 (d, *J*= 8.7 Hz, 1H)
	nr	6.87 (d, *J*= 2.4 Hz, 1H)	6.88 (d, *J*= 2.3 Hz, 1H)
	nr	6.66 (dd, *J*= 8.7, 2.4 Hz, 1H)	6.68 (dd, *J*= 8.8, 2.6 Hz, 1H)
19	5.00 (q, J= 7 Hz, 1H)	5.24 (q, *J*= 6.6 Hz, 1H)	5.28 (q, *J*= 6.8 Hz, 1H)
	nr	4.10 (d, *J*= 8.3 Hz, 1H)	4.18 (bs, 1H)
Ar-OMe	3.58 (s, 3H)	3.73 (s, 3H)	3.74 (s, 3H)
	nr	3.53-3.40 (m, 3H)	3.60-3.46 (m, 3H)
	nr	3.20 (t, *J*= 2.0 Hz, 1H)	3.23 (bs, 1H)
	nr	2.88 (dd, *J*= 15.1, 5.0 Hz, 1H)	2.92 (dd, *J*= 15.2, 4.6 Hz, 1H)
	nr	2.45 (d, *J*= 5.5 Hz, 1H)	2.52 (d, *J*= 4.2, Hz, 1H)
	nr	2.41 (bs, 1H)	2.47 (bs, 1H)
	nr	1.97 (ddd, *J*= 22.3, 11.0, 1.3 Hz, 1H)	2.01 (dd, *J*= 11.0 Hz, 1H)
	nr	1.69 (dt, *J*= 12.4, 2.9 Hz, 1H)	1.74 (d, *J*= 12.8 Hz, 1H)
18	1.50 (d, J= 7.0 Hz, 3H)	1.56 (d, *J*= 6.7 Hz, 3H)	1.57 (dt, *J*= 7.0, 1.3 Hz, 3H)

[a] Solvent and frequency not reported [b]nr = not reported

[6] M. Plat, R. Lemay, J. Levren, M. M. Janot, C. Djerassi, H. Budzikiewicz, *Bull. Soc. Chem. Fr.*, **1965**, 2497-2501.

[7] C. R., Edwankar, R. V., Edwankar, J. R., Dechamps, J. M., Cook, *Angew. Chem. Int. Ed.* **2012**, *51,* 11762-11765.

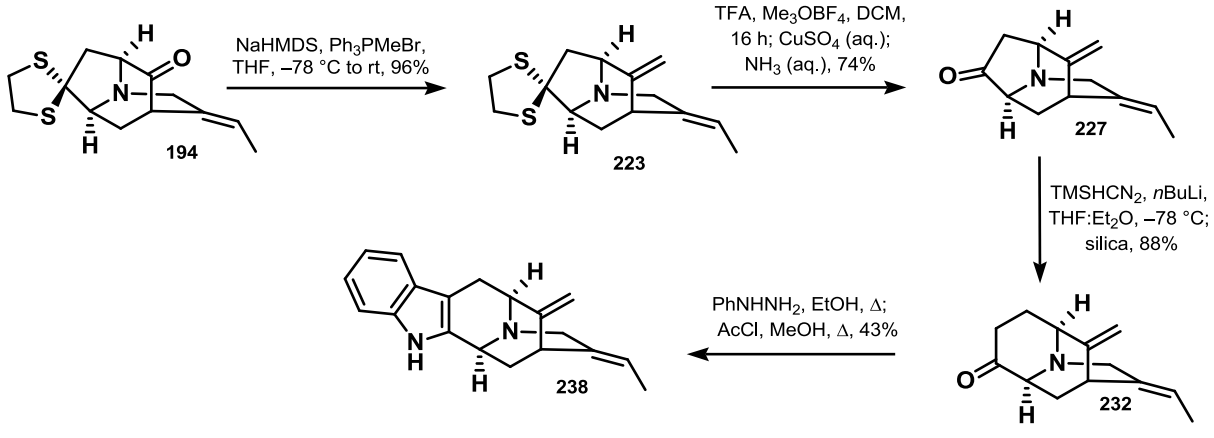
^{13}C-NMR-data:

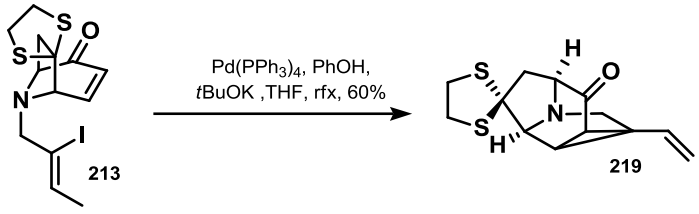
Nr	**Isolation** material[6] [ppm][a]	**Literature:** Synthetic material[7] [ppm] (75 MHz, DMSO-d_6)	**This work:** Synthetic material Gaich [ppm] (500 MHz, DMSO-d_6)
17	NOT REPORTED	204.0	203.54
		153.4	153.12
19		140.3	140.85
		136.4	135.64
		131.5	131.22
19		127.8	127.31
		115.6	-[b]
Ar-OMe		112.0	111.75
		110.5	110.37
		102.5	102.07
		100.2	99.94
		55.7	55.34
		55.6	54.99
		54.8	54.20
		50.2	50.02
		50.0	49.78
		33.2	32.63
		27.3	26.70
		26.7	26.16
		12.7	12.41

[a] No ^{13}C-NMR-data reported

[b] This signal is detected by HMBC

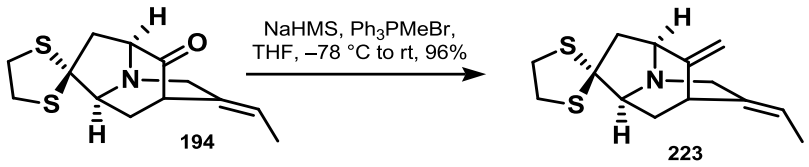
Graphical Overview II





Experiments

E-6-ethylidene-9-methylenehexahydro-2*H*-spiro[3,7-methanoindolizine-1,2'-[1,3]dithiolane] (**223**)

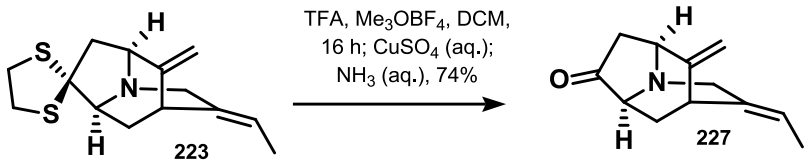


Methyltriphenylphosphonium bromide (204 mg, 571 µmol, 1.1 eq) was dispensed in THF (5.2 mL) under an inert atmosphere, and the mixture was cooled to –78 °C. NaHMDS (0.29 mL of a 2.0 M solution in THF, 580 µmol, 1.1 eq.) was then added, and the mixture was stirred for 15 minutes at –78 °C, before being warmed to 0 °C for 15 minutes. The yellow solution was then cooled back to –78 °C, followed by the addition of ketone **194** (139 mg, 520 µmol, 1.0 eq.) in THF (5.2 mL). The reaction mixture was stirred at –78 °C for one hour, before being warmed to ambient temperature for 6 hours. The reaction mixture was then diluted with 2 M NaOH solution and EtOAc. The mixture was transferred to a separation funnel, and water and solid NaCl were added. The phases were separated, and the aqueous layer was extracted two more times with EtOAc. The combined organic layers were dried over $MgSO_4$, the solvent was removed under reduced pressure and the remains were redissolved in EtOAc/DCM (10 mL/10 mL). The organic layer was extracted three times with 1 M HCl solution (25 mL total). The organic phase containing the non-aminic remains was then discarded. The acidic phase was adjusted to basic pH with 2 M NaOH solution (40 mL) and solid NaCl was added. The now basic phase was extracted three times with EtOAc (250 mL total). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure to yield 132 mg (96%) of olefin **223** as a pale oil without significant impurities by ^{1}H-NMR. An analytically pure sample can be obtained using preparative thin-layer chromatography using 3:1 PE:EtOAc as eluent.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.13–5.05 (qt, *J*=6.8, 1.8 Hz, 1H), 4.80–4.76 (m, 1H), 4.64–4.62 (m, 1H), 3.79 (d, *J*=8.0 Hz, 1H), 3.66–3.53 (m, 2H), 3.38–3.12 (m, 6H), 3.09 (ddd, *J*=14.3, 8.2. 0.9 Hz, 1H), 2.22 (dd, *J*=14.3, 1.4 Hz, 1H), 2.06 (dt, *J*=13.7, 3.4 Hz, 1H), 1.86 (ddd, *J*=13.8, 9.7, 2.3 Hz, 1H), 1.61 (dt, *J*=6.8, 2.1 Hz, 3H) ppm. **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 155.8, 140.1,

112.6, 105.8, 72.6, 68.2, 61.5, 52.3, 49.9, 40.0, 39.9, 35.9, 31.9, 12.4 ppm. **IR (neat sample):** 3064, 2918, 2859, 1740, 1653, 1437, 1376, 1315, 1270, 1218, 1125, 1078, 1053, 1006, 953, 885, 812 cm^{-1}. **MS:** calc. for [$C_{14}H_{19}NS_2$+H]: 266.1037, found: 266.1037, **R_f:** 0.30 (5:1 PE:EtOAc).

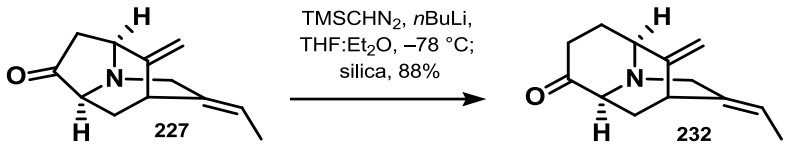
E-6-ethylidene-9-methylenehexahydro-3,7-methanoindolizin-1(5*H*)-one (**227**)



Me_3OBF_4 (89.2 mg, 603 µmol, 4.0 eq.) was weighed out in a glovebox. Olefin **223** (40.0 mg, 151 µmol, 1.0 eq.) was dissolved in a solution of TFA in DCM (1.5 mL of a solution of 0.23 mL TFA in 15 mL DCM, 2.0 eq.). The protonated amine solution was then added to the neat Meerwein salt, and the reaction mixture was stirred at ambient temperature for 16 hours. The reaction mixture was cooled to 0 °C, before 3% $CuSO_4$ solution (5 mL) was added. The reaction mixture was stirred at 0 °C for 30 minutes and was then allowed to warm to room temperature. A yellow precipitate formed upon warming to room temperature. After 1.5 hours at ambient temperature 25% ammonia solution (3 mL) was added, causing a deep blue color and leading to dissolving of the precipitate. The reaction mixture was then transferred to a separation funnel and was diluted with EtOAc. 2 M NaOH solution was added, as well as solid NaCl. The phases were separated, and the aqueous layers was extracted two more times with EtOAc. The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The remains were redissolved in EtOAc (20 mL). The organic layer was extracted three times with 1 M HCl solution (25 mL total). The organic phase containing the non-aminic remains was then discarded. The acidic phase was adjusted to basic pH with 2 M NaOH solution (40 mL) and solid NaCl was added. The now basic phase was extracted three times with EtOAc (250 mL total). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified *via* preparative thin-layer chromatography using 4:1 PE:EtOAc (aluminium oxide) to yield 21 mg (74%) of ketone **227** as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.18 (qt, *J*=6.8, 2.0 Hz, 1H), 4.95 (d, *J*=2.2 Hz, 1H), 4.73 (d, *J*=1.7 Hz, 1H), 4.08 (dd, *J*=6.9, 1.4 Hz, 1H), 3.77–3.56 (m, 2H), 3.42–3.37 (m, 1H), 3.35 (dd, *J*=4.0, 1.3 Hz, 1H), 2.80–2.72 (m, 1H), 2.22 (d, *J*=17.2 Hz, 1H), 2.04–1.96 (m, 1H), 1.76 (ddd, *J*=13.5, 4.0, 2.5 Hz, 1H), 1.61 (dt, *J*=6.8, 2.2 Hz, 3H) ppm. **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 216.7, 152.5, 138.2, 114.0, 108.4, 61.5, 60.9, 49.5, 46.5, 36.5, 30.4, 12.3 ppm. **IR (neat sample):** 2925, 2863, 1757, 1652, 1236, 1268, 1293, 1217, 1167, 1107, 1075, 1055, 992, 959, 893, 867, 841, 814 cm^{-1}. **MS:** calc. for [$C_{12}H_{15}NO$+H]: 190.1232, found: 190.1228, **R_f:** 0.33 (EtOAc, silica).

E-3-ethylidene-1-methylenehexahydro-1*H*-2,6-methano-quinolizin-7(2*H*)-one (**232**)

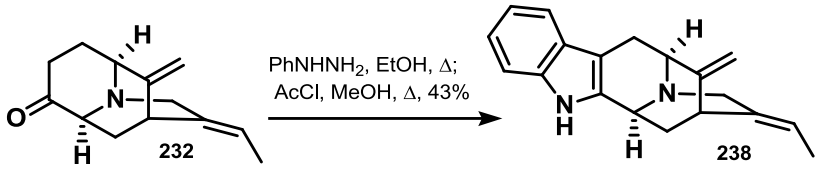


*n*BuLi (30 µL of a 2.5 M solution in hexanes, 75 µmol, 1.8 eq.) was added to Et_2O (1 mL) at –78 °C, followed by the addition of $TMSCHN_2$ (40 µL of a 2 M solution, 80 µmol, 1.9 eq.). The mixture was stirred for 15 minutes, before ketone **227** (8.0 mg, 42.3 µmol, 1.0 eq.) was added in THF (2.0 mL). The reaction mixture was stirred for 45 minutes at –78 °C, before the addition of MeOH (1 mL MeOH in 1 mL THF) at –78 °C quenched the reaction by *C*-protonation. The reaction mixture was diluted with EtOAc/Et_2O and water, and solid NaCl was added. The layers were separated, and the aqueous layer was extracted two more times with EtOAc. The combined organic layers were dried over $MgSO_4$ and silica gel (0.5 g) was added to the solution. The mixture was stirred for 30 minutes, leading to homologation and resulting in a mixture of homologated ketone **41** and its enol-ether derivative. The solvent was removed under reduced pressure. The remains were redissolved in EtOAc (20 mL). The organic layer was extracted three times with 1 M HCl solution (25 mL total). The organic phase containing the non-aminic remains was then discarded. The acidic phase was adjusted to basic pH with 2 M NaOH solution (40 mL) and solid NaCl was added. The now basic phase was extracted three times with EtOAc (250 mL total). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified *via*

preparative thin-layer chromatography using 4:1 PE:EtOAc as eluent (aluminium oxide plates) to yield 7.6 mg (88%) of ketone **232** as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.24 (qt, *J*=6.8, 2.0 Hz, 1H), 5.05 (d, *J*=2.8 Hz, 1H), 4.85 (d, *J*=2.2 Hz, 1H), 3.66 (brs, 1H), 3.60–3.51 (m, 1H), 3.51–3.40 (m, 3H), 2.74–2.63 (m, 1H), 2.30–2.03 (m, 4H), 1.70–1.61 (m, 4H) ppm. **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 208.9, 151.2, 136.8, 115.5, 106.6, 63.8, 56.7, 55.7, 36.6, 31.6, 31.1, 28.6, 12.5 ppm. **IR (neat sample):** 2924, 2859, 1715, 1653, 1435, 1319, 1290, 1267, 1242, 1126, 1098, 1063, 949, 883, 812 cm^{-1}. **MS:** calc. for [$C_{13}H_{17}NO$+H]: 204.1388, found: 204.1390, **R_f:** 0.30 (EtOAc, silica).

E-9-ethylidene-11-methylene-5,6,8,9,10,11,11a,12-octahydro-6,10-methanoindolo[3,2-*b*]-quinolizine (**238**)

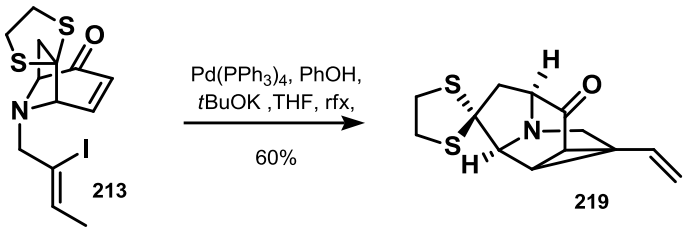


Ketone **232** (15.8 mg, 77.7 µmol, 1.0 eq.) was dissolved in EtOH (0.5 mL) under an inert atmosphere, and 0.5 mL of a stock solution of phenylhydrazine (10.1 mg, 93.4 µmol, 1.2 eq.) in EtOH was added. The reaction mixture was heated to reflux for two hours, before the solvent was removed under reduced pressure. The crude remains were redissolved in a 2.5 M solution of HCl in MeOH (1.0 mL), and the reaction mixture was heated to reflux for one hour. The mixture was diluted with 2 M NaOH solution and EtOAc and was then transferred to a separation funnel, to which solid NaCl was added. The phases were separated, and the aqueous layers was extracted two more times with EtOAc. The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified *via* preparative thin-layer chromatography using 5% MeOH:DCM as eluent to yield 9.0 mg (42%) of indole **238** as a brown solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.38 (brs, 1H), 7.49–7.44 (m, 1H), 7.22–7.18 (m, 1H), 7.13–7.08 (m, 2H), 5.24 (q, *J*=6.7 Hz, 1H), 4.82 (dd, *J*=3.8, 2.6 Hz, 2H), 3.93–3.83 (m, 2H), 3.68–3.53 (m, 2H), 3.27 (dd, *J*=4.0, 1.5 Hz, 1H), 3.16 (dd, *J*=15.4, 5.5 Hz, 1H), 2.98 (dd, *J*=15.5, 1.4, 1H),

2.00 (ddd, *J*=12.0, 10.1, 1.6 Hz, 1H), 1.85–1.77 (m, 1H), 1.63 (dt, *J*=6.8, 1.9 Hz, 3H) ppm. **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 152.2, 137.6, 137.0, 136.5, 127.7, 121.5, 119.4, 118.2, 115.1, 111.2, 105.5, 104.9, 56.8, 55.7, 50.4, 36.8, 36.2, 26.4, 12.5 ppm. **IR (neat sample):** 2053, 2924, 1707, 1647, 1570, 1452, 1383, 1341, 1321, 1302, 1169, 1121, 1009, 883, 854 cm^{-1}. **MS:** calc. for [$C_{19}H_{20}N_2$+H]: 277.1705, found: 277.1702, **R_f:** 0.24 (25:1 DCM:MeOH).

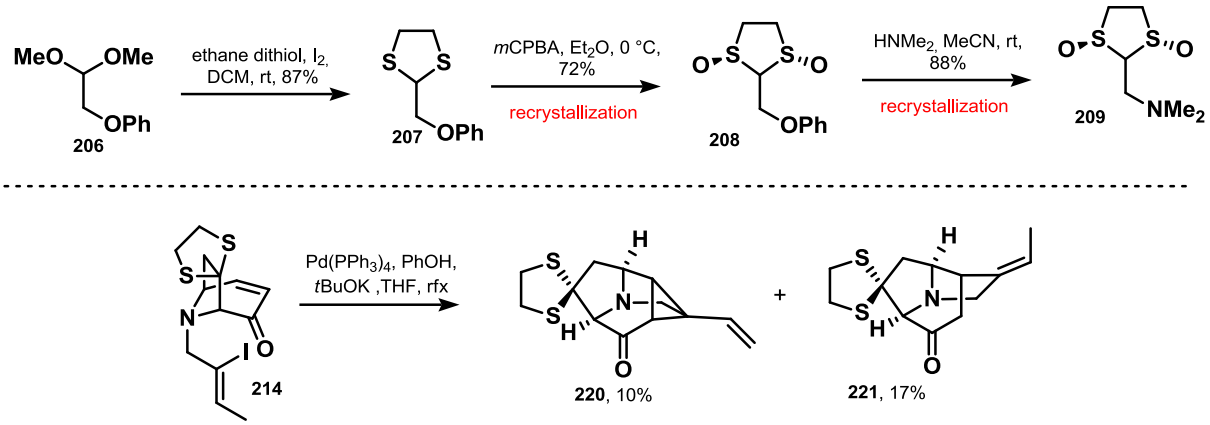
1a-vinylhexahydro-1*H*-spiro[1,4-methanocyclo-propa[*a*]-pyrrolizine-6,2'-[1,3]dithiolan]-7-one (**219**)



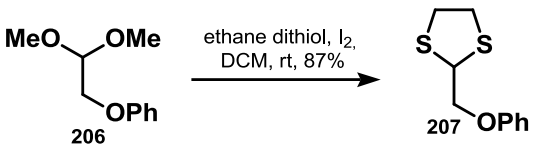
Enone **213** (87.0 mg, 221 µmol, 1.0 eq.) was dissolved in THF (8.0 mL) under an inert atmosphere, followed by the addition of $Pd(PPh_3)_4$ (25.0 mg, 21.6 µmol, 0.1 eq.) in THF (1.0 mL) and PhOK (prepared in another flask from PhOH (41.0 mg, 436 µmol, 2.0 eq.) and *t*BuOK (33.0 mg, 294 µmmol, 1.3 eq.) in THF (2.0 mL)). The resulting mixture was heated to reflux for 5 hours, before being cooled down to ambient temperature. The cold mixture was diluted with ice-water and EtOAc as well as solid NaCl and 2 M NaOH solution. The phases were separated and the aqueous phase was extracted two more times with EtOAc. The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude remains were purified *via* flash column chromatography using 1:1 EtOAc:PE as eluent to yield 35.0 mg (60%) of vinylcyclopropane **219** as a clear oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.76–5.68 (m, 1H), 5.17–5.10 (m, 2H), 4.04 (d, *J*=2.3 Hz, 1H), 3.45 (dt, *J*=11.3, 4.2 Hz, 1H), 3.40–3.27 (m, 4H), 3.25–3.17 (m, 1H), 3.15 (d, *J*=12.6 Hz, 1H), 2.89 (dd, *J*=14.6, 8.5 Hz, 1H), 2.47 (d, *J*=14.6 Hz, 1H), 2.36 (dd, *J*=7.2, 2.4 Hz, 1H), 2.17 (d, *J*=7.1 Hz, 1H) ppm. **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 206.3, 134.4, 115.8, 78.0, 69.3, 67.3, 52.6, 48.9, 42.4, 40.9, 37.7, 32.0 ppm. **IR (neat sample):** 2924, 1701, 1632, 1429, 1298, 1279, 1234, 1173, 1140, 1109, 1076, 1038, 1022, 988, 897, 854 cm^{-1}. **MS:** calc. for [$C_{13}H_{15}NOS_2$+H]: 266.0673, found: 266.0669, **R_f:** 0.34 (1:1 EtOAc:PE).

Graphical Overview III



2-(Phenoxymethyl)-1,3-dithiolane (**207**)

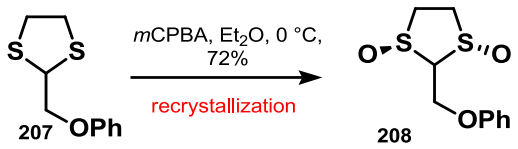


Acetal **206** (10.0 g, 54.88 mmol, 1.0 eq.) was dissolved in DCM (100 mL), followed by the addition of 1,2-ethanedithiol (4.8 mL, 5.2 g, 54.88 mmol, 1.0 eq.). Iodine (1.4 g, 5.5 mmol, 0.1 eq.) was added and the reaction mixture was stirred at ambient temperature. After four hours and incomplete consumption of starting material another 0.2 eq of ethanedithiol (0.96 mL, 1.04 g, 10.98 mmol, 0.2 eq) was added. The reaction mixture was stirred at ambient temperature for another 16 hours, followed by the addition of sat. sodium thiosulfate solution and 0.1 M sodium hydroxide solution. The phases were separated, and the aqueous phase was extracted two more times with DCM. The combined organic layers were dried

over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified *via* flash chromatography using 30:1 to 15:1 PE:EtOAc as eluent to give 10.1 g (87%) of desired dithiolane **207** as a clear oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.34–7.27 (m, 2H), 7.01–6.96 (m, 1H), 6.96–6.91 (m, 2H), 4.81 (t, *J*=7.0 Hz, 1H), 4.07 (d, *J*=7.0 Hz, 2H), 3.28 (s, 4H) ppm. **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 158.4, 129.6 (2C), 121.4, 115.0 (2C), 73.0, 51.2, 38.3 ppm. **IR (neat sample):** 3036, 2923, 2860, 1598, 1492, 1453, 1291, 1235, 1206, 1172, 1078, 1034, 843 cm^{-1}. **R_f:** 0.66 (9:1 PE:EtOAc).

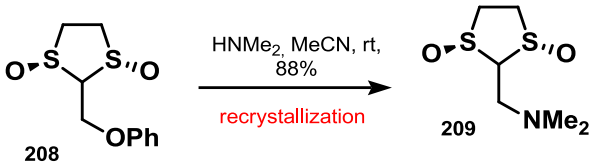
2-Benzyloxmethyl-1,3-dithiolane-1,3-dioxide (**208**)



Dithiolane **207** (10.1 g, 47.43 mmol, 1.0 eq.) was dissolved in Et_2O (95 mL) and the solution was cooled to 0 °C. *m*CPBA (25.7 g of 70% purity, 104.34 mmol, 2.2 eq.) was dissolved in Et_2O (140 mL) and was added through an addition funnel over 45 minutes. After the addition of 50 mL of the *m*CPBA solution the reaction mixture turned cloudy as a white precipitate formed. After two more hours the precipitate was filtered off, followed by recrystallization from ethyl acetate to give 8.4 g (72%) of desired bissulfoxide **208** as a white solid.

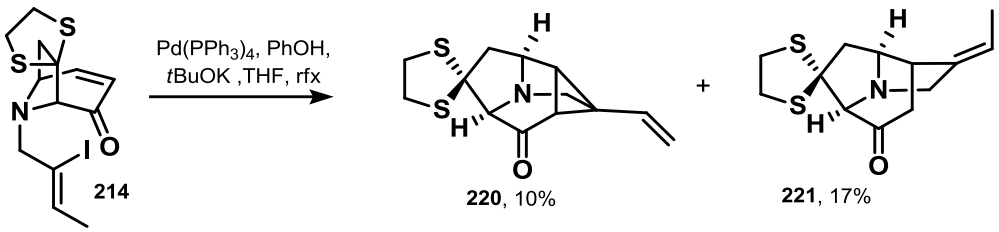
^{1}H-NMR (400 MHz, methanol-d_4): δ = 7.34–7.28 (m, 2H), 7.04–6.97 (m, 3H), 4.68–4.62 (m, 1H), 4.61–4.51 (m, 2H), 3.99–3.92 (m, 1H), 3.88–3.75 (m, 2H) ppm. **^{13}C-NMR (100 MHz, methanol-d_4):** δ = 159.3, 130.7 (2C) 123.0, 116.0 (2C), 90.0, 61.8, 52.9, 52.5 ppm. **IR (neat sample):** 2938, 1599, 1585, 1493, 1463, 1387, 1292, 1239, 1096, 1019, 841 cm^{-1}. **MS:** calc. for $[C_{10}H_{12}O_3S_2Na^+]$: 267.0126, found: 267.0125. **MP:** 105-108 °C. **R_f:** 0.41 (10% MeOH:EtOAc).

2-*N*,*N*'-dimethylaminomethyl-1,3-dithiolane-1,3-dioxide (**209**)



Bisulfoxide **208** (8.4 g, 34.4 mmol, 1.0 eq.) was suspended in MeCN (30 mL), followed by the addition of $HNMe_2$ (18 mL, 1.05 eq, 2.0 M solution in THF). After the complete addition of the $HNMe_2$ solution the reaction mixture was a clear solution and was stirred for 5 minutes. The solution was concentrated under reduced pressure to approximately 5 mL, followed by the addition of 50 mL ethylether. A white precipitate formed, and the mixture was transferred to a freezer for 3 hours to ensure complete precipitation. The white precipitate was then filtered off and was washed with 10 mL ethylether to yield 5.9 g (88%) of desired amine **209** as a white solid. The spectral data matches those reported in the literature.[2.51a]

(4'*S*,6a'*S*)-1a'-vinylhexahydro-4'*H*-spiro[[1,3]dithiolane-2,5'-[1,4]methanocyclopropa[*a*]pyrrolizin]-7'-one (**220**) and **221**



Unsaturated Ketone **214** (117 mg, 0.30 mmol, 1.0 eq.) was dissolved in degassed THF (12 mL, overall concentration 0.02 M) followed by the addition of $Pd(PPh_3)_4$ (35 mg, 0.03 mmol, 10 mol%) in THF (1 mL) and a mixture of KO*t*Bu (51 mg, 0.45 mmol, 1.5 eq.) and PhOH (56 mg, 0.60 mmol, 2.0 eq.) in THF (2 mL). The resulting mixture was heated to reflux for 5 h, before being cooled down to room temperature. The cold mixture was diluted with ice-water and EtOAc as well as solid NaCl and 2 M NaOH solution. The phases were separated and the aqueous phase was extracted two more times with EtOAc. After column chromatography

(PE/EtOAc 1.5:1) cyclopropane **220** (8.0 mg, 10%) and five membered **221** (13.0 mg, 17%) were isolated.

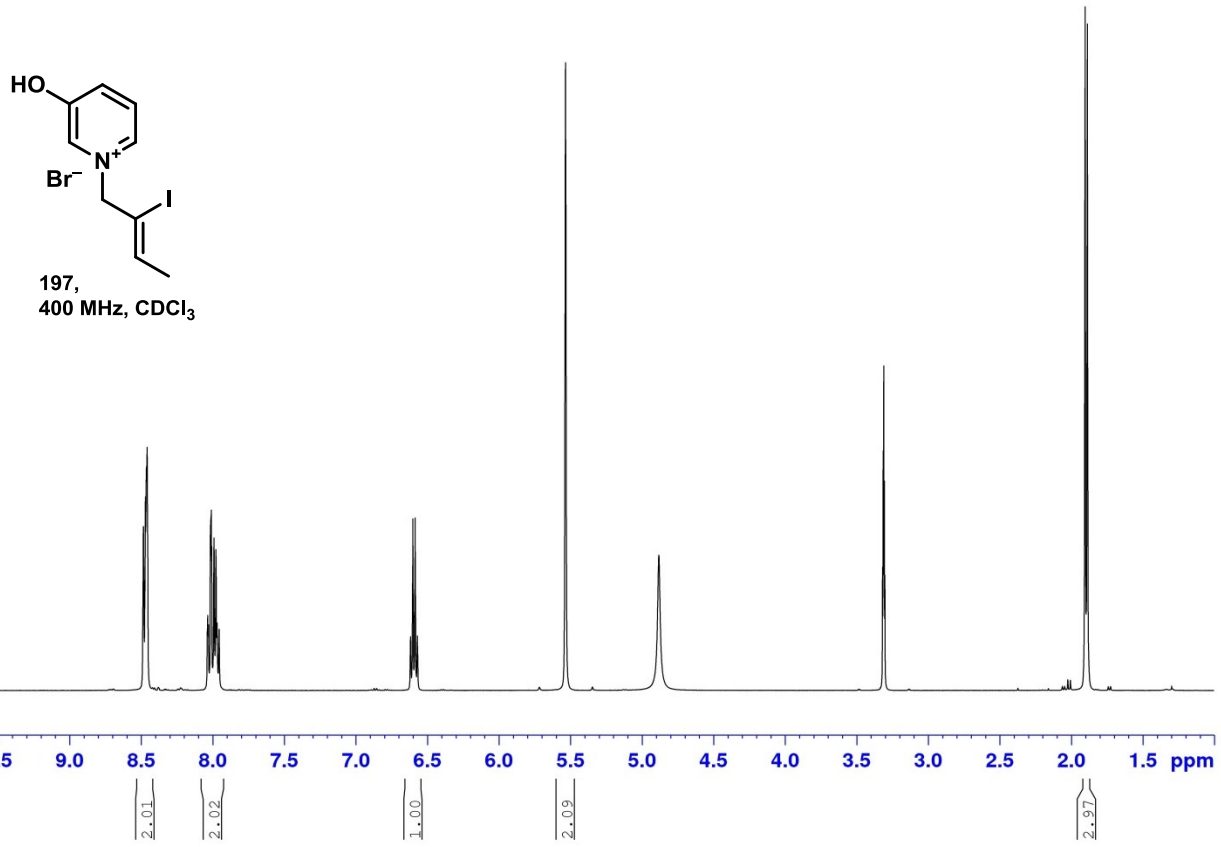
Cyclopropane **220**:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.72 (dd, *J*=17.6, 10.6 Hz, 1H), 5.17–5.11 (m, 2H), 3.91 (d, *J*=7.7 Hz, 1H), 3.42–3.23 (m, 6H), 3.18 (d, *J*=12.7 Hz, 1H), 2.91 (ddd, *J*=14.5, 7.6, 1.0 Hz, 1H), 2.51 (dd, *J*=14.5, 2.0 Hz, 1H), 2.18 (dd, *J*=7.1, 2.5 Hz, 1H), 2.09–2.03 (m, 1H) ppm. **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 202.7, 134.4, 115.8, 80.3, 69.5, 62.0, 52.4, 45.3, 44.2, 40.3, 39.9, 36.8, 34.3 ppm. **IR (neat sample):** 2922, 2851, 1694, 1634, 1447, 1308, 1290, 1227, 1140, 1103, 984, 876, 856 cm^{-1}. **MS:** calc. for [$C_{13}H_{15}NOS_2$+H]: 266.0673, found: 266.0677.

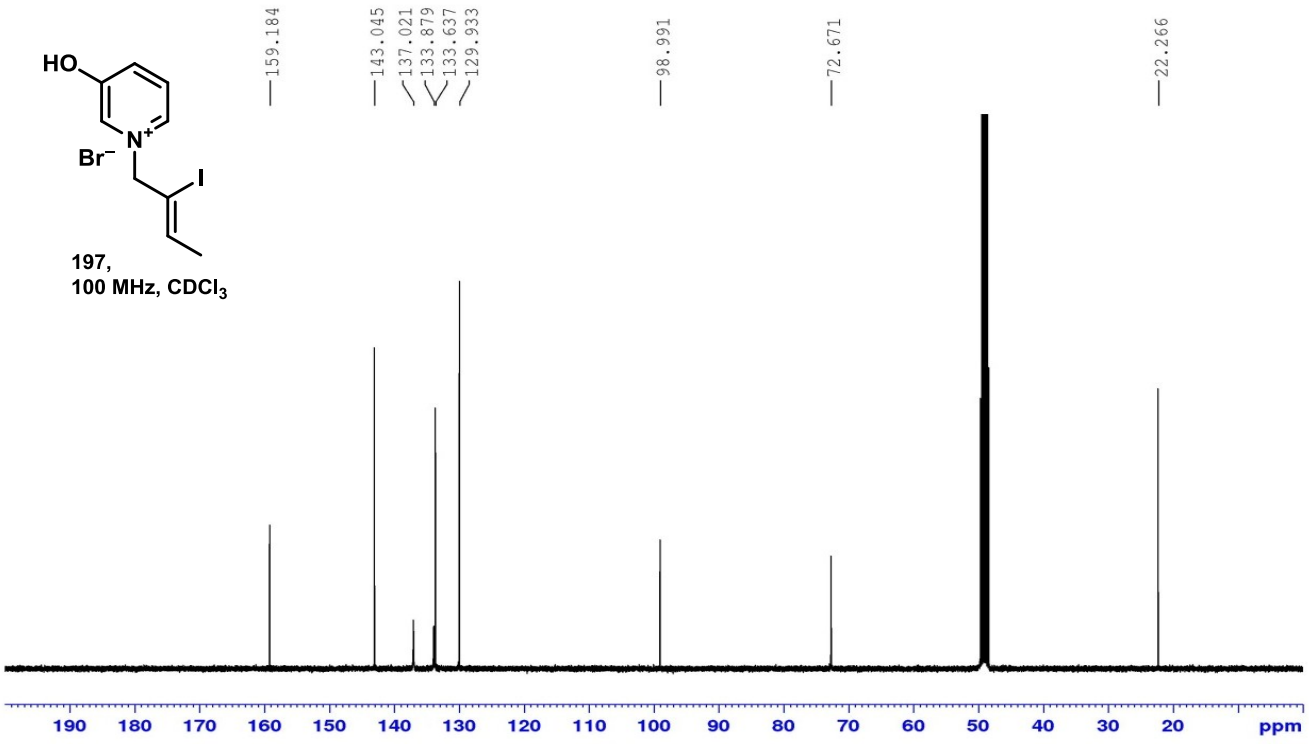
Five membered ring **221**:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.32–5.25 (m, 1H), 3.71 (dt, *J*=16.9, 2.2 Hz, 1H), 3.62–3.53 (m, 2H), 3.48–3.36 (m, 3H), 3.30–3.15 (m, 3H), 3.05–2.99 (m, 1H), 2.85–2.77 (m, 2H), 2.27 (dq, *J*=15.9, 2.2 Hz, 1H), 1.62 (dt, *J*=6.8, 2.1 Hz, 3H) ppm. **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 210.0, 143.5, 116.4, 86.7, 69.2, 64.8, 53.6, 44.7, 42.8, 40.6, 40.2, 39.9, 14.9 ppm. **IR (neat sample):** 2918, 2857, 1719, 1454, 1418, 1288, 1192, 1126, 1101, 1074, 975, 930, 860, 812 cm^{-1}.

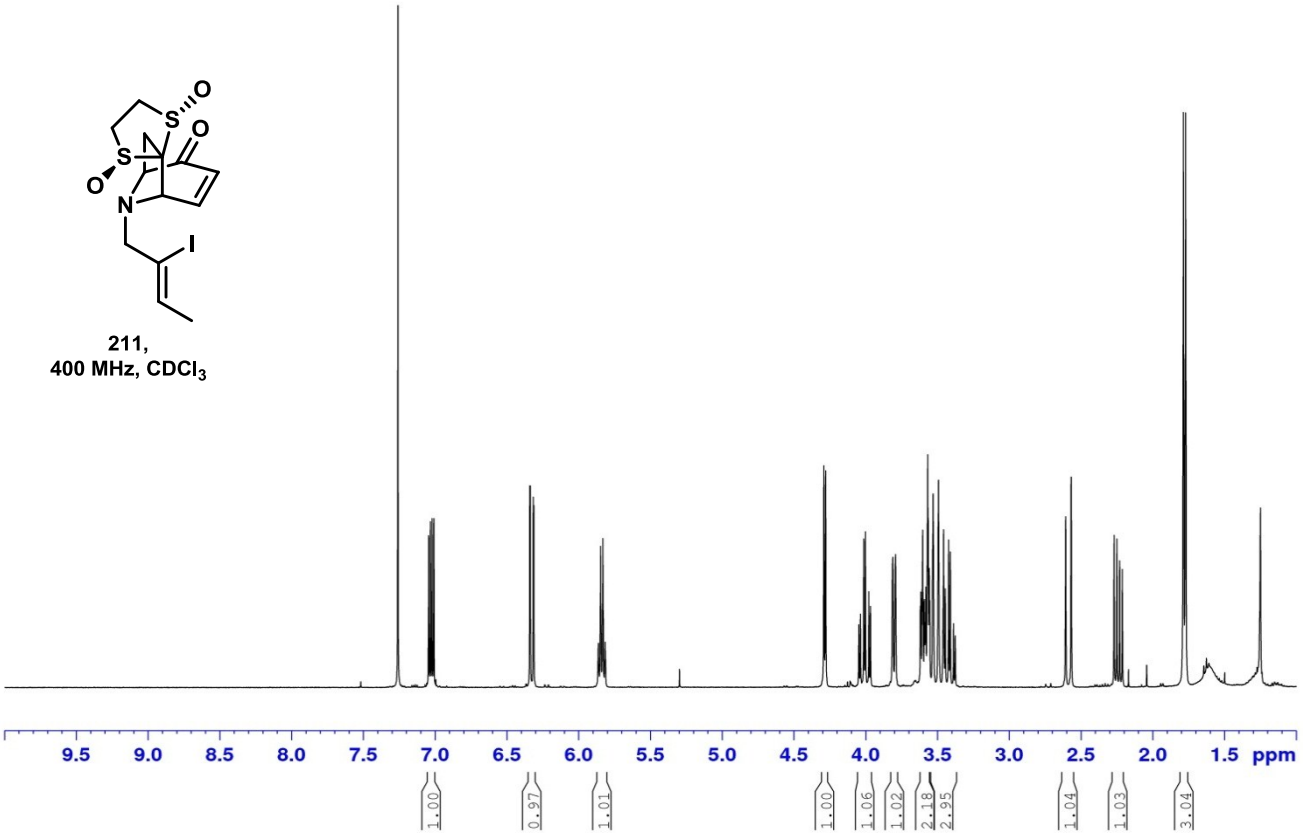
2.11 Spectra



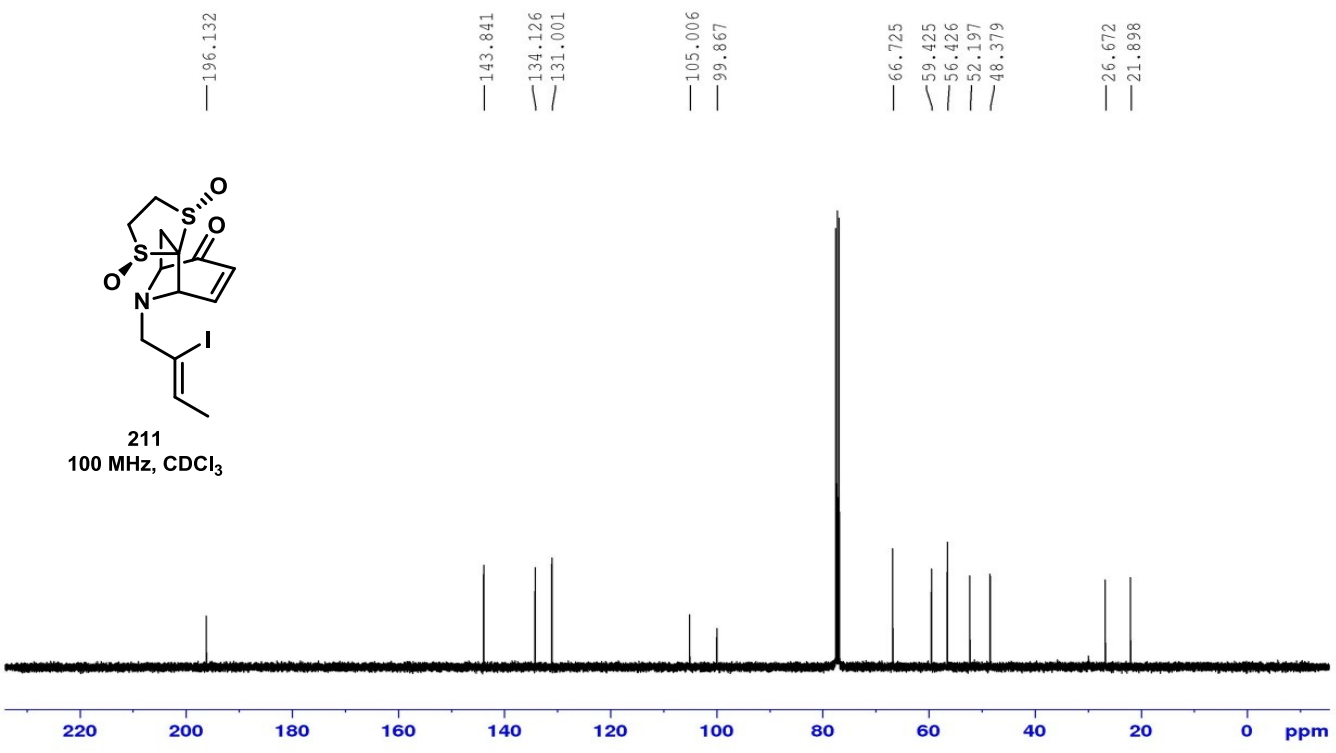
197,
400 MHz, $CDCl_3$



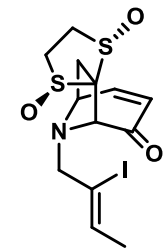
197,
100 MHz, $CDCl_3$



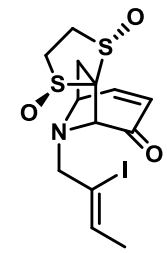
211,
400 MHz, $CDCl_3$



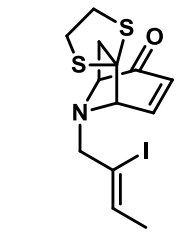
211
100 MHz, $CDCl_3$



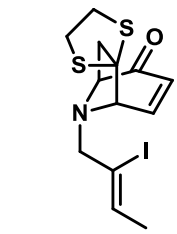
212
400 MHz, $CDCl_3$



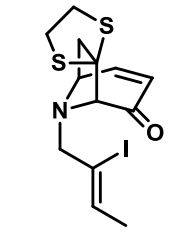
212
100 MHz, $CDCl_3$



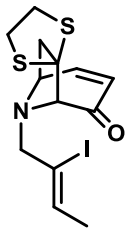
213
400 MHz, $CDCl_3$



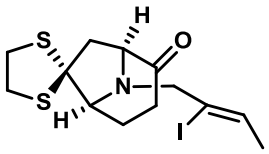
213
100 MHz, $CDCl_3$



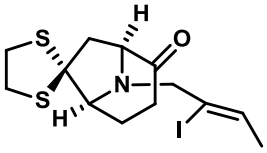
214
400 MHz, $CDCl_3$



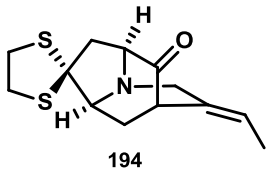
214
100 MHz, $CDCl_3$



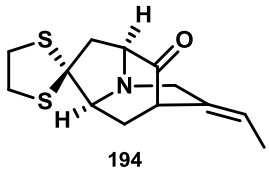
195
400 MHz, $CDCl_3$



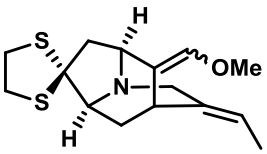
195
100 MHz, $CDCl_3$



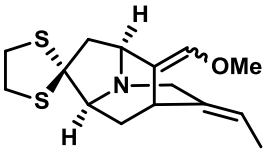
194
400 MHz, $CDCl_3$



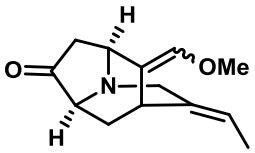
194
100 MHz, $CDCl_3$



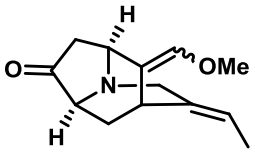
major DB-isomer **239**
500 MHz, $CDCl_3$



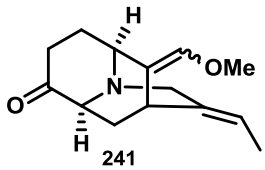
major DB-isomer **239**
125 MHz, $CDCl_3$



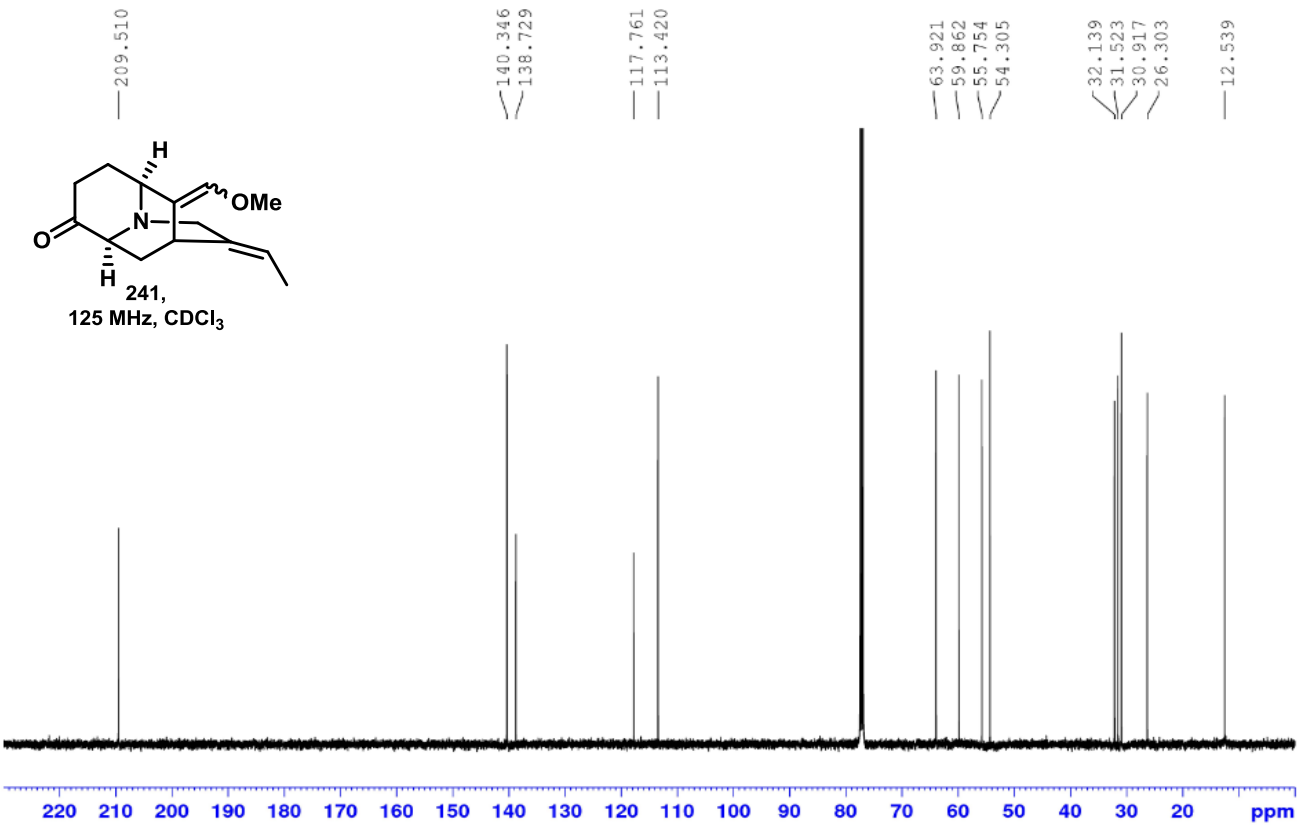
240
500 MHz, $CDCl_3$



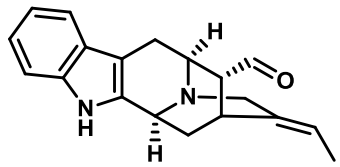
240
125 MHz, $CDCl_3$



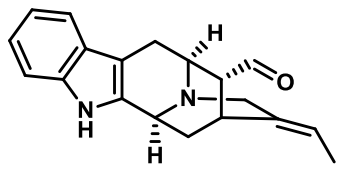
241
500 MHz, $CDCl_3$



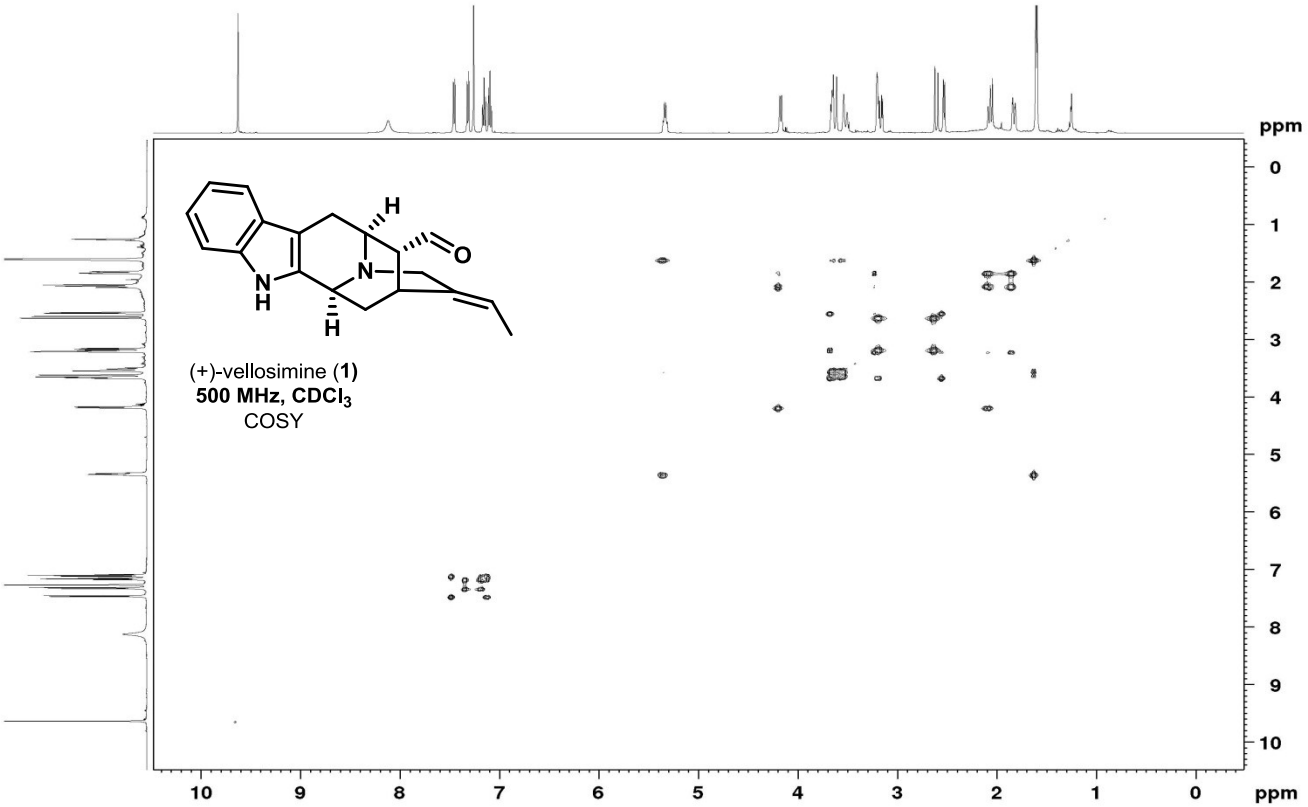
241,
125 MHz, $CDCl_3$



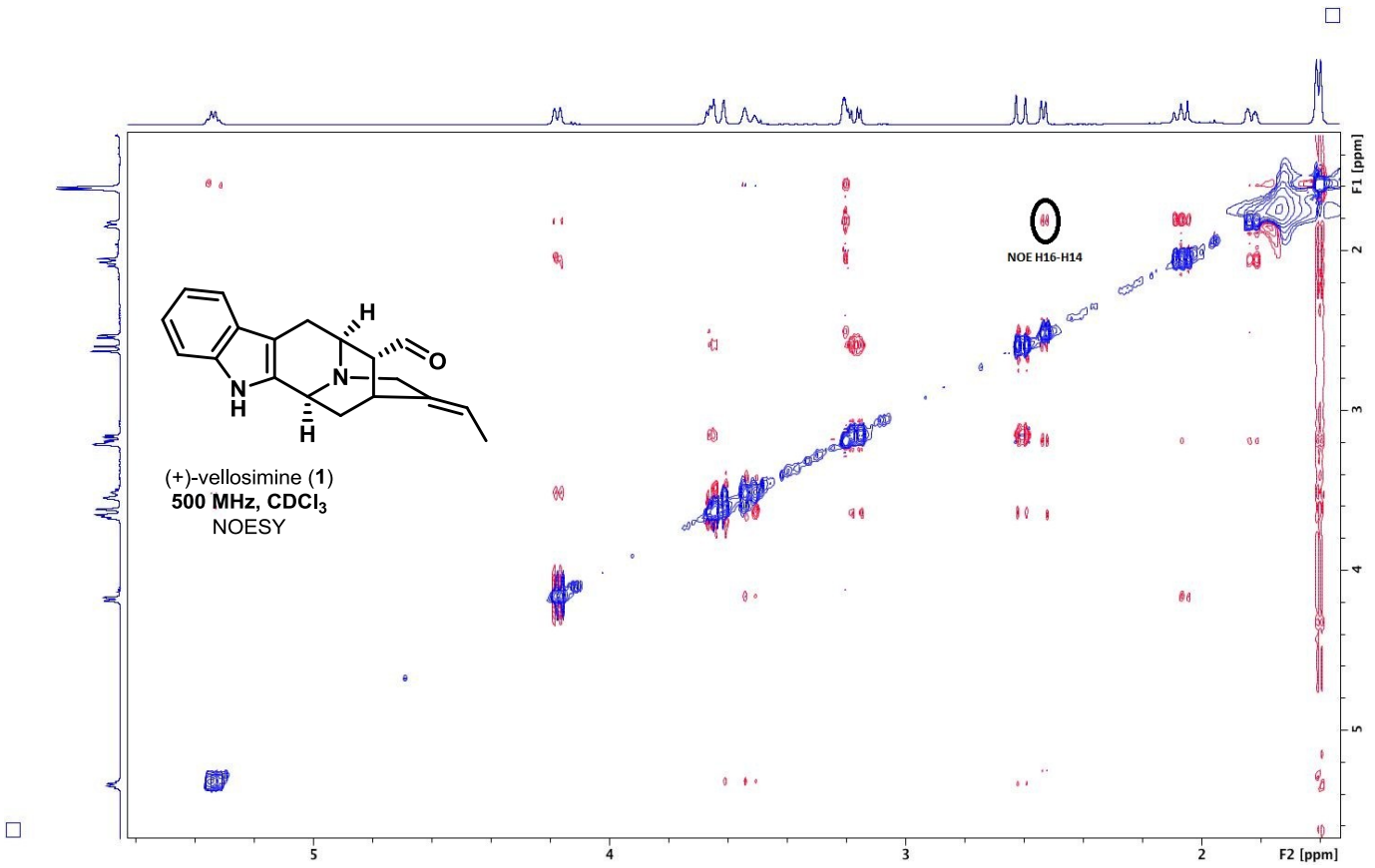
(+)-vellosimine (**1**)
500 MHz, $CDCl_3$



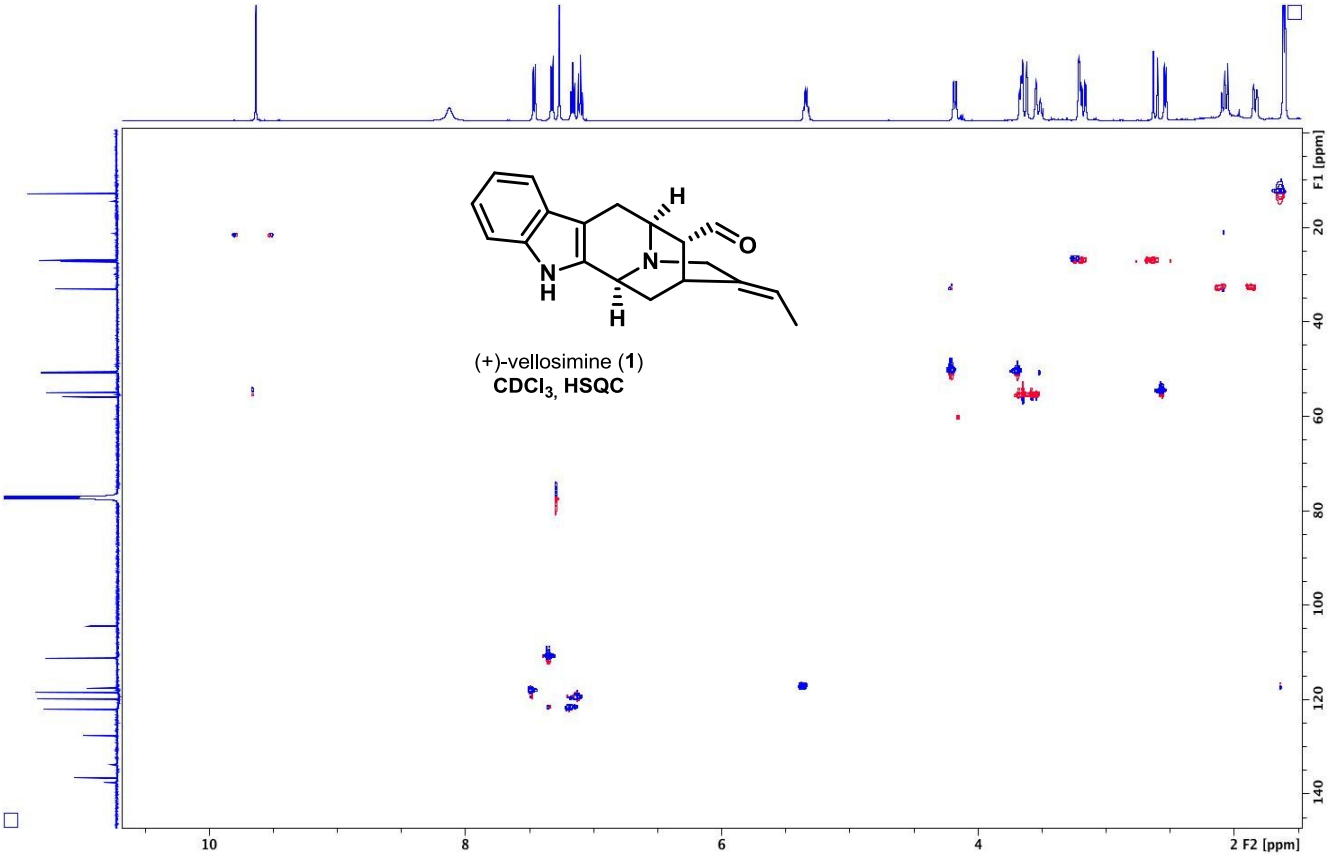
(+)-vellosimine (**1**)
125 MHz, $CDCl_3$



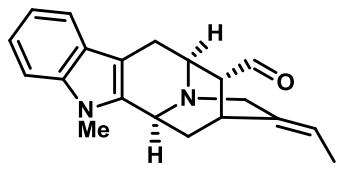
(+)-vellosimine (**1**)
500 MHz, $CDCl_3$
COSY



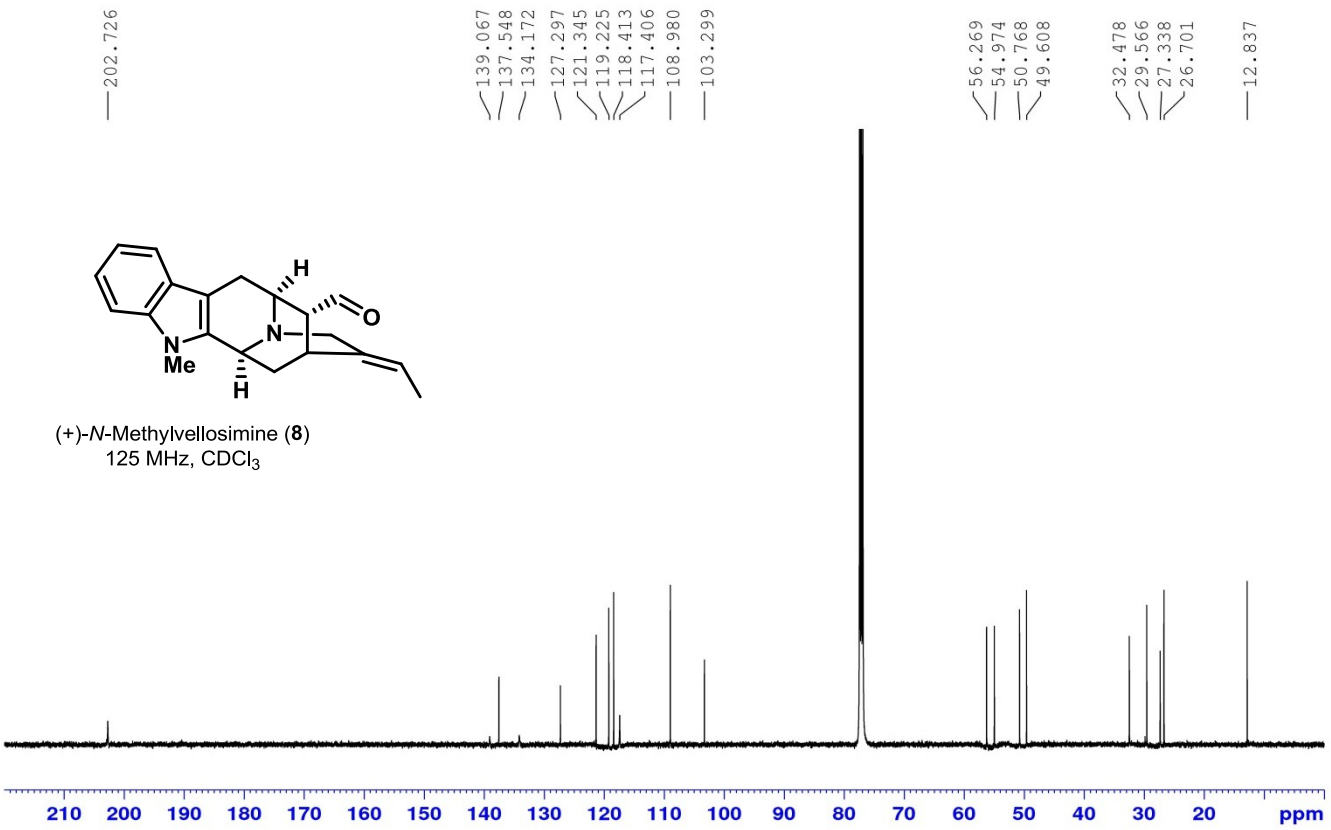
(+)-vellosimine (**1**)
500 MHz, $CDCl_3$
NOESY



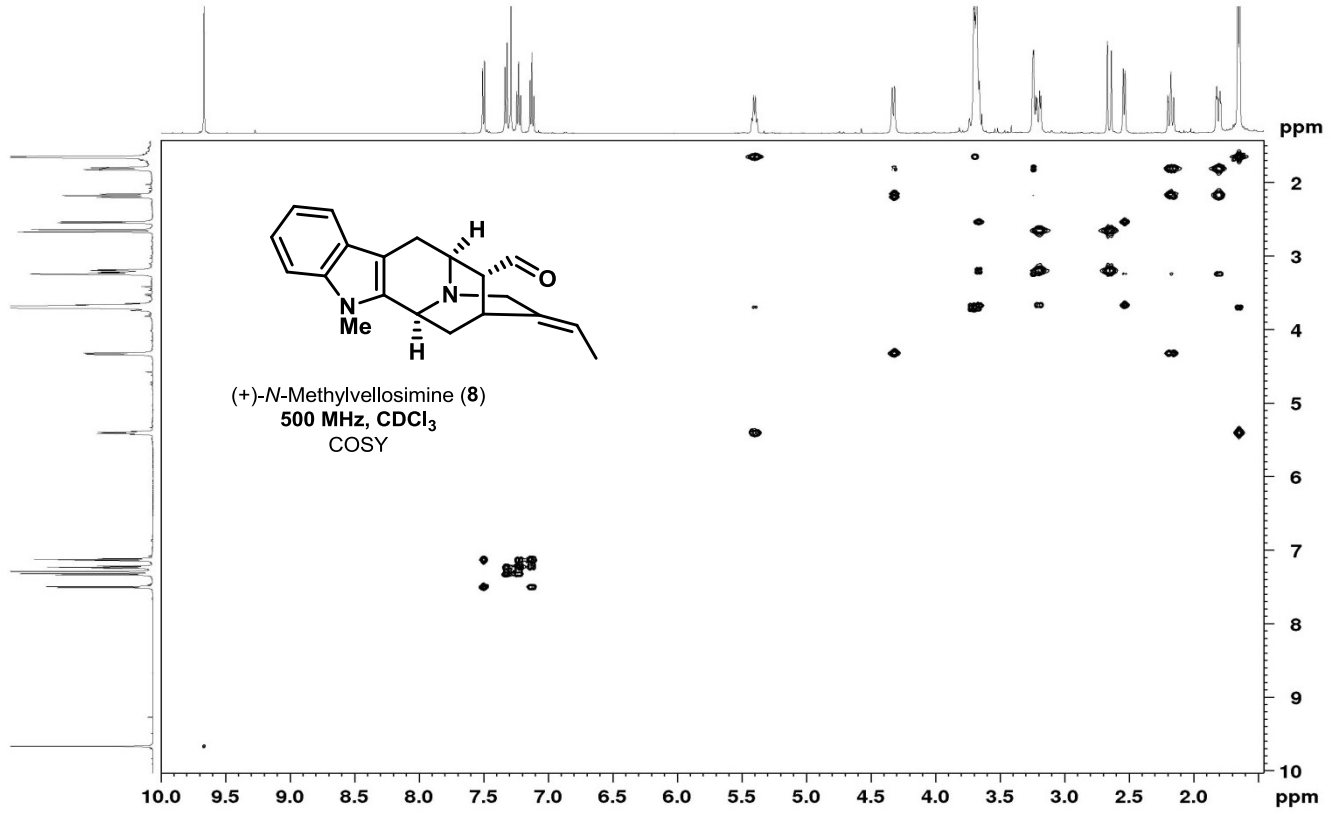
(+)-vellosimine (**1**)
$CDCl_3$, HSQC



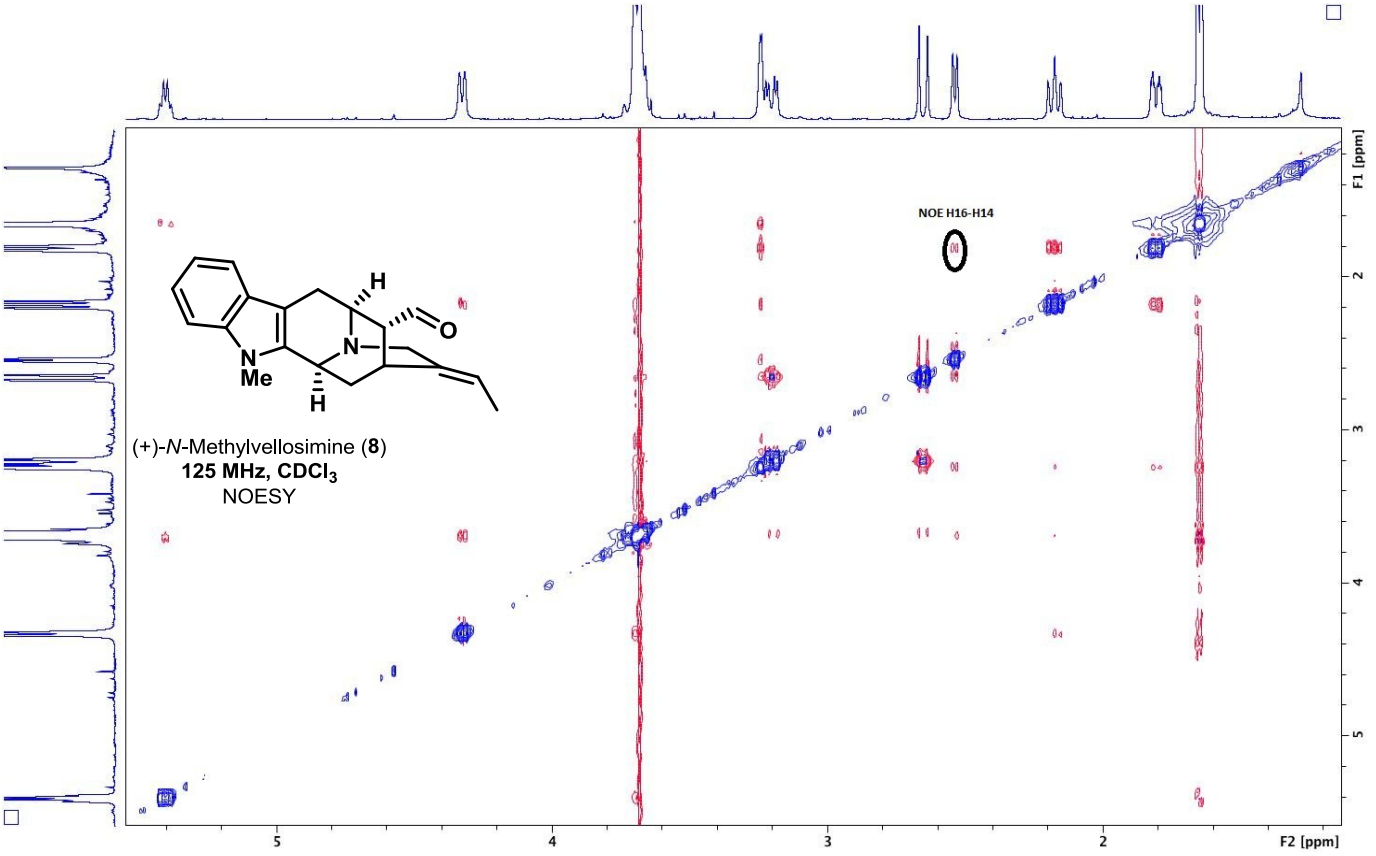
(+)-*N*-Methylvellosimine (**8**)
500 MHz, $CDCl_3$

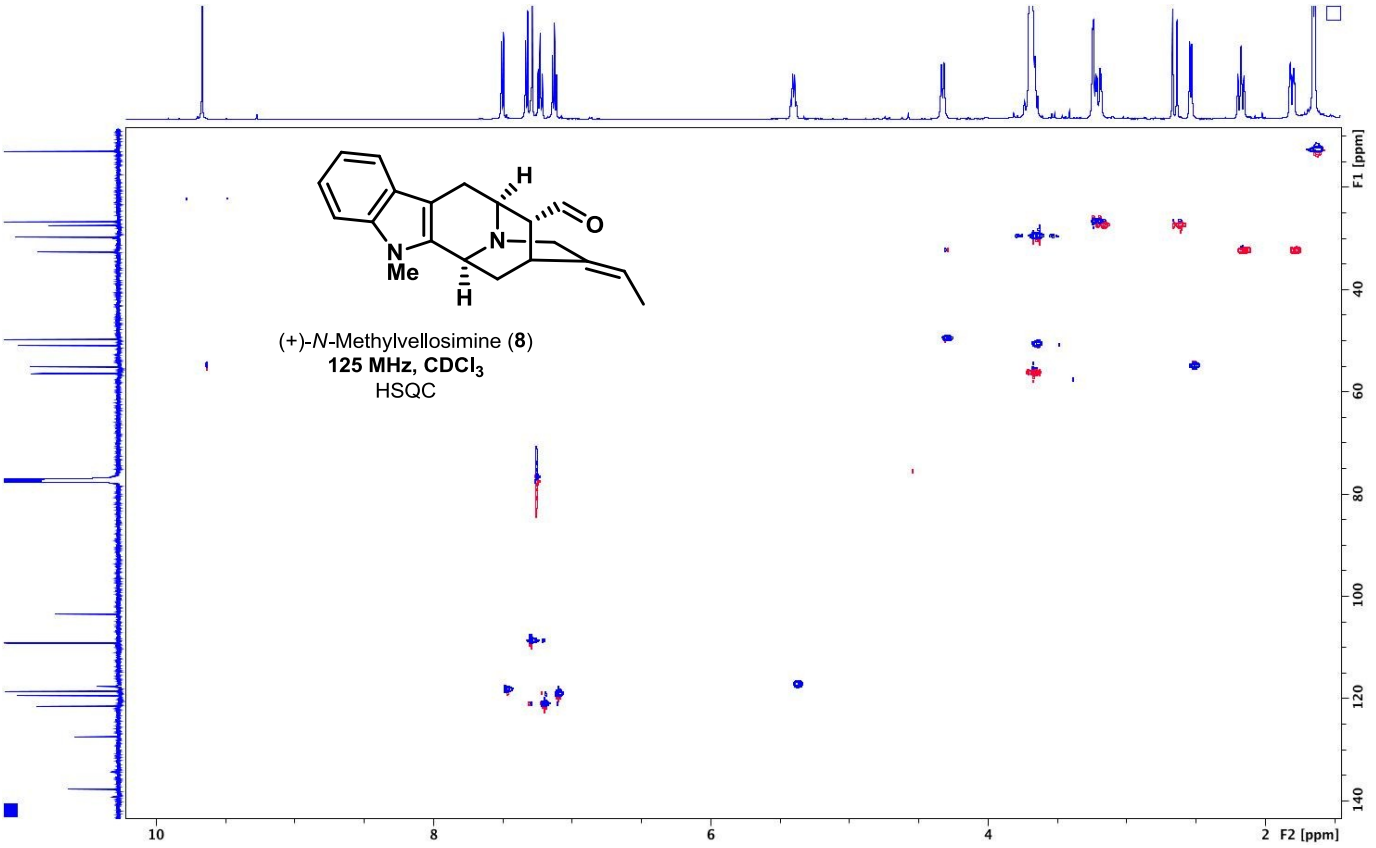


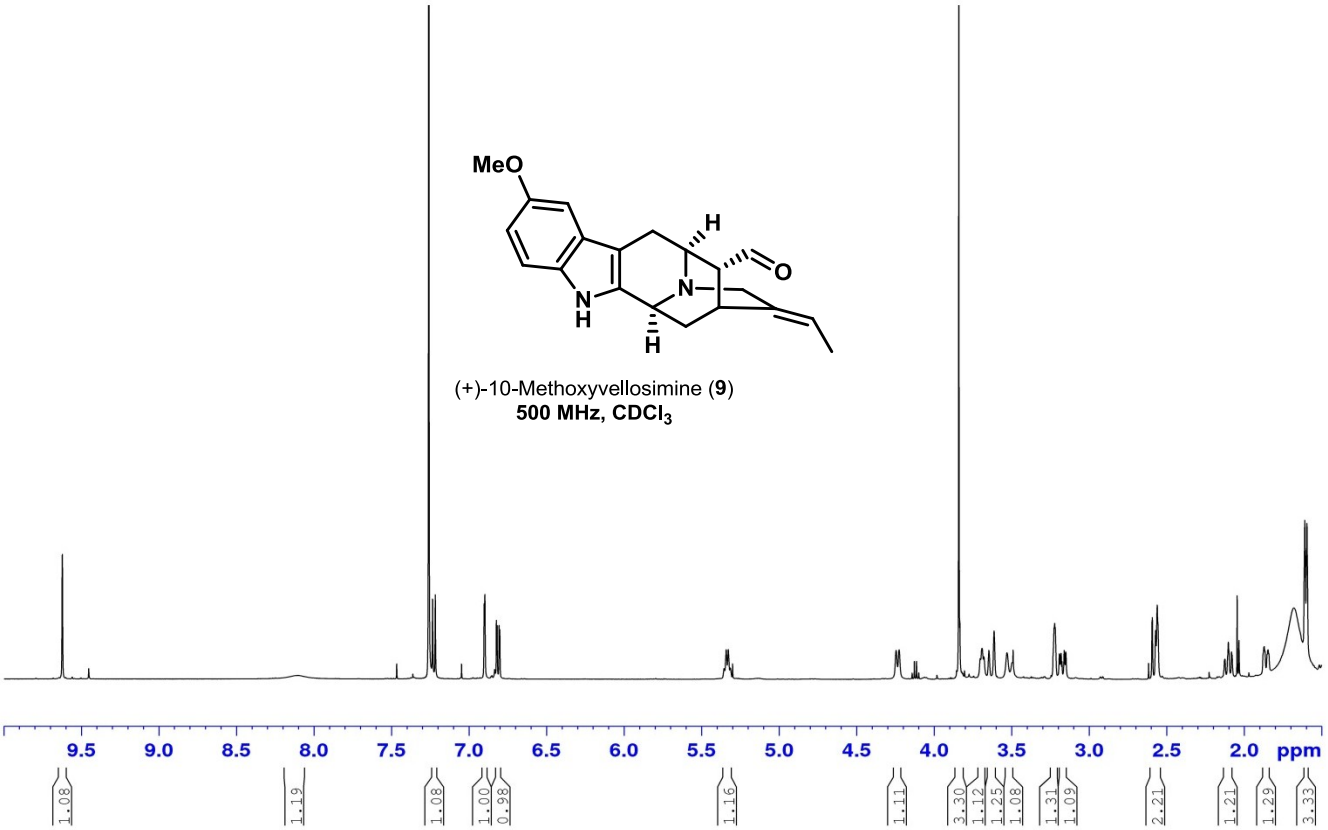
(+)-*N*-Methylvellosimine (**8**)
125 MHz, $CDCl_3$



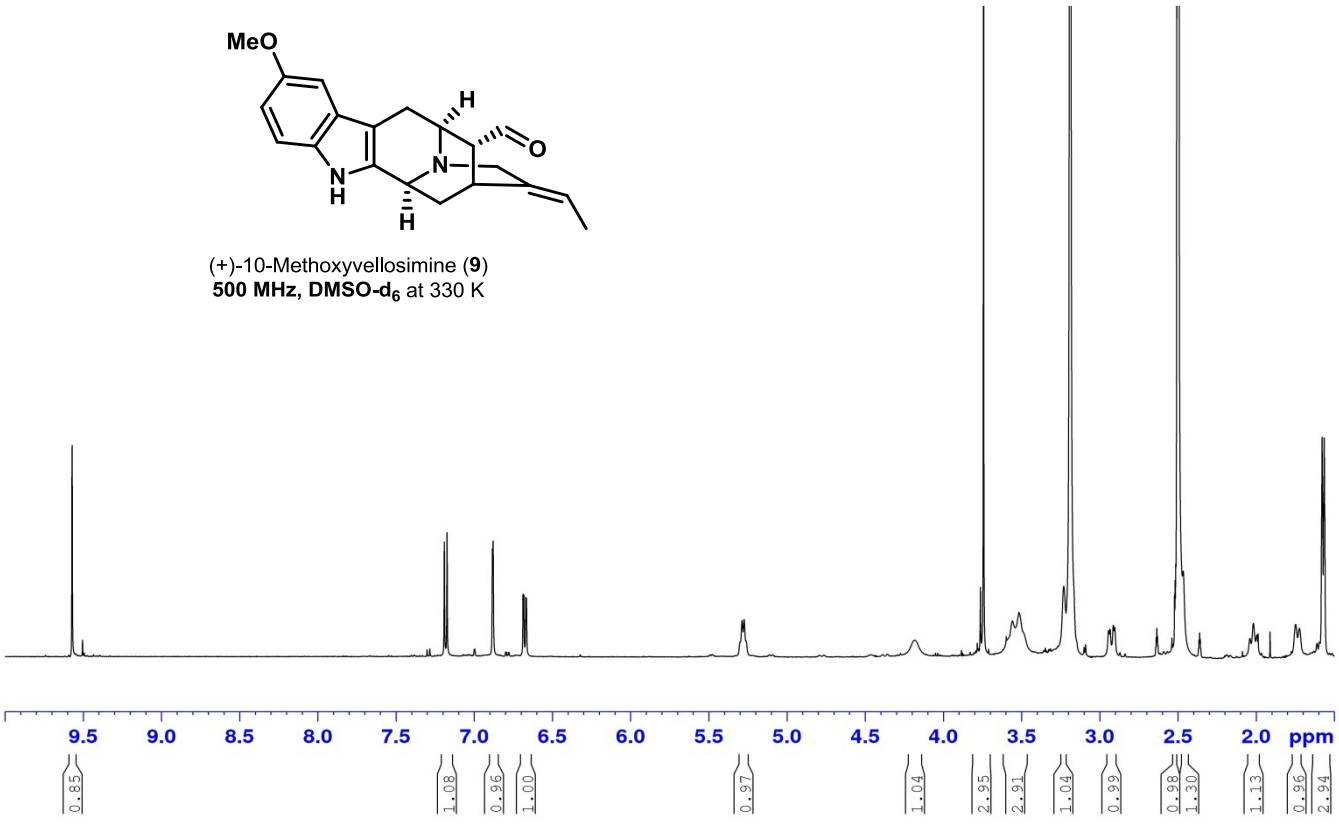
(+)-*N*-Methylvellosimine (**8**)
500 MHz, $CDCl_3$
COSY


NOE H16-H14
F1 [ppm]
F2 [ppm]
(+)-*N*-Methylvellosimine (**8**)
125 MHz, $CDCl_3$
NOESY

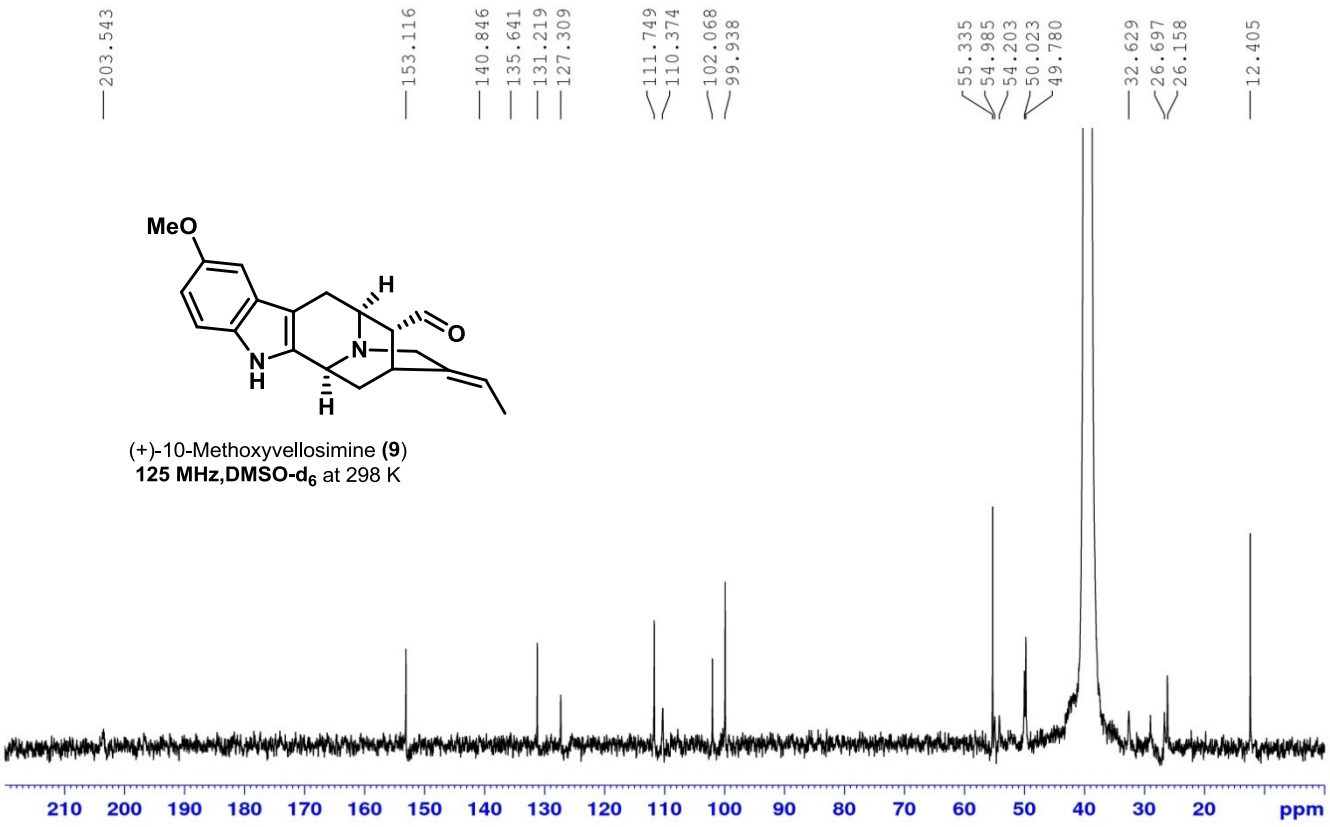

F1 [ppm]
F2 [ppm]
(+)-*N*-Methylvellosimine (**8**)
125 MHz, $CDCl_3$
HSQC



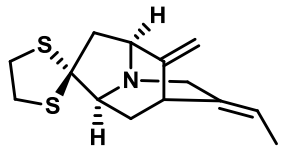
(+)-10-Methoxyvellosimine (**9**)
500 MHz, $CDCl_3$



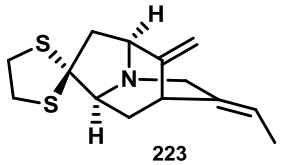
(+)-10-Methoxyvellosimine (**9**)
500 MHz, DMSO-d_6 at 330 K



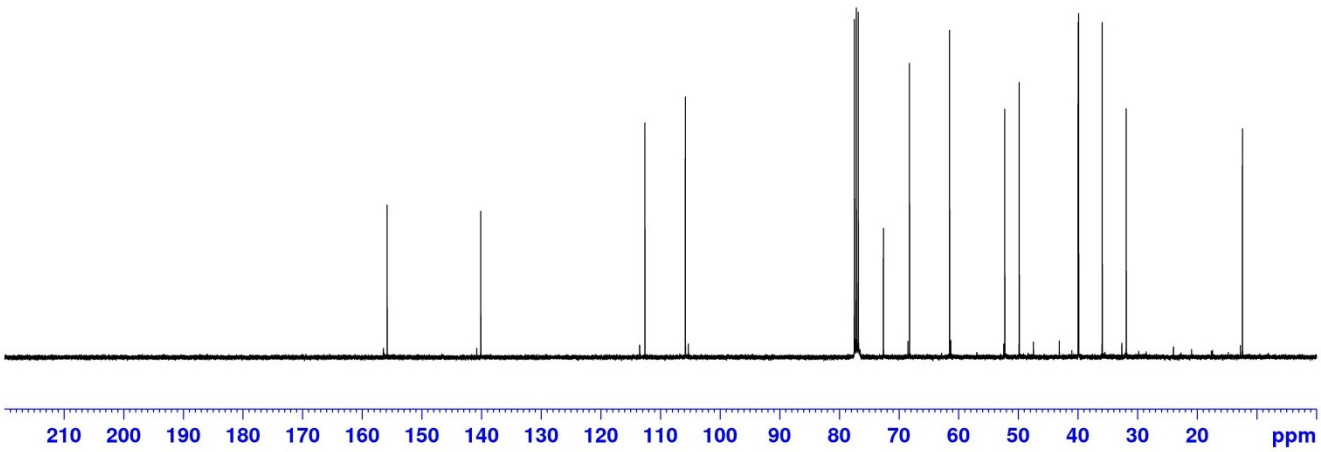
(+)-10-Methoxyvellosimine (**9**)
125 MHz,DMSO-d_6 at 298 K

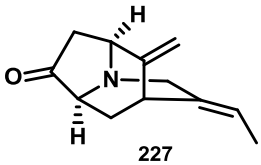


223
400 MHz, $CDCl_3$

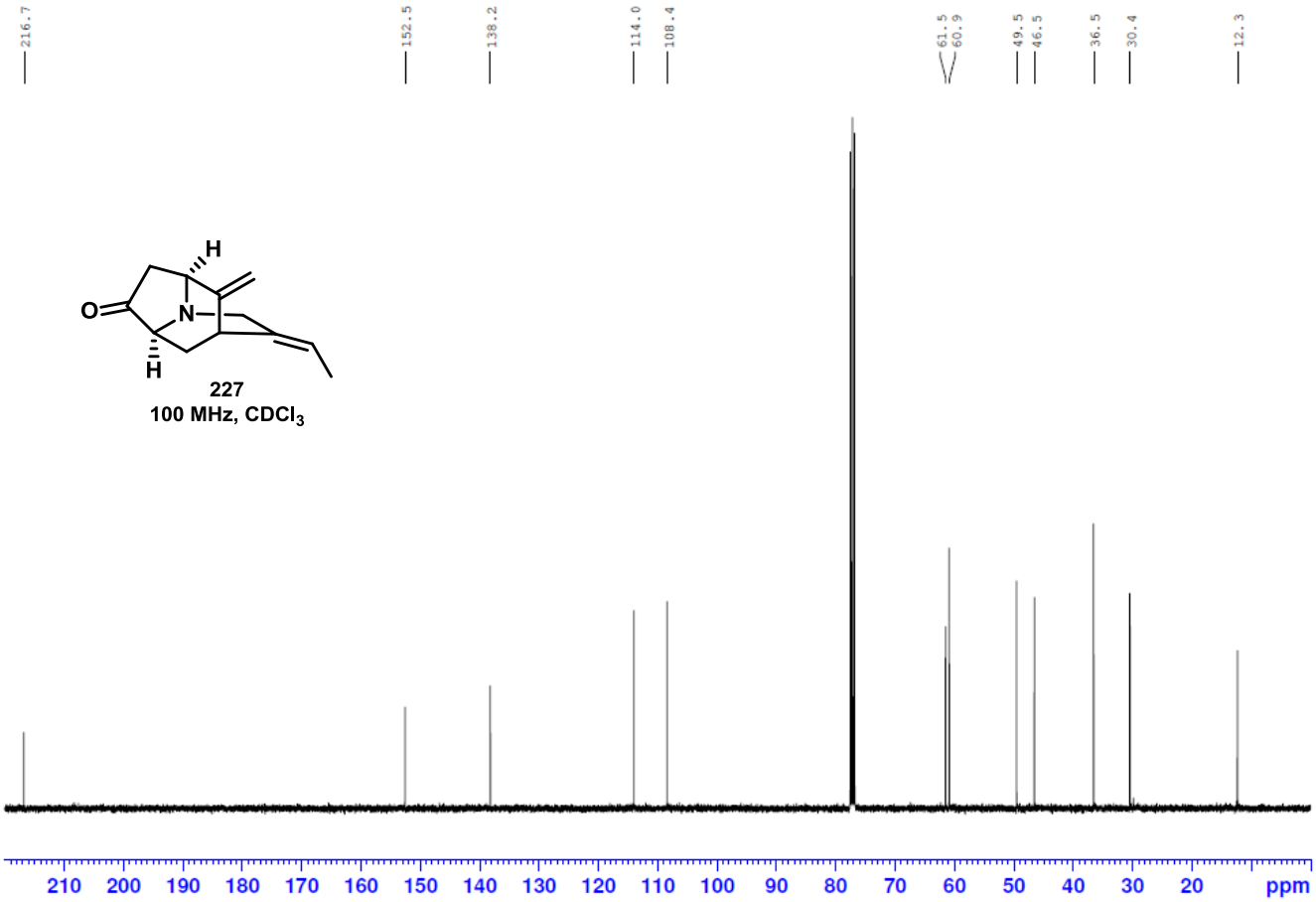


223
100 MHz, $CDCl_3$

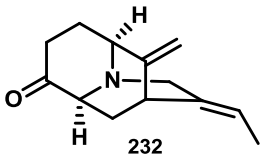




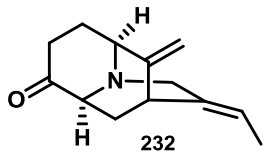
227
400 MHz, $CDCl_3$



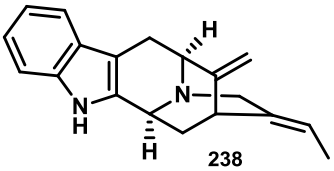
227
100 MHz, $CDCl_3$



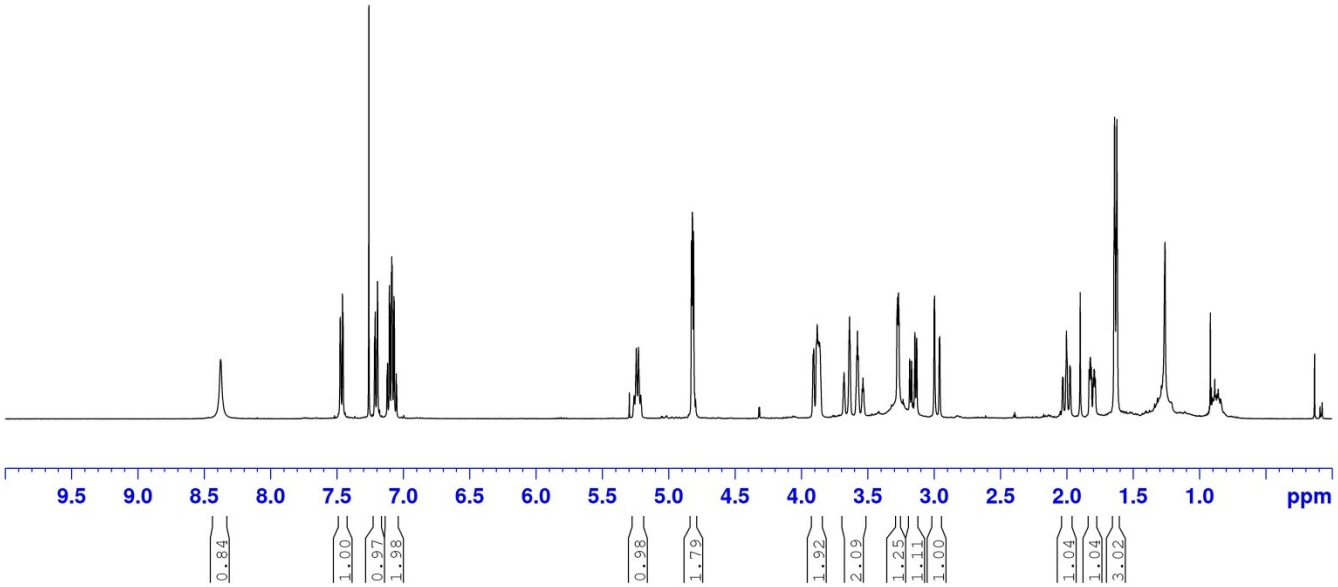
232
400 MHz, $CDCl_3$

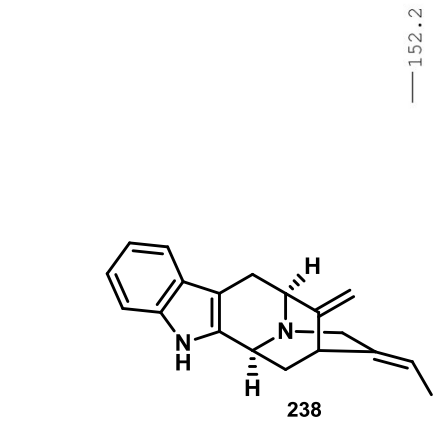


232
100 MHz, $CDCl_3$

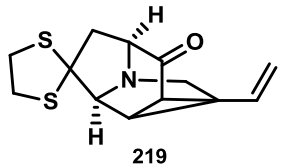


238
400 MHz, $CDCl_3$

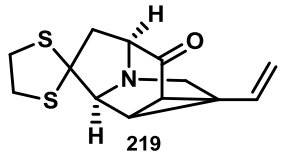




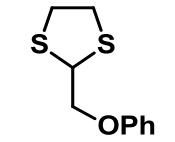
238
100 MHz, $CDCl_3$



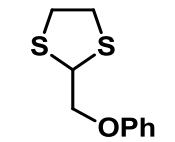
219
400 MHz, $CDCl_3$



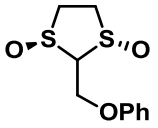
219
100 MHz, $CDCl_3$



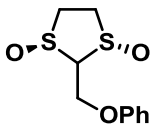
207
400 MHz, $CDCl_3$



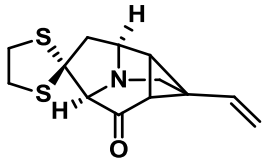
207
100 MHz, $CDCl_3$



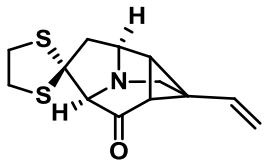
208
400 MHz, $CDCl_3$



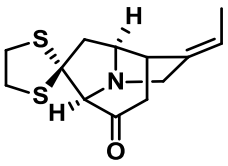
100 MHz, $CDCl_3$



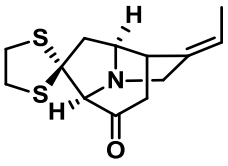
220,
400 MHz, $CDCl_3$



220,
100 MHz, $CDCl_3$



221,
400 MHz, $CDCl_3$



221,
100 MHz, $CDCl_3$

2.12 References

[2.1] C. Weiming, V. Yaping, L. Xiaotian, *Planta Med.* **1983**, *49*, 62.

[2.2] L. Douzoua, M. Mansourm M. M. Debray, L. Le Men-Oliver, J. Le Men, *Phytochemistry*, **1974**, *13*, 1974–1995.

[2.3] H. Rapaport, T. Onak, N. A. Hughes, M. G. Reineke, *J. Am. Chem. Soc.* **1958**, *80*, 1601–1604.

[2.4] A. M. A. G. Nasser, W. E. Court, *J. Ethnopharmacol.* **1984**, *11*, 99–117.

[2.5] M. M. A. Amer, W. E. Court., *Planta Med. Suppl.* **1980**, 8–12.

[2.6] M. A. Amer, W. E. Court, *Phytochemistry*, **1981**, *20*, 2569–2573.

[2.7] P. Sierra, L. Novotny, Z. Samek, M. Budesinsky, L. Dolejs, K. Blaha, *Collect. Czech. Chem. Commun*. **1982**, *47*, 2912–2921.

[2.8] H. L. Lastra, M. Palacios, R. Menendez, M. Larionova, F. Rodriguez, V. Fuste, *Rev. Cub. Farm.* **1982**, *16*, 316–328.

[2.9] H. R. Arthur, S. R. Johns, J. A. Lamberton, S. N. Loo. *J. Austr. Chem*. **1968**, *21*, 1399–1401.

[2.10] M. Ohashi, H. Budzikiewicz, J. M. Wilson, C. Djerassi, J. Levy, J. Gosset, J. Le Men, M.-M. Janot, *Tetrahedron*, **1963**, *19*, 2241–2246.

[2.11] M. Lounasmaa, P. Hanhinen, M. Westersund, *„The Sarpagine Group of Indole Alkaloids"*, in: *The Alkaloids*, Vol. 52, Ed.:G. A. Cordell, Academic Press, San Diego, **1999.**

[2.12] P. Clivio, B. Richard, J.-R. Deverre, T. Sevenet, M. Zeches, L. Le Men-Olivier, *Phytochemistry*, **1991**, *30*, 3785–3792.

[2.13] Y. Sheludko, I. Gerasimenko, H. Kolshorn, J. Stöckigt, *J. Nat. Prod.* **2002,** *65,* 1006–1010.

[2.14] Y. Gao, D.-S. Zhou, L.-M. Kong, P. Hai, Y. Li, F. Wang, J.-K. Liu, *Nat. Prod. Bioprospect.* **2012**, *2*, 65–69.

[2.15] for the isolation of *Z*-affinisine see: S.-H. Lim, Y.-Y. Low, S. K. Sinniah, K.-T. Yong, K.-S. Sim, T.-S. Kam, *Phytochemistry*, **2014**, *98*, 204–215.

[2.16] L. Pan, C. Terrazas, U. Munoz Acuna, T. Ninh, H. Chai, E. J. Carcache de Blanco, D. D. Soejarto, A. R. Satoskar, A. D. Kinghorn, *Phytochemistry Letters*, **2014**, *10*, liv–lix.

[2.17] M. Kitajima, H. Kobayashi, N. Kogure, H. Takayama, *Tetrahedron*, **2010**, *66*, 5987–5992.

[2.18] N. Kogure, C. Nishiya, M. Kitajima, H. Takayama, *Tetrahedron Letters*, **2005**, *46*, 5857–5861.

[2.19] S.-H. Lim, S.-J. Tan, Y.-Y. Low, T.-S. Kam, *J. Nat. Prod.* **2011**, *74*, 2556−2562.

[2.20] C.-Y. Gan, Y.-Y. Low, W. T. Robinson, K. Komiyama, T.-S. Kam, *Phytochemistry*, **2010**, *71*, 1365–1370.

[2.21] S. Liang, C.-Y. He, L. F. Szabó, Y. Feng, X. Lin, Y. Wang, *Tet. Lett.* **2013**, *54*, 887–890.

[2.22] H. Takayama, W. Nitta, M. Kitajima, N. Aimi, S.-I. Sakai, *J. Nat. Prod.* **1994**, *57*, 521–523.

[2.23] S. E. O'Connor, J. J. Maresh, *Nat. Prod. Rep.* **2006**, *23*, 532–547.

[2.24] L. Yang, M. Hill, M. Wang, S. Panjikar, J. Stöckigt, *Angew. Chem. Int. Ed.* **2009**, *48*, 5211–5213.

[2.25] M. Ruppert, X. Ma, J. Stöckigt, *Curr. Org. Chem.* **2005**, *9*, 1431–1444.

[2.26] A. Pfitzner, J. Stöckigt, *J. Chem. Soc., Chem. Commun.* **1983**, 459−460.

[2.27] for a review, see: J. Stöckigt, S. Panjikar, M. Ruppert, L. Barleben, X. Ma, E. Loris, M. Hill, *Phytochem. Rev.* **2007**, *6*, 15−34.

[2.28] E. E. van Tamelen, L. K. Olivier, *J. Am. Chem. Soc.* **1970**, *92*, 2136−2137.

[2.29] E. E. van Tamelen, V. B. Haarstad, R. L. Orvis, *Tetrahedron*, **1968**, *24*, 687−704.

[2.30] E. E. van Tamelen, L. K. Olivier, *Bioorg. Chem.* **1976**, *5*, 309−326.

[2.31] E. E. van Tamelen, J. P. Yardley, M. Miyano, W. B. Hinshaw Jr., *J. Am. Chem. Soc.* **1969**, *91*, 7349−7359.

[2.32] M. Lousnamaa, P. Hanhinen, *Tetrahedron*, **1996**, *52*, 15225−15242.

[2.33] J. S. Cannon, L. E. Overman, *Angew. Chem. Int. Ed.* **2012**, *51*, 4288−4311.

[2.34] M. Mentel, M. Peters, J. Albering, R. Breinbauer, *Tetrahedron*, **2011**, *67*, 965−970.

[2.35] J. Warneke, E. Winterfeldt, *Chem. Ber*. **1972**, *105*, 2120−2125.

[2.36] S. E. Lewis, *Tetrahedron,* **2006**, *62*, 8655−8681.

[2.37] P. Magnus, B. Mugrage, M. DeLuca, G. A. Cain, *J. Am. Chem. Soc.* **1989**, *111*, 789−789.

[2.38] Z. Liu, F. Xu, *Tetrahedron Lett.* **1989**, *30*, 3457−3460.

[2.39] C. E. Edwankar, R. V. Edwankar, O. A. Namjoshi, X. Liao, J. M. Cook, *J. Org. Chem.* **2013**, *78*, 6471−6487.

[2.40] a. J. Yu, T. Wang, X. Liu, J. Deschamps, J. Flippen-Anderson, X. Liao, J. M. Cook, *J. Org. Chem.* **2003**, *68*, 7565−7581; b. M. Quaisuddin, *Bangladesh J. Sci. Ind. Res*. **1980**, *15*, 35.

[2.41] W. Yin, S. Kabir, Z. Wang, S. K. Rallapalli, J. Ma, J. M. Cook, *J. Org. Chem.* **2010**, *75*, 3339−3349.

[2.42] S. Zhao, X. Liao, T. Wang, J. Flippen-Anderson, J. M. Cook, *J. Org. Chem.* **2003**, *68*, 6279−6295.

[2.43] X. Liao, H. Zhou, J. Yu, J. M. Cook, *J. Org. Chem.* **2006**, *71*, 8884−8890.

[2.44] C. E. Edwankar, R. V. Edwankar, J. R. Deschamps, J. M. Cook, *Angew. Chem. Int. Ed.* **2012**, *51*, 11762−11765.

[2.45] D. D. I. Kingston, B. B. Gerhart, F. Ionescu, M. M. Mangino. S. M. Sami, *J. Pharm. Sci.* **1978**, *67*, 249−251.

[2.46] R. Verpoorte, L. Bohlin, D. Dwuma-Badu, W. Rolfsen, J. Strömbom, *J. Nat. Prod.* **1983**, *46*, 572–575.

[2.47] M. Harada, Y. Ozaki, *Chem. Pharm. Bull.* **1978**, *26*, 48−52.

[2.48] A. Nören-Müller, W.Wilk, K. Saxena, H. Schwalbe, M. Kaiser, H. Waldmann, *Angew. Chem. Int. Ed.* **2008**, *47*, 5973−5977.

[2.49] D. Solé, X. Urbaneja, J. Bonjoch, *Adv. Synth. Catal.* **2004**, *346*, 1646−1656.

[2.50] D. Solé, E. Peidro, J. Bonjoch, *Org. Lett.* **2000**, *2*, 2225−2228.

[2.51] a. V. K. Aggarwal, J. Drabowcz, R. S. Grainger, Z. Gultekin, M. Lightowler, P. L. Spargo, *J. Org. Chem.* **1995**, *60*, 4962−4963; b. V. K. Aggarwal, R. S. Grainger, G. K. Newton, P. L. Spargo, A. D. Hobson, H. Adams, *Org. Biomol. Chem.* **2003**, *1*, 1884−1893.

[2.52] K. V. Radhakrishnan, *Top. Heterocycl. Chem.* **2008**, *13*, 71−98.

[2.53] A. R. Katritzky, N. Dennis, *Chem. Rev.* **1989**, 827−861.

[2.54a] M. E. Jung, Z. Longmei, P. Tangsheng, Z. Huiyan, L. Yan, S. Jingyu, *J. Org. Chem.* **1992**, *57*, 3528−3530.

[2.54b] Y. Zhang, L. S. Liebeskind, *J. Am. Chem. Soc.* **2006**, *128*, 465–472.

[2.55] K. M. Peese, D. Y. Gin, *J. Am. Chem. Soc*. **2006**, *128*, 8734−8735.

[2.56] E. R. Ashley, E. G. Cruz, B. M. Stoltz, *J. Am. Chem. Soc.* **2003**, *125*, 15000−15001.

[2.57] M. P. Smith, C. George, A. P. Kozikowski, *Tet. Lett.* **1998**, *39*, 197−200.

[2.58] A. P. Kozikowski, G. L. Araldi, R. G. Ball, *J. Org. Chem.* **1997**, *62*, 503−509.

[2.59] M. J. Sung, H. I. Lee, Y. Chong, J. K. Cha, *Org. Lett.* **1999**, *1*, 2017−2019.

[2.60] A. G. Steinig, A. de Meijere, *Eur. J. Org. Chem.* **1999**, 1333−1344.

[2.61] Z. Owczaczyk, F. Lamaty, E. J. Vawter, E. Negishi, *J. Am. Chem. Soc.* **1992**, *114*, 10091−10092.

[2.62] F. E. Meyer, P. J. Parsons, A. de Meijere, *J. Org. Chem.* **1991**, *56*, 6487−6488.

[2.63] K. C. Nicolaou, C. J. N. Mathison, T. Montagnon, *J. Am. Chem. Soc.* **2004**, *126*, 5192−5201.

[2.64] F. F. Fleming, L. Funk, R. Altundas, Y. Tu, *J. Org. Chem.* **2001**, *66*, 6502−6504.

[2.65] N. C. Ganguly, P. Mondal, *Synth. Commun.* **2011**, *41*, 2374−2384.

[2.66] for a review see: T. E. Burghardt, *J. Sulfur Chem.* **2005**, *26*, 411−427.

[2.67] T. Oishi, H. Takechi, K. Kamemoto, Y. Ban, *Tetrahedron Lett.* **1974**, *15*, 11−14.

[2.68] T. Oishi, K. Kamemoto, Y. Ban, *Tetrahedron Lett.* **1972**, *13*, 1085−1088.

[2.69] H. Liu, C. Sun, N. Lee, R. Henry, D. Lee, *Chem. Eur. J.* **2012**, *18*, 11889−11893.

[2.70] for more information on DMNB see chapter four.

[2.71] for more information about diazo-insertion using scandium(III) triflate see chapter four.

[2.72] J. Garcia, N. Casamitjana, J. Bonjoch, J. Bosch, *J. Org. Chem.* **1994**, *59*, 3939−3951.

[2.73] S. Krüger, T. Gaich, *Angew. Chem. Int. Ed.* **2014,** *54*, 315**–**317.

3 The Parvineostemonine Project

3.1 Occurence

Parvineostemonine (**2**, figure 25 displays the (+)-enantiomer of the natural product, see experimentals for details) has been isolated in the chinese province Hainan by Ye and co-workers from the stems and leaves of *stemona parviflora* in 2003.[3.1] The rotational value and the amount of the natural product isolated was not reported. The occurrence of further *stemona* alkaloids is not discussed here, see references 3.2 and 3.3 for details.

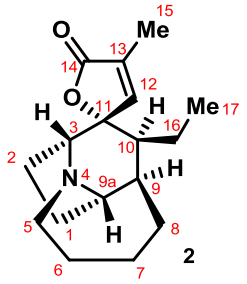


Figure 25: Structure of (+)-parvineostemonine (**2**).

3.2 Structures

Due to the large structural variety of the *stemona* alkaloids there is not even a unified classification system for these alkaloids.

In the first summary of this class of alkaloid, Pilli and co-workers[3.2] tried to classify the *stemona* alkaloids into eight different subgroups (see figure 26). Accoring to their classification, most s*temona* alkaloids bear a signature octahydro-1*H*-pyrrolo[1,2-*a*]azepine core (**249**, n=1), which is present in nearly all of the isolated natural products. Pilli and co-workers tried to order the *stemona* alkaloids based on their skeletal features, with six subgroups (stenine group **250**, stemoamide group **251**, tuberostemospironine group **252**, stemonamine group **253**, parvistemoline group **254** and stemofoline group **255**) bearing the signature pyrroloazepine **249** (n=1). These six classes are differentiated according to their remaining substitution pattern, without regard of the biosynthesis of these alkaloids.

The alkaloids of the stemocurtisine group (**256**) have a decahydropyrido[1,2-*a*]azepine core (**249**, n=2) in common. All alkaloids that do not fit into one of the seven classes (like parvineosteomine **2**) belong to the miscellaneous group of *stemona* alkaloids. In their summary they identified 68 alkaloids as part of the *stemona* alkaloids in 2005.

As a large number of the *stemona* alkaloids have been isolated after their review, their classification is outdated by now.

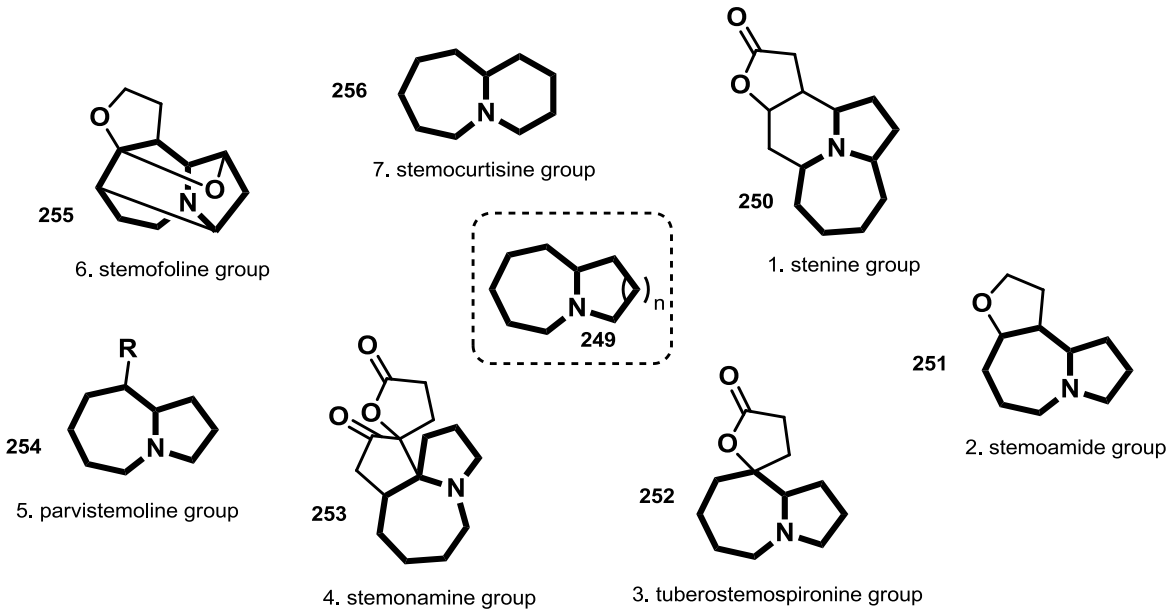


Figure 26: Classification of the *stemona* skeletons according to Pilli *et al*.[3.2]

As a large variety of further alkaloids belonging to the *stemona* alkaloids have been isolated after the review of Pilli and co-workers, a complete new summary was neccessary.

Wang and Chen classified 82 *stemona* alkaloids into two classes with fourteen types nine years later in 2014.[3.3] The two classes are “hemiterpenoid pyrrolidine” (structural motives **A1**-**A4**, figure 27) and “terpenoid pyrrolidine” (structural motives **B1** and **B2**), depending on the length of the terpene unit.

The R-moiety within these classes can be another hemiterpene rest, so a hemiterpenoid pyrrolidine *stemona* alkaloid can contain up to three non-connected hemiterpene subunits (in the case of **A4** with an additional hemiterpene rest **R**).

The classification does not include the linear carbon tether length (usually C3 (black in **A1**, **A2**, **B1**, **B3**)), but sometimes C2 (yellow) or C4 (red).

In the terpenoid pyrrolidine class **B2** a rearranged terpene unit occurs (highlighted in green). The terpenoid pyrrolidine classes **B1** and **B2** comprise the vast majority of *stemona* alkaloids. *Stemona* alkaloids containing a decahydropyrido[1,2-*a*]azepine core (**249**, n=2, figure 23) are classified within the 14 types according to their biosynthesis. For the 14 subclasses see figures 28 and 29.

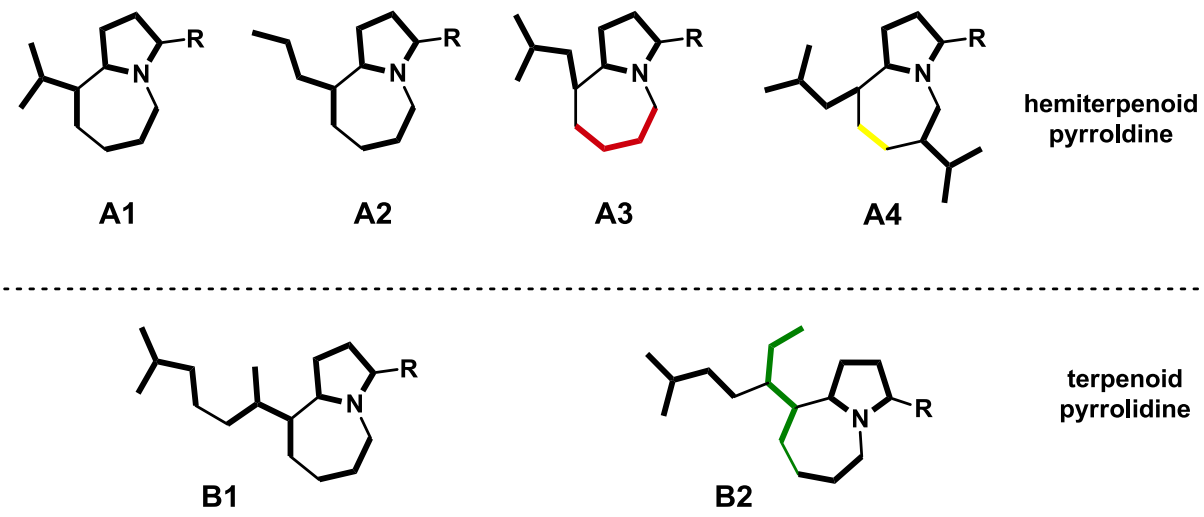


Figure 27: Classes of *stemona* alkaloids according to Wang and Chen.[3.3]

According to their differentiation into types, most stemona alkaloids are assembled from three different parts (see figure 28 and 29):

- at least one hemiterpene or terpene unit (not including the rest R in figure 27)
- a pyrrolidine moiety
- a linear carbon tether (usually C3, but C2 or C4 are possible too).

The 14 subtypes are the stemonamide type (with the three structural motives (sm) **257**-**259**, see figure 24), the croomine type (sm **260**, **261**), the sessifoliamine type (sm **262**), the protostemonine type (sm **263**, **264**), the steomamine type (sm **265**, **266**), the stemofoline type (sm **267**), the stemocurtisine type (sm **268**, **269**), the cochinchistemonine type (sm **270**), the stichoneurine type (sm **271**-**273**), the stemona-amine C type (sm **274**, see figure 26), the tuberostemonamide type (sm **275**-**278**), the stenine type (sm **279**-**281**), the seco-stenine type (sm **282**-**284**), and the rearranged steinine type (sm **285**-**288**). Parvineosteomine (**2**) is proposed to be derived from stemonamide type **258**.

This classification seems lengthy and complicated with two classes, fourteen types and 32 structural motives within these types for 82 alkaloids in total, but that has to be attributed to the vast amount of structural diversity within these alkaloids. The biosynthetic machinery producing these alkaloids seems to be very flexible concerning the starting materials and the three-dimensional outcome.

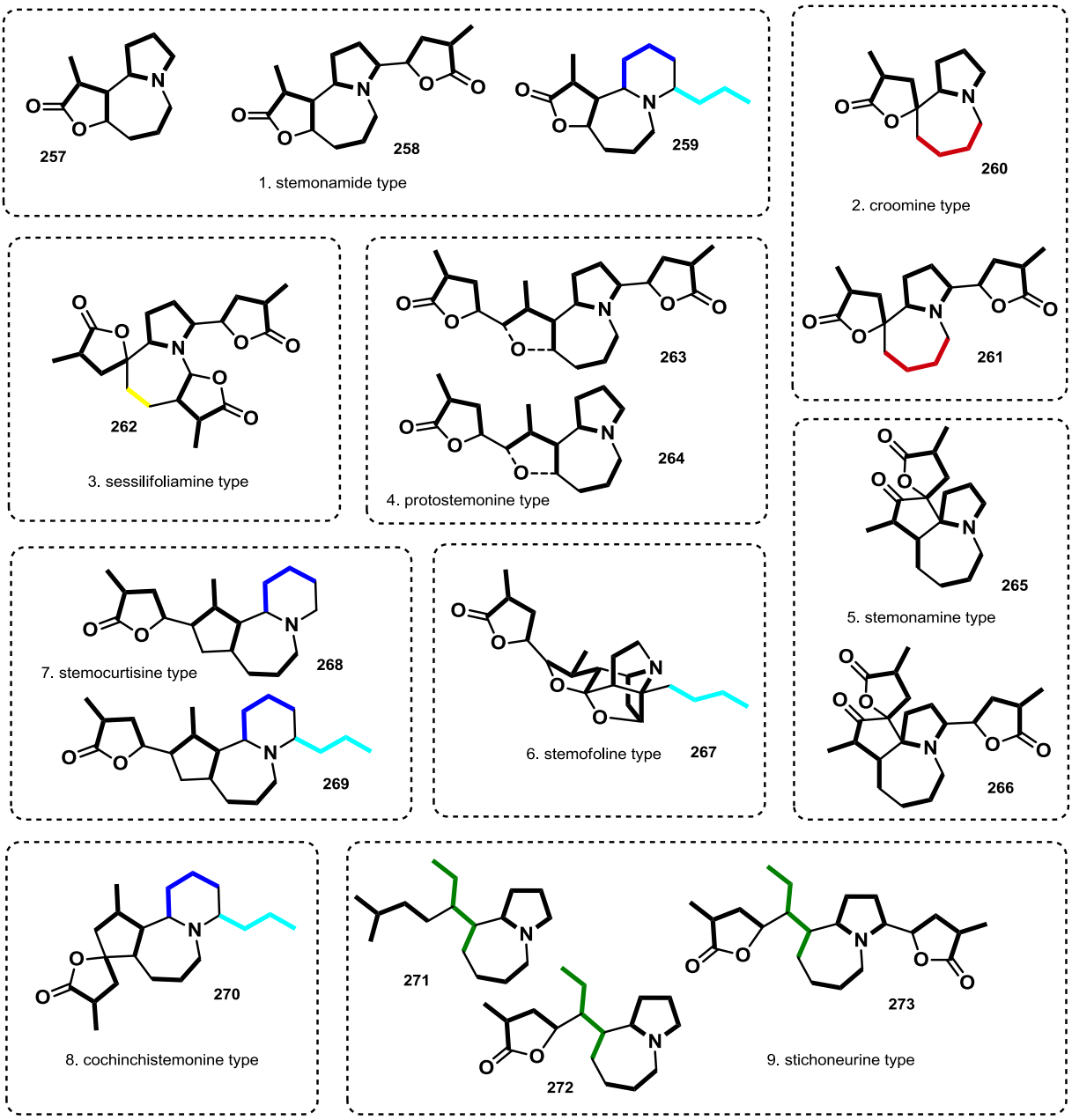


Figure 28: Classification of *stemona* alkaloids according to Wang and Feng, part 1.[3.3]

Certain different structural elements are reoccurring, such as a C4 moiety within the azepane ring (croomine type aklakoids (**260**, **261**), highlighted in red), shortened carbon side-chains (stemoamide type **259**, stemofoline type **267**, stemocurtisne type **269**, conchinstemonine type **270**, highlighted in turquoise), linear hemiterpene subunits (stichoneurone type **271**-**273**, stemona-amine type **274**, tuberostemonine type **275**-**278**, stenine type **279**-**281**, seco-stenine type **282**-**284**, rearranged stenine type **285**-**288**, highlighted in green), and a piperidine moiety (stemoamide type **259**, stemocurtisine type **268**, **269**, conchininstemonine type **270**, rearranged stenine type **287**, **288**, highlighted in blue).

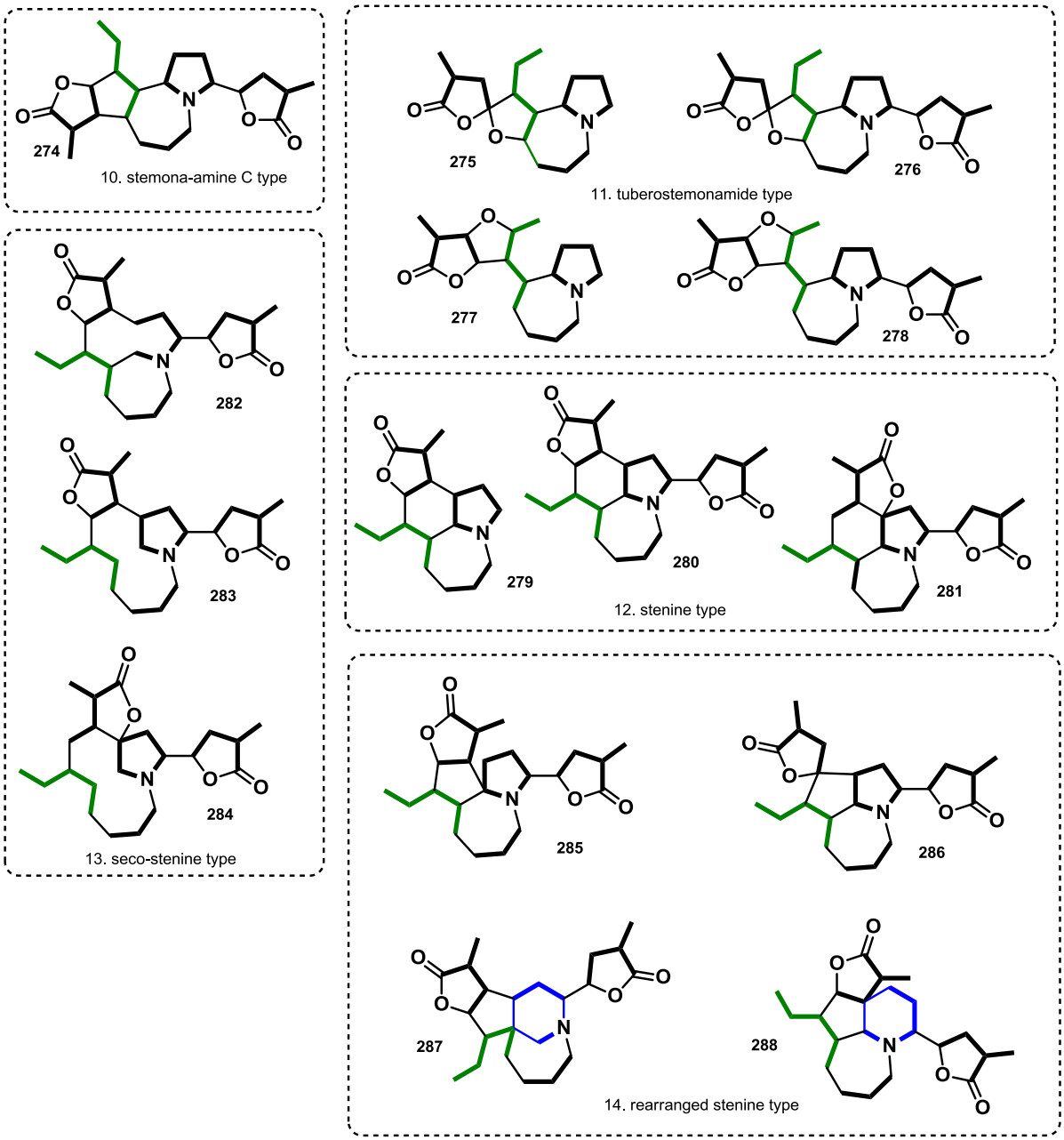


Figure 29: Classification of *stemona* alkaloids according to Wang and Feng, part 2.[3.3]

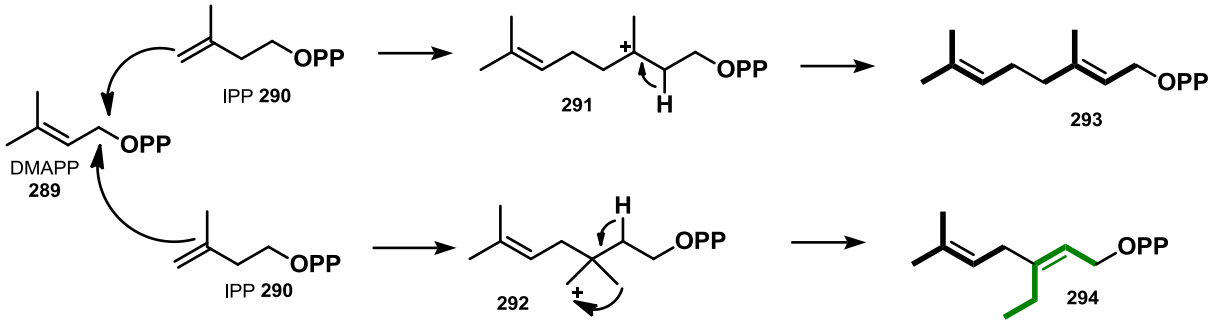
As a complete biosynthetic discussion about the *stemona* alkaloids would be extremely difficult, due to the small amount of publications on the subject, and far too long for this chapter, the following discussion will focus on the biosynthesis of the common building blocks.

A biosynthesis of a *stemona* alkaloid will be explained in the context of the biosynthesis of parvineostemonine (**2**), which is suggested to be assembled *via* other *stemona* alkaloids.

3.3 Biosynthesis

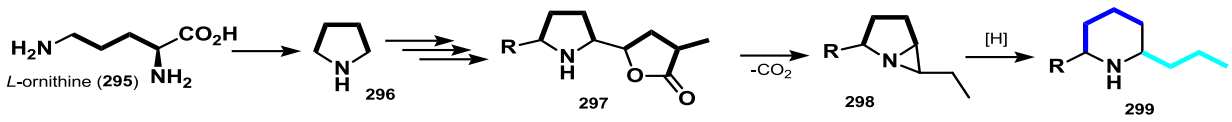
The C5-building blocks originate from the terpene biosynthetic pathway *via* the elongation of IPP **290** and DMAPP **289** (see scheme 34). Nucleophilic displacement of the pyrophosphate of **289** by the double bond of **290** leads to carbocation **291**, which undergoes proton-elimination to form geraniol pyrophosphate **293**.

The rearranged terpene **294** probably results from the less likely attack of the more substituted end of the double bond of **290** onto **289**. The less stable carbocation **292** is formed, subsequent methyl shift results in transposition of the positive charge, final deprotonation leads to the formation of **294**.



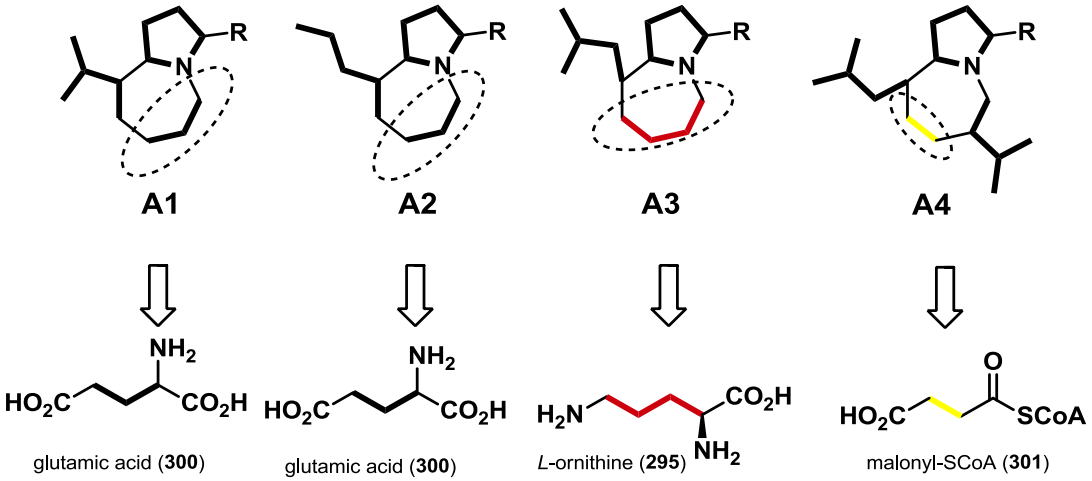
Scheme 34: Biosynthesis of **293** and **294** from DMAPP **289** and IPP **290**.

The pyrrolidine moiety of the *stemona* alkaloids (**296**, see scheme 35) is most likely build up from *L*-ornithine (**295**). The piperidine moiety (**299**) is generated from pyrrolidine precursor **296**, which is elongated with an oxidized hemiterpene to form **297**. Loss of carbon diooxide leads to the formation of aziridine **298**, subsequent rearrangement yields pipieridine **299**.[3.3]



Scheme 35: Biosynthesis of the pyrrolidine- and the piperidine core (**296–299**).

The linear carbon tethers (see scheme 36) is thought to come from glutamic acid (**300**, three carbon atoms, **A1**, **A2**), *L*-ornithine (**295**, four carbon atom, **A3**) and malonyl-SCoA (**301**, two carbon atoms, **A4**).[3.3]



Scheme 36: Biosynthetic origin of the linear starter units of *stemona* alkaloids.

According to these three starting units, the *stemona* alkaloids can be further divided into three groups, according to their biosynthetic origin:

1. *L*-ornithine **295** (for the construction of **296**), glutamic acid **300** (as the linear tether), and at least one hemi- or monoterpene (classes **A1**, **A2, B1, B2**)
2. *L*-ornithine **295** (2x, both for the construction of **296** and as the linear tether), and at least one hemi- or monoterpene (class **A3**)
3. *L*-ornithine **295** (for the construction of **296**), malonyl-SCoA **301** (as the linear tether), and at least two hemiterpenes (class **A4**).

The first group comprises nearly all members of the *stemona* alkaloids (see scheme 25), whereas the second group comprises the croomine type (**260**, **261**) of *stemona* alkaloids. The only member of group three is sessilifoliamine **262**. [3.3]

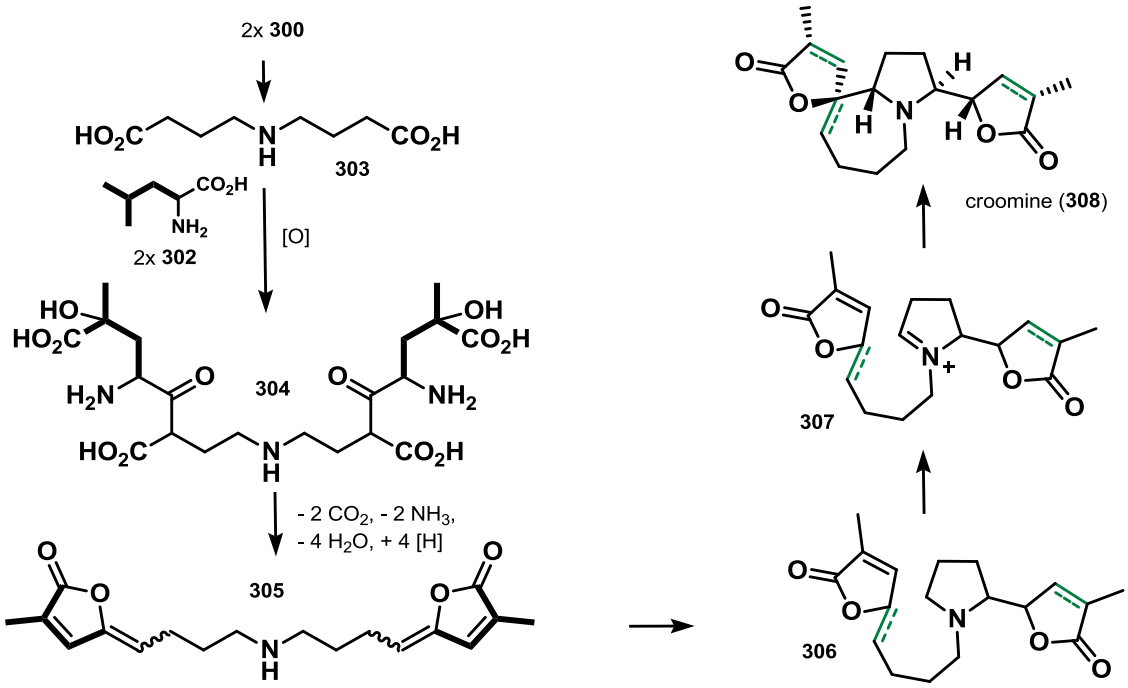
Parvineostemonine (**2**) is classified to belong to class **A1** according to Wang and Feng, but they describe the biosynthetic transformation involved as "extremely uncommon". [3.3]

The proposed biosynthesis of parvineostemonine (**2**) in this thesis would lead to a classification of the alkaloid into the **A3** or **B2** class.

The biosynthesis of parvineostemonine (**2**) is unknown, not even suggestions have been made. Scientific work on the biosynthesis of *stemona* alkaloids is rare, and limited to five publications only.[3.3-3.7] In this chapter, a biosynthesis is proposed based on an intramolecular Michael addition of a croomine-derivative and subsequent reductive decarboxylation. Therefore, the suggested biosyntheses of croomine are discussed first. Greger and co-

workers[3.4,3.5] (see scheme 37) have proposed a biosynthetic origin of croomine **308** based on the concomitant isolation of pandanamines (like **305**).

Two equivalents of of glutamine (**300**) are connected to form linear precursor **303**, followed by the addition of two equivalents of leucine (**302**) and oxidation to give **304**. Double decarboxylation, with loss of ammonia and water followed by reduction yields pandanamine **305**. 1,6-Michael addition of the secondary amine yields pandamarilactonine **306**. Generation of imminium ion **307** can then yield croomine (**308**) after attack of the furanone enolate. The dashed double bonds are reduced somewhere during the cyclization processes.



Scheme 37: Possible biosynthesis of croomine **308** by Greger and co-workers.[3.4,3.5]

A closer look at the croomine type subclass of *stemona* alkaloids reveals a certain flexibility concerning the stereochemistry at the pyrrolidine moiety (figure 30).

In stemonidine (**309**) the hydrogens are *cis*-aligned, in dehydrocroomine (**310**) they are *trans*-aligned. During the biosynthesis of croomine (**308**) from pandanamine **305** several double bonds are reduced in unknown steps, in dehydrocroomine (**310**) a part of the former unsaturation remains in the final natural product.

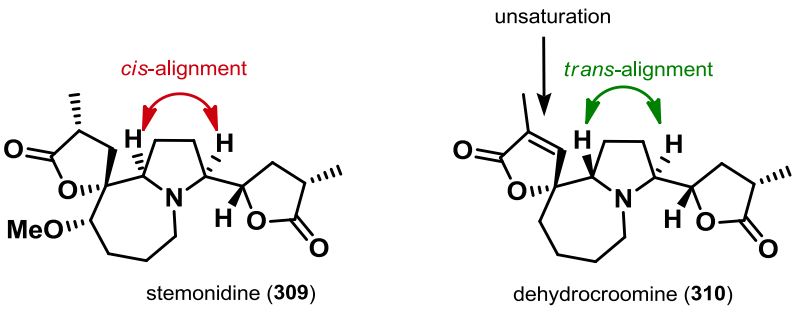
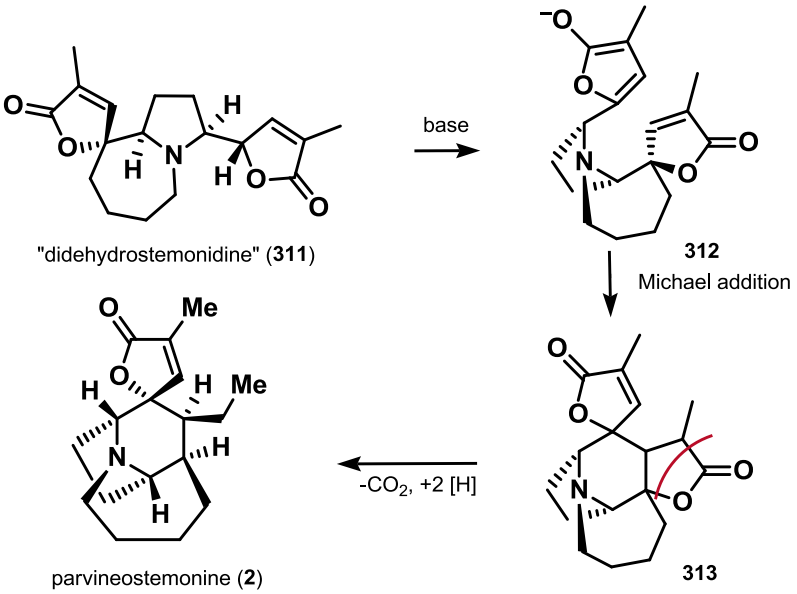


Figure 30: Variations on the croomine skeleton.

Taking into account, that the final skeleton-constructing Mannich reaction might not be stereospecific (**307** to **308**, scheme 37), and a high degree of unsaturation seems to disappear during the biosynthesis, it is plausible to propose parvineostemonine's biosynthetic precursor to be "didehydrostemonidine" **311** (not an isolated natural product, see scheme 38).

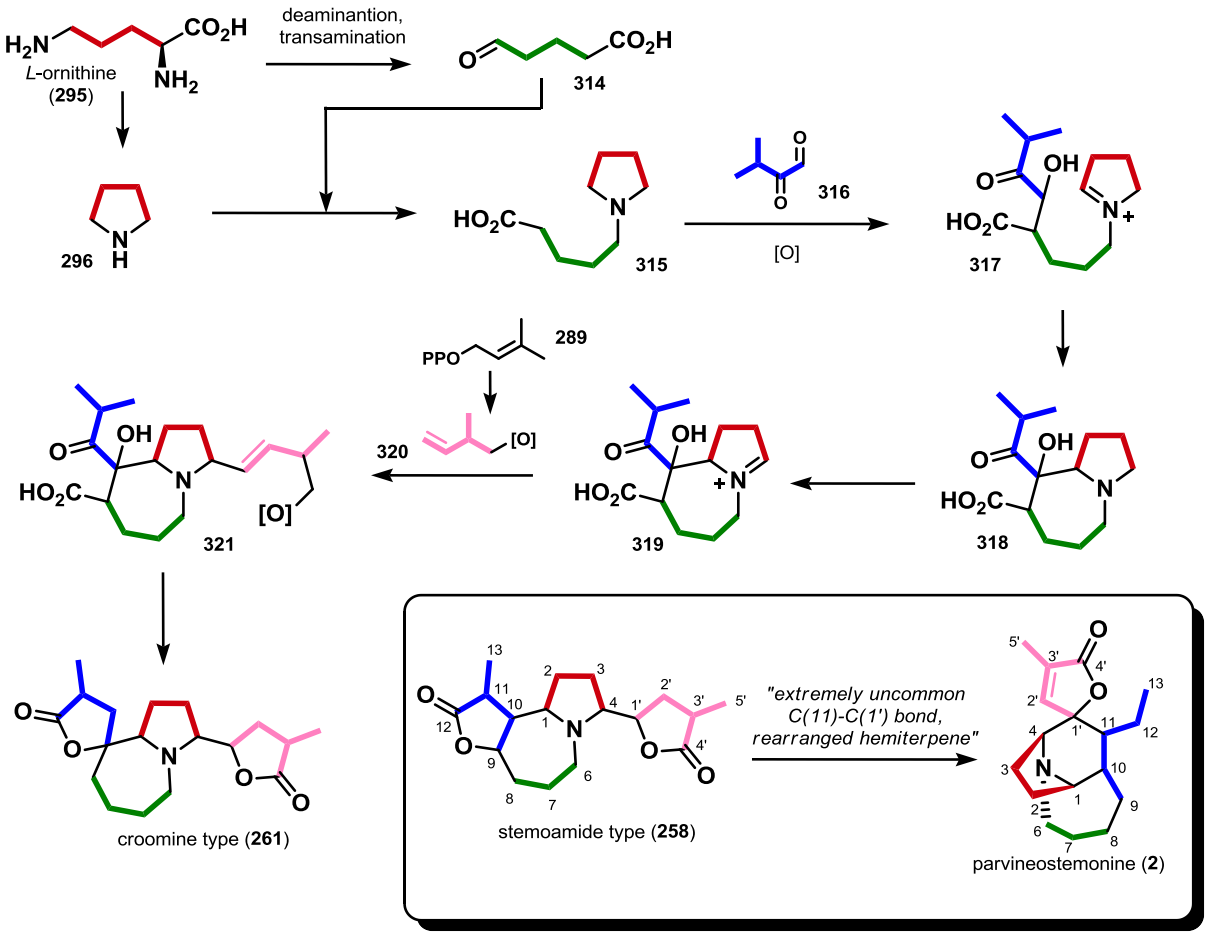
Deprotonation at the only acidic center forms furanone enolate **312**, which can undergo intramolecular Michael addition to give polycyclic **313**. Reductive decarboxylation finally finishes the biosynthesis of parvineostemonine (**2**). Since no biosynthetic investigation has been carried out, this is only a proposal. Parvineostemonine (**2**) could also result from stichoneurine type **273** under the loss of a furanone moiety.



Scheme 38: Proposed biosynthesis of parvineosteomine (**2**) from the hypothetic intermediate didehydrostemonidine (**311**).

Wang and Chen[3.3] have put forward a unified approach to the biosynthesis of *stemona* alkaloids. They proposed the biosynthesis of croomine type **261** (see scheme 39) to originate

from two equivalents of the C4-unit *L*-ornithine (**295**), and of two hemiterpene units (**316** and **320**). *L*-Ornithine **295** is first transformed into pyrrolidine **296** and into aldehyde **314** after deamination and transamination. Those two compounds are condensed to form amine **315**. After attack of **315** onto keto-aldehyde **316** to yield imminium ion **317** the second ring is build up *via* Mannich reaction, yielding **318**. Another imminium ion (**319**) is formed, which is trapped by olefin **320** in a Prins-type addition followed by deprotonation and elimination yielding **321**. Olefin **320** is supposed to originate from DMAPP **289**. Final reduction-state adjustments furnish the croomine skeleton **261**. Albeit this biosynthesis seems plausible, the classification of parvineostemonine (**2**) as arising from stemoamide type (**258**) seems not. The authors indicate, that the neccessary new bond would be extremely uncommon, and a methyltransposition has to take place afterwards. It seems more reasonable to classify parvineostemonine **2** to be derived from croomine type **261** or from stichoneurine type **273**.



Scheme 39: Biosynthesis of croomine type **261**, stemoamide typ **258** and comment on the possible biosynthesis of parvineostemonine **2**.

All in all, it seems likely, that parvineostemonine (**2**) is build up from a croomine type **261** like unisolated intermediate or from stichoneurine type **273**. Both publications[3.3,3.4] agree on the fact that croomine seems to be build up from two C4-units, which contain the nitrogen atom and two C5 units, which build up the furanone moieties. Both approaches include a Mannich reaction as the key step to build up the azepane ring.

3.4 Synthetic Efforts

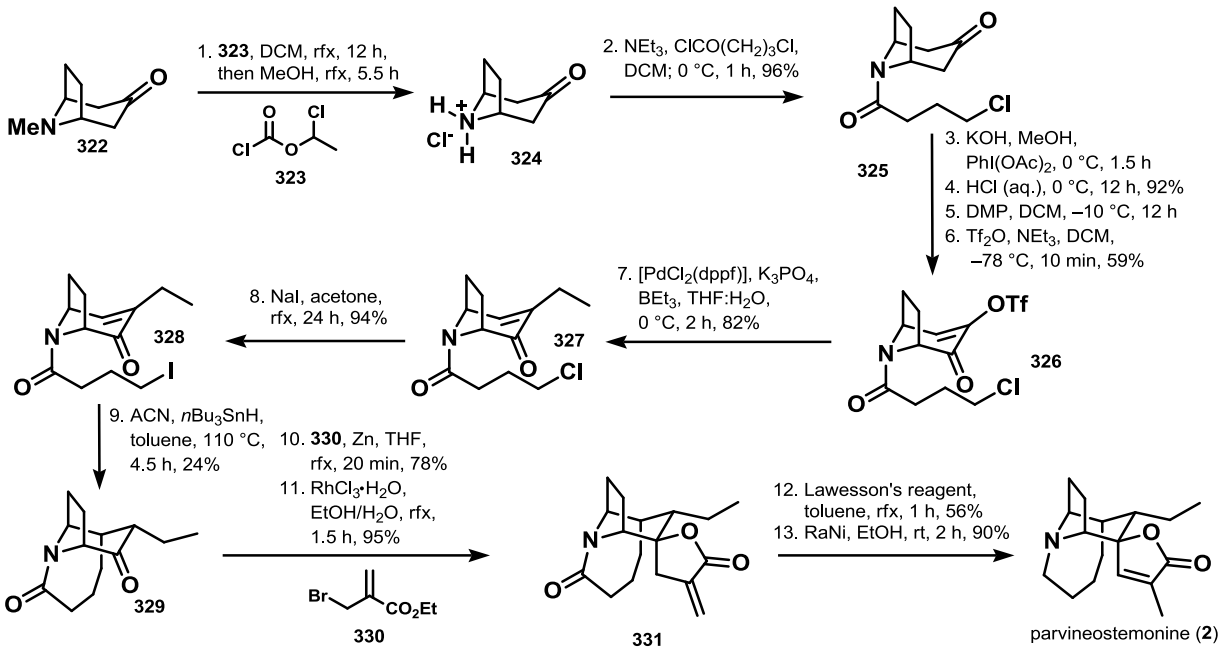
Tu and co-workers[3.8] have accomplished the total synthesis of racemic parvineostemonine (**2**, see scheme 40). Starting from commercially available tropinone **322**, demethylation was achieved using compound **323** and methanol under reflux conditions to yield **324** as the corresponding HCl salt.

Next in line was the formation of amide **325**, with a chloride handle for later radical cyclization. A two step oxidation protocol was then utilized to install an α–hydroxy moiety, followed by oxidation to the instable corresponding bisketone.

Transformation into the corresponding vinyltriflate **326** was achieved using triflic anhydride. The ethyl side chain of parvineostemonine was then attached under Suzuki conditions, obtaining compound **327**.

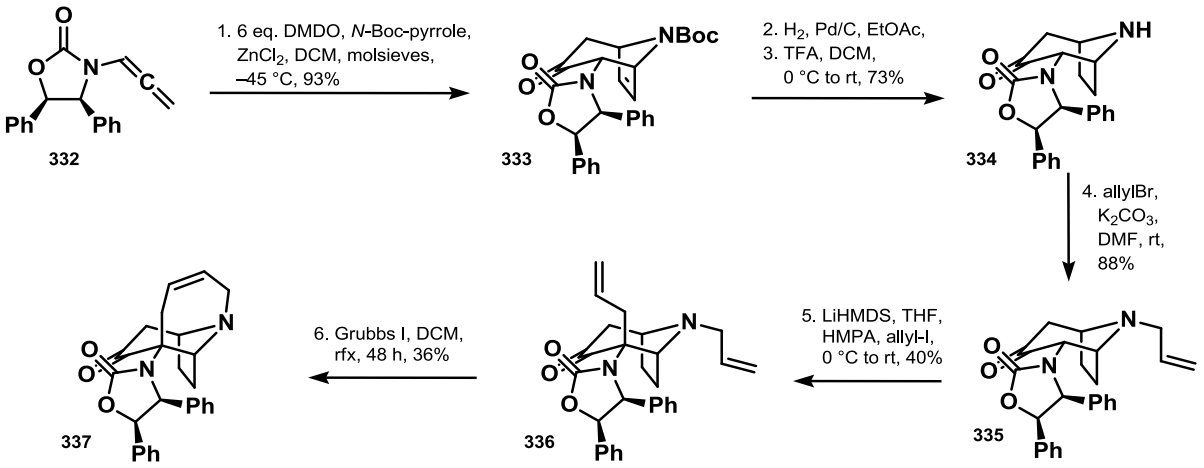
Transformation of the chloride moiety into iodide **328** to facilitate the upcoming radical cyclization under Finkelstein conditions. Subjection to a radical initiator in refluxing toluene yielded the desired ring closing product **329** in low yield, accompanied by the undesired epi-isomer.

The missing lactone was then installed using Reformatzky conditions, followed by double bond shift under rhodium catalysis to give furanone **331**. Reduction of the amide moiety was achieved *via* formation of the corresponding thio-amide and subsequent reduction using Raney nickel to yield the desired natural product parvineostemonine **2** after 13 steps from commercially available tropinone **322**.



Scheme 40: Tu's synthesis of parvineostemonine (**2**) from tropinone **322**.[3.8]

Hsung and co-workers[3.9] furnished the parvineostemonine skeleton **337** based on their newly developed [4+3] cycloadditon (see scheme 41). Addition of DMDO to allene **332** produced an intermediate oxyallyl cation, which reacted with Boc-protected pyrrole to give tricycle **333** in a chiral fashion. Reduction of the double bond was then achieved, followed by removal of the Boc-protecting group to give amine **334**. Allylation of the secondary amine was next to give **335**, followed by allylation at the more hindered α-position of the ketone, furnishing compound **336**. The final seven-membred ring was then installed *via* RCM using 20 mol% Grubbs I catalyst in moderate yield to give polycylce **337**.



Scheme 41: Hsung and co-worker's approach to the parvineostemonine skeleton **337** *via* [4+3] cycloadditon.[3.9]

3.5 Bioactivities

Parvineostemonine **2** has not been evaluated regarding any bioactivity profile.

However, tuberostemonine **348** (see figure 31) was investigated in regard of its bioactivity, and the anthelminthic activity against three worms species (*Angiostrongylus catonensis*, *Dipylidium canium*, *Faciola hepatica*) was determined, with glutamate inhibition being the mode of action.[3.2,3.10] Tuberostemonine **348** was furthermore proven to possess insecticidal activities against the larvae of *Spodoptera littoralis*.[3.11] In the same series of experiments, the insecticidal activities for 16,17-didehydroxy-16(*E*)-stemofoline **343** was assessed, which was superior to that of stemofoline (**344**) and 2'-hydroxystemofoline (**345**).[3.11,3.12]

The insecticidal activity of several *stemona* alkaloids was examined by Greger and co-workers, with dehydroprotostemonine **339** and oxystemokerrin **340** showing the highest reactivities. They were furthermore able to show that the potential for insecticidal activity strongly depends on the 4-methoxy-3-methyl-2-furanone (highlighted in green), as the closely related compounds stemocochinin **341** and parvistemonine **342** showed much weaker reactivities.[3.2,3.13]

Stemofoline **344** was determined to be much more potent than stemonine **346** and stemospironine **347** in regard of their insecticidal activities against the fourth instar silk worm larvae (*Bombix mori* L).[3.2,3.14]

Several extracts from different *stemona* species have been evaluatued in regard of their insecticidal, antitumor or anticough activities. Remarkable insecticidal/larvicidal activities were observed using the leaf extraxcts of *Stemona janponica*[3.14], the leaf and root extracts of *Stemona curtisii,*[3.13,3.15] and *Stemona cochinchinensis.*[3.13]

The antitussive activities from the roots extracts of *Stemona tuberosa* have been observed,[3.16] with the alkaloid neotuberostemonine (**348**) being the most active. Less active alkaloids were found to be isostenine (**349**), tuberostemonine H (**350**) and tuberosteomonine J (**351**). *Stemona tuberosa* showed antitumoral activity against MTC (medullary thyroid carcinoma) by enhancing apoptosis.[3.17]

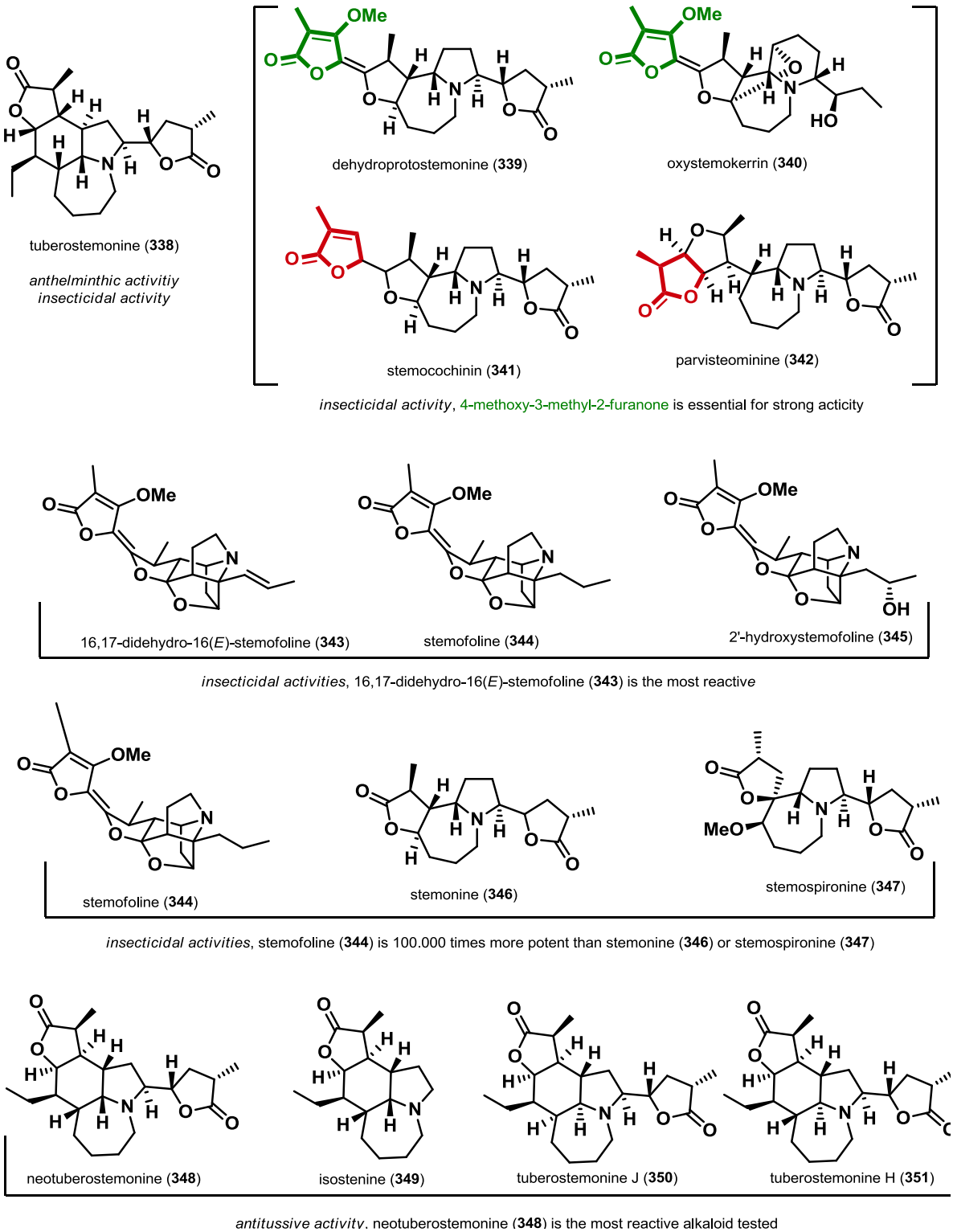


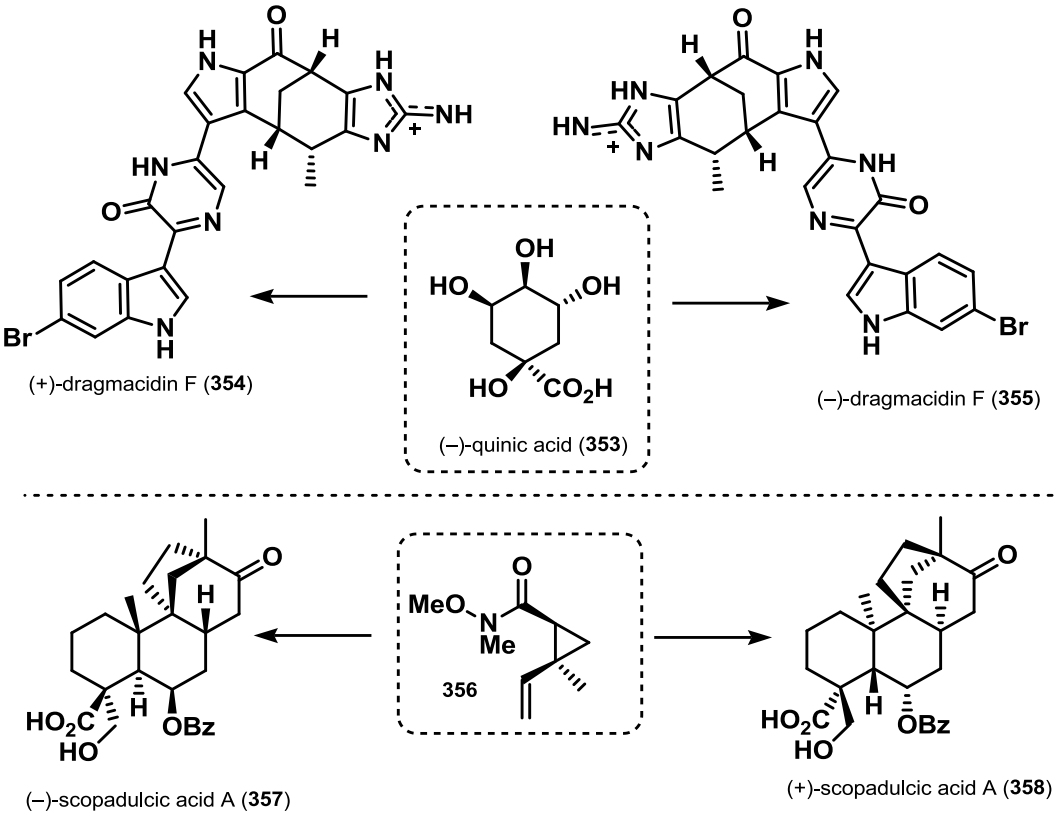
Figure 31: Bioactivities of *stemona* alkaloids.

3.6 Enantiodivergent Total Synthesis

Enantiodivergent total synthesis relies on the concept of accessing both antipodes of a natural product from one single intermediate isomer. This concept shows its full utility if one intermediate enantiomer is easily accessible, in contrast to the other.[3.18] In case of parvineosteomine **2**, an enantiodivergent total synthesis was most desirable, as no rotation values were published in the original isolation paper.[3.1]

The power of enantiodivergence has been beautifully showcased in the total synthesis of dragmacidin F (**354**/**355**) by Garg and Stoltz (see scheme 42).[3.19] They converted commercially available (–)-quinic acid (**353**) into both enantiomers of dragmacidine F.

Another impressive example is the total synthesis of both antipodes of scopadulcic acid A (**357**/**358**) by Overman and co-workers[3.20] *via* a divinylcyclopropane-cycloheptadiene rearrangement, through intermediate **356**.[3.21] A variety of enantiodivergent syntheses were conducted in recent years.[3.22-3.25]

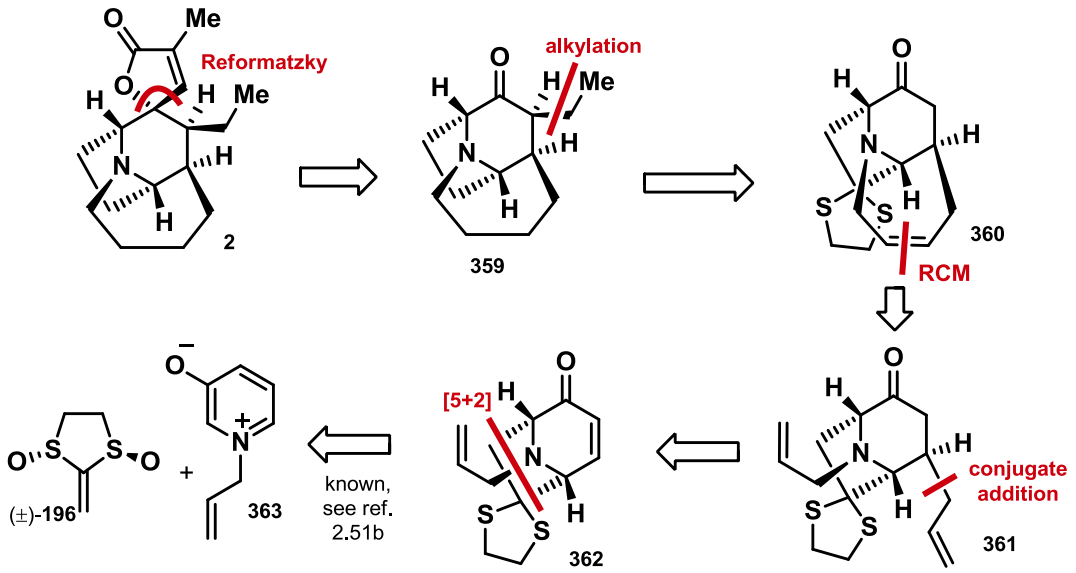


Scheme 42: Examples for enantiodivergent total synthesis of complex natural products.

3.7 Synthetic Planning

This project has been subject to three different approaches, each based on the lessons learned from the last one. Note that the first and second attempt were carried out in a racemic fashion, and the third attempt in a chiral fashion.

First attempt In the beginning, we were eager to gain access to parvineostemonine (**2**) in a racemic fashion. We intended to dissect parvineosteomine (**2**) in a retrosyntheic fashion to ketone **359** (see scheme 43), which would serve as a handle for a Reformatzky-based furanone synthesis. Ketone **359** could be obtained *via* alkylation of ketone **360**. Azepane **360** should be accessible *via* ring closing metathesis from bisolefin **361**. This compound would be traced back to tricycle **362** *via* conjugate addition of an allyl moiety. This tricycle **362** has been earlier prepared by Aggarwal and co-workers in a chiral fashion.[2.51b]

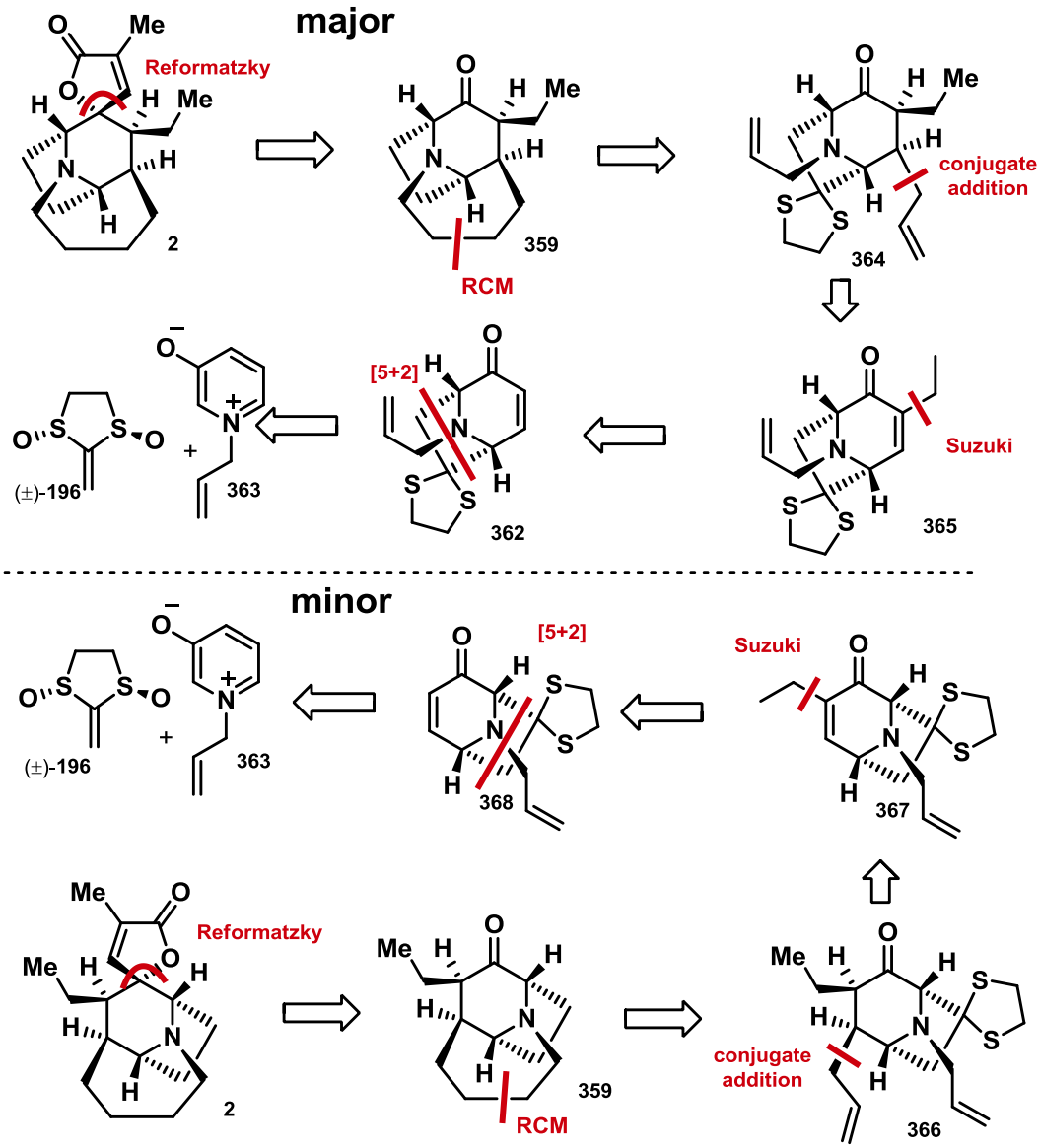


Problem: Unsuccessfull introduction of the ethyl side chain.

Scheme 43: First retrosynthesis and the resulting problem.

Second attempt Having realized that the ethyl side-chain proved to be cumbersome to install at a late stage *via* alkylation, we decided to introduce it at an earlier stage. At this point we decided to explore chemistry for both the major and the minor [5+2] cyclization product (**362** and **368**, see scheme 44). Reformatzky-based furanone formation would lead us back to ketone **359** (for the major cycloaddition product), already containing the necessary ethyl side chain. The azepane moiety of **359** would again be prepared *via* ring-closing

metathesis arising from bisolefin **364**. The allyl handle should be installed *via* conjugate addition to enone **365**. The ethyl side chain should be installed *via* Suzuki coupling of the vinyl iodide derivative of enone **362**. Enone **362** can again be prepared according to literature procedure.[2.51b] The retrosynthesis for both antipodes of parvineostemonine (**2**) is the same. Compounds **362** and **368** are regioisomers, which can be separated from each other. After the removal of the dithiolanes to obtain ketones **359** those compounds are enantiomers.

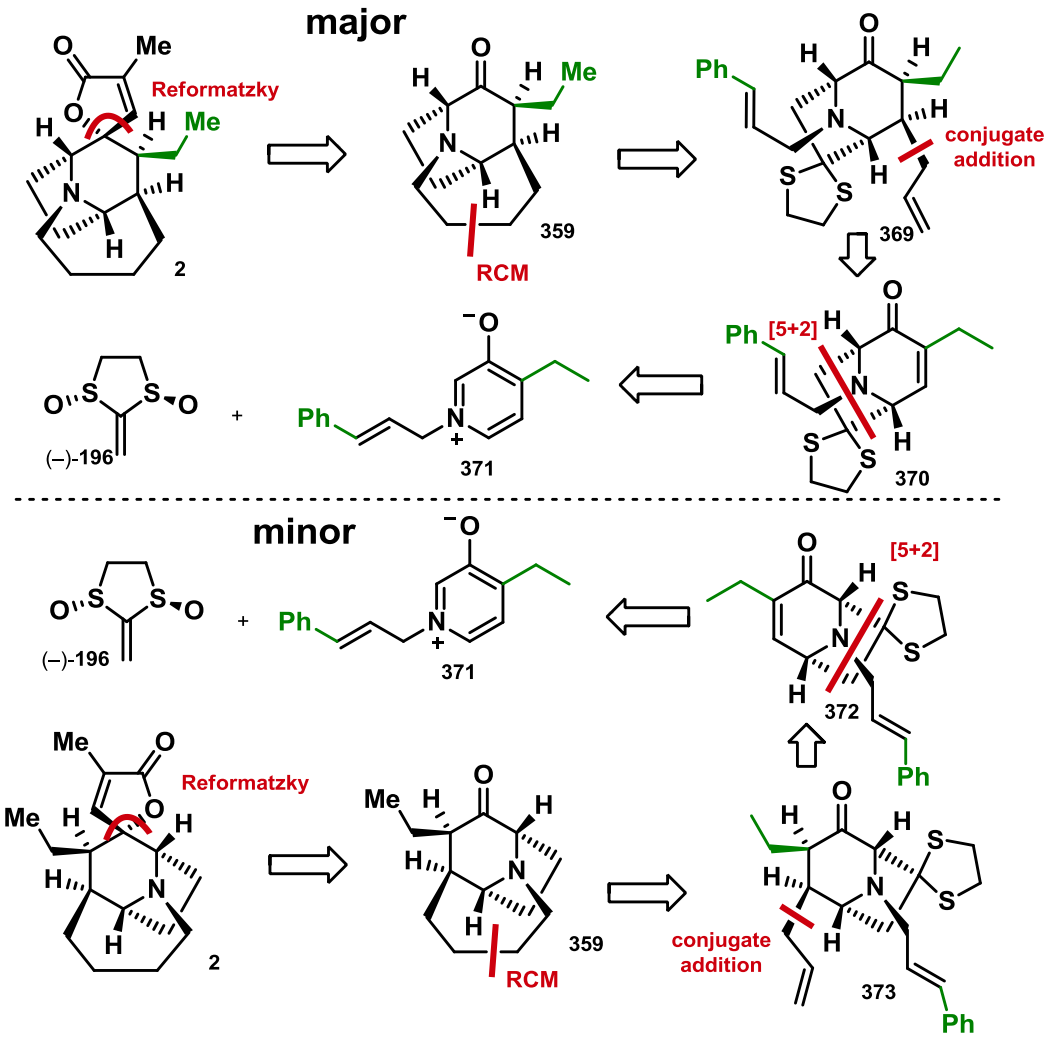


Problem: Low-yielding ring closing metathesis.

Scheme 44: Second retrosynthesis, employing the enantiodivergent concept.

Third Attempt As the ring closing metathesis has proven to be the synthetic bottleneck in the previous approach, we decided to fix this issue by adding a phenyl substituent to

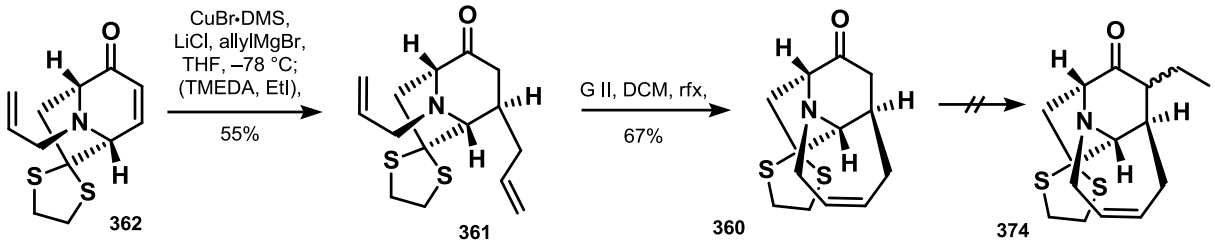
one double bond. In this fashion, the initial Grubbs carbene is reformed after the catalytic cycle, and the RCM would not start at the allyl amine moiety.[3.26-3.28] Furthermore, we aimed at introducing the crucial ethyl-side chain before the [5+2] cycloaddition to shorten the synthetic sequence. We used chiral bissulfoxide (–)-**196** (the other enantiomer as in the *sarpagine* synthesis) in this approach. Again, the final molecule **2** (see scheme 45) should be assembled *via* a Reformatzky. Ketone **359** would be obtained after ring-closing metathesis from bisolefins **369/373**, now containing an additional phenyl substituent. The allyl moiety of compounds **369**/**373** could be obtained from conjugate addition to enones **370**/**372**. These Michael acceptors will be obtained from a [5+2] cycloadditon. Pyridinium betaine **371** can be obtained from the addition of known 4-ethylpyridin-3-ol[3.29,3.30] to cinnamyl bromide.



Scheme 45: Third retrosynthetic approach.

3.8 Results

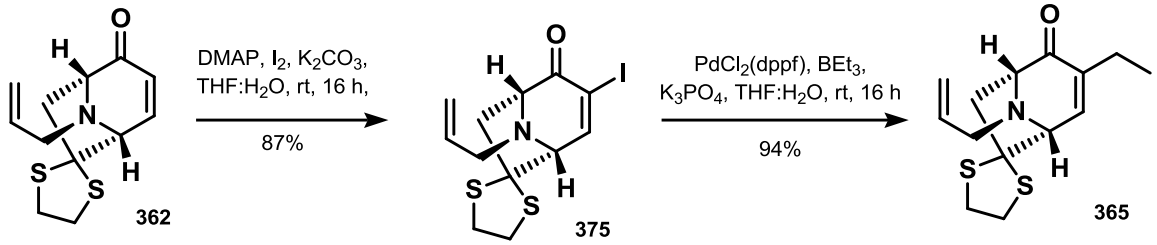
After preparation of racemic **362** (see scheme 46), we examined the conjugate addition of an allyl substituent and found the conditions from Lipshutz[3.31] well applicable. We obtained ketone **361** (tetramethylethylenediamine (TMEDA) and ethyl iodide were used to attempt one-pot alkylation) in acceptable yield. Inspired by Hsung and co-workers,[3.9] we then achieved ring closing metathesis using Grubbs second generation catalyst in good yield to give olefin **360**. However, we had to dismiss this synthetic route due to the failure of multiple alkylation attempts to obtain **374**, including a variety of bases (LiHMDS, KHMDS, LDA), ethyl iodide and various temperatures (–78 °C to ambient temperature). The immediate addition of the ethyl side chain under the conjugate addition attempts failed as well.



Scheme 46: First synthetic attempts terminated by an unsucessfull alkylation.

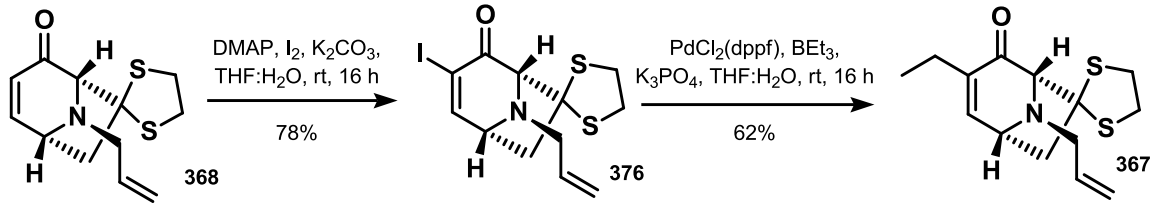
Having realized that the ethyl side-chain proved to be cumbersome to install at a late stage *via* alkylation due to large steric bulk around the ketone moiety, we decided to introduce it at an earlier stage (see scheme 45 for the retrosynthesis). We commenced our studies using the major cycloaddition product **362** (see scheme 47), as its reactivity proved to be superior to the minor one using the designed synthetic sequence. Transformation of enone **362** into vinyliodide **375** was cleanly achieved using the conditions developed by Kraft and co-workers.[3.32]

The crucial ethyl side chain was then installed using Suzuki coupling conditions developed by Maulide and co-workers[3.33] and applied on a similar system by Tu's group.[3.8] The palladium catalyst showed remarkable selectivity, as the allyl amine moiety and the dithiolane were essentially untouched under these reaction conditions and we were able to obtain the desired coupling product **365** in excellent yield.



Scheme 47: Introdution of the ethyl side chain under palladium catalysis.

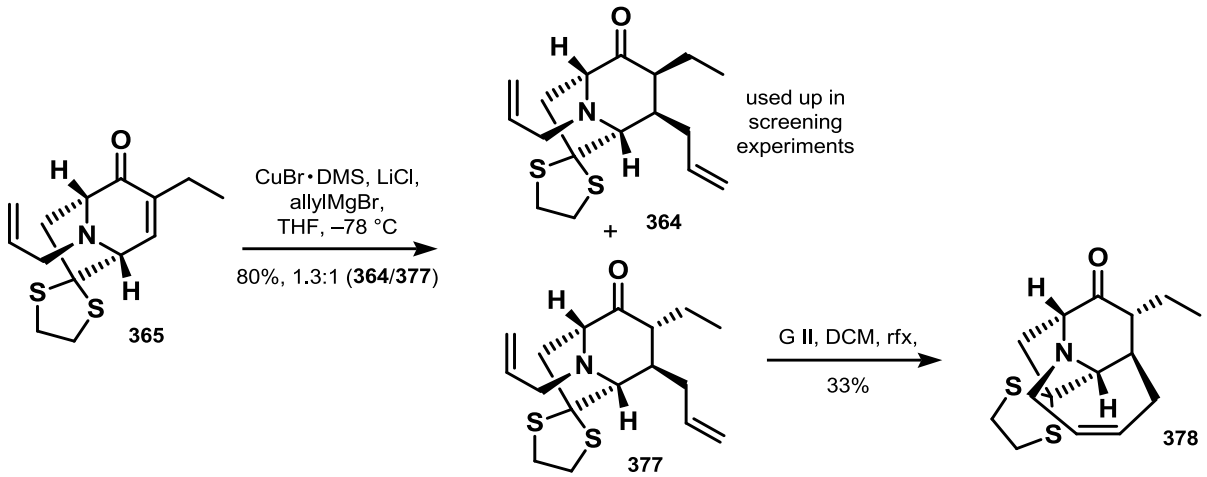
We were surprised to find differences in reactivity when we attempted the same reaction sequence with the minor regioisomer **368** (see scheme 48). The α-iodination protocol delivered almost the same yield for compound **376**, but the Suzuki coupling worked to a diminished degree to give ethyl containing compound **367**. Albeit this yield remains unoptimized, the initial attempts using the major regioisomer **362** were more successfull. At this point, we decided to focus our synthetic studies on the major regioisomer **362**. If necessary, the Suzuki coupling can be optimized using freshly bought triethylborane and by prolonging the reaction times.



Scheme 48: Installation of the ethyl side chain on the minor regioisomer, slightly less successful.

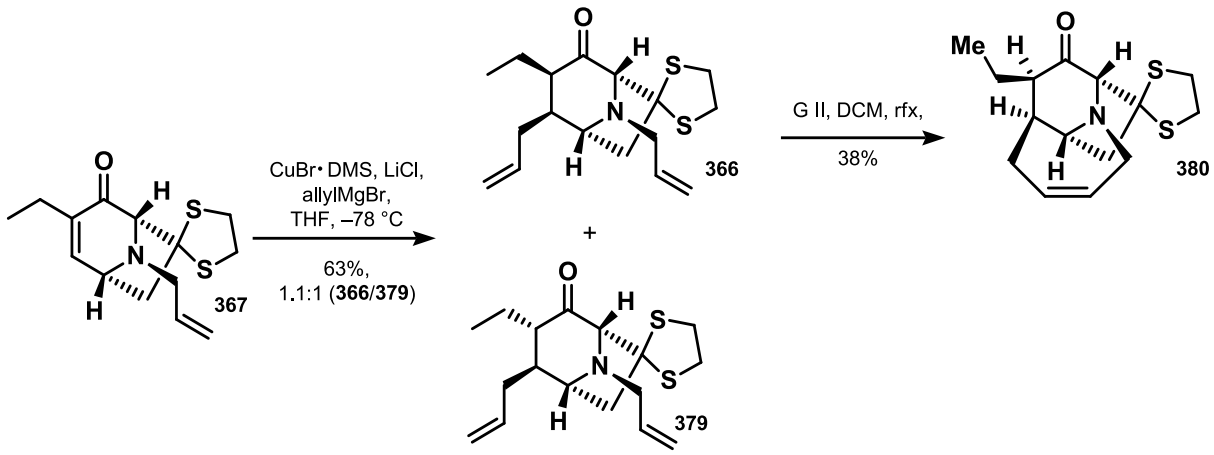
We then attempted the conjugate addition of an allyl moiety to enone **365**, which proved to be high yielding using the Lipshutz protocol (see scheme 49).[3.31] The alternative Sakurai reaction[3.34] was not examined, due to the expected incompatibility of the system with Lewis-acids (complexation of the LA between the *N*/*S*-lone pairs, see chapter 2 for examples). Quenching the reaction mixture with 2 M NaOH solution led to an improved ratio of the desired equatorial compound **364** in favor of **377**. We later established the orientation of the ethyl groups in **364** and **377** *via* NOeSY experiments of polycyclic **378.**

Unfortunately, the desired compound **364** was used up in screening experiments for the subsequent metathesis recation. We later found that ring-closing metathesis of **377** using Grubbs second generation catalyst worked in moderate yield to give olefin **378**, but unfortunately the yield dropped significantly compared to nor-ethyl compound **374**.



Scheme 49: First synthetic attempts to form bisolefins **364** and **377**.

The conjugate allyl addition worked less well for minor regioisomer **367** (see scheme 50), but nevertheless yielded desired **366** and undesired **379** with close to no selectivity. With a better understanding of the ethyl orientation, we conducted the subsequent ring-closing metathesis with the desired compound **366** and obtained olefin **380** in moderate yield, which could not be improved.

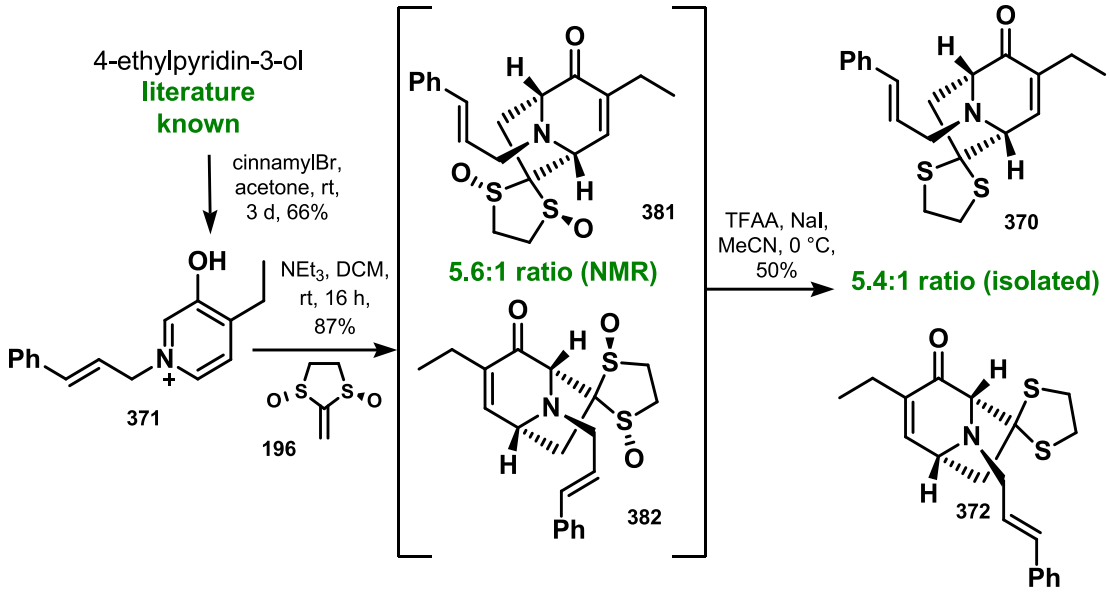


Scheme 50: Synthetic attempts with minor **367**.

At this stage, we conducted several (probably successful, but on a exceptionally small scale) experiments with **359** towards parvineostemonine (**2**) and finally ran out of material. As we were keen to furnish an enantiodivergent synthesis, we decided to bring up chiral material using chiral **196** (the opposing antipode as in the sarpagine synthesis) and fix several flaws in the synthetic sequence.

As the ring-closing metathesis of **377** to **378** or from **366** to **380** did only proceed in moderate yields and could not be improved, we needed to optimize this reaction by the choice of different substituents at the double bonds. As the allyl amine could potentially undergo side reactions we added a phenyl-substituent in order to initiate metathesis at the remaining ally handle. The use of a phenyl substituent would furthermore regenerate the more reactive initial Grubbs carbene.[3.26-3.28] Furthermore, we aimed at introducing the crucial ethyl side chain before the [5+2] cycloaddition to shorten the synthetic sequence.

Starting from known 4-ethylpyridin-3-ol[3.29,3.30] (see scheme 51) we readily obtained pyridinium salt **371** after recrystallization. Subjection of this salt to basic conditions in the presence of chiral vinylbissulfoxide **196** led to a 5.6:1 mixture of regioisomeric cycloaddition products **381**/**382** in good yield. The mixture of **381** and **382** could not be separated. We then reduced the bisdioxodithiolane to the corresponding dithiolanes **370**/**372** which could be easily separated, and a 5.4:1 mixture of regioisomers **370**/**372** was obtained.

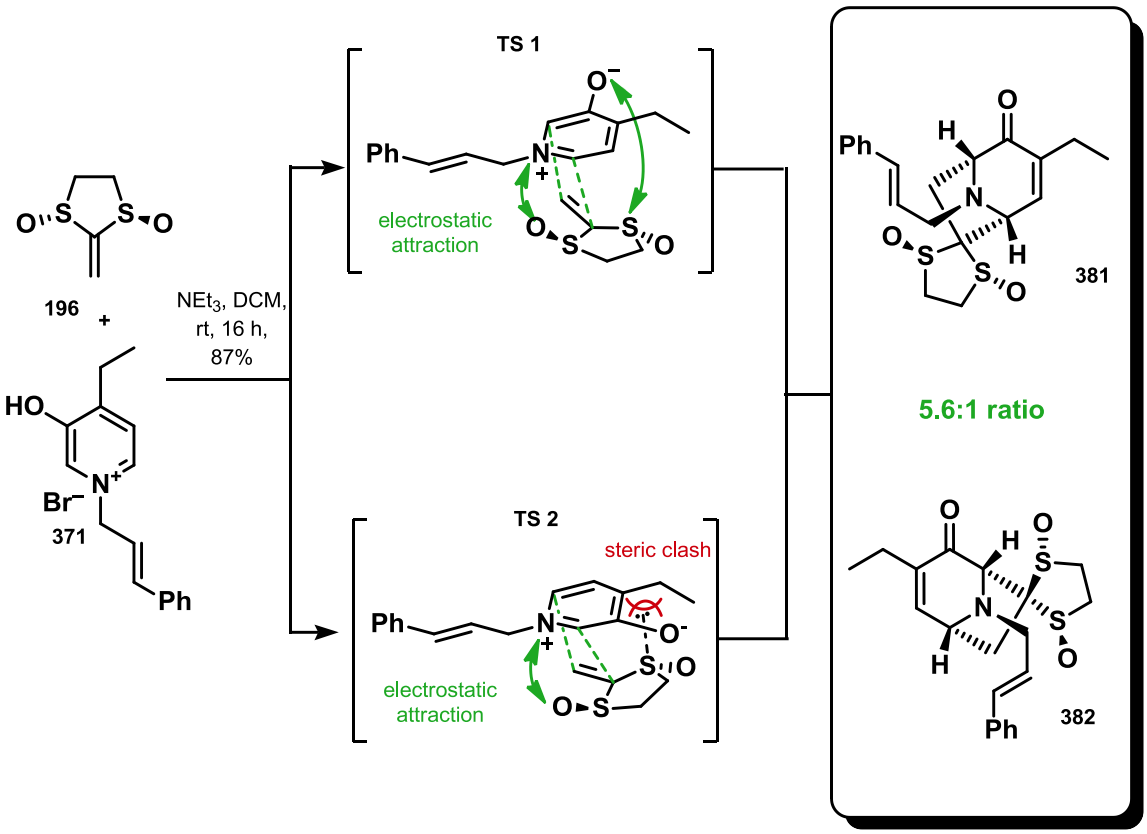


Scheme 51: From 4-ethylpyridin-3-ol to dithiolanes **370** and **372**.

The regioselectivity for this [5+2] cycloaddition (see schemes 51 and 52) increased drastically compared to the one discussed earlier in the *sarpagine* synthesis (see scheme 23), favouring the major isomer **381** over the minor isomer **382**. Due to the position of the side chain (*para* to the pyridinium nitrogen) we expected the change in selectivity to be very small if occurring at all, because the ethyl side is far away from the reactive positions of the oxidopyridinium ion. As Aggarwal and coworkers[2.51b] have only investigated the effect of *ortho*- and *me-*

ta-substitution in the pyridinium cycloaddition, this finding comprises a new and unexpected result.

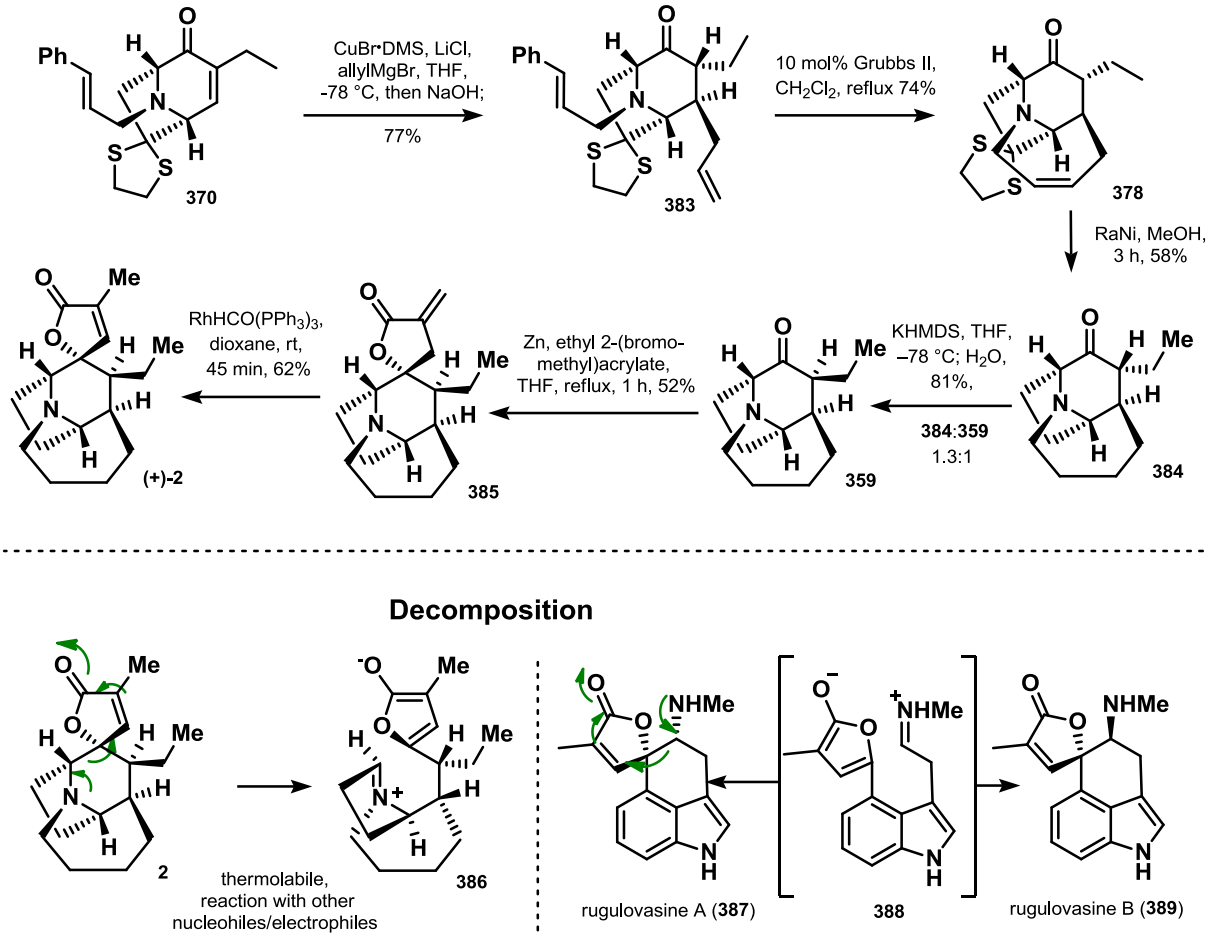
For the favoured transition state (**TS 1**) no additional destabilization occurs, both possible charge interactions are intact. For the less favoured **TS 2** the second (usually less important) interaction between the pyridinium oxygen and the positively charged sulfur is sterically disfavoured, as the remaining *S*-lone pair suffers from steric clash with the ethyl chain. As **TS 1** is usually favoured anyway, the additional destabilization of **TS 2** leads to a large increase of selectivity for cycloaddition product **381**.



Scheme 52: Regioselectivity of the [5+2] cycloaddition with an additional ethyl side chain.

After separation of regioisomer **370** (see scheme 53), we carried out the conjugate allyl-addition, this time yielding the undesired axial ethyl orientation **383** exclusively in good yield. Quenching the reaction with NaOH results in the formation of **383** exclusively. Ring-closing metathesis yielded desired polycycle **378**, this time in good yield due to our improvements. Reduction of dithiolane **378** with Raney nickel proceeded smoothly with concomitant reduction of the double bond to yield ketone **384**. As we had selectively obtained the undesired stereochemistry of the ethyl side chain, we had to invert this stereocenter to

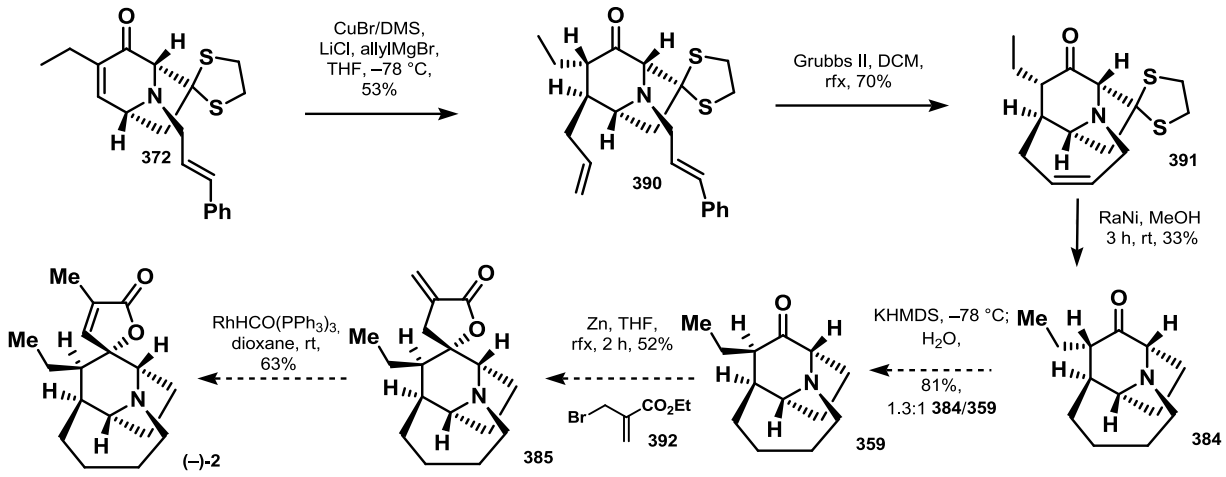
obtain desired ketone **359**. This works in good yield and acceptable selectivity, although the selectivity proved to be inconsistent (1.3:1 to 6.0:1 (**384**:**359**)). The missing furanone moiety was then installed in a two step process. All remaining atoms were attached using Reformatzky type addition of etyhyl 2-(bromomethyl)acrylate[3.35] to obtain **385**, followed by double bond shift with $RhHCO(PPh_3)_3$ to finally yield (+)-parvineostemonine **2**.[3.36] Isomerization attempts using elevated temperatures[3.37,3.38] led to decomposition of the starting material **385**, probably according to the indicated decomposition pathway in scheme 54. After double bond shift yielding **2**, the amine is able to form an imminium ion with concomitant formation of a furanone (**386**), which is then further reduced or degraded. Similar fragmentations have been suggested for the interconversion between rugulovasine A **387** and rugolovasine B **389** *via* a vinylogous retro-Mannich reaction to form **388** followed by vinylogous Mannich addition without stereocontrol.[3.39]



Scheme 53: End of the total synthesis and suggested decomposition pathway of parvineostemonine **2** along the lines of the interconversion between the rugulovasines A/B (**387**/**389**).

We then conducted the same synthetic route with the minor cycloaddition product **372** (see scheme 54). The copper mediated conjugate addition to yield compound **390** works less efficient, probably due to slightly decomposed starting material. The following ring closing metathesis yields the desired olefin **391** in a comparable fashion. Removal of the dithiolane under Raney nickel conditions works less well for the formation of **384**, but was only carried out once. As compound **384** (scheme 55) is the enatiomer of compound **384** (scheme 54), we have thereby established an enantiodivergent access to parvineostemonine (**2**).

(–)-Parvineostemonine **2** can be obtained through the same steps as discussed earlier. Equilibration of the etyl side chain would give **359**, attachment of **392** leads to **385**. Final double bond shift will yield the (–)-parvineostemonine **2.**



Scheme 54: Processing of the minor regioisomer into (–)-parvineostemonine (**2**).

3.9 Summary and Outlook

With the presented synthesis we have gained an enantiodivergent, protecting group free access to the *stemona* alkaloid parvineostemonine **2**. The synthesis can be carried out in a very rapid fashion using both regiosomers arising from the 3-oxidopyridinium [5+2] cycloaddition as the point of enantiodivergence. Both enantiomers can be prepared in only nine steps from known starting materials.

The major drawback of the presented synthesis is the very limited amount of time in which it was conducted. High quality, publishable spectra of parvineostemonine **2** and a more accurate rotation value have still to be obtained.[3.40] The final spectrum of parvineostemonine **2**

was obtained on the very last day of synthetic work. Together with the optimization of some steps this work will be continued at the University of Konstanz.

The broadening of the synthetic utility of the 3-oxidopyridinium [5+2] cycloaddition to now the *sarpagine* alkaloids and the *stemona* alkaloids has been fulfilled. In contrast to the *sarpagine* alkaloids, where most members will be accessible *via* our synthetic approach, not every *stemona* alkaloid can be obtained in this fashion.

Figure 32 sums up the *stemona* alkaloids containing a tropanone core. These alkaloids can be accessed *via* the 3-oxidopyridinium [5+2] cycloaddition. For references see [3.3]. In total, we should be able to gain synthetic access to nearly one quarter of the *stemona* alklaloids through further synthetic endeavours with the already developed methodology.

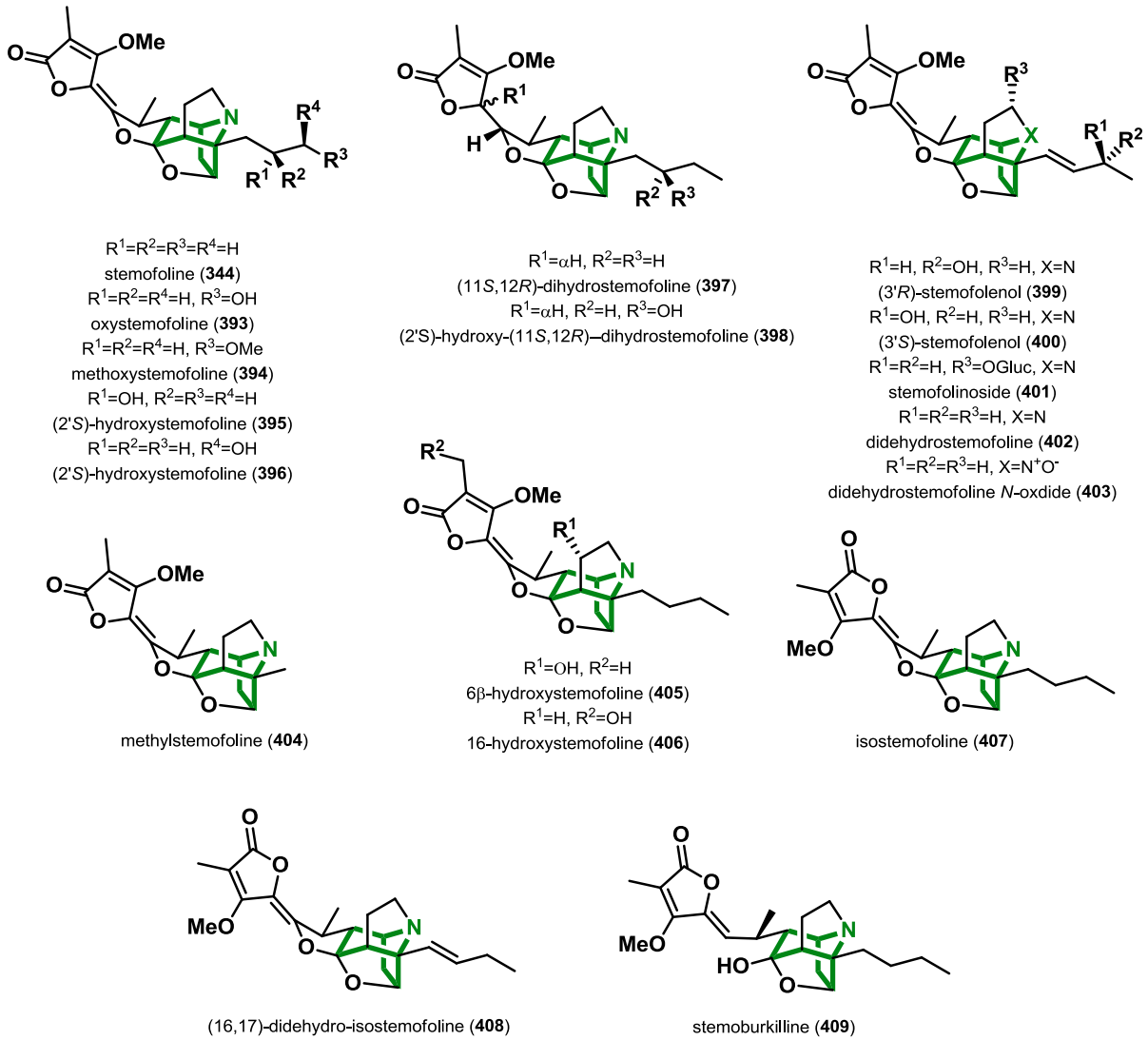


Figure 32: Further *stemona* alkaloids possesing the tropanone skeleton arising from the 3-oxidopyridinium [5+2] cycloaddition.

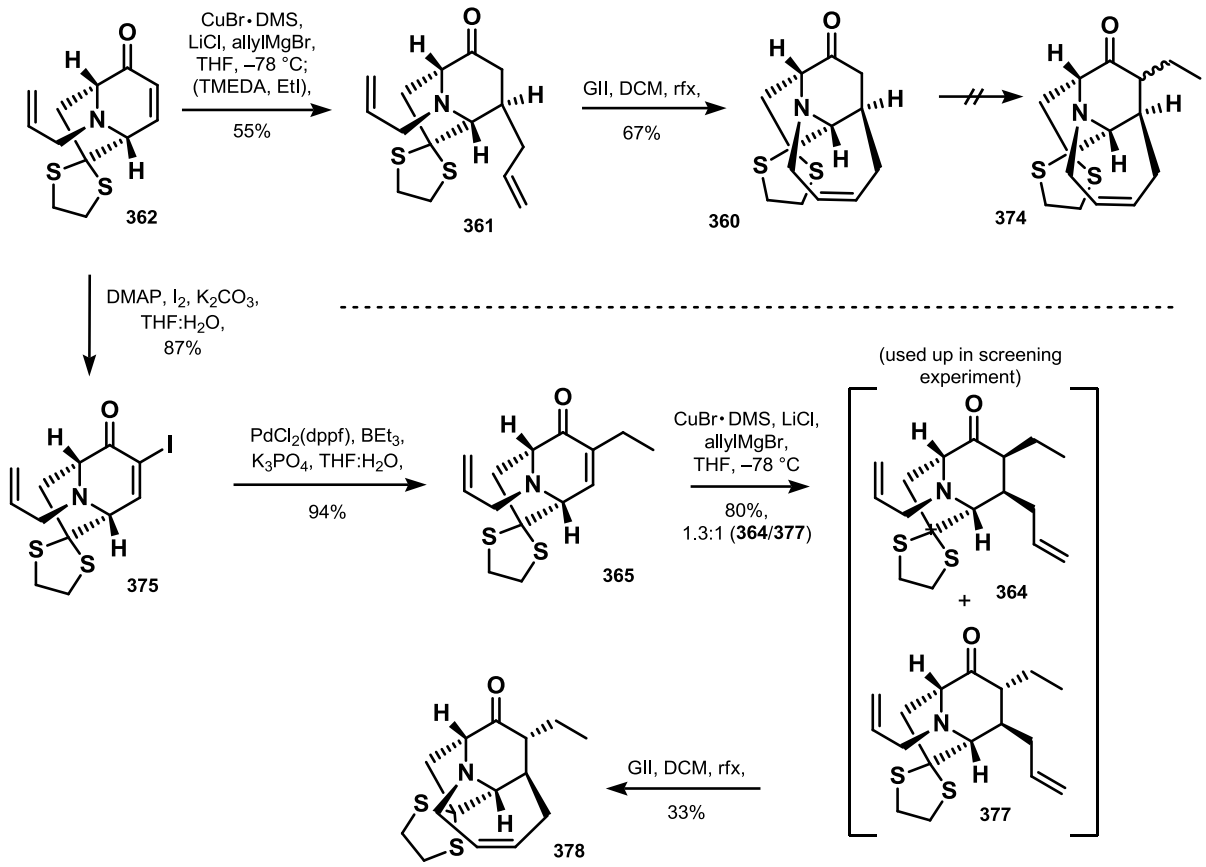
3.10 Experimentals

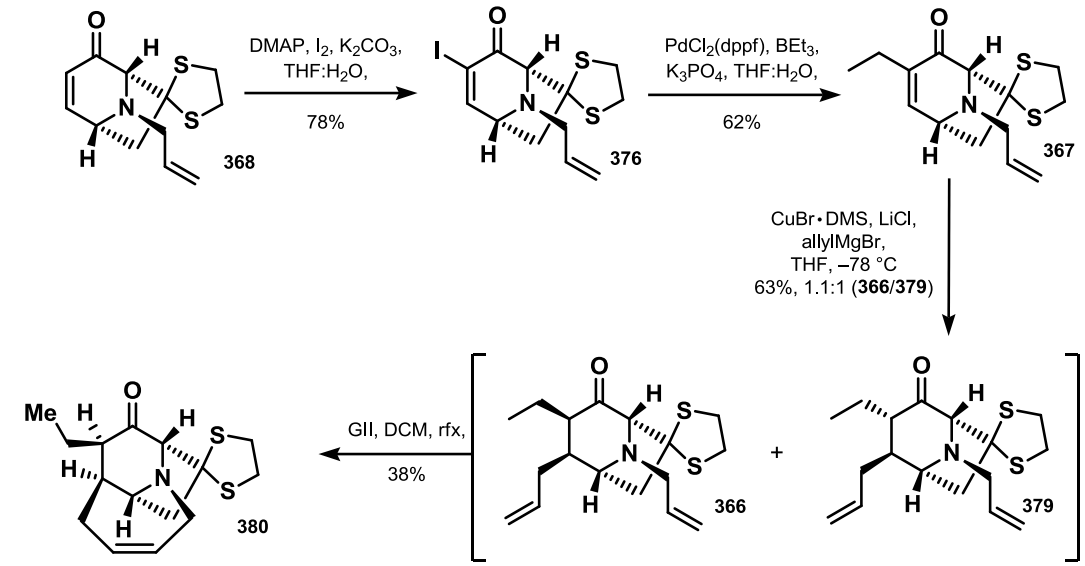
General

All reactions were performed under an inert atmosphere using Argon as the inert gas, using oven-dried glassware unless stated otherwise. Chemicals were used as bought from chemical suppliers. Solvents were used as bought from chemical suppliers or obtained from a dispensory system. THF was used dry after being distilled from Na/benzophenone or as bought from Acros Organics, 99,5% over molsieves, stabilized. DCM was used after distillation over CaH_2 or as bought from chemical suppliers. Acetonitrile was used as bought from Acros Organics 99.9% over molsieves. Acetone was used as bought from Acetone: VMR, technical grade. NEt_3 was used after distillation over CaH_2 or as bought from chemical suppliers. No difference in reactivities/yields was observed using different solvent sources. THF for Pd-catalyzed enolate coupling was used after sparging the solvent with argon for 30 minutes under ultrasonication. TLC was carried out using Macherey-Nagel, ALUGRAM Xtra SIL G/UV_{254}, Aluminium plates, silica 60. Silica gel-chromatography was carried out using Macherey-Nagel, Silica 60M, 0.04-0.083 mm mesh. Preparative thin layer chromatography was carried out using Macherey-Nagel, ADAMANT UV_{254}, Glass plates, silica 60. NMR-measurements were carried out using Bruker DPX 200 MHz, Bruker AV 400 MHz, Bruker DPX 400 MHz and Bruker DRX 500 MHz. All NMR-spectra are referenced to 7.26 ppm ($CDCl_3$, ^1H) and 77.16 ppm ($CDCl_3$, ^{13}C), 3.31 ppm (methanol-d_4, ^1H) and 49.00 ppm (methanol-d_4, ^{13}C) or 2.50 ppm (DMSO-d_6, ^1H) and 39.52 (DMSO-d_6, ^{13}C). IR measurements were carried out using Bruker Vector 22 or Shimadzu IRAffinity-1S. UPLC-MS Spectra were recorded using Waters QTOF-Premier (Waters Aquity Ultra Performance, electron spray ionization). HR-EI-MS were obtained using Micromass GCT. Optical rotations were measured using Perkin Elmer Polarimeter 341.

.

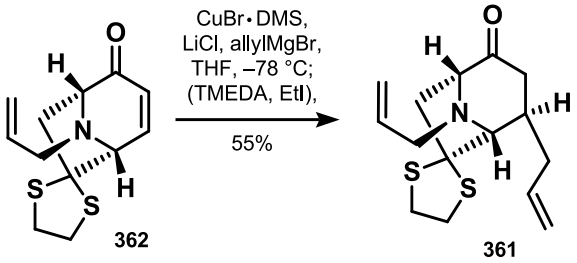
Graphical Overview IV





Procedures

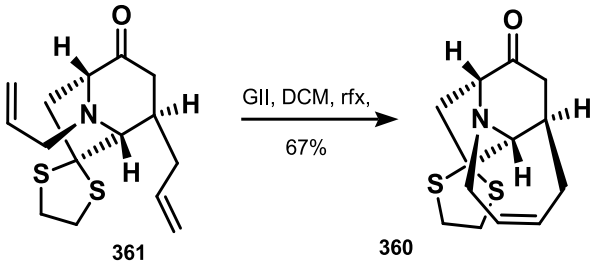
4,8-diallyl-8-azaspiro[bicyclo[3.2.1]octane-6,2'-[1,3]dithiolan]-2-one (**361**)



CuBr/DMS (343 mg, 1.67 mmol mmol, 1.0 eq.) was weighed out into a schlenk flask, which was then transferred to a glove box. LiCl (141 mg, 3.34 mmol, 2.0 eq.) was added to the schlenk flask, and the flask was then transferred out of the glove box. THF (3.0 mL) was added, and the resulting mixture was cooled to –78 °C. Allyl magnesiumbromide solution (3.3 mL of a 1.0 M solution in ethyl ether, 3.34 µmol, 2.0 eq.) was then added to the solution, followed by immediate dropwise addition of Michael acceptor **362** (381 mg, 1.50 mmol, 0.9 eq.). The solution was then allowed to stir for 10 minutes, followed by the addition of TMEDA (0.25 mL, 1.67 mmol, 1.0 eq.) and EtI (1.04 g, 6.68 mmol, 4.0 eq.). The mixture was allowed to stir for 5 hours at –78 °C, before 2 M NaOH was added and the mixture was stirred for one hour. EtOAc was then added, as well as water and solid NaCl. The phases were separated, and the aqueous phase was extracted two more times with EtOAc. The combined organic layers were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude mixture was purified using 10:1 PE:EtOAc as eluent to yield 245 mg (55%) of ketone **361** as a clear oil. The desired ethylation did not occur in a significant fashion.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.84–5.62 (m, 2H), 5.21 (dq, *J*=17.2, 1.6 Hz, 1H), 5.12 (dq, *J*=10.2, 1.4 Hz, 1H), 5.08–4.93 (m, 2H), 3.48–3.31 (m, 5H), 3.31–3.24 (m, 3H), 2.98 (dd, *J*=15.2, 7.9 Hz, 1H), 2.63–2.52 (m, 2H), 2.41 (d, *J*=15.4 Hz, 1H), 2.33–2.24 (m, 1H), 2.22–2.15 (m, 2H) ppm.

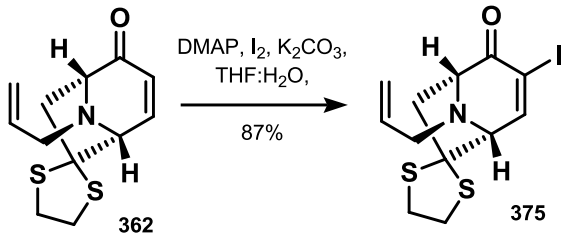
2,3,5,8,9,9a-hexahydrospiro[3,9-ethanopyrrolo[1,2-*a*]azepine-1,2'-[1,3]dithiolan]-11-one (**360**)



Bisolefin **361** (180 mg, 611 µmol, 1.0 eq) was dissolved in degassed DCM (15 mL) and Grubbs II catalyst (63 mg, 74.2 µmol, 0.25 eq) was added in DCM (15 mL). The reaction mixture was heated to reflux for six hours. The solvent was then evaporated and the crude remains were subjected to flash column chromatography using 9:1 PE:EtOAc as eluent to give 109 mg (67%) of olefin **360** as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.84–5.71 (m, 2H), 3.85–3.74 (m, 1H), 3.71–3.61 (m, 1H), 3.49–3.37 (m, 2H), 3.35 (s, 1H), 3.34–3.16 (m, 3H), 3.11–3.04 (m, 1H), 2.99 (dd, *J*=14.9, 8.0 Hz, 1H), 2.68 (dd, *J*=17.1, 8.2 Hz, 1H), 2.45–2.34 (m, 1H), 2.34–2.19 (m, 2H), 1.98 (d, *J*=17.4 Hz, 1H) ppm. **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 212.2, 133.0, 131.0, 77.1, 70.9, 68.2, 48.3, 47.7, 40.6, 39.9, 38.8, 36.3, 34.1 ppm. **IR (neat sample):** 3017, 2920, 2835, 1711, 1414, 1356, 1325, 1277, 1261, 1234, 1194, 1155, 1130, 1082, 1055, 1009, 968, 955, 937, 908, 874, 853, 812 cm^{-1}.

8-allyl-3-iodo-8-azaspiro[bicyclo[3.2.1]oct[3]ene-6,2'-[1,3]dithiolan]-2-one (**375**)

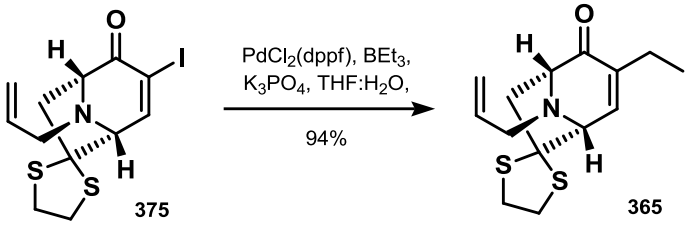


Enone **362** (658 mg, 2.60 mmol, 1.0 eq) was dissolved in a 1:1 mixture of water:THF (15 mL). Potassium carbonate (431 mg, 3.12 mmol, 1.2 eq) was added, followed by the addition of iodine (857 mg, 3.38 mmol, 1.3 eq.) and DMAP (63.0 mg, 520 µmol, 0.2 eq). The reaction

mixture was allowed to stirr overnight, and was then diluted with ether. The mixture was then washed with sat. sodium thiosulfate solution, followd by separation of the organic layer. The organic layer was then washed with 0.1 M HCl. The organic layer was then dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude remains were purified *via* column chromatography using 5:1 PE:EtOAc as eluent to yield 860 mg (87%) of **375** as a bright yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.69 (d, *J*=5.3, 1H), 5.90–5.68 (m, 1H), 5.31–5.05 (m, 2H), 3.87 (d, *J*=8.0 Hz, 1H), 3.75 (d, *J*=5.3 Hz, 1H), 3.46–3.35 (m, 2H), 3.34–3.19 (m, 4H), 3.11 (dd, *J*=15.0, 8.0 Hz, 1H), 2.37 (d, *J*=15.0 Hz, 1H) ppm. **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 192.0, 156.7, 134.1, 118.3, 100.6, 72.7, 70.8, 67.3, 51.7, 45.0, 40.7, 40.4 ppm. **HRMS** (ESI, *m/z*): calc. for [$C_{12}H_{14I}NOS_2$+H]: 397.9640, found: 397.9640. **IR (neat sample):** 2961, 2920, 2822, 1694, 1574, 1443, 1420, 1331, 1300, 1279, 1236, 1134, 1053, 991, 928, 887 cm^{-1}. **R_f:** 0.44 (5:1 PE:EtOAc).

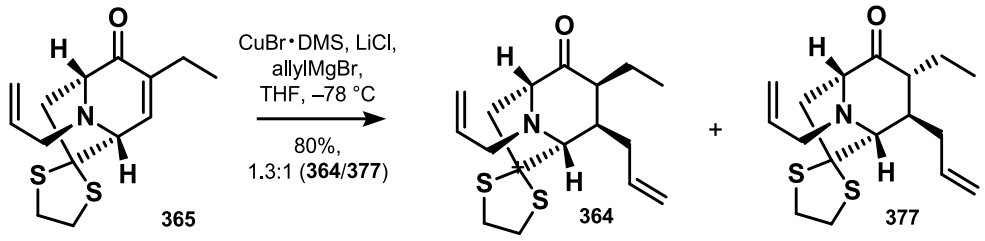
8-allyl-3-ethyl-8-azaspiro[bicyclo[3.2.1]oct[3]ene-6,2'-[1,3]dithiolan]-2-one (**365**)



Vinyliodide **375** (100 mg, 264 µmol, 1.0 eq.), $PdCl_2$(dppf) (21.0 mg, 26.0 mol, 0.1 eq.) and K_3PO_4 (168 mg, 791 µmol, 3.0 eq.) were put in a schlenk flask and the flask was purged with argon. A 10:1 mixture of THF:H_2O was then added, and the mixture was cooled to 0 °C. The addition of BEt_3 solution (0.32 mL of a 1.0 M solution in THF, 316 µmol, 1.2 eq.) occurred next and the reaction mixture was then allowed to stirr overnight while warming to ambient temperature. The mixture was then diluted with EtOAc and water. The organic layer was separated, and the aqueous layer was extracted two more times with EtOAc. The combined organic layers were then washed with brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude remains were purified *via* flash chromatography using 5:1 PE:EtOAc as eluent to yield 70 mg (94%) of **365** as a bright yellow oil.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 6.62 (dt, *J*=5.1, 1.3 Hz, 1H), 5.82 (ddt, *J*=16.8, 14.5, 6.0 Hz, 1H), 5.28–5.05 (m, 2H), 3.80 (d, *J*=5.0 Hz, 1H), 3.60 (d, *J*= 8.0 Hz, 1H), 3.51–3.17 (m, 6H), 3.07 (dd, *J*=14.8, 8.0 Hz, 1 H), 2.39–2.17 (m, 3H), 1.06 (t, *J*=7.5 Hz, 3H) ppm. **IR** (neat sample): 2963, 2924, 1874, 1682, 1445, 1420, 1373, 1335, 1277, 1136, 993, 924, 889 cm^{-1}. **HRMS** (ESI, *m/z*): calc. for [$C_{14}H_{19}NOS_2$+H]: 282.0986, found: 282.0986. **R_f:** 0.55 (5:1 PE:EtOAc).

4,8-diallyl-3-ethyl-8-azaspiro[bicyclo[3.2.1]octane-6,2'-[1,3]dithiolan]-2-one (**364**)



CuBr/DMS (102 mg, 500 µmol mmol, 1.0 eq.) was weighed out into a schlenk flask, which was then transferred to a glove box. LiCl (68 mg, 1.60 mmol, 3.5 eq.) was added to the schlenk flask, and the flask was then transferred out of the glove box. THF (4.0 mL) was added, and the resulting mixture was cooled to –78 °C. Allyl magnesiumbromide solution (1.00 mL of a 1.0 M solution in ethyl ether, 1.00 µmol, 2.0 eq.) was then added to the solution, followed by immediate dropwise addition of Michael acceptor **365** (126.7 mg, 450 µmol, 0.9 eq.). The solution was then allowed to stir for 10 minutes, before the addition of 2 M NaOH at –78 °C quenched the reaction. The mixture was allowed to stirr for an hour at ambient temperature, before the mixture was transferred to a separation funnel. EtOAc was added, as well as neat NaCl, and the aqueous phase was extracted three times with EtOAc. The combined organic layers were then washed with brine, followed by drying over $MgSO_4$. The solvent was removed under reduced pressure, and the obtained crude oil was purified *via* silica flash chromatography using 10:1 PE:EtOAc as eluent to yield 115.5 mg (80%) of enones **364**/**377** in a 1.3:1 mixture of **364** to **377** as a clear oil.

Desired isomer **364**:

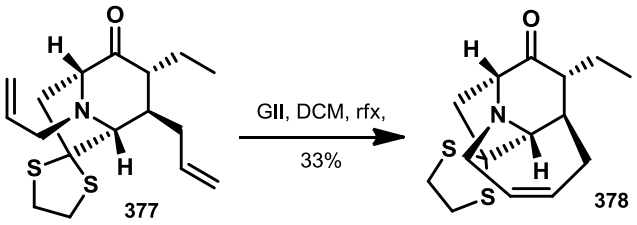
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.91–5.73 (m, 2H), 5.25 (dq, *J*=17.2, 1.6 Hz, 1H), 5.20–5.08 (m, 3H), 3.51 (dt, *J*=8.2, 1.4 Hz, 1H), 3.49–3.45 (m, 1H), 3.43–3.30 (m, 3H), 3.29–3.17 (m, 3H),

2.90 (dd, *J*=14.7, 8.0 Hz), 2.41–2.28 (m, 2H), 2.27–2.07 (m, 3H), 1.69–1.55 (m, 2H), 0.94 (t, *J*=7.4 Hz, 3H) ppm. **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 213.9, 136.7, 135.7, 118.1, 117.6, 74.5, 71.2, 70.0, 55.2, 50.6, 48.4, 40.8, 40.3, 40.2, 39.2, 21.4, 12.2 ppm. **IR (neat sample):** 2961, 2924, 2845, 1717, 1447, 1420, 1337, 1275, 1142, 1103, 1049, 995, 918 cm^{-1}. **R_f:** 0.67 (5:1 PE:EtOAc).

Undesired isomer **377**:

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 5.93–5.78 (m, 2H), 5.26–5.12 (m, 4H), 3.53 (d, *J*=4.8 Hz, 1H), 3.47–3.08 (m, 7H), 2.90 (dd, *J*=14.8, 1.0 Hz), 2.96–2.54 (m, 3H), 2.41–2.09 (m, 4H), 1.06 (t, *J*=7.4 Hz, 3H) ppm. **IR** (neat sample): 3073, 2961, 2918, 2874, 2828, 1715, 1639, 1420, 1331, 1277, 1125, 1053, 995, 972, 917, 972 cm^{-1}. **R_f:** 0.50 (5:1 PE:EtOAc).

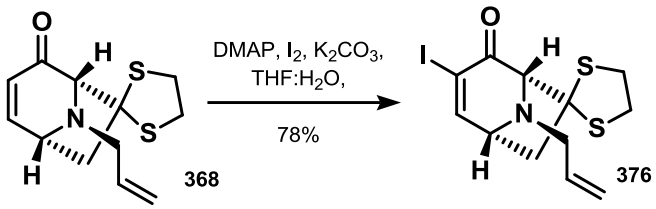
10-ethyl-2,3,5,8,9,9a-hexahydrospiro[9,3-ethanopyrrolo[1,2-*a*]azepine-1,2'-[1,3]dithiolan]-11-one (**378**)



Bisolefin **377** (10.6 mg, 32.7 µmol, 1.0 eq) was dissolved in degassed DCM (1.5 mL) and Grubbs II catalyst (2.8 mg, 3.27 µmol, 0.1 eq) was added in DCM (1.5 mL). The reaction mixture was heated to reflux for six hours. The solvent was then evaporated and the crude remains were subjected to flash column chromatography using 9:1 PE:EE as eluent to give 3.2 mg (33%) of olefin **378** as a white solid.

For spectral data see page 150.

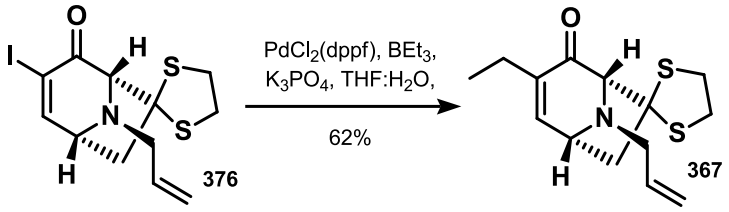
8-allyl-3-iodo-8-azaspiro[bicyclo[3.2.1]oct[2]ene-6,2'-[1,3]dithiolan]-4-one (**376**)



Enone **368** (50.0 mg, 197 µmol, 1.0 eq) was dissolved in a 1:1 mixture of water:THF (2.0 mL). Potassium carbonate (33.0 mg, 236 µmol, 1.2 eq) was added, followed by the addition of iodine (75.0 mg, 296 µmol, 1.5 eq.) and DMAP (5.0 mg, 39.0 µmol, 0.2 eq). The reaction mixture was allowed to stirr overnight, and was then diluted with ether. The mixture was then washed with sat. sodium thiosulfate solution, followed by separation of the organic layer. The organic layer was then washed with 0.1 M HCl. The organic layer was then dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude remains were purified *via* column chromatography using 5:1 PE:EtOAc as eluent to yield 58.0 mg (78%) of **376** as a bright yellow solid.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.58 (d, *J*=5.3 Hz, 1H), 5.80 (ddt, *J*=17.3, 10.0, 6.2 Hz, 1H), 5.27–5.11 (m, 2H), 4.00 (d, *J*=1.3 Hz, 1H), 3.82–3.73 (m, 1H), 3.50–3.33 (m, 2H), 3.33–3.08 (m, 4H), 2.88 (dd, *J*=15.6, 6.3 Ht, 1H), 2.45 (d, *J*=13.6 Hz, 1H) ppm. **R_f:** 0.36 (5:1 PE:EtOAc).

8-allyl-3-ethyl-8-azaspiro[bicyclo[3.2.1]oct[2]ene-6,2'-[1,3]dithiolan]-4-one (**367**)

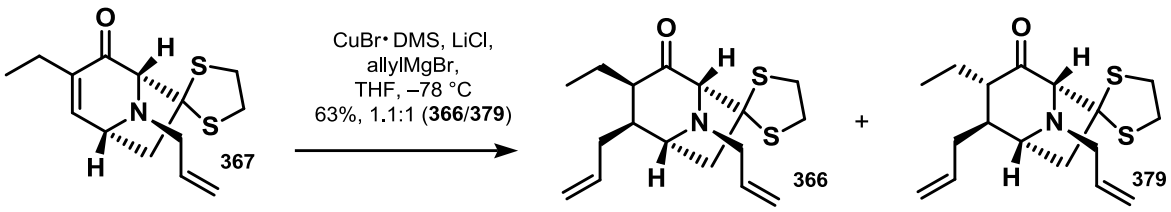


Vinyliodide **376** (94.0 mg, 248 µmol, 1.0 eq.), $PdCl_2$(dppf) (20.0 mg, 25.0 mol, 0.1 eq.) and K_3PO_4 (158 mg, 744 µmol, 3.0 eq.) were put in a schlenk flask and the flask was purged with argon. A 10:1 mixture of THF:H_2O was then added, and the mixture was cooled to 0 °C. The addition of BEt_3 solution (0.3 mL of a 1 M solution in THF, 298 µmol, 1.2 eq.) occurred next

and the reaction mixture was then allowed to stirr overnight while warming to ambient temperature. The mixture was then diluted with EtOAc and water. The organic layer was separated, and the aqueous layer was extracted two more times with EtOAc. The combined organic layers were then washed with brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude remains were purified *via* flash chromatography using 5:1 PE:EtOAc as eluent to yield 43 mg (62%) of **367** as a bright yellow oil.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 6.55 (dt, *J*=5.3, 1.5 Hz, 1H), 5.81 (ddt, *J*=17.3, 10.0, 6.2 Hz, 1H), 5.24–5.14 (m, 2H), 3.86–3.74 (m, 1H), 3.67 (d, *J*=1.3 Hz, 1H), 3.48–3.05 (m, 6H), 2.88 (dd, *J*=13.4, 6.2 Hz, 1H), 2.36 (d, *J*=13.3Hz, 1H), 2.22 (qd, *J*=7.4, 1.3 Hz, 2H), 1.05 (t, *J*=7.4 Hz, 3H) ppm.

2,8-diallyl-3-ethyl-8-azaspiro[bicyclo[3.2.1]octane-6,2'-[1,3]dithiolan]-4-one (**366**)



CuBr/DMS (67 mg, 326 µmol, 1.0 eq.) was weighed out into a schlenk flask, which was then transferred to a glove box. LiCl (28 mg, 652 µmol, 2.0 eq.) was added to the schlenk flask, and the flask was then transferred out of the glove box. THF (1.5 mL) was added, and the resulting mixture was cooled to –78 °C. Allyl magnesiumbromide solution (10.65 mL of a 1.0 M solution in ethyl ether, 652 µmol, 2.0 eq.) was then added to the solution, followed by immediate dropwise addition of Michael acceptor **367** (83 mg, 293 µmol, 0.9 eq.). The solution was then allowed to stir for 10 minutes, before the addition of 2 M NaOH at –78 °C quenched the reaction. The mixture was allowed to stirr for an hour at ambient temperature, before the mixture was transferred to a separation funnel. EtOAc was added, as well as neat NaCl, and the aqueous phase was extracted three times with EtOAc. The combined organic layers were then washed with brine, followed by drying over $MgSO_4$. The solvent was removed under reduced pressure, and the obtained crude oil was purified

via silica flash chromatography using 10:1 PE:EtOAc as eluent to yield 59.4 mg (63%) of enones **366**/**379** in a 1.1:1 mixture of **366** to **379** as a clear oil.

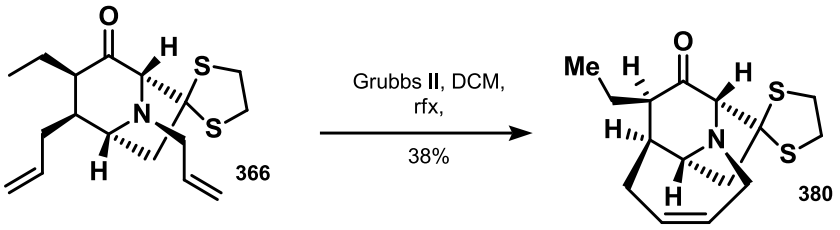
Desired isomer **366**:

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 5.88–5.68 (m, 2H), 5.29–5.07 (m, 4H), 4.77 (s, 1H), 3.92 (d, *J*=2.3 Hz, 1H), 3.54–3.25 (m, 6H), 2.93 (dd, *J*=14.3, 6.3 Hz, 1H), 2.39–2.05 (m, 5H), 1.65–1.52 (m, 2H), 0.86 (t, *J*=7.8 Hz, 3H) ppm.

Undesired isomer **379**:

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 5.91–5.64 (m, 2H), 5.27–4.99 (m, 4H), 3.72 (d, *J*=1.5 Hz, 1H), 3.53–3.24 (m, 7H), 2.93 (dd, *J*=14.8, 7.3 Hz, 1H), 2.27–1.96 (m, 4H), 1.83–1.58 (m, 2H), 1.39–1.34 (m, 1H), 1.00 (t, *J*=7.4 Hz, 3H) ppm.

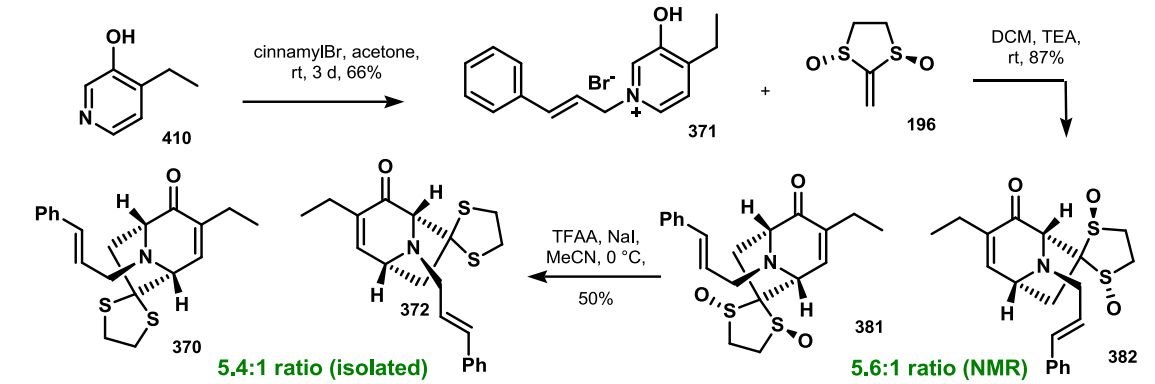
10-ethyl-1,3,5,8,9,9a-hexahydrospiro[9,3-ethanopyrrolo[1,2-*a*]azepine-2,2'-[1,3]dithiolan]-11-one (**380**)

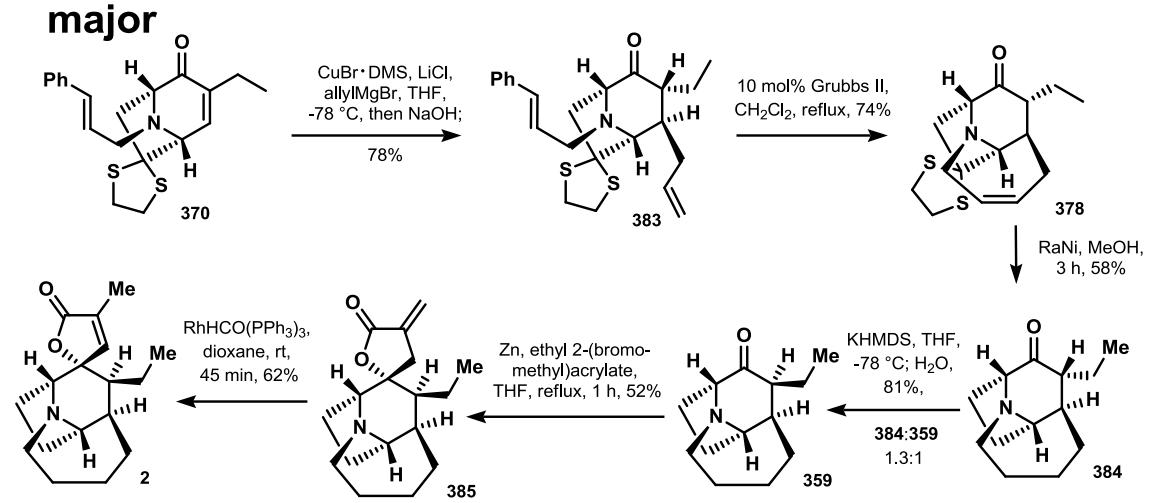


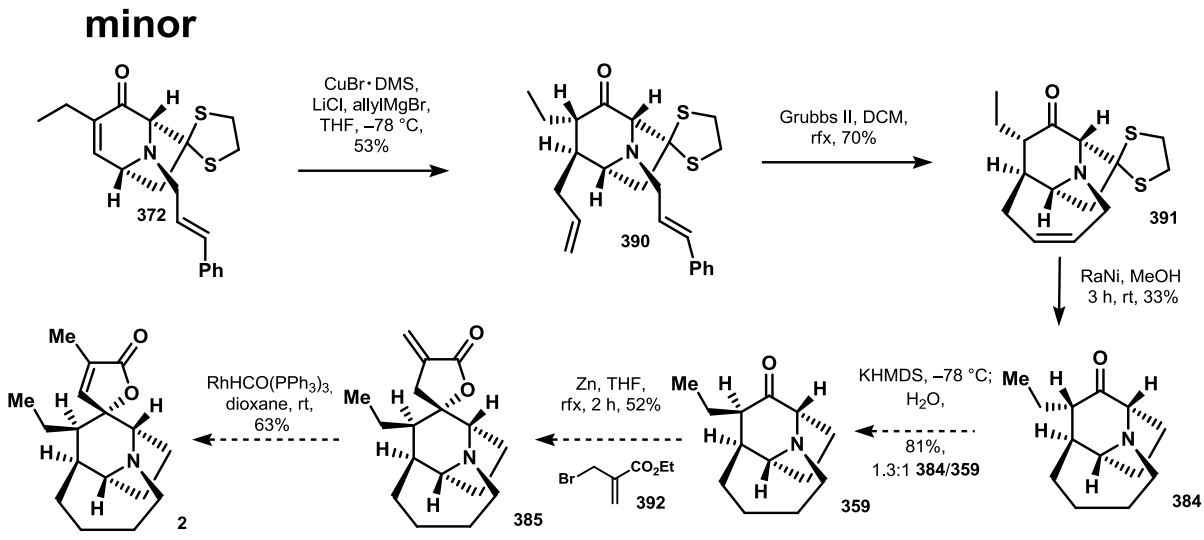
Bisolefin **366** (18 mg, 55.6 µmol, 1.0 eq) was dissolved in degassed DCM (1.0 mL) and Grubbs II catalyst (12.0 mg, 1.41 µmol, 0.25 eq) was added in DCM (1.0 mL). The reaction mixture was heated to reflux for six hours. The solvent was then evaporated and the crude remains were subjected to flash column chromatography using 9:1 PE:EE as eluent to give 6.2 mg (38%) of olefin **380** as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.76 (t, *J*=3.3 Hz, 2H), 3.85–3.78 (m, 1H), 3.67–3.58 (m, 2H), 3.49–3.45 (m, 2H), 3.43–3.35 (m, 2H), 3.27–3.22 (m, 2H), 3.18–3.11 (m, 1H), 2.97 (dd, *J*=14.6, 7.3 Hz, 1H), 2.57–2.45 (m, 2H), 2.41–2.27 (m, 1H), 2.04–1.95 (m, 1H), 0.94 (t, *J*=7.4 Hz, 3H) ppm. **HRMS** (ESI, *m/z*): calc. for [$C_{15}H_{21}NOS_2$+H]: 296.1143, found: 296.1144.

Graphical Overview V

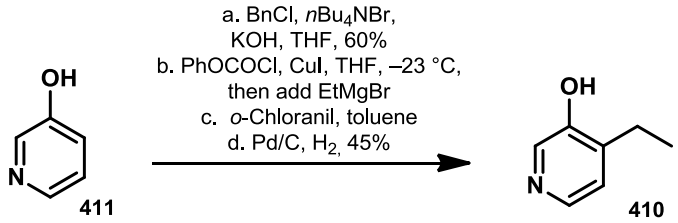






Procedures

4-ethylpyridin-3-ol (**410**)



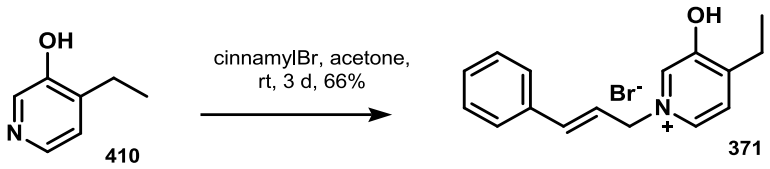
3-hydroxypyridine **411** was *O*-benzylated using the procedure of Kozikowski and coworkers.[3.29]

4-ethylpyridin-3-ol **410** was obtained using the procedure of Commins and coworkers.[3.30]

[3.29] A. P. Kozikowski *et al*. *J. Org. Chem.* **1997**, *62*, 503–509.

[3.30] D. L. Commins *et al. J. Heterocyclic Chem.* **1985**, *22*, 1419–1420.

1-cinnamyl-4-ethyl-3-hydroxypyridin-1-ium bromide (**371**)

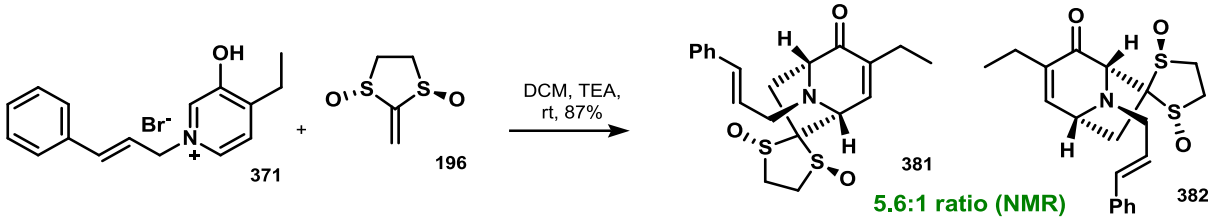


4-ethylpyridin-3-ol **410** (3.99 g, 32.4 mmol, 1.0 eq.) was dissolved in acetone (32 mL), followed by the addition of cinnamylbromide (6.38 g, 32.4 mmol, 1.0 eq.) in acetone (32 mL). The solution was stirred for 3 days, after which 5.91 g (57%) of the desired product **371** was filtered off. The remaining brown oil was recrystallized from EtOAc/MeOH/Et_2O to give another 906 mg (9%) of the desired compound **371**.

^{1}H-NMR (400 MHz, methanol-d_4): δ = 8.45 (dd, *J*=6.1, 1.4 Hz, 1H), 8.30 (d, *J*=1.4 Hz, 1H), 7.83 (d, *J*=6.1 Hz, 1H), 7.54–7.46 (m, 2H), 7.39–7.26 (m, 3H), 6.99 (d, *J*=15.7 Hz, 1H), 6.53 (dt, *J*=15.8, 7.1 Hz, 1H), 5.30 (d, *J*=7.2 Hz, 2H), 2.88 (q, *J*=7.5 Hz, 2H), 1.31 (t, *J*=7.5 Hz, 3H) ppm. **^{13}C-NMR (100 MHz, methanol-d_4):** δ = 156.7, 152.6, 139.7, 136.9, 136.7, 130.0, 129.9, 128.5, 128.1, 122.0, 63.7, 24.2, 12.4 ppm. **IR (neat sample):** 3339, 3026, 2974, 2936, 1626, 1582,

1528, 1474, 1373, 1310, 1281, 1134, 1059, 976, 878, 841 cm^{-1}. **MP:** 123-125 °C. **HRMS** (ESI, *m/z*): calc. for [$C_{16}H_{18}NO^{+}$]: 240.1383, found: 240.1388.

(1*R*,5*R*)-8-cinnamyl-3-ethyl-8-azaspiro[bicyclo[3.2.1]oct[3]ene-6,2'-[1,3]dithiolan]-2-one 1',3'-dioxide (**381**) and (1*R*,5*R*)-8-cinnamyl-3-ethyl-8-azaspiro[bicyclo[3.2.1]oct[2]ene-6,2'-[1,3]dithiolan]-4-one 1',3'-dioxide (**382**)



Bissulfoxide **196** (445 mg, 2.97 mmol, 1.6 eq.) was dispersed in DCM (18 mL) under an inert atmosphere, followed by the addition of solid pyridinium salt **371** (590 g, 1.84 mmol, 1.0 eq.) and NEt_3 (0.28 mL, 2.02 mmol, 1.1 eq.). The reaction vessel was wrapped in aluminium foil and the reaction mixture was stirred at ambient temperature for 24 hours. The remaining solvent was then removed under reduced pressure and the crude remains were purified using silica gel chromatography eluting with acetone to yield 626 mg (87%) of regioisomeric tricycles **381** and **382** (5.6:1 ratio **381**:**382**) as a yellow solid. The mixture of regioisomers was used directly in the next step as separation could not be achieved.

Major regioisomer (**381**)

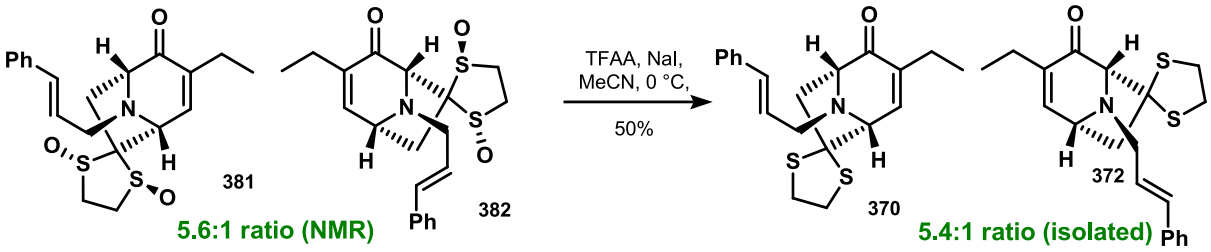
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.36–7.31 (m, 2H), 7.30–7.23 (m, 2H), 7.22–7.16 (m, 1H), 6.62 (dt, *J*=5.1, 1.4 Hz, 1H), 6.47 (d, *J*=16.0 Hz, 1H), 6.12 (dt, *J*=16.0, 6.2 Hz, 1H), 4.29 (d, *J*=5.1 Hz, 1H), 3.91–3.82 (m, 2H), 3.54–3.46 (m, 2H), 3.42–3.31 (m, 3H), 2.45 (d, *J*=15.4 Hz, 1H), 2.30 (q, *J*=7.5 Hz, 2H), 2.20 (dd, *J*=15.5, 7.7 Hz, 1H), 1.07 (t, *J*=7.3 Hz, 3H) ppm.

Minor regioisomer (**382**)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.36–7.31 (m, 2H), 7.30–7.23 (m, 2H), 7.22–7.16 (m, 1H), 6.77 (td, *J*=5.5, 1.4 Hz, 1H), 6.49–6.45 (m, 1H), 6.17–6.09 (m, 1H), 4.15 (br.s., 1H), 4.06 (t, *J*=5.5 Hz, 1H), 3.69–3.62 (m, 1H), 3.91–3.32 (m, 6H), 2.62 (d, *J*=14.3 Hz, 1H), 2.43–2.37 (m, 1H), 2.29–2.24 (m, 2H), 1.08–1.04 (m, 3H) ppm.

IR (neat sample, mixture): 2968, 2932, 2832, 1684, 1599, 1495, 1449, 1373, 1234, 1138, 1092, 1065, 1040, 968, 835 cm^{-1}. **R_f:** 0.78 (acetone). **HRMS (mixture of regioisomers)** (ESI, *m/z*): calc. for $[C_{20}H_{23}NO_3S_2+H]$ 390.1198, found: 390.1201.

(1*R*,5*R*)-8-cinnamyl-3-ethyl-8-azaspiro[bicyclo[3.2.1]oct[3]ene-6,2'-[1,3]dithiolan]-2-one (**370**) and (1*R*,5*R*)-8-cinnamyl-3-ethyl-8-azaspiro[bicyclo[3.2.1]oct[2]ene-6,2'-[1,3]dithiolan]-4-one (**372**)



Regiosiomeric mixture of bissulfoxides **381/382** (5.6:1 mixture of major/minor by NMR, 1.95 g, 5.00 mmol, 1.0 eq.) was dissolved in actetonitrile (100 mL) and the solution was cooled to 0 °C. NaI (2.25 mg, 15.00 mmol, 3.0 eq.) was added in one portion, followed by the dropwise addition of TFAA (2.1 mL, 15.00 mmol, 3.0 eq.). The reaction mixture was stirred at 0 °C for 2 hours before the addition of sat. $Na_2S_2O_3$ solution followed by the addition of 2 M NaOH solution quenched the reaction. The mixture was diluted with DCM and transferred to a separation funnel. The phases were separated, and the aqueous layer was extracted two more times with DCM. The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude mixture was purified *via* silica gel chromatography using 10:1 (PE:EtOAc) as eluent to give 898 mg (50%, isolated 5.4:1 ratio of regioisomers **370**/**372**) as a yellow oil.

Major regioisomer **370**:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.40–7.38 (m, 2H), 7.34–7.28 (m, 2H), 7.26–7.20 (m, 1H), 6.64 (dt, *J*=5.1, 1.4 Hz, 1H), 6.53 (d, *J*=16.0 Hz, 1H), 6.26–6.15 (m, 1H), 3.85 (d, *J*=5.1 Hz, 1H), 3.65 (d, *J*=8.2 Hz, 1H), 3.49–3.37 (m, 3H), 3.35–3.31 (m, 1H), 3.29–3.20 (m, 2H), 3.10 (dd, *J*=14.7, 7.9 Hz, 1H), 2.37–2.22 (m, 2H), 1.09 (t, *J*=7.5 Hz, 3H) ppm. **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 198.9, 140.1, 139.9, 136.9, 132.5, 128.6, 127.7, 126.5, 126.4, 71.2, 69.8, 68.1, 50.9, 45.6,

40.5, 40.4, 21.1, 12.6 ppm. **IR (neat sample):** 3024, 2963, 2922, 2872, 2827, 1680, 1597, 1578, 1495, 1447, 1371, 1335, 1304, 1277, 1206, 1070, 966, 934, 910, 891, 854 cm^{-1}. **$[\alpha]_D^{20}$**: -59 (c= 0.61; $CHCl_3$).

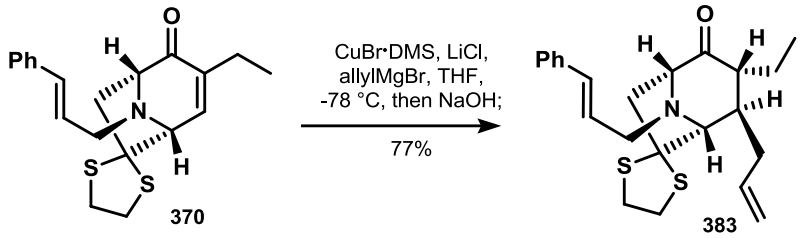
Minor regioisomer **372**:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.40–7.35 (m, 2H), 7.34–7.28 (m, 2H), 7.25–7.21 (m, 1H), 6.59 (dt, *J*=5.2, 1.5 Hz, 1H), 6.51 (d, *J*=16.0 Hz, 1H), 6.22 (dt, *J*=15.7, 6.5 Hz, 1H), 3.87 (t, *J*=5.8 Hz, 1H), 3.74 (d, *J*=0.7 Hz, 1H), 3.52–3.32 (m, 4H), 3.29–3.21 (m, 1H), 3.20–3.12 (m, 1H), 2.93 (dd, *J*=13.5, 6.3 Hz, 1H), 2.40 (d, *J*=13.7 Hz, 1H), 2.26 (q, *J*=7.1 Hz, 2H), 1.09 (t, *J*=7.3 Hz, 3H) ppm. **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 195.8, 141.1, 140.3, 136.9, 133.1, 128.7, 127.8, 126.6, 126.2, 83.9, 65.4, 58.6, 52.1, 45.3, 41.0, 39.0, 21.2, 12.3 ppm. **IR (neat sample):** 3024, 2963, 2930, 1682, 1494, 1449, 1371, 1275, 1221, 1134, 1053, 1011, 968, 881 cm^{-1}. **$[\alpha]_D^{20}$**: -116 (c= 0.61; $CHCl_3$)

HRMS (mixture of regioisomers) (ESI, *m/z*): calc. for [$C_{20}H_{23}NOS_2$+H]: 358.1299, found: 358.1299. **R_f:** major: 0.40, minor: 0.30 (both 6:1 PE/EtOAc).

major

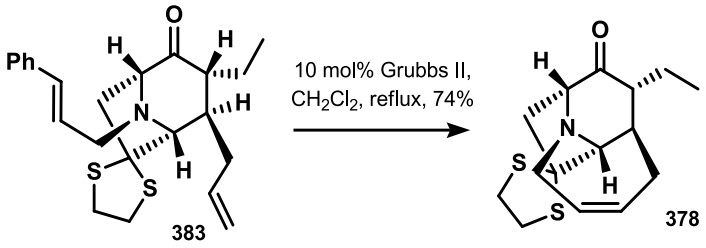
(1*R*,3*R*,4*R*,5*R*)-4-allyl-8-cinnamyl-3-ethyl-8-azaspiro[bicyclo[3.2.1]octane-6,2'-[1,3]dithiolan]-2-one (**383**)



CuBr/DMS (301 mg, 1.47 mmol, 1.0 eq.) was weighed out into a schlenk flask, which was then transferred to a glove box. LiCl (124 mg, 2.93 mmol, 1.8 eq.) was added to the schlenk flask, and the flask was then transferred out of the glove box. THF (6.5 mL) was added, and the resulting mixture was cooled to –78 °C. Allyl magnesiumbromide solution (2.6 mL of a 1.0 M solution in ethyl ether, 2.64 mmol, 1.8 eq.) was then added to the solution, followed by immediate dropwise addition of Michael acceptor **370** (470 mg, 1.32 mmol, 0.9 eq.). The solution was then allowed to stir for 10 minutes, before the addition of 2 M NaOH at –78 °C quenched the reaction. The mixture was allowed to stir for an hour at ambient temperature, before the mixture was transferred to a separation funnel. EtOAc was added, as well as neat NaCl, and the aqueous phase was extracted three times with EtOAc. The combined organic layers were then washed with brine, followed by drying over $MgSO_4$. The solvent was removed under reduced pressure, and the obtained crude oil was purified *via* silica flash chromatography using 10:1 PE:EtOAc as eluent to yield 405 mg (77%) of **383** as a clear oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.43–7.35 (m, 2H), 7.35–7.28 (m, 2H), 7.25–7.20 (m, 1H), 6.59 (d, *J*=16.0 Hz, 1H), 6.23 (dt, *J*=15.8, 6.6 Hz, 1H), 5.78 (dddd, *J*=16.5, 10.8, 8.5, 5.1 Hz, 1H), 5.08–4.91 (m, 2H), 3.61–3.38 (m, 5H), 3.33–3.24 (m, 1H), 3.24–3.17 (m, 2H), 2.96 (dd, *J*=14.7, 7.8 Hz, 1H), 2.44–2.33 (m, 2H), 2.30–2.18 (m, 1H), 2.18–2.11 (m, 2H), 1.72–1.59 (m, 2H), 0.96 (t, *J*=7.5 Hz, 3H) ppm. **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 213.9, 137.0, 136.6, 133.2, 128.7 (2C), 127.7, 127.1, 126.5 (2C), 117.8, 74.5, 71.2, 70.1, 54.6, 50.7, 48.5, 40.8, 40.5, 40.3, 39.2, 21.4, 12.3 ppm. **IR (neat sample):** 3024, 2961, 2924, 2874, 1715, 1639, 1597, 1495, 1449, 1375, 1342, 1275, 1148, 1105, 1047, 966, 912 cm^{-1}. **$[\alpha]_D^{20}$**: -44 (c= 0.83; $CHCl_3$). **R_f:** 0.41 (10:1 PE/EtOAc). **HRMS** (ESI, *m/z*): calc. for $[C_{23}H_{29}NOS_2+H]$: 400.1769, found: 400.1766.

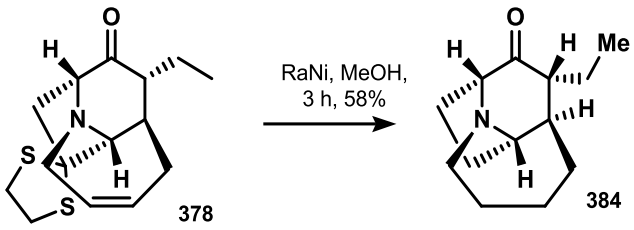
(3*R*,4*S*,9*R*,9a*R*,10*R*)-10-ethyl-2,3,5,8,9,9a-hexahydrospiro[9,3-ethanopyrrolo[1,2-*a*]azepine-1,2'-[1,3]dithiolan]-11-one (**378**)



Bisolefin **383** (202 mg, 505 µmol, 1.0 eq) was dissolved in degassed DCM (35 mL) and Grubbs II catalyst (43 mg, 51.0 µmol, 0.1 eq) was added in DCM (15 mL). The reaction mixture was heated to reflux for six hours. The solvent was then evaporated and the crude remains were subjected to flash column chromatography using 9:1 PE:EE as eluent to give 110 mg (74%) of olefin **378** as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.70–5.56 (m, 2H), 3.98–3.89 (m, 1H), 3.64–3.55 (m, 1H), 3.45–3.27 (m, 5H), 3.24–3.17 (m, 1H), 3.01–2.89 (m, 2H), 2.36–2.24 (m, 3H), 2.00–1.93 (m, 1H), 1.83–1.70 (m, 2H), 1.00 (t, *J*=7.2 Hz, 3H) ppm. **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 214.7, 130.6, 129.1, 76.2, 71.8, 67.8, 52.2, 49.3, 45.6, 41.1, 39.8, 38.9, 37.6, 28.7, 12.8 ppm. **IR (neat sample):** 2961, 2920, 1705, 1449, 1423, 1277, 1244, 1163, 1136, 972, 951, 818 cm^{-1}. **$[\alpha]_D^{20}$**: -164 (c= 0.18; $CHCl_3$). **R_f:** 0.50 (6:1 PE:EtOAc). **HRMS** (ESI, *m/z*): calc. for [$C_{15}H_{21}NOS_2$+H]: 296.1143, found: 296.1145.

(3*R*,4*R*,9*R*,9a*S*,10*R*)-10-ethyloctahydro-1H-9,3-ethanopyrrolo[1,2-*a*]azepin-11-one (**384**)

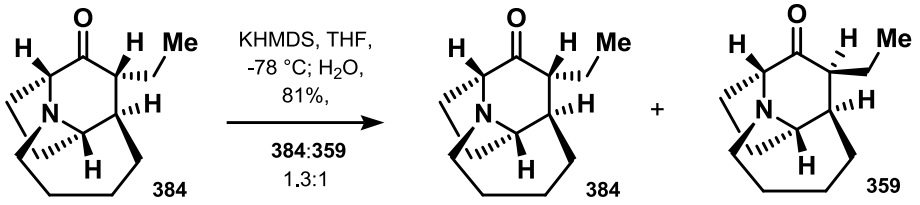


An aqueous dispersion of Raney nickel in water (1 pipet) was washed 3 three times with MeOH, and the waste solvent was discarded. Dithiolane **378** (20 mg, 67.7 µmol) was added in MeOH (2 mL), and the reaction mixture was stirred for 3 h at ambient temperature. Raney

nickel was then filtered off, and the solvent was removed under reduced pressure. The crude oil was subjected to flash column chromatography using 25:1 DCM:MeOH as eluent to give 8.2 mg (58%) of amine **384** as a clear oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.50 (d, *J*=7.2 Hz, 1H), 3.47–3.41 (m, 1H), 3.37 (d, *J*=7.9 Hz, 1H), 2.45 (td, *J*=12.0, 2.1 Hz, 1H), 2.28–2.17 (m, 1H), 2.17–2.06 (m, 1H), 2.00–1.90 (m, 3H), 1.84–1.52 (m, 8H), 1.51–1.38 (m, 1H), 0.91 (t, *J*=7.5 Hz, 3H) ppm. **^{13}C-NMR (125 MHz, $CDCl_3$):** δ= 217.1, 70.1, 59.2, 51.2, 49.0, 45.3, 34.5, 31.0, 27.5, 27.1, 26.5, 26.4, 11.8 ppm. **IR (neat sample):** 2924, 1705, 1456, 1377, 1281, 1159, 1148, 1134, 986, 816, 799**,** cm^{-1}. **$[\alpha]_D^{20}$**: -171 (c= 0.22; $CHCl_3$). **R_f:** 0.50 (25:1 DCM:MeOH). **HRMS** (ESI, *m/z*): calc. for [$C_{13}H_{21}NO$+H]: 208.1701, found: 208.1701.

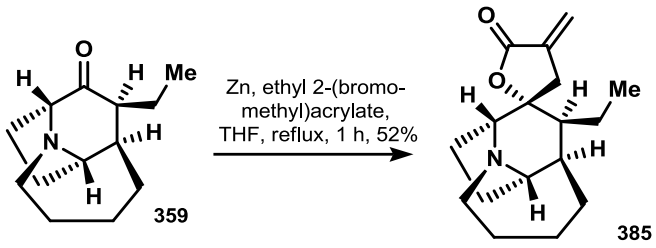
(3*R*,4*R*,9*R*,9a*S*,10*R*)-10-ethyloctahydro-1H-9,3-ethanopyrrolo[1,2-*a*]azepin-11-one (**384**) and (3*R*,4*R*,9*R*,9a*S*,10*S*)-10-ethyloctahydro-1H-9,3-ethanopyrrolo[1,2-*a*]azepin-11-one (**359**)



NaHMDS (0.08 mL, 164 µmol, 2.0 eq.) was added to THF at –78 °C. Ketone **384** (17.0 mg, 82 µmol 1.0 eq.) was added to this solution in THF and was stirred for one hour, before the ad–dition of water (0.1 mL) quenched the reaction. The mixture was dried over $MgSO_4$ and the solvent was evaporated. The crude remains were purified *via* flash column chromatography using 50:1 DCM:MeOH as eluent to obtain 13.7 mg (81%) of a 1.3:1 mixture of **384** and **359** as colourless oil. As the desired ketone **359** decomposes rapidly, the obtained product was immediately used in the next step.

R_f: desired: 0.53 (25:1 DCM:MeOH) undesired: 0.50

(2'*R*,3*R*,4*R*,9*R*,9a*S*,10*S*)-10-ethyl-4'-methyleneoctahydro-1H,3'H-spiro[9,3-ethanopyrrolo[1,2-*a*]azepine-11,2'-furan]-5'(4'*H*)-one (**385**)

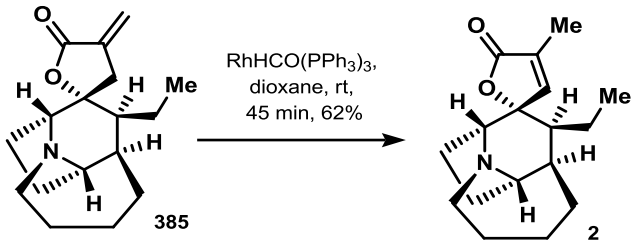


359 385

A stock solution (obtained *via* refluxing the two components in THF for 20 minutes) of Zn (9.4 mg, 144.3 µmol, 2.6 eq.) and ethyl 2-(bromomethyl)acrylate (13.9 mg, 72.1 µmol, 1.3 eq., in 1 mL THF) was added to neat ketone **359** (11.5 mg, 55.6 µmol, 1.0 eq), and the mixture was heated to reflux for one hour. After 40 minutes, another 0.2 mL of the stock solution was added. After one hour, the mixture was cooled to ambient temperature, and water was added. The mixture was stirred for one minute, followed by the addition of DCM. $MgSO_4$ was added, and the mixture was filtered. The solution was evaporated to dryness, and was purified *via* silica gel chromatography using 25:1 DCM:MeOH as eluent to yield 8.0 mg (52%) of **385** as a white semi-solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 6.32 (t, *J*=3.0 Hz, 1H), 5.76 (t, *J*=2.7 Hz, 1H), 4.39 (d, *J*=4.0 Hz, 1H), 4.25 (t, *J*=13.0 Hz, 1H), 4.08 (d, *J*=6.1 Hz, 1H), 3.85 (d, *J*=13.1 Hz, 1H), 2.97–2.83 (m, 2H), 2.78–2.73 (m, 2H), 2.34–2.25 (m, 1H), 2.17–2.14 (m, 2H), 2.04–1.95 (m, 3H), 1.87–1.76 (m, 4H), 1.69–1.66 (m, 1H), 1.49–1.41 (m, 1H), 1.38–1.30 (m, 1H), 0.94 (t, *J*=7.3 Hz, 3H) ppm. **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 168.4, 131.8, 124.0, 83.1, 67.4, 60.7, 47.6, 42.9, 38.6, 37.4, 25.3, 24.0, 23.8, 23.6, 21.5, 16.7, 11.6 ppm. **IR (neat sample):** 2920, 2882, 2849, 1769, 1717, 1458, 1396, 1267, 1167, 1119, 1076, 1059, 1030, 1003, 984, 908 cm^{-1}. **$[\alpha]_D^{20}$**: 20 (c= 0.13; $CHCl_3$). **R_f:** 0.39 (25:1 DCM:MeOH). **HRMS** (ESI, *m/z*): calc. for [$C_{17}H_{25}NO_2$+H]: 276.1964, found: 276.1962.

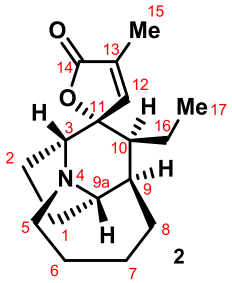
(+)-parvineostemonine **2**



Exo-metyhlene compound **385** (1.9 mg, 6.9 µmol, 1.0 eq) was put in a Schlenk flask and the flask was sparged with argon. A stock solution of $RhCOH(PPh_3)_3$ (3.2 mg, 3.4 µmol, 0.5 eq) in dioxane (1.0 mL) was then added, and the reaction mixture was stirred for 45 minutes. The solvent was removed under reduced pressure, and the remains were purified *via* column chromatography using (25:1 DCM:MeOH) as eluent to yield 1.2 mg (63%) of (+)-parvineosteomine **2** as a white solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 6.89 (d, *J*=1.6 Hz, 1H), 3.72 (br.s, 1H), 3.62 (br.s, 1H), 3.12 (br.s, 1H), 2.98 (br.s, 1H), 2.03–1.95 (m, 4H), 1.93 (d, *J*=1.1 Hz, 3H), 1.90–1.82 (m, 3H), 1.77–1.70 (m, 3H), 1.34–1.29 (m, 2H), 1.03 (br. s., 1H), 0.81 (t, *J*=7.8 Hz, 3H) ppm. Missing peak at 1.58–1.52 concealed by water can be seen in COSY. **^{13}C-NMR (125 MHz, $CDCl_3$):** δ = 132.2, 66.2, 57.0, 46.6, 38.4, 38.1, 29.6, 29.5, 25.8 (2C), 22.8, 17.2, 11.9, 10.8 ppm (signals missing due to bad signal to noise ratio). **IR (neat sample):** 2961, 2920, 2862 1751, 1734, 1717, 1653, 1558, 1541, 1506, 1456, 1248, 1153, 1136, 1088, 1070, 997 cm^{-1}. **MS:** calc. for $[C_1H_{25}NO_2+H]$: 276.1964, found: 276.1964. **$[\alpha]_D^{20}$**: 47 (c= 0.06; $CHCl_3$). **R_f:** 0.46 (25:1 DCM:MeOH).

Spectral Comparison of (+)-parvineostemonine



IR: (**[1] Y. Ye *et al.***) 1735, 1458, 1248 cm^{-1}. (**[2] J. Tu *et al.***) 2923, 1747, 997, 731 cm^{-1}. **(this work):** 2961, 2920, 2862 1751, 1734, 1717, 1653, 1558, 1541, 1506, 1456, 1248, 1153, 1136, 1088, 1070, 997 cm^{-1}.

^{1}H-NMR-data

Nr.	**Isolation:**[1] [ppm] (400 MHz, $CDCl_3$)	**Literature:**[2] Synthetic material [ppm] (400 MHz, $CDCl_3$)	**This work:** Synthetic material (500 MHz, $CDCl_3$)
1	1.55, m; 2.06, m	1.58–1.52 (m, 1H), 2.10–1.94 (m, 1H)	first peak visible in COSY, 2.03–1.95 (m, 1H)
2	1.67, m; 1.94, m	1.78–1.64 (m, 1 H), 2.10–1.94 (m, 1H)	1.74 (m, 1H), 2.03–1.95 (m, 1H)
3	2.97 (bd, *J* = 6.9)	2.99–2.97 (d, J=6.8 Hz, 1 H)	2.98 (m, 1H)
4	-	-	-
5	3.12, m; 3.61, m	3.15–3.11 (ddd, J=12.0, 3.2, 3.2 Hz, 1H), 3.66–3.59 (dt, J=12.8, 3.6 Hz, 1 H)	3.12 (m, 1H), 3.62 (m, 1H)
6	1.75, m; 1.89, m	1.78–1.64 (m, 1 H), 1.89–1.81 (m, 1H),	1.77–1.70 (m, 1H), 1.90–1.82 (m, 1H)
7	1.71, m; 2.02, m	1.78–1.64 (m, 1 H), 2.10–1.94 (m, 1H)	1.77–1.70 (m, 1H), 2.03–1.95 (m, 1H)
8	1.34, m; 1.87, m	1.39–1.23 (m, 1H), 1.89–1.81 (m, 3H),	1.34–1.29 (m, 1H), 1.90–1.82 (m, 1H)
9	1.81, m	1.89–1.81 (m, 1H)	1.90–1.82 (m, 1H)
9a	3.72 (bd, *J*=6.9)	3.73–3.72 (d, J=6.8 Hz, 1H),	3.72 (m, 1H)
10	1.98, m	2.10–1.94 (m, 1H)	2.03–1.95 (m, 1H)
11	-	-	-
12	6.88, (d, *J*=1.4)	6.88–6.87 (d, J=1.6 Hz, 1H)	6.89, (d, *J*=1.6, 1H)
13	-	-	-
14	-	-	-
15	1.92 (d, *J*=1.4)	1.92–1.91 (d, J=1.2 Hz, 3 H)	1.93 (d, *J*=1.1 Hz, 3H).
16	1.01, m; 1.26, m	1.04–0.98 (m, 1 H), 1.39–1.23 (m, 1H),	1.03 (br. s., 1H), 1.34–1.29 (m, 1H)
17	0.80 (t, *J* = 7.4)	0.82–0.78 ppm (t, J=7.2 Hz, 3H)	0.81 (t, *J*=7.8 Hz, 3H)

^{13}C-NMR-data:

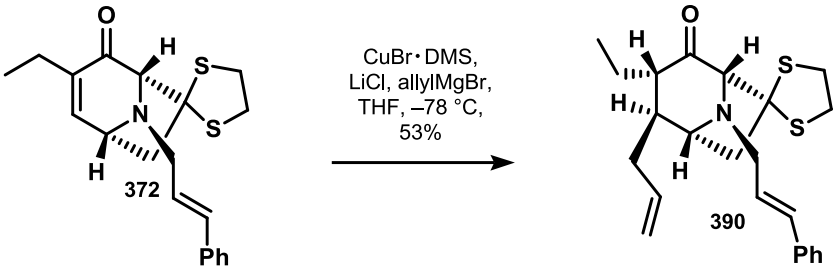
Nr.	**Isolation:**[1] [ppm] (100 MHz, $CDCl_3$)	**Literature:**[2] Synthetic material [ppm] (100 MHz, $CDCl_3$)	**This work:** Synthetic material (125 MHz, $CDCl_3$)
1	28.2	28.1	29.6
2	27.1	26.9	25.8
3	66.2	66.0	66.2
4	-	-	-
5	46.6	46.5	46.6
6	28.3	28.2	29.5
7	24.2	24.0	22.8
8	27.3	27.1	25.8
9	38.4	38.2	38.4
9a	57.0	56.9	57.0
10	38.1	37.9	38.1
11	89.6	89.4	to weak s/n
12	153.0	152.8	to weak s/n
13	130.6	130.6	132.2
14	174.2	174.0	to weak s/n
15	10.7	10.6	10.8
16	17.2	17.1	17.2
17	11.9	11.7	11.9

[1] Y. Ye *et al. Chinese Chemical Letters*, **2003**, *14*, 173–175.

[2] J. Tu *et al. Chem. Asian J.* **2012**, *7*, 2199–2202.

minor

(1*R*,2*S*,3*S*,5*R*)-2-allyl-8-cinnamyl-3-ethyl-8-azaspiro[bicyclo[3.2.1]octane-6,2'-[1,3]dithiolan]-4-one (**390**)

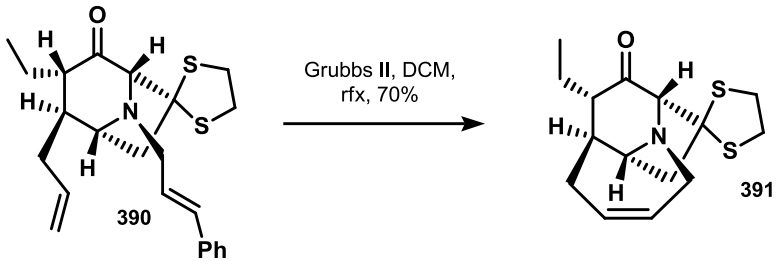


CuBr/DMS (103 mg, 502 µmol mmol, 1.0 eq.) was weighed out into a schlenk flask, which was then transferred to a glove box. LiCl (44 mg, 1.04 mmol, 2.0 eq.) was added to the schlenk flask, and the flask was then transferred out of the glove box. THF (6.5 mL) was added, and the resulting mixture was cooled to –78 °C. Allyl magnesiumbromide solution (0.94 mL of a 1.0 M solution in ethyl ether, 936 µmol, 1.8 eq.) was then added to the solution, followed by immediate dropwise addition of Michael acceptor **372** (167 mg, 468 µmol, 0.9 eq.). The solution was then allowed to stir for 10 minutes, before the addition of 2 M NaOH at –78 °C quenched the reaction. The mixture was allowed to stir for an hour at ambient temperature, before the mixture was transferred to a separation funnel. EtOAc was added, as well as neat NaCl, and the aqueous phase was extracted three times with EtOAc. The combined organic layers were then washed with brine, followed by drying over $MgSO_4$. The solvent was removed under reduced pressure, and the obtained crude oil was purified *via* silica flash chromatography using 10:1 PE:EtOAc as eluent to yield 98.6 mg (53%) of **390** as a clear oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.40–7.35 (m, 2H), 7.31 (t, *J*=7.5 Hz, 2H), 7.26–7.19 (m, 1H), 6.55 (d, *J*=16.0 Hz, 1H), 6.18 (dt, *J*=15.7, 6.5 Hz, 1H), 5.73 (dddd, *J*=16.8, 10.4, 8.1, 6.0 Hz, 1H), 5.03–4.90 (m, 2H), 3.80–3.77 (m, 1H), 3.65–3.57 (m, 1H), 3.54–3.43 (m, 3H), 3.36–3.28 (m, 3H), 2.98 (dd, *J*=14.9, 7.3 Hz, 1H), 2.28–2.12 (m, 3H), 2.06 (q, *J*=6.0 Hz, 1H), 1.86–1.74 (m, 1H), 1.73–1.60 (m, 1H), 1.39 (dt, *J*=8.1, 5.9 Hz, 1H), 1.01 (t, *J*=7.5 Hz, 3H) ppm. **^{13}C-NMR (100 MHz, $CDCl_3$):** δ= 207.1, 137.0, 136.3, 133.0, 128.7 (2C), 127.6, 127.3, 126.4 (2C), 117.6, 84.7, 67.9, 62.4, 55.4, 49.9, 46.8, 43.1, 40.5, 40.4, 39.9, 25.0, 12.7 ppm. **IR (neat sample):** 2961,

2928, 1713, 1449, 1375, 1250, 1194, 1113, 1061, 968, 917 cm^{-1}. **$[\alpha]_D^{20}$**: -16 (c= 0.14; $CDCl_3$). **R_f:** 0.29 (10:1 PE:EtOAc). **HRMS** (ESI, *m/z*): calc. for [$C_{23}H_{29}NOS_2$+H]: 400.1769, found: 400.1766.

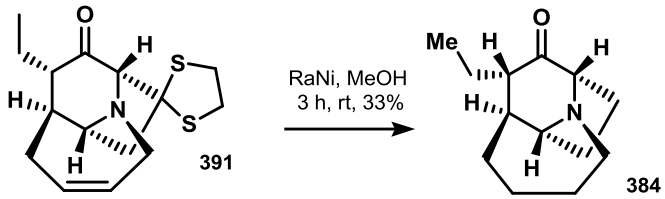
(3*R*,4*S*,9*S*,9a*R*,10*S*)-10-ethyl-1,3,5,8,9,9a-hexahydrospiro[9,3-ethanopyrrolo[1,2-*a*]azepine-2,2'-[1,3]dithiolan]-11-one (**391**)



Bisolefin **390** (100.0 mg, 250 µmol, 1.0 eq) was dissolved in degassed DCM (15 mL) and Grubbs II catalyst (21.0 mg, 25.0 µmol, 0.1 eq) was added in DCM (10 mL). The reaction mixture was heated to reflux for 5.5 hours. The solvent was then evaporated and the crude remains were subjected to flash column chromatography using 10:1 to 7:1 PE:EtOAc to as eluent to give 52.0 mg (70%) of olefin **391** as a clear oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.75–5.62 (m, 2H), 3.89 (d, *J*=17.1 Hz, 1H), 3.63 (dd, *J*=17.1, 5.8 Hz, 1H), 3.55 (d, *J*=7.2 Hz, 1H), 3.43–3.31 (m, 2H), 3.31–3.21 (m, 2H), 3.19–3.10 (m, 1H), 2.98 (dd, *J*=14.7, 7.9 Hz, 1H), 2.45 (d, *J*=15.0 Hz, 1H), 2.39–2.35 (m, 1H), 2.31–2.27 (m, 1H), 2.25–2.20 (m, 1H), 2.00–1.83 (m, 2H), 1.73–1.62 (m, 1H), 1.02 (t, *J*=7.0 Hz, 3H) ppm. **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 212.9, 130.7 (2C), 82.8, 69.2, 62.2, 53.2, 48.8, 47.0, 43.4, 40.5, 39.1, 36.2, 30.4, 13.1 ppm. **IR** (neat sample)**:** 2959, 2922, 2874, 1695, 1456, 1437, 1425, 1319, 1279, 1184, 1163, 1128, 976, 818 cm^{-1}. **$[\alpha]_D^{20}$**: 106 (c= 0.11; $CHCl_3$). **R_f:** 0.23 (10:1 PE:EtOAc). **HRMS** (ESI, *m/z*): calc. for [$C_{15}H_{21}NOS_2$+H]: 296.1143, found: 296.1141.

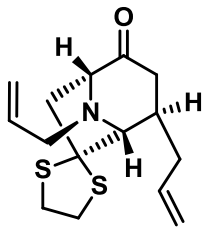
(3*S*,4*S*,9*S*,9a*R*,10*S*)-10-ethyloctahydro-1H-9,3-ethanopyrrolo[1,2-a]azepin-11-one (**384**)



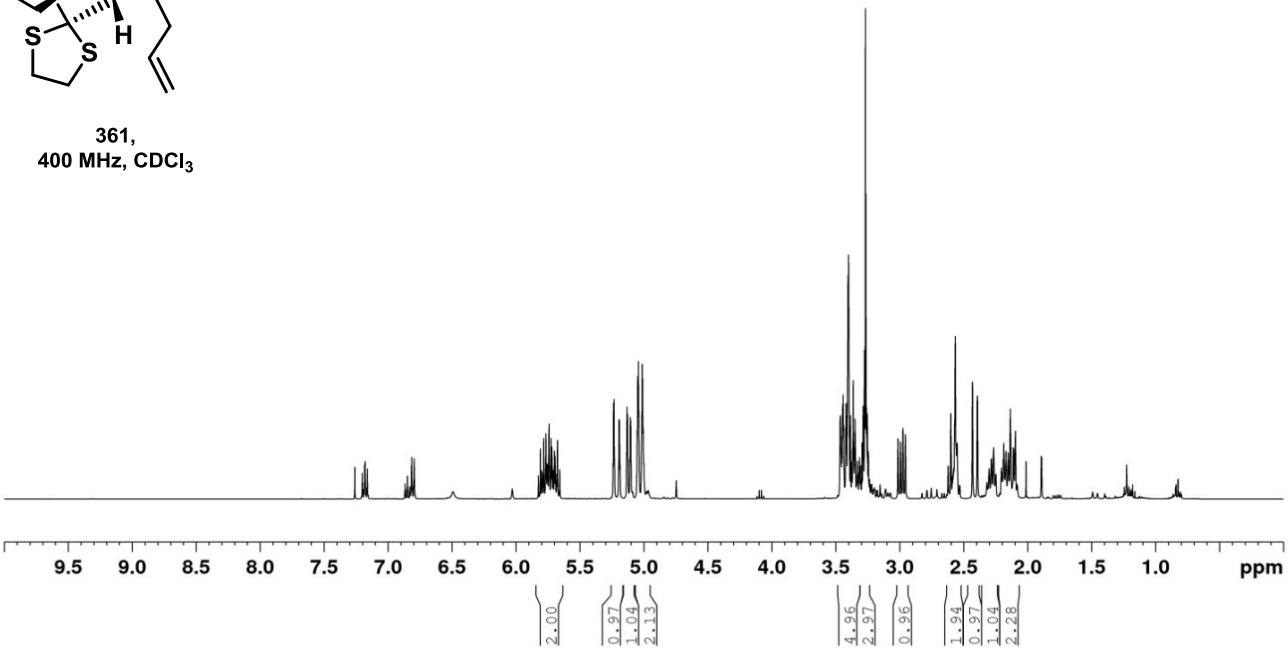
An aqueous dispersion of Raney nickel in water (3 pipets) was washed 3 three times with MeOH, and the waste solvent was discarded. Dithiolane **391** (30 mg, 101 µmol mmol, 1.0 eq) was added in MeOH (1 mL), and the reaction mixture was stirred for 3 h at ambient temperature. Raney nickel was then filtered off, and the solvent was removed under reduced pressure. The crude oil was subjected to flash column chromatography using 25:1 DCM:MeOH as eluent to give 7.0 mg (33%) of amine **384** as a clear oil.

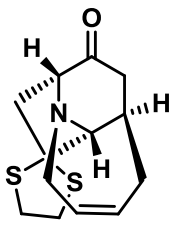
$[\alpha]_D^{20}$: 129 (c= 0.10; $CHCl_3$). For more data see the enantiomer at pages 150–151.

3.11 Spectra

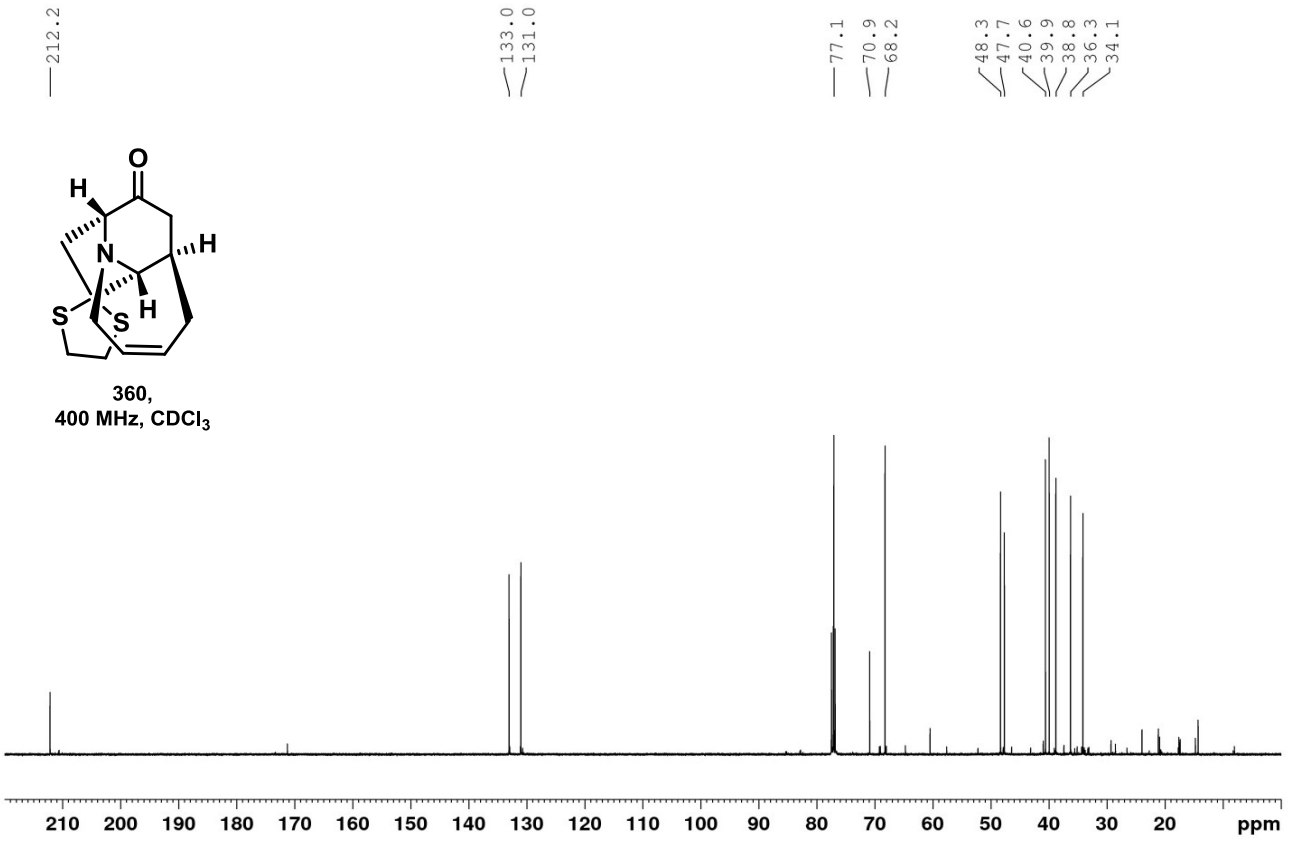


361,
400 MHz, $CDCl_3$

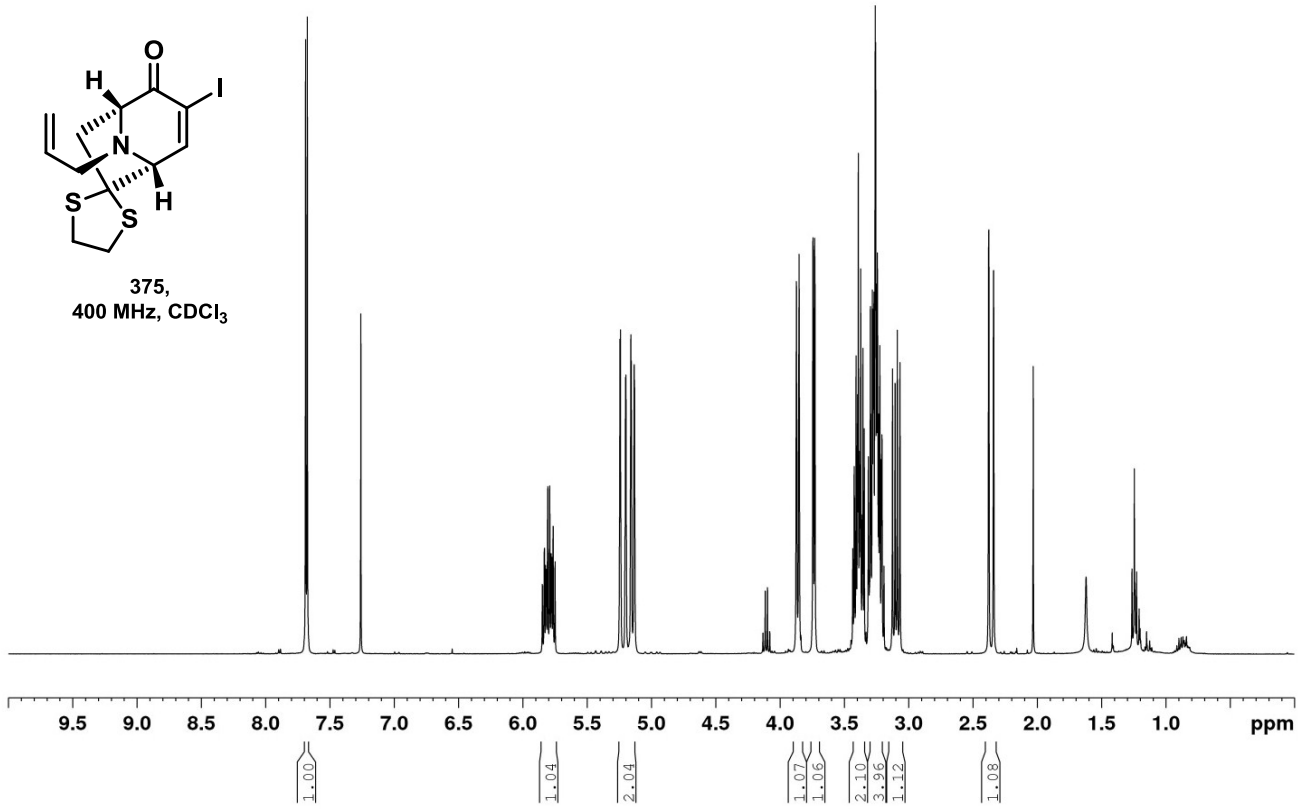




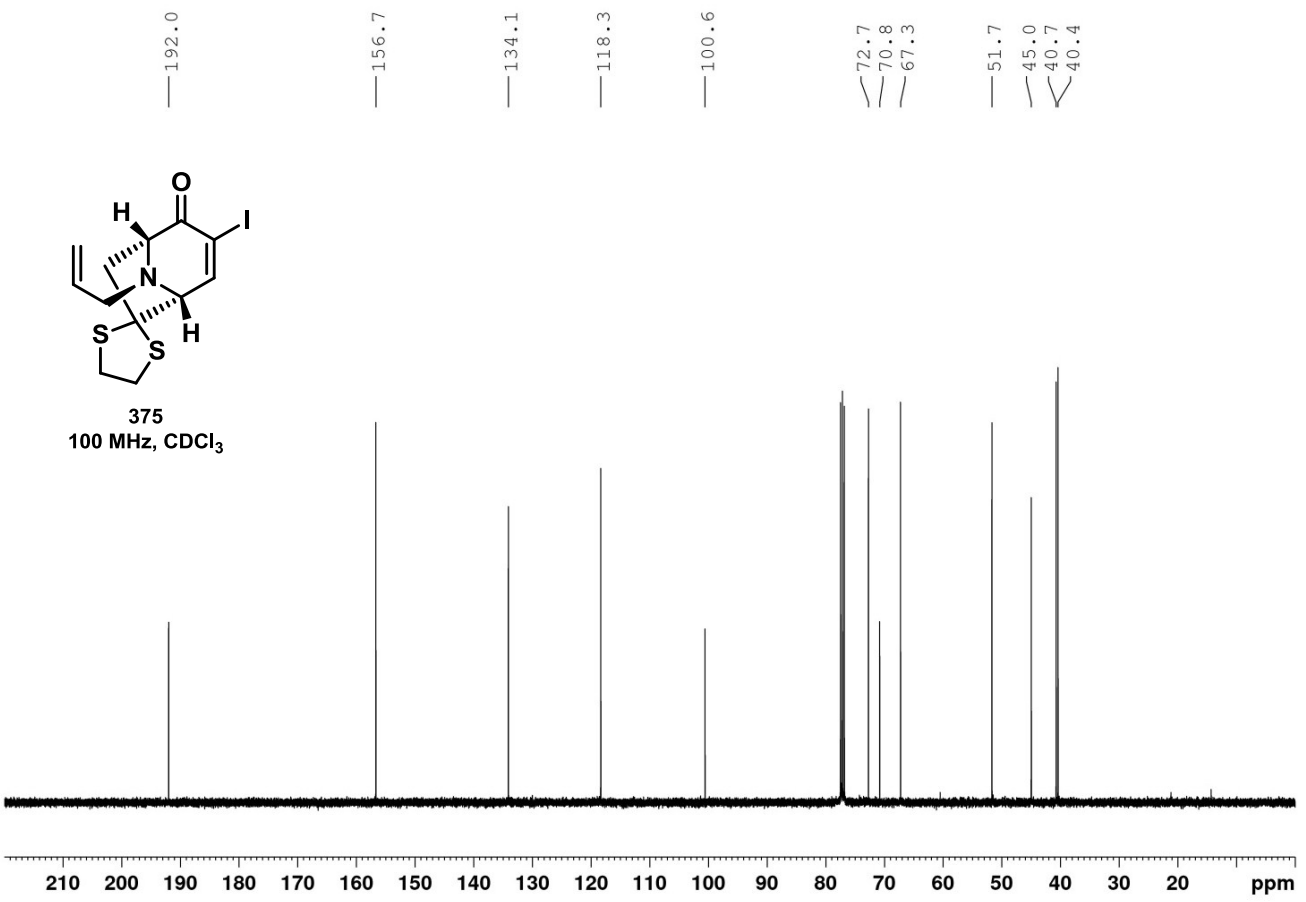
360,
400 MHz, $CDCl_3$



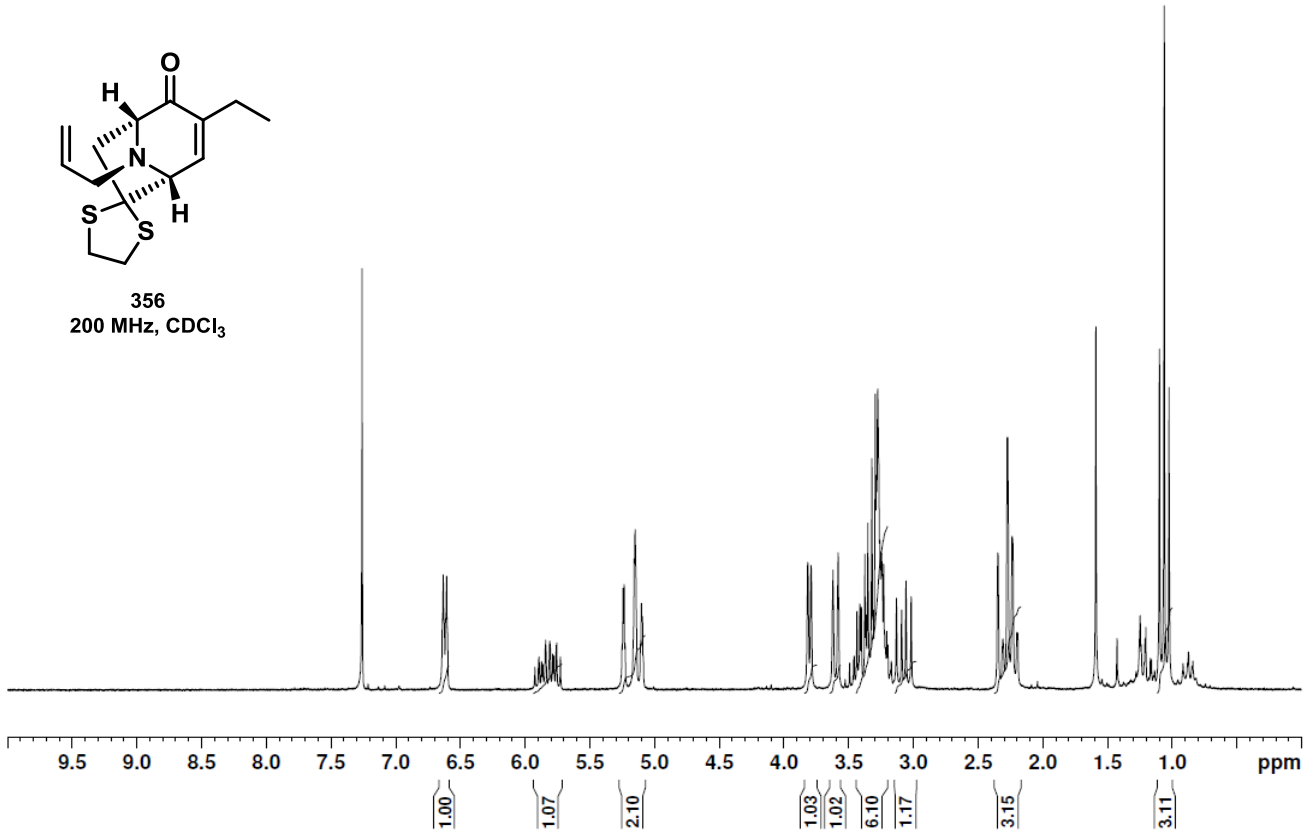
360,
400 MHz, $CDCl_3$



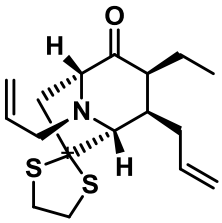
375,
400 MHz, $CDCl_3$



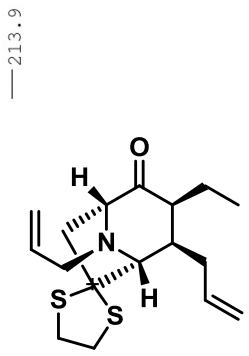
375
100 MHz, $CDCl_3$



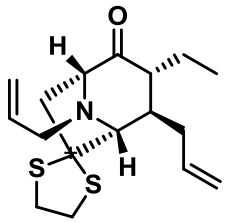
356
200 MHz, $CDCl_3$



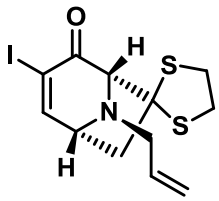
364,
400 MHz, $CDCl_3$



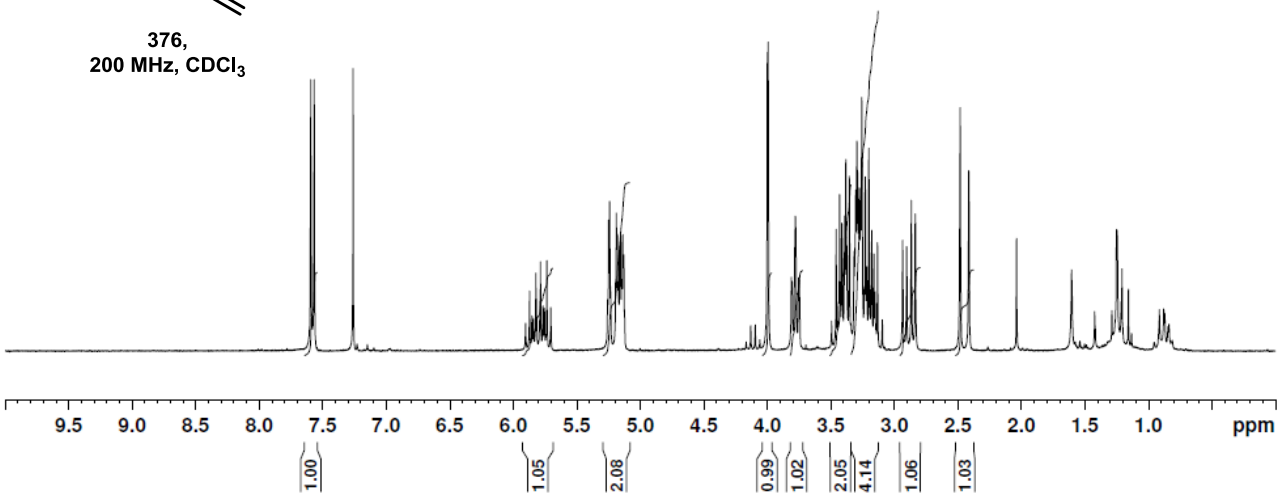
364
100 MHz, $CDCl_3$

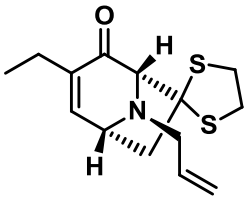


377,
400 MHz, $CDCl_3$

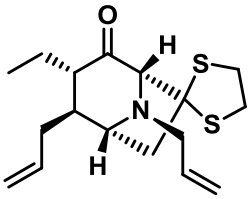


376,
200 MHz, $CDCl_3$

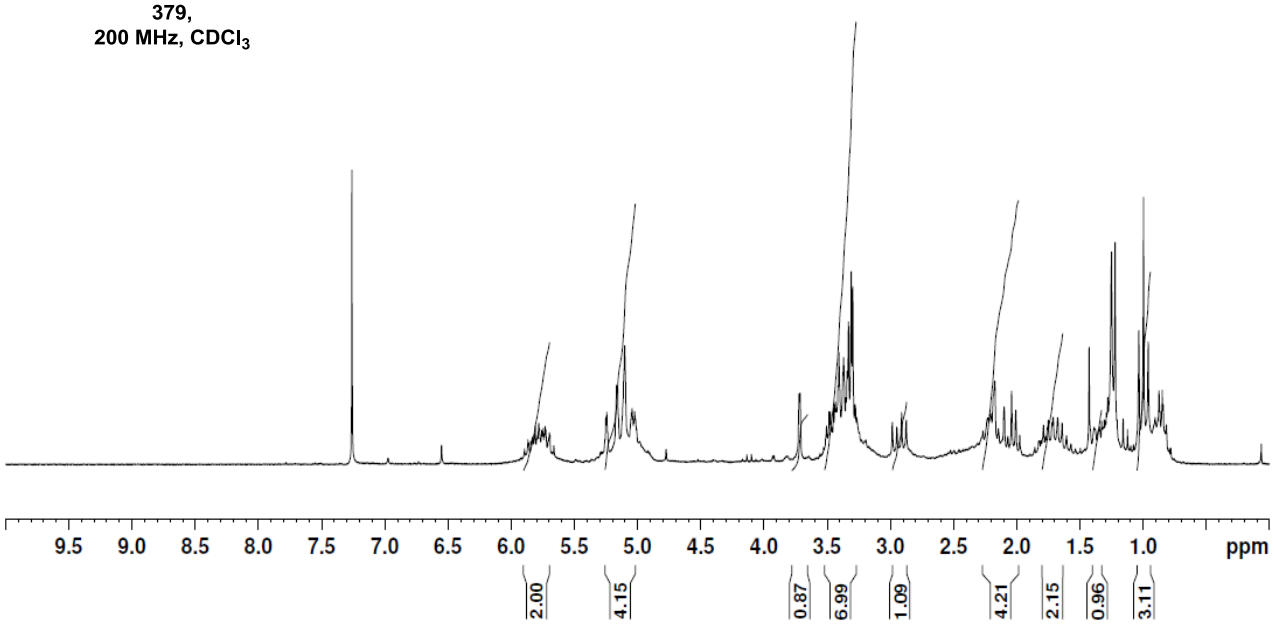


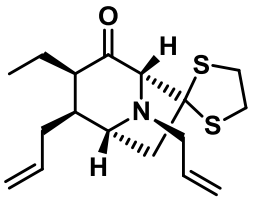


367,
200 MHz, $CDCl_3$

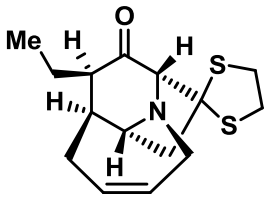


379,
200 MHz, $CDCl_3$

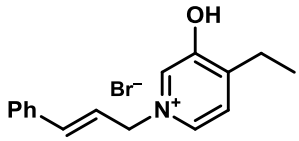




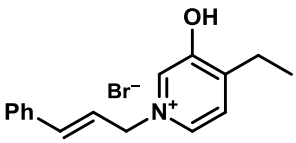
366,
200 MHz, $CDCl_3$



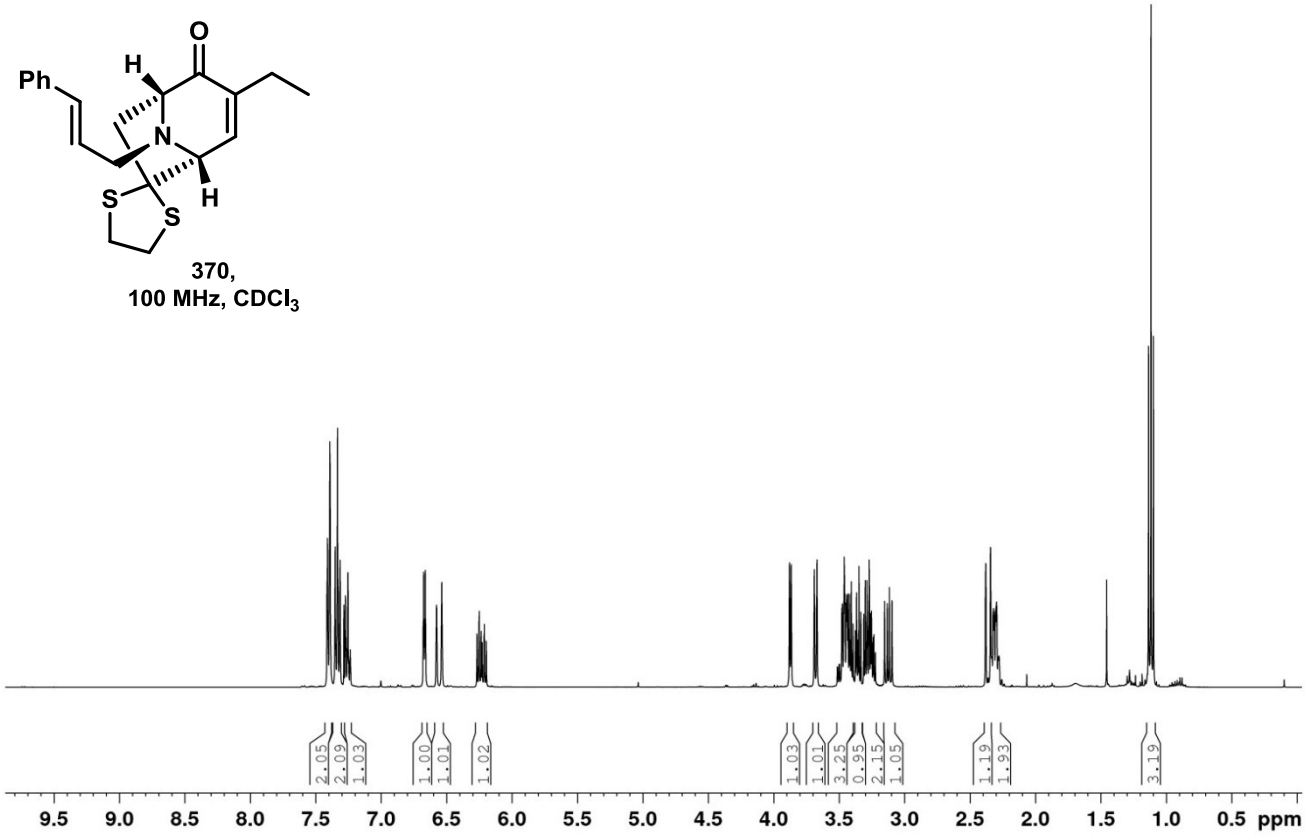
380,
400 MHz in $CDCl_3$



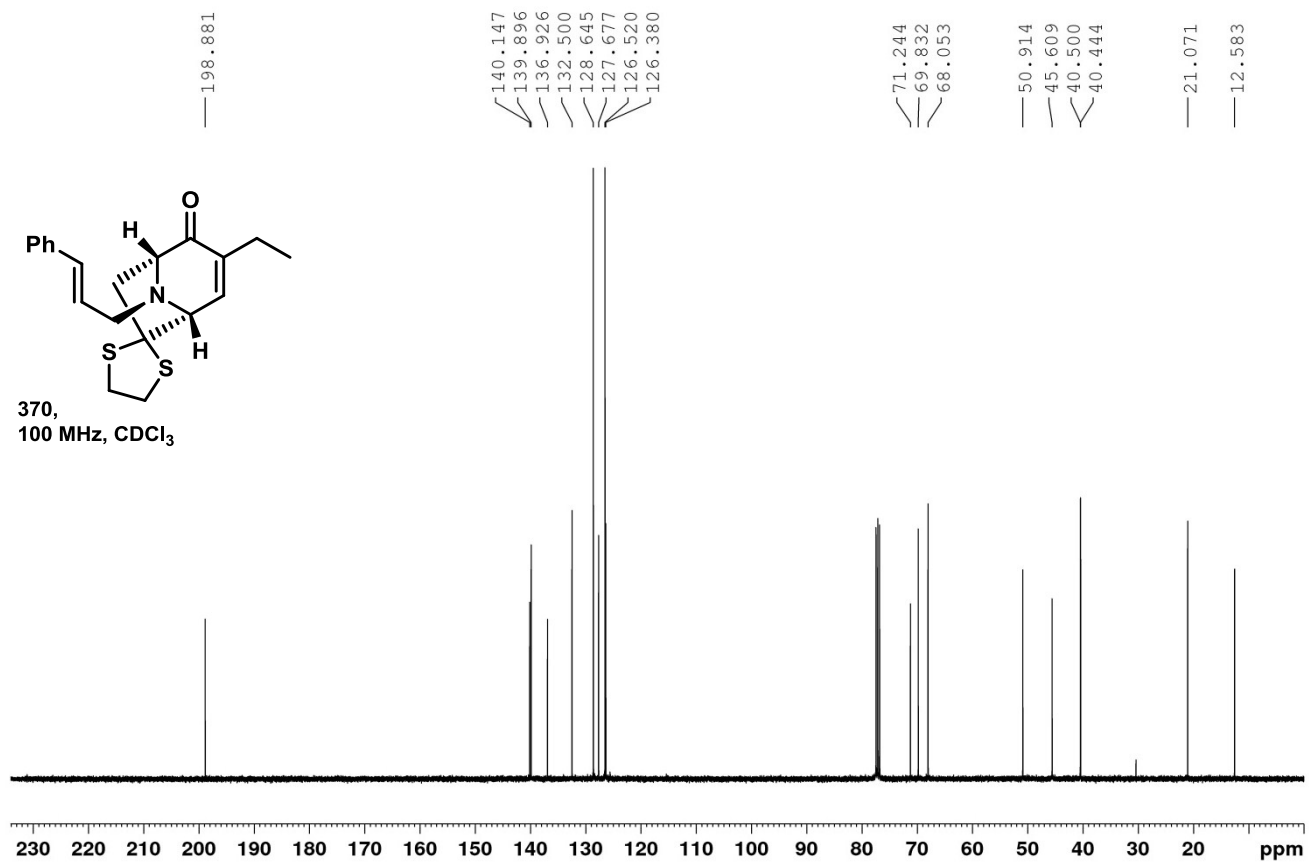
400 MHz, MeOD-d_4



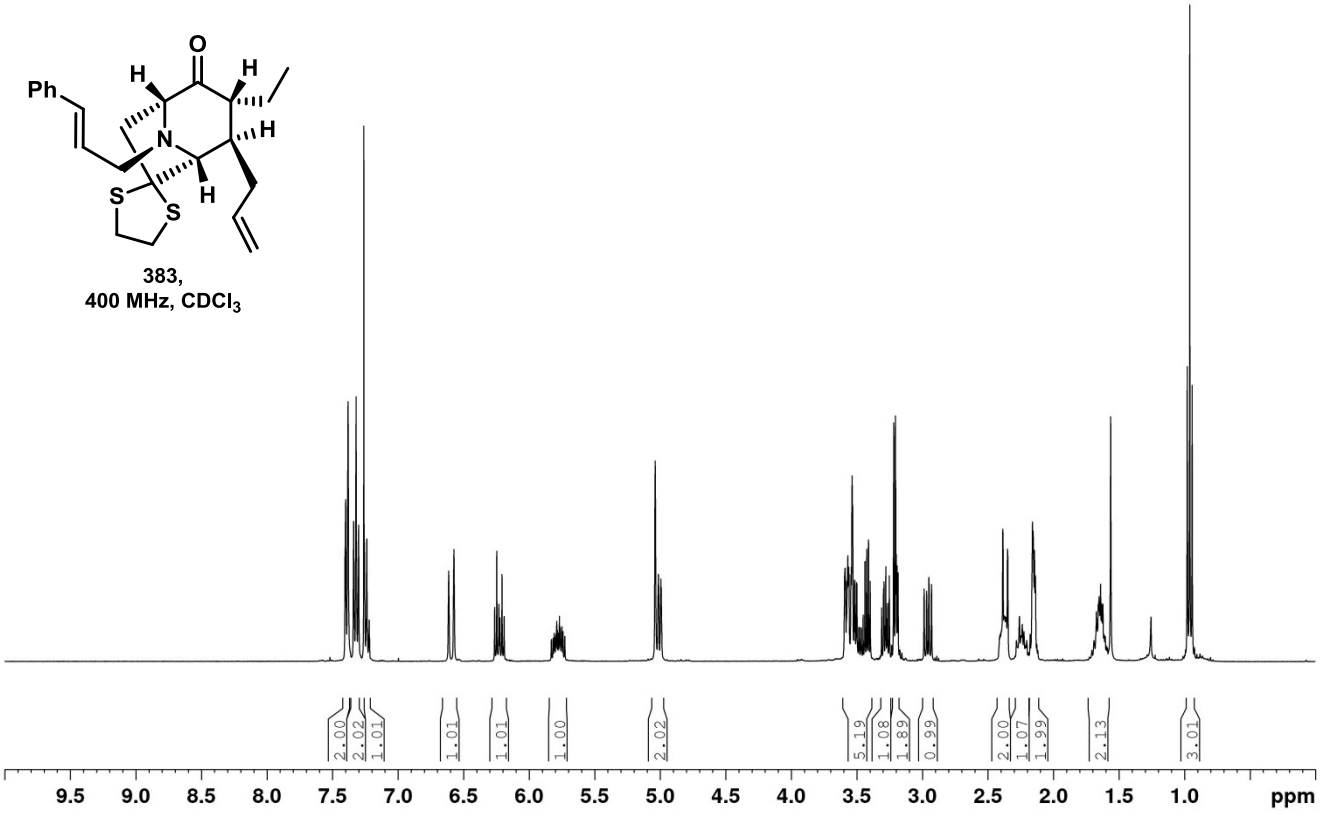
100 MHz, MeOD-d_4



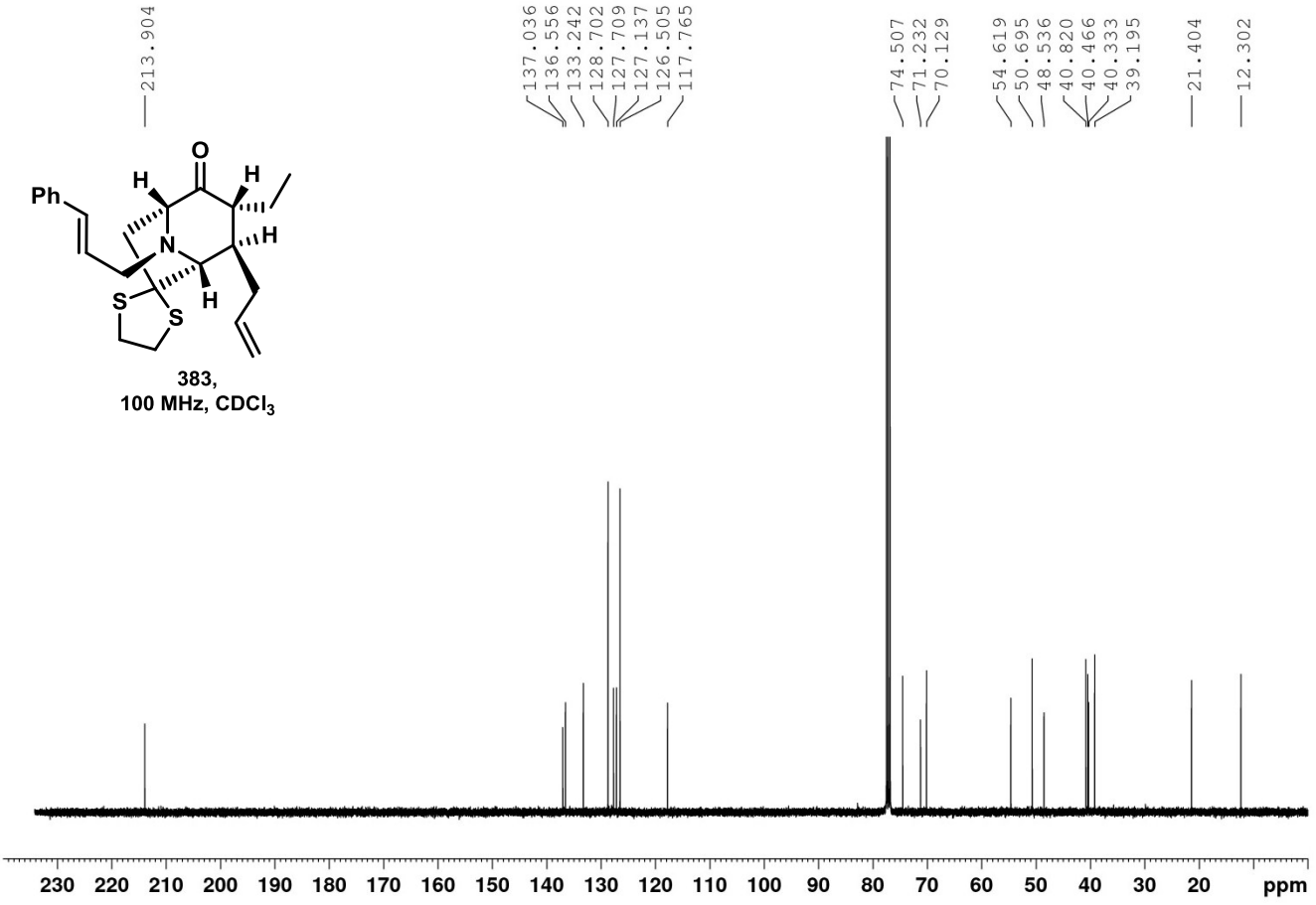
370,
100 MHz, $CDCl_3$



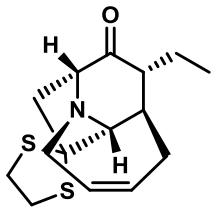
370,
100 MHz, $CDCl_3$



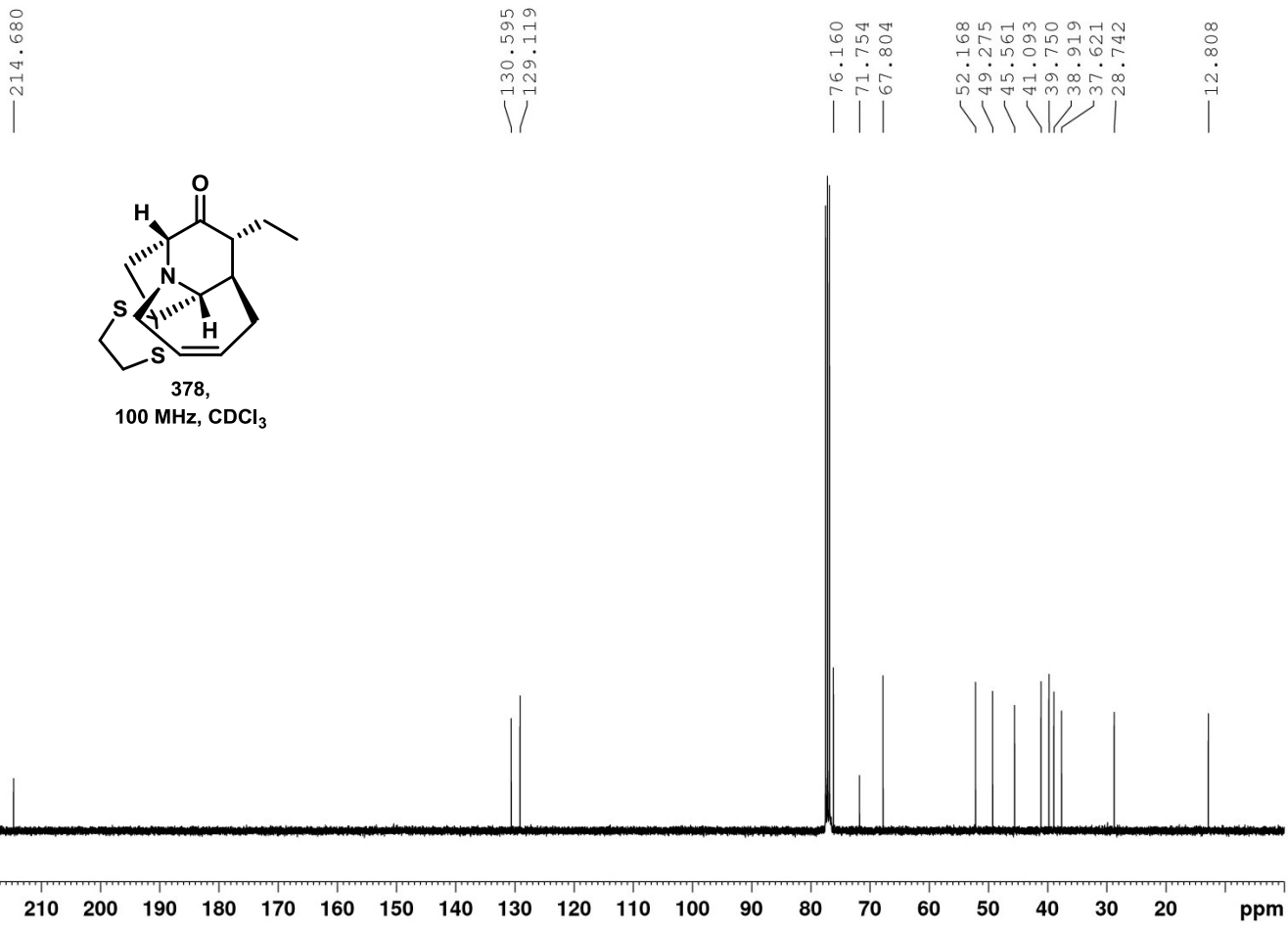
383,
400 MHz, $CDCl_3$



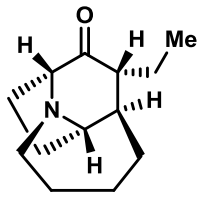
383,
100 MHz, $CDCl_3$



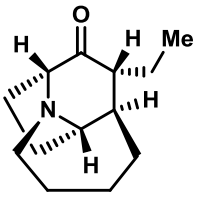
378,
400 MHz, $CDCl_3$



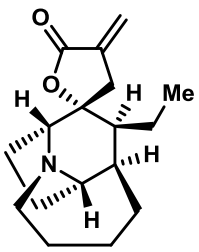
378,
100 MHz, $CDCl_3$



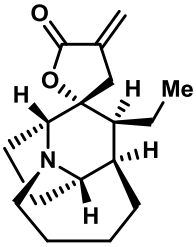
384,
400 MHz, $CDCl_3$



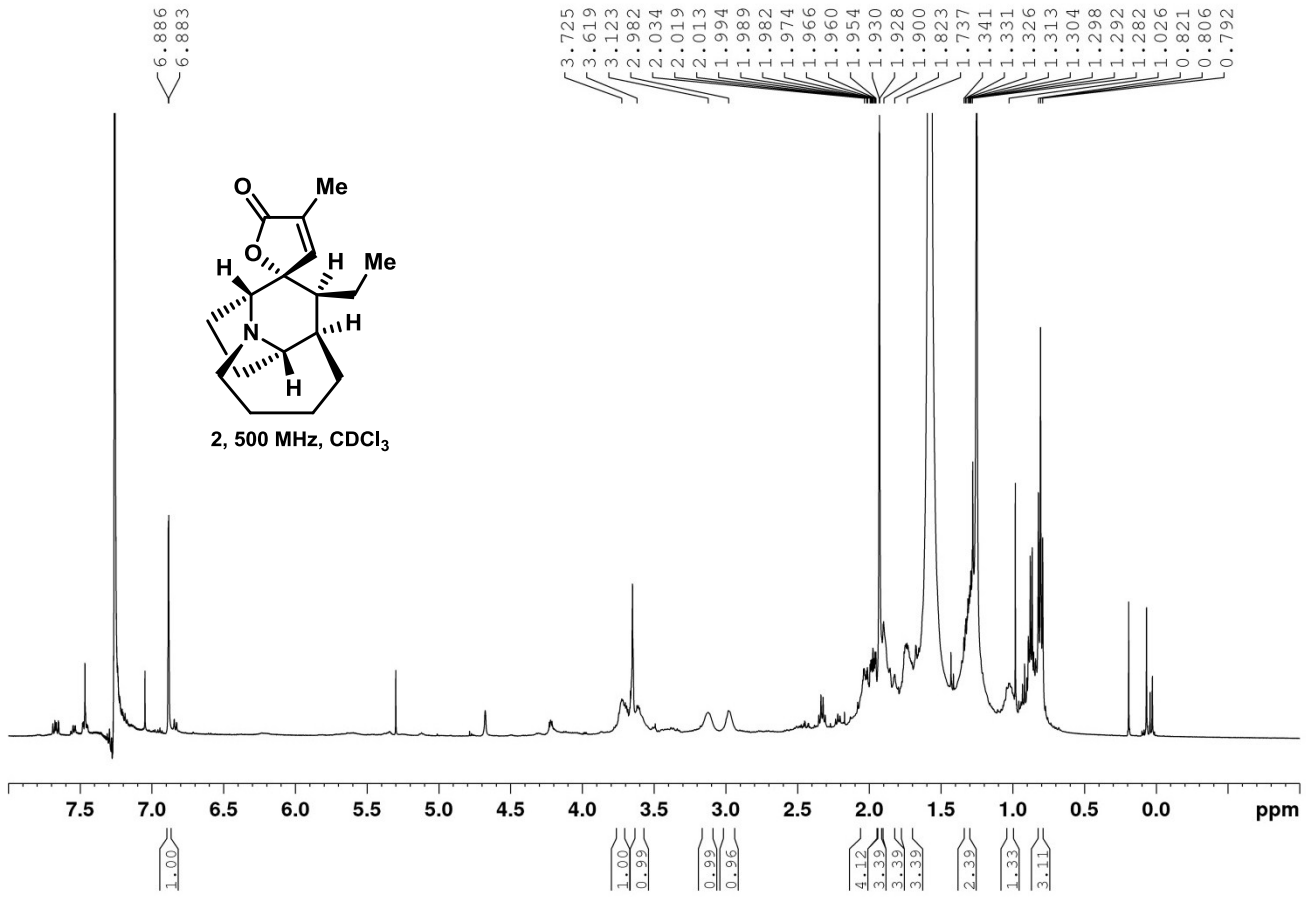
100 MHz, $CDCl_3$



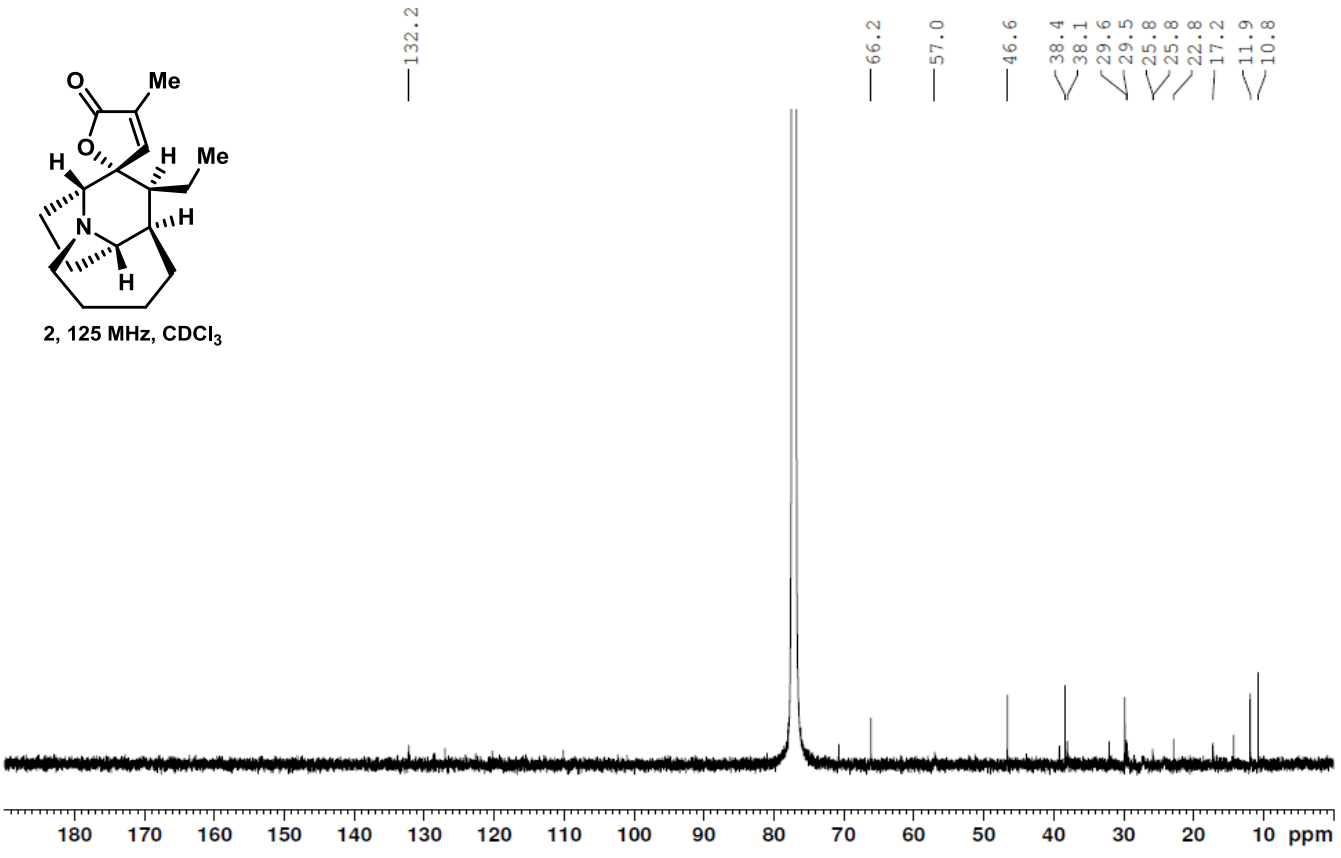
385,
400 MHz, $CDCl_3$



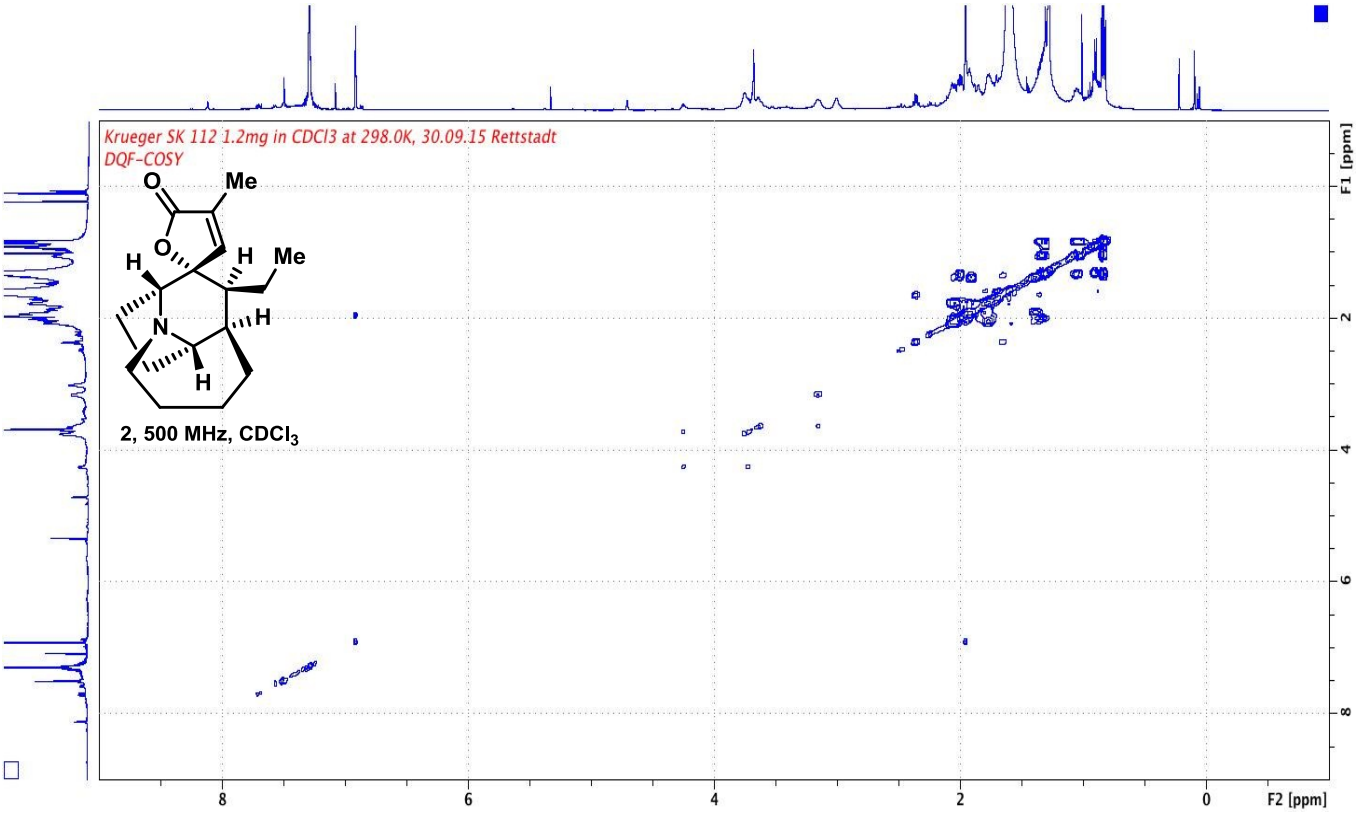
385,
100 MHz, $CDCl_3$

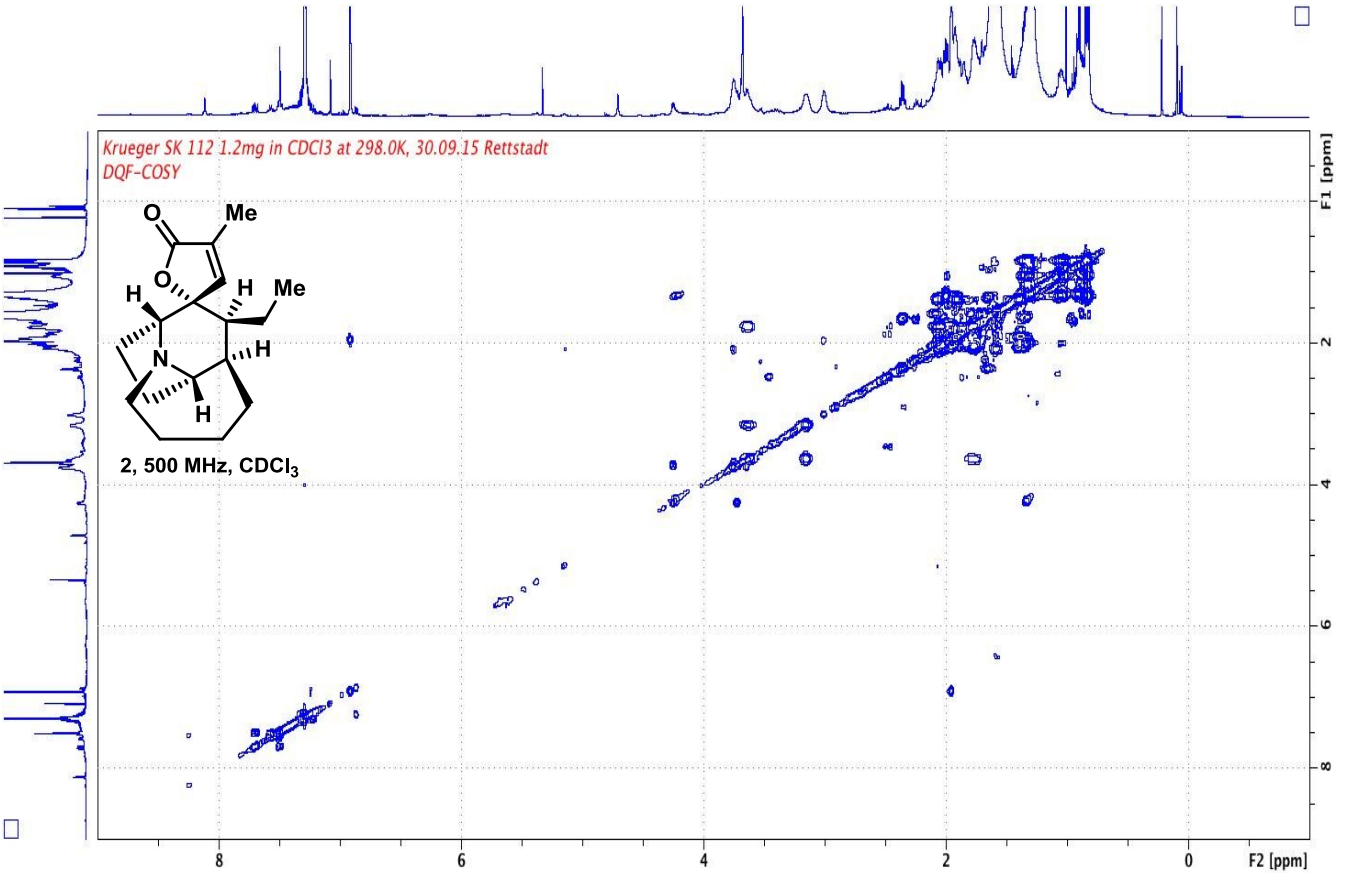


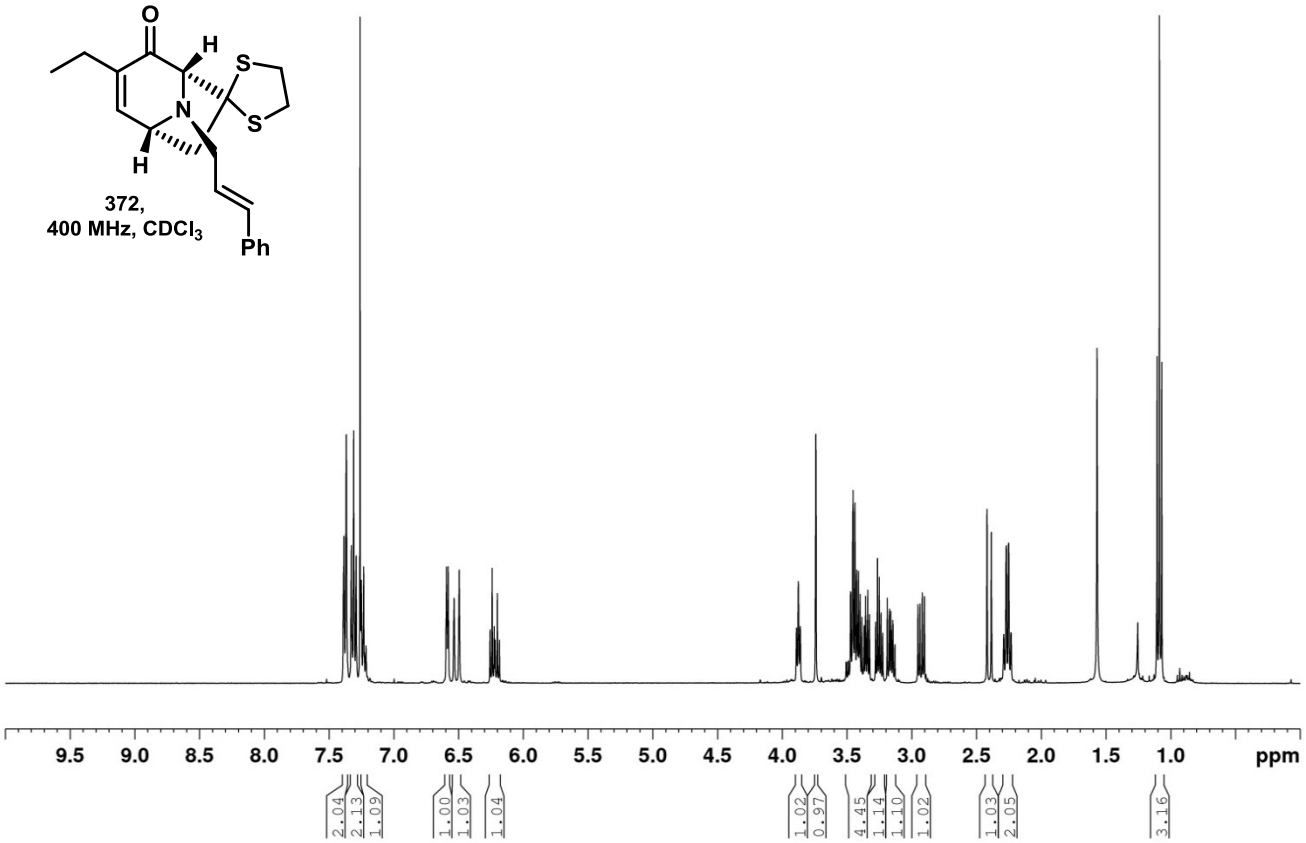
2, 500 MHz, $CDCl_3$

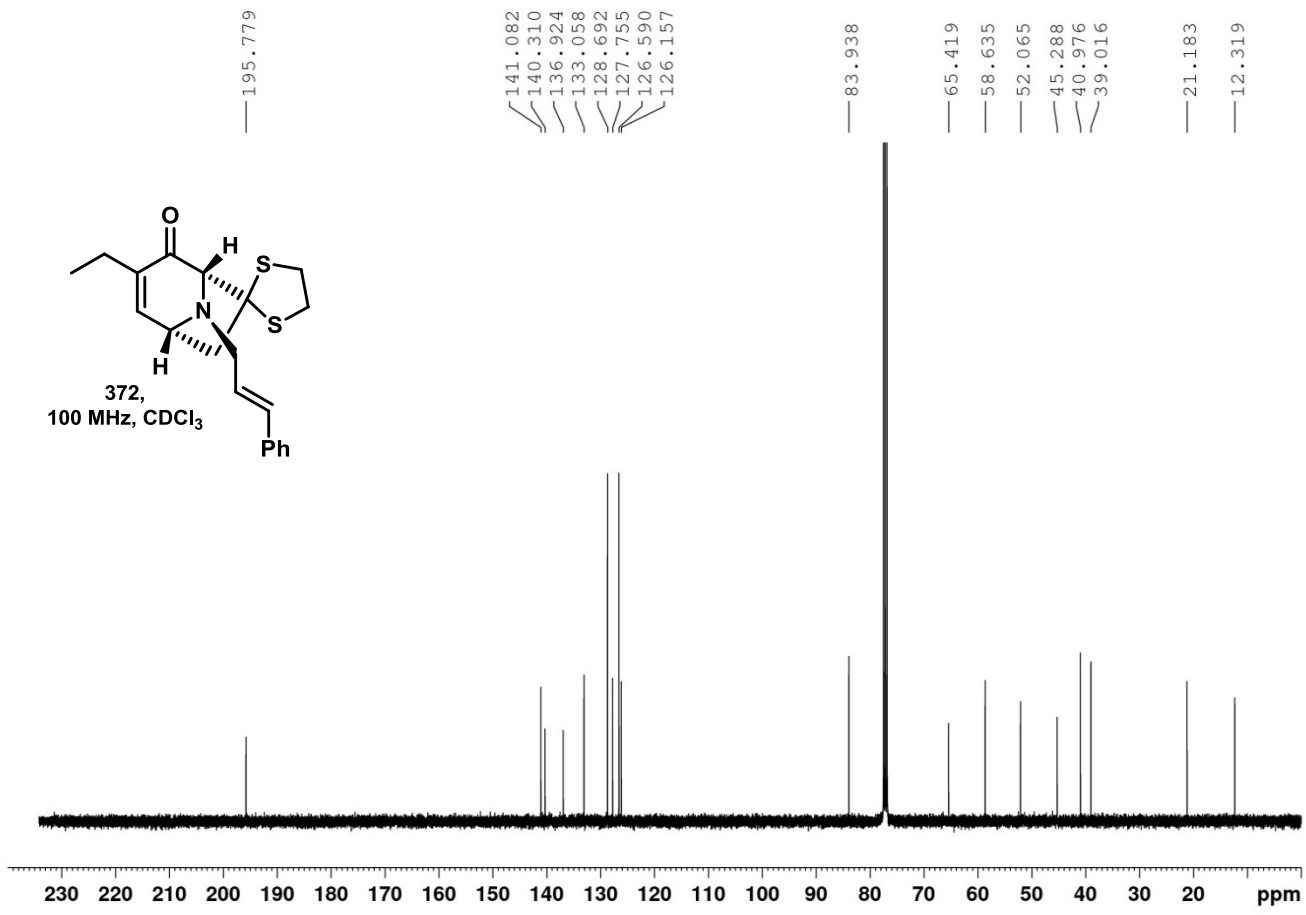


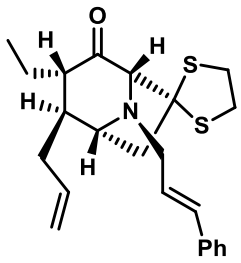
2, 125 MHz, $CDCl_3$


Krueger SK 112 1.2mg in CDCl3 at 298.0K, 30.09.15 Rettstadt
DQF-COSY
O
Me
O
H
H
Me
N
H
H
2, 500 MHz, CDCl3
F1 [ppm]
F2 [ppm]
8
6
4
2
0

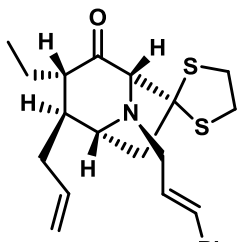

Krueger SK 112 1.2mg in CDCl3 at 298.0K, 30.09.15 Rettstadt
DQF-COSY
O
Me
O
H
H
Me
N
H
H
2, 500 MHz, CDCl3
F1 [ppm]
F2 [ppm]
8
6
4
2
0


O
H
S
N
S
H
Ph
372,
400 MHz, CDCl3
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
2.04 2.13 1.09 1.00 1.03 1.04 1.02 0.97 4.45 1.14 1.10 1.02 1.03 2.05 3.16

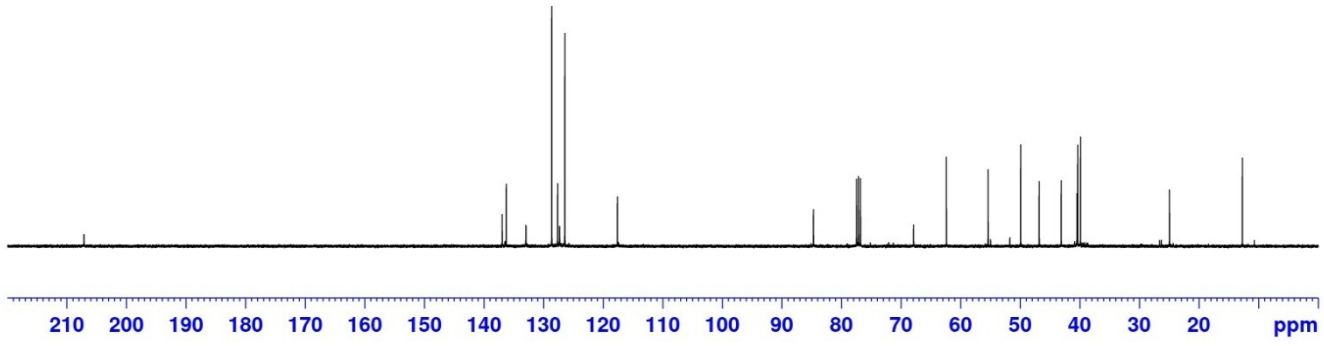

195.779
141.082
140.310
136.924
133.058
128.692
127.755
126.590
126.157
83.938
65.419
58.635
52.065
45.288
40.976
39.016
21.183
12.319
O
H
S
N
S
H
Ph
372,
100 MHz, CDCl3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

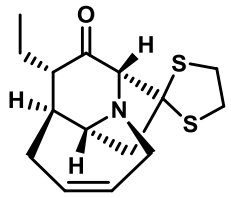


390,
400 MHz, $CDCl_3$

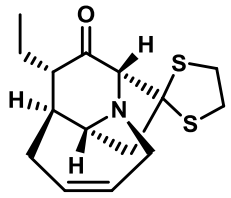


390,
100 MHz, $CDCl_3$





391,
400 MHz, $CDCl_3$



391,
100 MHz, $CDCl_3$

3.12 References

[3.1] C. Q. Ke, Z. S. He, Y. P. Yang, Y. Ye, *Chin. Chem. Lett.* **2003**, *14*, 173–175.

[3.2] R. A. Pilli, G. B. Rosso, M. da Conceicao F. de Oliveira, *"The Stemona Alkaloids"*, in: *The Alkaloids*, Vol. 62, Ed.: G. A. Cordell, Academic Press, San Diego, **2005**, 77–173.

[3.3] F.-P. Wang, Q.-H. Chen, *Natural Product Communications*, **2014**, *9*, 1809–1822.

[3.4] C. Seger, K. Mereiter, E. Kaltenegger, T. Pacher, H. Greger, O. Hofer, *Chemistry&Bio-diversity*, **2004**, *1*, 265–279.

[3.5] H. Greger, K. Schinner, S. Vajrodaya, L. Brecker, O. Hofer, *J. Nat. Prod*. **2009**, *72*, 1708–1711.

[3.6] P. Mungkorsawakul, H. Mattews, A. T. Ung, S. G. Pyne, A. Jatisatienr, W. Lie, B. W. Skelton, A. H. White, *ACGC Chemical Research Communications*, **2005**, *19*, 30–33.

[3.7] S. G. Pyne, A. T. Ung, A. Jatisatienr, P. Mungkorsawakul, *Maejo International Journal of Science and Technology*, **2007**, *1*, 157–165.

[3.8] Z.-H. Chen, J.-M. Tian, Z.-M. Chen, Y.-Q. Tu, *Chem. Asian J.* **2012**, *7*, 2199–2202.

[3.9] J. E. Antoline, R. P. Hsung, J. Huang, Z. Song, G. Li, *Org. Lett.* **2007**, *9*, 1275–1278.

[3.10] H. Shinozaki, M. Ishida, *Brain Res*. **1985**, *334*, 33–40.

[3.11] B. Brem, C. Seger, T. Pacher, O. Hofer, S. Vajrodaya, G. Greger, *J. Agric. Food Chem*. **2002**, *50*, 6383–6388.

[3.12] S. Jiwajinda, N. Hirai, K. Watanabe, V. Satisopasri, N. Chuensamarnyart, K. Koshimizu, H. Ohigashi, *Phytochemistry*, **2002**, *56*, 693–695.

[3.13] E. Kaltenegger, B. Brem, K. Mereiter, H. Kalchauser, H. Kählig, O. Hofer, S. Vajrodaya, H. Greger, *Phytochemistry*, **2003**, *63*, 803–816.

[3.14] K. Sakata, A. Aoki, C.-F. Chang, A. Sakurai, S. Tamura, S. Murakoshi, *Agric. Biol. Chem*. **1978**, *42*, 457–463.

[3.15] P. Mungkornasawakul, S. G. Pyne, A. Jatisatienr, D. Supyen, C. Jatisatienr, W. Lie, A. T. Ung, B. W. Skelton, A. H. White, *J. Nat. Prod*. **2004**, *67*, 675–677.

[3.16] H.-S. Chung, P.-M. Ho, G. Lin, P.P.-H. But, H. Dong, *Planta Med*. **2003**, *69*, 914–920.

[3.17] B. Rinner, V. Siegl, P. Pürstner, T. Efferth, B. Brem, H. Greger, R. Pfragner, *Anticancer Res*. **2004**, *24*, 495–500.

[3.18] D. D. Caspi, "Recent Advances in Enantiodivergent Strategies", https://www.organicdivision.org/ama/orig/Fellowship/2005_2006_Awardees/Essays/Caspi.pdf

[3.19] N. K. Garg, D. D. Caspi, B. M. Stoltz, *J. Am. Chem. Soc.* **2005**, *127*, 5970–5978.

[3.20] M. E. Fox, C. Li, J. P. Marino, L. E. Overman, *J. Am. Chem. Soc.* **1999**, *121*, 5467–5480.

[3.21] S. Krüger, T. Gaich, *Beilstein J. Org. Chem.* **2014**, *10*, 163–193.

[3.22] K. Nakata,T. Tokumaru, H. Iwamoto, Y. Nishigaichi, I. Shiina, Asian *J. Org. Chem.* **2013**, *2*, 920–922.

[3.23] S. Takano, M. Moriya, K. Ogasawara, *J. Chem. Soc. Chem. Commun.* **1993**, 614–615.

[3.24] T. Hudlicky, J. **D.** Price, F. Rulin, T. Tsunoda, *J. Am. Chem. Soc.* **1990,** *112,* 9439–9440.

[3.25] F. J. Sardina, M. H. Howard, M. Morningstar, H. Rapoport, *J. Org. Chem.* **1990**, *55*, 5025–5033.

[3.26] P. Wipf, S. R. Rector, H. Takahash, *J. Am. Chem. Soc.* **2002**, *124*, 14848–14849.

[3.27] W. Janse van Rensburg, P. J. Steynberg, W. H. Meyer, M. M. Kirk, G. S. Forman, *J. Am. Chem. Soc.* **2004**, *126*, 14332–14333.

[3.28] B. Alcaide, P. Almendros, J. M. Alonso, M. F. Aly, *Org. Lett*. **2001**, *3*, 3781–3784.

[3.29] A. P. Kozikowski, G. L. Araldi, R. G. Ball, *J. Org. Chem.* **1997**, *62*, 503–509.

[3.30] D. L. Commins, E. D. Stroud, *J. Heterocyclic Chem.* **1985**, *22*, 1419–1420.

[3.31] B. H. Lipshutz, C. Hackmann *J. Org. Chem.* **1994**, *59*, 7437–7444.

[3.32] M. E. Krafft J. W. Cran, *Synlett*, **2005**, *8*, 1263–1266.

[3.33] F. Frébault, M. T. Oliveira, E. Wöstefeld, N. Maulide et al, *J. Org. Chem.*, **2010**, *75*, 7962–7965.

[3.34] A. Hosomi, H. Sakurai, *J. Am. Chem. Soc.* **1977**, *99,* 1673–1675.

[3.35] E. Öhler, K. Reininger, U. Schmidt, *Angew. Chem. Int. Ed*. **1970**, *6*, 457–458

[3.36] T. F. Murray, E. G. Samsel, V. Varma, J. R. Norton, *J. Am. Chem. Soc.* **1981,** *103,* 7520-7528.

[3.37] P. Grieco, M. Ni shizawa, N. Marinovic, W. J. Ehmann, *J. Am. Chem. Soc*. **1976**, *98*, 7102 – 7104.

[3.38] Y.-A. Zhang, Q. liu, C. Wang, Y. Jia, *Org. Lett*. **2013**, *15*, 3662–3665.

[3.39] J. Rebek, Y. K. Shue, *J. Am. Chem. Soc*. **1980**, *102*,5426–5427.

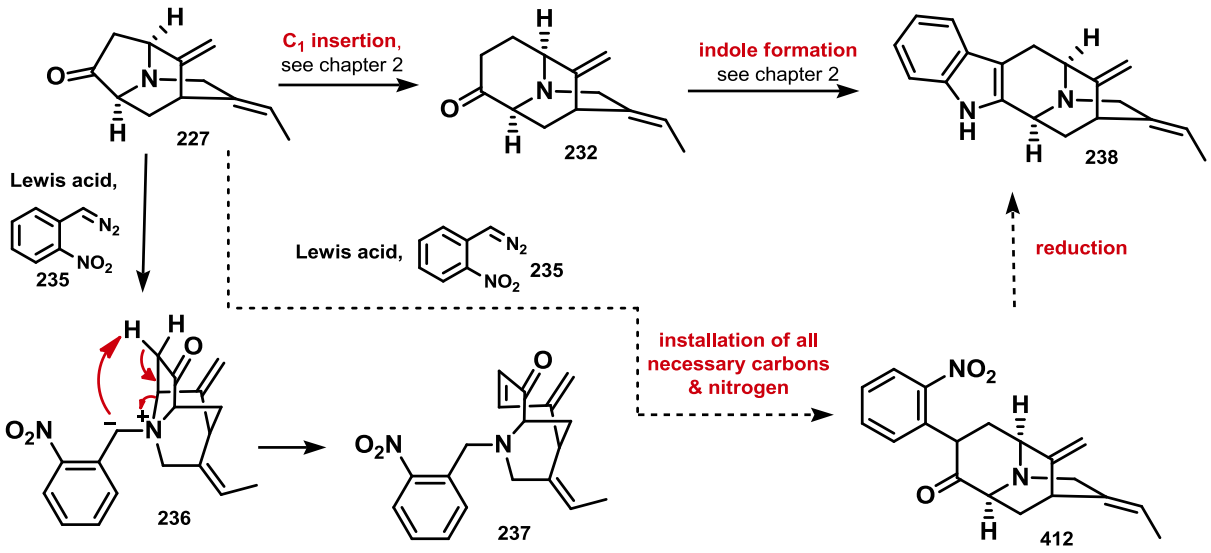
[3.40] see the experimental part (chapter 3.9) for an extensive comparsion of the spectral data for parvineostemonine.

4 The DMNB Project

This project has been in part conducted within the Master Thesis of Lukas Dempwolff at the Leibniz University of Hanover under the supervision of the author of this thesis.[4.1]

4.1 Introduction

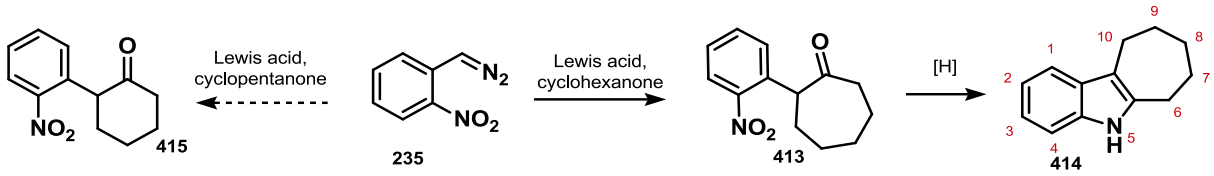
We stumbled upon the diazo-insertion based indole formation through a synthetic challenge occurring during the *sarpagine* total synthesis (see scheme 29). At some point, we had to achieve a one carbon homologation from ketone **227** to enlarged ketone **232** (see scheme 55). Next followed the introduction of the indole core *via* Fischer indole synthesis to give **238**. As this proved to be a challenging task, we explored the possibility to conduct both the C1 enlargement and the introduction of the remaining atoms for the indole nucleus in one operation. We envisioned the use of 1-(diazomethyl)-2-nitrobenzene (**235**, from now on DMNB) to obtain α-aryl species **412** under Lewis-acid catalysis. This compound should be converted into the desired indole **238** *via* simple reduction of the nitro group and subsequent dehydration. This idea turned out to be a dead end for the total synthesis of *sarpagine* alkaloids, due to the formation of betaine **236**, and subsequent fragmentation to unsaturated **237**.



Scheme 55: How to stumble upon an indolization methodology.

Before we attempted this reaction on advanced ketone **227**, the unknown reaction was examined on a test system consisting of cyclohexanone (see scheme 56). Cyclohexanone readily underwent the desired diazo insertion to give **413** and could easily be transformed into indole **414**. When we later explored the scope of the reaction, we realized that we had acci-

dentally chosen the best test system possible, as the reaction does not occur with cyclopentanone. Therfore, compound **415** cannot be obtained in good yields.



Scheme 56: Successful test system and unsuccessfull example with cyclopentanone.

Having realized that we can easily access saturated hexahydrocyclohepta[*b*]indoles like **414**, we focussed on the development of our new methodology towards this ring system. Cyclohepta[*b*]indoles and their heteroatom-substituted derivatives are frequently encountered in both natural products and biologically active molecules (see figure 33). The natural products ervatamine (**416**)[4.2,4.3] and actinophyllic acid (**417**)[4.4] both contain a cyclohepta[*b*]indole motif. Actinophyllic acid acts as a CPU inhibitor, which can be useful for the treatment of thrombotic diseases. Vincamajorine B (**418**)[4.5] and catharanthine (**419**)[4.6] contain heteroatom-substitution within the heptacycle. Catharanthine (**419**) is one of the biosynthetic[4.7] and chemical[4.8] precursors of highly reactive vincristine. The SIRT inhibitor 1 (**420**)[4.9] is heavily investigated due to its gene-silencing activities and contains the cyclohepta[*b*]indole core. The A FABP inhibitor (**421**)[4.10] is a biologically active molecule containing this structural motif as well. Due to the inhibition of the fatty-acid-binding protein, compounds like (**421**) have been investigated at large due to the reduced risk to suffer from hypertriglyceridemia, type 2 diabetes and coronary heart disease.[4.11]

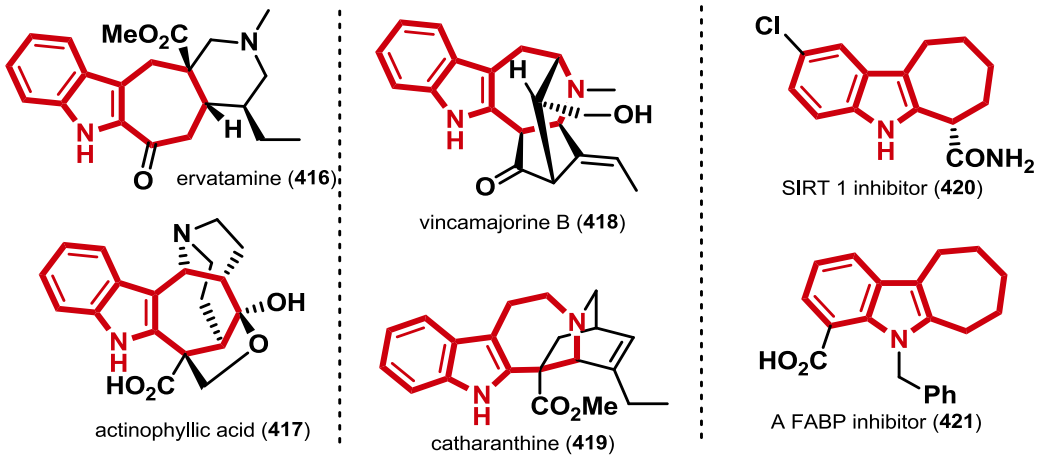


Figure 33: Natural products containing the cyclohepta[*b*]indole motif.

4.2 Diazo Insertion and Alpha Arylation

Although the original Tiffeneau-Demjanow rearrangement (aminoalcohol **422** was converted to diazocompound **423**, which rearranged to cycloheptanone **434**, scheme 57) dates back to the beginning of the 20th century, its usefullness was limited.

A synthetically much more usefull variation was developed by Roskamp and co-workers[4.12,4.13] by employing stabilized diazo-compounds like **425** and aldehydes (like benzaldehyde) in order to generate β-ketoesters like **426**.

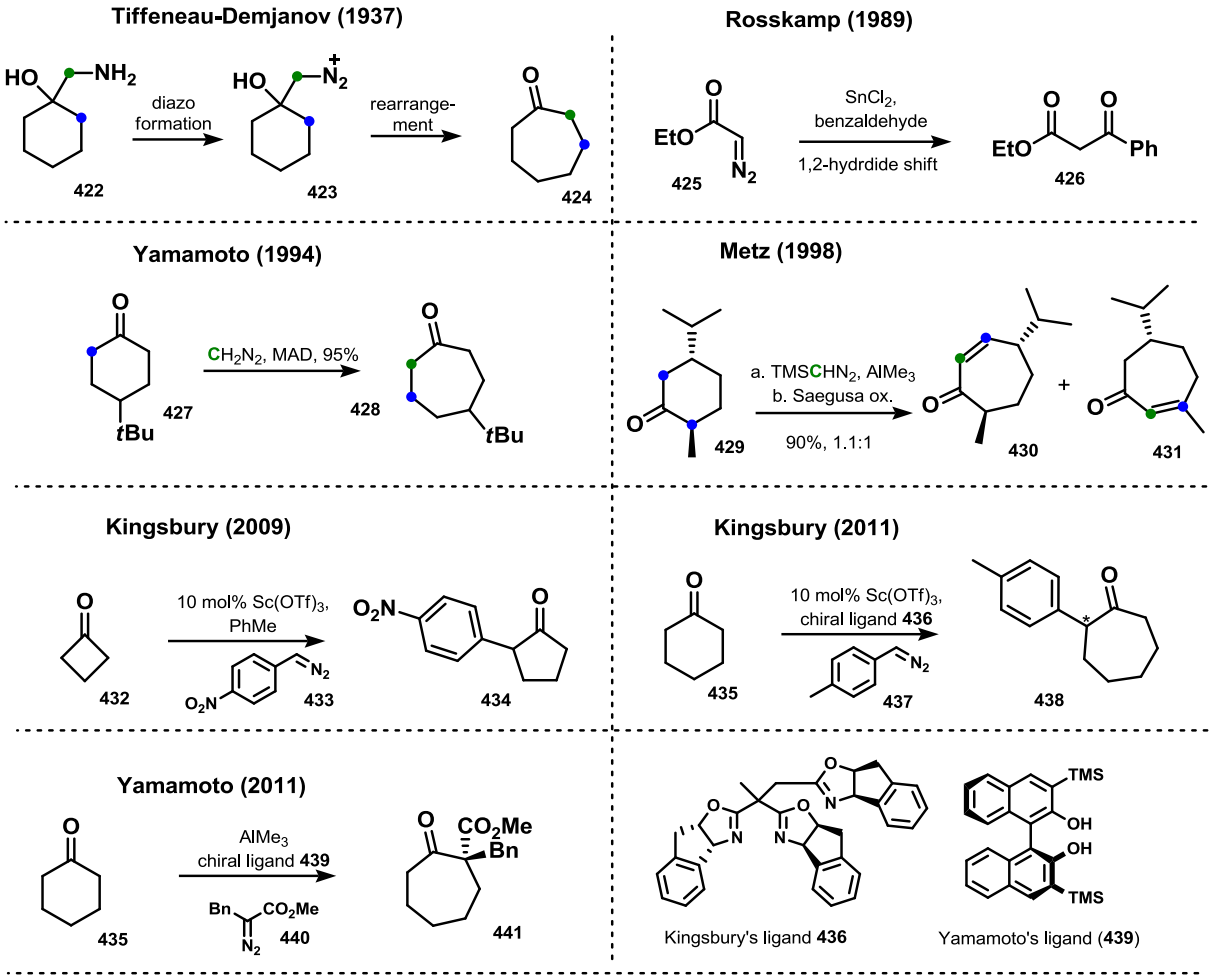
From thereon, the diazo mediated ring expansion was heavily investigated spear-headed by Yamamoto in 1994.[4.14] In order to achieve the ring expansion of *tert*-butyl-cyclohexanone **427** with diazomethane they screened several aluminium based Lewis-acids, in the end favouring MAD (methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide)) as the highest yielding reagent for the preparation of cycloheptanone **428**.

Metz demonstrated the TMS-diazomethane based C1-carbon enlongation using trimethylaluminium as Lewis acid.[4.15] They could convert ketone **429** into the two enones **430**/**431** *via* diazo insertion using TMS-diazomethane. They obtained two intermediate silyl enol ethers, which were converted to the desired compounds **430**/**431** *via* Saegusa oxidation in good yield without any selectivity.

Kingsbury developed diazo insertion chemistry around the strong Lewis acid scandium(III) triflate in 2009,[4.16] which was further developed into an asymmetric variant. In 2009 they were able to achieve the diazo insertion of a variety of substituted phenyldiazo species, including *para*-nitro compound **433** to yield cyclopentanone **434** from cyclobutanone **432**. The use of 1-(diazomethyl)-2-nitrobenzene (DMNB) itself has not been reported by Kingsbury, probably due to the fact that DMNB decomposes rapidly in the presence of $Sc(OTf)_3$.

In 2011, the same group published the insertion of phenyldiazo species like **437** with a number of different cyclic ketones like cyclohexanone **435**. They again utilized scandium(III) catalysis, employing chiral trisbenzoxazole **436**, to obtain α-chiral ketones like **438**.[4.17,4.18]

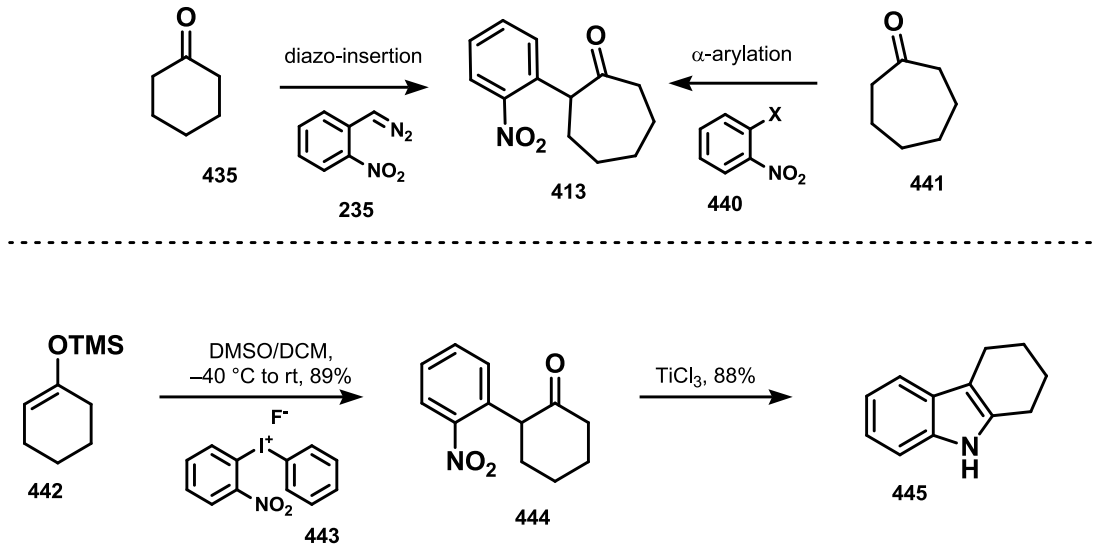
The pioneering group of Yamamoto[4.19] developed an asymmetric variant of their aluminium based diazo insertion chemistry, using stabilized diazocompounds like **440** to insert into cyclohexanone **435**. They were able to obtain chiral cycloheptanone derivative **441** *via* the use of trimethylaluminium and chiral BINOL-ligand **439**. For further examples of diazo-insertion chemistry see the review from Zhang and Wang.[4.20]



Scheme 57: Examples of diazoinsertions from Tiffeneau-Demjanov to today.

The diazo-insertion of DMNB has not been reported, not even the (unsucessfull) use of DMNB in such reactions has been described. However, the same α-arylated cycloheptanone **413** arising from the diazo insertion of DMNB **235** to cyclohexanone **435** could be obtained by α-arylation using nitrobenzenderivative **440** and cycloheptanone **441** (see scheme 58 and 56). Indeed, a fairly close example of this reaction has been published by the Rawal group[4.21] using hypervalent iodine reagent *ortho*-nitrophenylphenyliodonium fluoride **443** and silyl enol ether **442**. The fluoride liberates the protected enolate, without scrambling of the enolate position, enabling the enolate to perform a nucleophilic aromatic substitution under the realease of iodobenzene. The less electron rich aryl moiety is transferred selectively in this reaction. They obtained α-arylated cyclohexanone **444**, which could be converted into cyclohexa[*b*]indole **445** in good yield using titanium(III) chloride. They did not apply their system to cycloheptanones, but used it in the total synthesis of the *aspidosperma* alkaloid tabersonine.[4.22]

For further information on α-arylation using hypervalent iodine compounds the review from Olofsson and co-worker is recommended.[4.23]



Scheme 58: Comparison of diazo-insertion vs. α-arylation, and application from the Rawal group.

4.3 DMNB

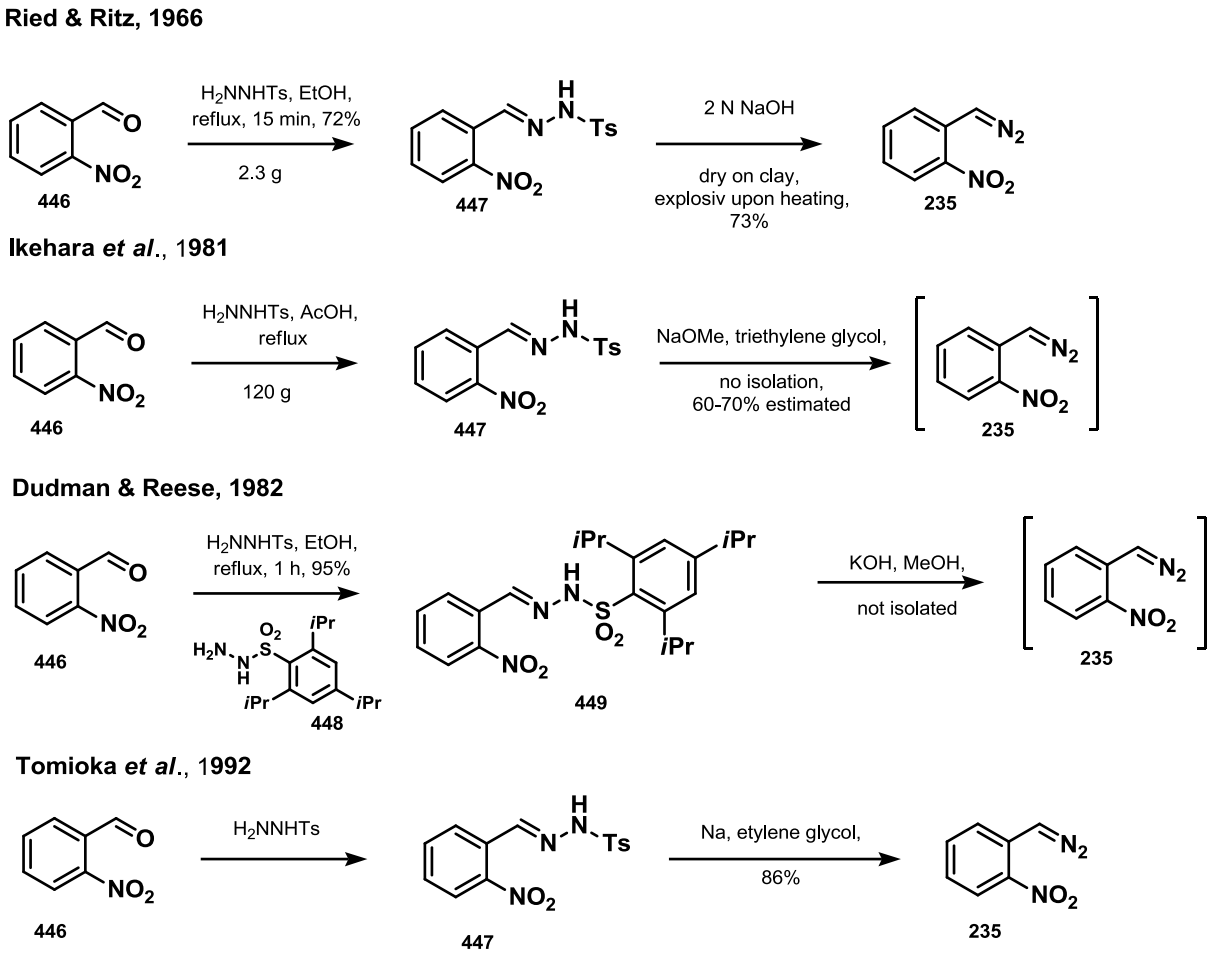
DMNB **235** has been prepared in 1966 for the first time by Ritz and Ried (see scheme 59).[4.24] They reacted *ortho*-nitrobenzaldehyde **446** with tosylhydrazine, obtaining hydrazone **447**. The corresponding diazo compound **235** was then prepared by α-elimination in a sodium hydroxide solution. The product was dried on clay and was obtained in 73% yield.

Ikehara and coworkers[4.25] prepared tosylhydrazone **447** by the reaction of **446** and tosylhydrazine in acetic acid in large quantities in 1981. They furnished DMNB **235** after treatment of hydrazone **447** with sodium methoxide. Although they did not isolate the product in its pure form, they state a yield of 60-70% estimated by the reaction of DMNB with 3,5-dinitrobenzoic acid (see scheme 61).

Dudman and Reese[4.26] prepared hydrazone **449** from *ortho*-nitrobenzaldehyde **446** and hydrazide **448** in good yield, and obtained DMNB **235** after α-elimination. Again, the desired compound was not isolated.

Tomioka *et al*.[4.27] prepared tosylhydrazone **447** in the common fashion (hydrazone formation with aldehyde **446**) and obtained DMNB **235** after subjection of hydrazone **447** to sodium in ethylene glycol in 86%.

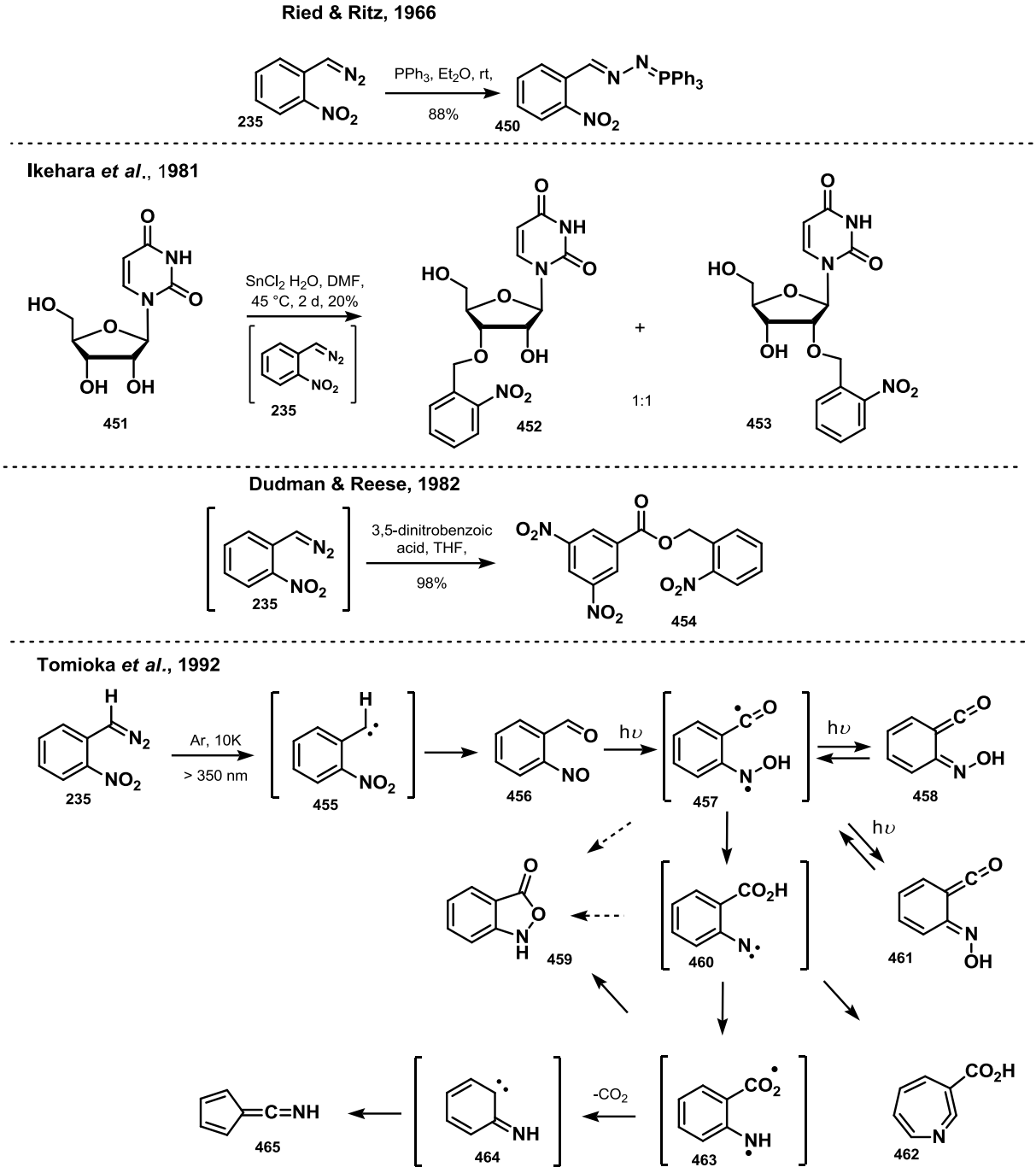
Neither of the presented accesses to DMNB **235** was feasible enough to obtain large quantities in short time, especially the isolation of neat DMNB **235** was troublesome.



Scheme 59: Preparation of DMNB (**235**) over the years.

DMNB **235** was prepared by Ried and Ritz[4.24] to form the corresponding phospazine **450** (see scheme 60), which could be accessed by treating **235** with triphenylphosphine in good yield. Ikehara and co-workers[4.25] investigated the protection of the alcohol moieties of several DNA-bases, such as uridine (**451**), by treating the DNA bases with DMNB **235** in the presence of tin(II) chloride as a Lewis acid. They obtained compounds **452**/**453** in moderate yield without selectivity. Dudman and Reese[4.26] prepared DMNB **235** and established the calibration of the DMNB purity by its near quantitative reaction with 3,5-dinitrobenzoic acid to form ester **454**. Tomioka *et al.*[4.27] investigated the decomposition of **235** under irradiation using matrix isolation technique. In the first step, the diazo moiety is decomposed, forming intermediate carbene **455**, which is then intramolecularly trapped by one of the oxygens of the nitro group. The first isolable compound has been proven to be *ortho*-nitrosobenzaldehyde **456**, which is further decomposed by irradiation. Two major compounds are formed from this intermediate *via* the initial formation of biradical **457**. 2,1-benzisoxazol-3(1*H*)-one **459** is formed either from this biradical directly, or from nitrene

460, or from the other possible biradical **463**. The second major compound carbonylcyclopentadieneimine **465** is formed from biradical **463** *via* the loss of carbon dioxide and subsequent rearrangement. As side products, oxime ketenes **458** and **461** were isolated, which can be interconverted under irradiation conditions. A remaining side product was assigned to be 3-carboxy-1-aza-1,2,4,6-cycloheptatetraene **462**, which results from Buchner-like ring expansion from nitrene intermediate **460**.



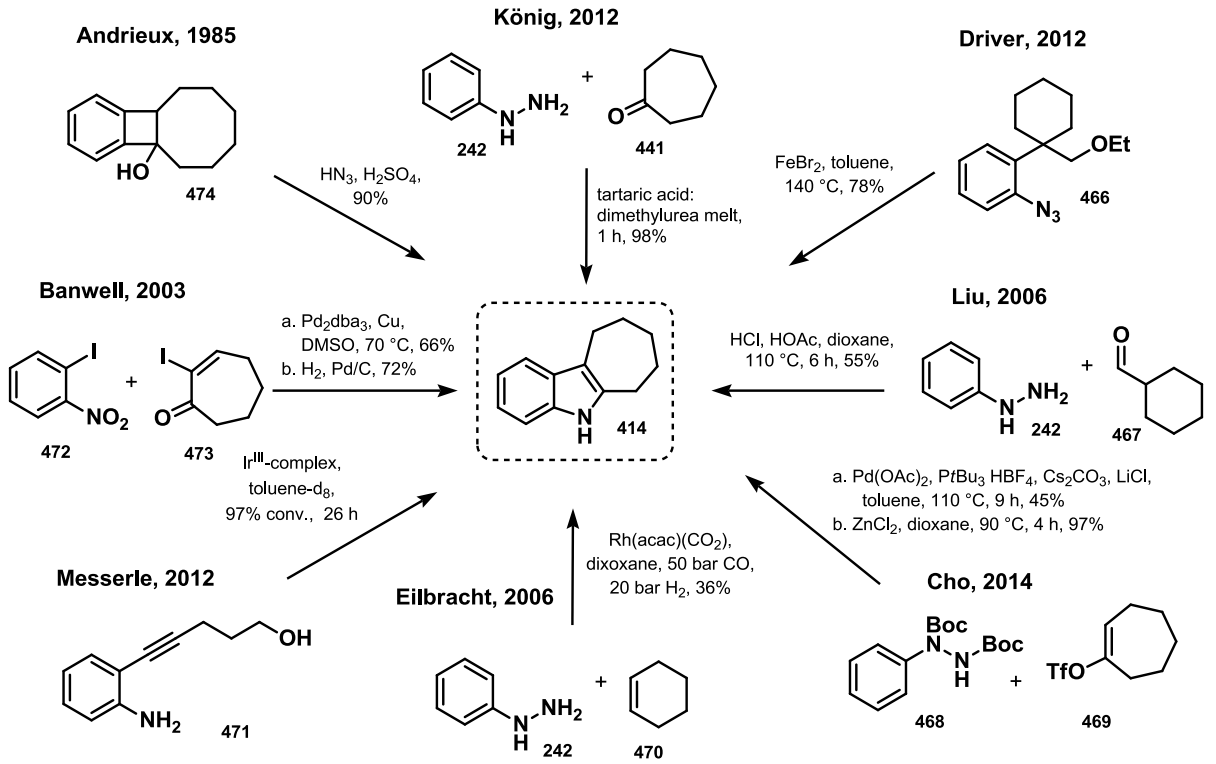
Scheme 60: Reactions of DMNB **235**.

4.4 Indole Forming Reactions

As a huge variety of possibilities exists for the formation of indoles,[4.28] this discussion is limited to the formation of cyclohepta[*b*]indoles, preferentially those occurring in this thesis.

Plain, unsubstituted hexahydrocyclohepta[*b*]indole **414** was recently prepared by König and co-workers (along with various other groups) *via* Fischer indole synthesis (see scheme 61).[4.29] They used a tartaric acid/dimethylurea melt as solvent and proton donor and phenylhyadrazine (**242**) and cycloheptanone (**441**). Driver and coworkers[4.30] used azide **466** under iron catalysis to form a transient indolenine, which underwent rearrangement to yield the desired product **414**. Liu and co-workers[4.31] investigated the Fischer indole synthesis of aldehydes (like **467**) and subsequent indolenine/indole rearrangement, which led to **414** in a mediocre yield. Cho *et al*.[4.32] used a palladium catalyzed cross coupling between vinyltriflate **469** and bis-Boc protected phenylhydrazine **468**, to generate an intermediate which underwent Fischer indolization and deprotection under zinc catalysis. Eilbracht *et al*.[4.33] pursued the same idea, but started with cyclohexene (**470**), which first undwent rhodium catalyzed hydroformylation, followed by the same reaction sequence from Liu's group. Their yield is not among the best for **414**, but nonetheless impressive for the overall transformation. Messerle and co-workers[4.34] used an advanced iridium(III) complex to generate hexahydrocyclohepta[*b*]indole **414** in one step from aminoalcohol **471**. This reaction proceeds *via* hydroamination and subsequent nucleophilic ring closure. Banwell and coworkers[4.35] coupled vinyliodide **473** and *ortho*-iodonitrobenzene **472** under Ullmann conditions, followed by reduction to obtain the desired compound **414** in good yield. Andrieux and co-workers[4.36] prepared hexahydrocyclohepta[*b*]indole **414** *via* tertiary alcohol **474**, which was first converted to an azide, which then decomposed and underwent ring enlargement.

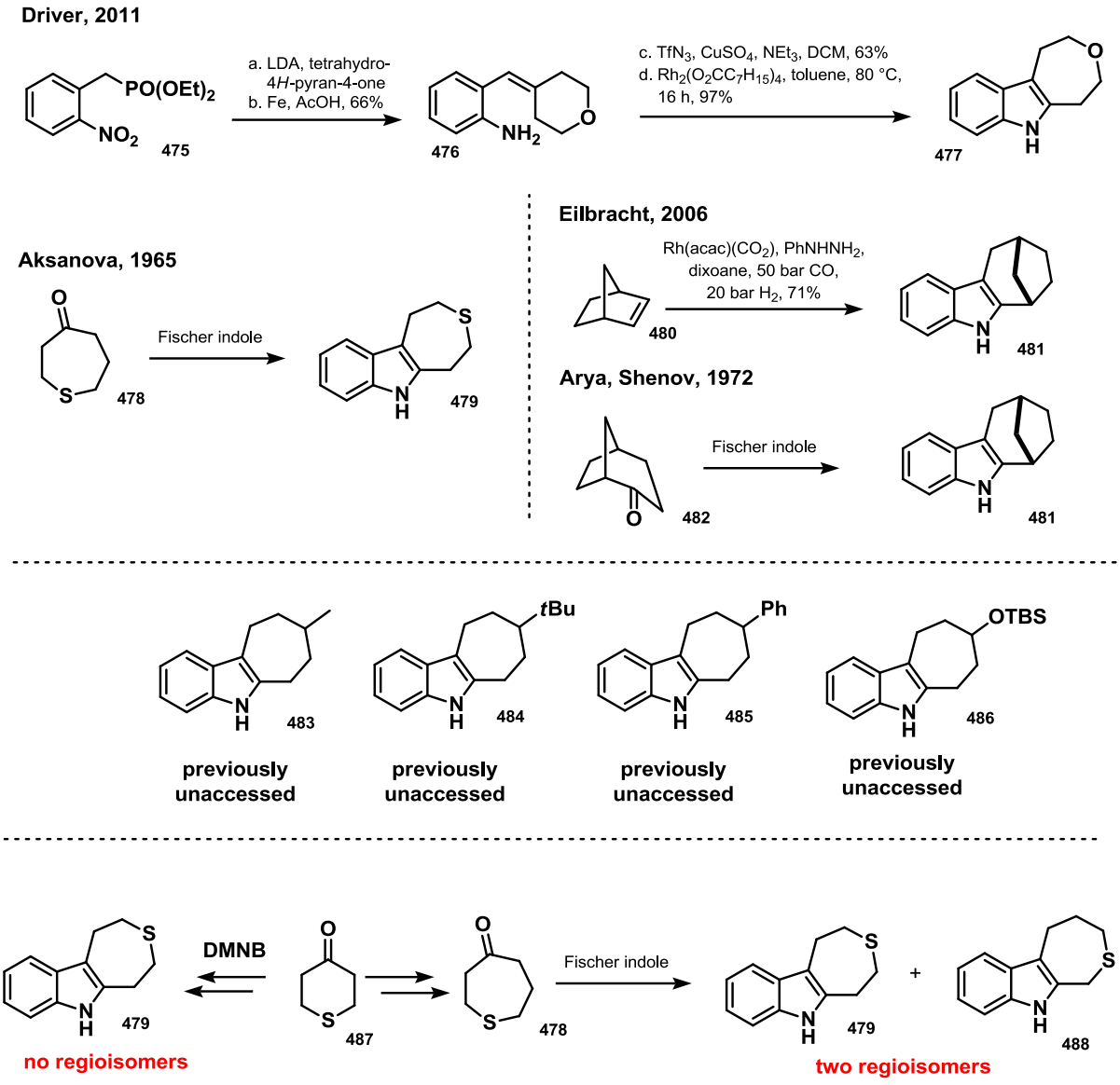
Several more methodologies for the construction of the cycylohepta[*b*]indole core have been put forward, without the preparation of any of the relevant molecules of this thesis. Gaich and co-workers used the divinylcyclopropane-cycloheptadiene rearrangement.[4.37] Hong and co-workers used an organocatalyzed Michael/double Friedel-Crafts alkylation strategy.[4.38] Li and co-workers used an impressive 3–oxidopyrrilium [5+2] cycloadditon to build up the cycylohepta[*b*]indole core.[4.39] Sinha and co-workers used the divinylcyclopropane-cycloheptadiene rearrangement as well.[4.40]



Scheme 61: Different recent synthetic appraoches towards hexahydrocyclohepta[*b*]indole **414**.

Driver and co-workers[4.41] were able to prepare 2,4,5,6-tetrahydro-1*H*-oxepino[4,5-*b*]indole **477** *via* a four step sequence (see scheme 62). In the first two steps, phosphonate **475** was converted to aniline **476** *via* Wittig reaction/reduction of the nitro group to yield aniline **476**. The formation of an intermediate azide *via* diazo transfer was followed by rhodium-catalyzed isomerization to give the desired indole **477**. The sulfur anologue 2,4,5,6-tetrahydro-1*H*-thiepino[4,5-*b*]indole **478** was prepared from ketone **479** *via* Fischer indole synthesis in 1965.[4.42] In the same fashion, hexahydro-6,9-methanocyclo-hepta[*b*]indole **481** was accessed in 1972 from tricyclic precursor **482**.[4.43] The same compound **481** could be accessed by Eilbracht and co-workers[4.32] *via* one-pot hydroformulation of olefin **480**, Fischer indole synthesis and final indolenine-indole rearrangement in good yield. No synthetic access has been developed for the preparation of indoles **483**-**486**. In principle all compounds, which are going to be discussed can be prepared from cyclohexanone derivatives like **487**, which are first subjected to a ring expansion (using diazomethane, TMS-diazomethane or ethyl diazoacetate (followed by decarboxylation) to give **478** and subsequent Fischer indole synthesis to yield **479** and **488**. Although this route might lead to all indoles but compound **486** (OTBS is probably unstable under most Fischer indole variants), the regioselectivity in the Fischer indole synthesis remains an unsolvable issue (formation of **479** and **488**). The

yield will not be above 50%. The same reaction from **487** directly to **479** *via* diazo-insertion circumvents this regioselectivity issue.



Scheme 62: Previous synthetic access to the other synthesized 8-substituted cyclohepta[*b*]indoles (for the numbering see scheme 57).

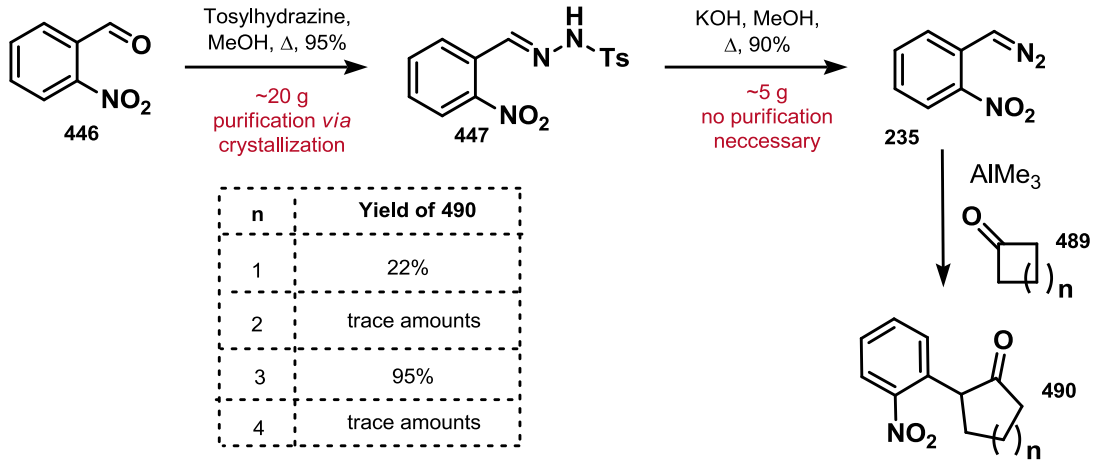
4.5 Adipocyte Fatty Acid Binding Protein (A FABP)

Adipocyte fatty acid binding proteins (A FABP, FABP4 or aP2) are capable of binding and transporting endogenous fatty acids through the cell membrane.[4.10] Spiegelmann and co-workers compared mice with null mutation of aP2 to control mice while fed with an obesity inducing diet. The knock-out mice behaved developmentally and metabolically stable, and became dietary obese like the control mice. However, they did not develop insulin resistence and diabetes like the control mice.[4.44] Mice with aP2 deficient macrophages showed protec-

tion against arteriosclerosis.[4.45] A FABP has been regarded as being important for understanding the molecular basis of the metabolic syndrome, and provides an attractive target for the prevention of ateriosclerosis.[4.45]

4.6 Results

DMNB **235** can be prepared most easily and in large quantities from commercially available *o*-nitrobenzaldehyde (**446**), which ins converted into hydrazone **447** and subsequent elimination. Those two steps require only one purification *via* crystallizaton (see scheme 63). DMNB **235** decomposes rapidly on silica gel, but only slowly and non-violent in its isolated form or in solution at ambient temperature or lower. Ried and Ritz[4.24] reported DMNB **235** to be explosive upon heating in its pure form. First attempts on the desired diazo-insertion yielded surprising results, as only cyclobutanone (**489**, n=1) and cyclohexanone (**489**, n=3) underwent the desired ring expansion to give **490**. Although the yield for cyclobutanone was only 22%, cyclopentanone and cycloheptanone failed to give any reasonable amount of insertion product. A variety of Lewis acids was screened for the diazo-insertion reaction ($SbCl_5$, $SnCl_2$, $SnCl_4$, $NiClO_4$, $Sc(OTf)_3$, BF_3) with trifluoroborate being the only Lewis acid to give any insertion product. Trimethylaluminium (in a stoichiometric fashion) proved to be the best Lewis acid for the diazo insertion, and three equivalents of DMNB **235** were usually employed to give best results. Dichloromethane gave the best yields, the reaction can be less efficiently carried out in THF and toluene. Less $AlMe_3$ and fewer equivalents of DMNB led to diminished yields. Trimethylaluminium has been reported to react with diazo compounds.[4.46,4.47]

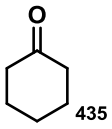
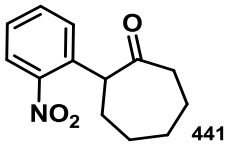
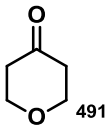
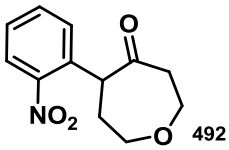
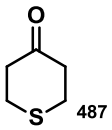
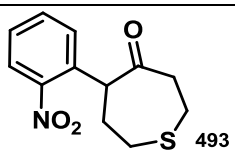


n	Yield of 490
1	22%
2	trace amounts
3	95%
4	trace amounts

Scheme 63: Preparation of DMNB **235** and initial screening for the desired diazo insertion to give **490**.

We then decided to develop this methodology exclusively for the formation of 8-substituted hexahydrocyclohepta[*b*]indoles (for the numbering see scheme 56), for which little synthetic access is known. We first examined the incorporation of heteroatoms in *para*-position to the ketone functionality (see table 1). Unsubstituted cyclohexanone **435** underwent the desired diazo insertion in almost quantitative yield to give **441** (entry 1), dihydropyran **491** gave compound **492** in good yield (entry 2). Dihydrothiopyran **487** underwent the desired reaction to **493** in almost the same yield as its oxygen analogue (entry 3).

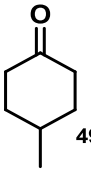
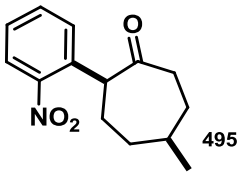
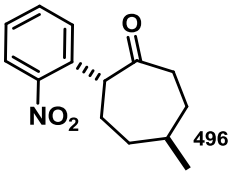
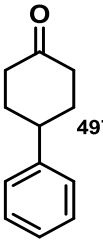
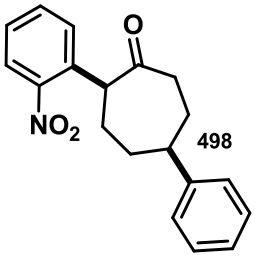
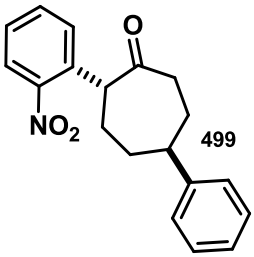
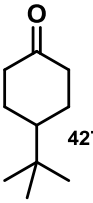
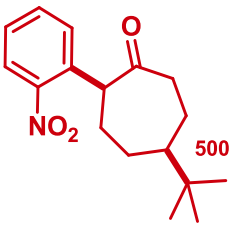
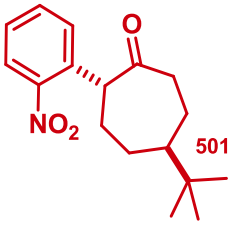
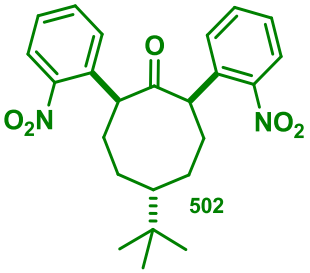
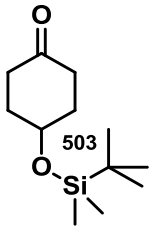
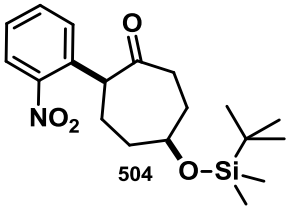
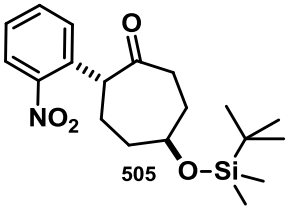
Table 1: Diazo insertion using cyclohexanone **435** and its heteroatomic analogues **491** and **487**.

Entry[a]	Starting material	Product	Yield
1	 435	 441	94
2	 491	 492	85
3	 487	 493	84

a=conditions: ketone at –78 °C in DCM, add 1.0 eq. $AlMe_3$, then add 3.0 eq. DMNB, warm to rt over 16 h.

We then shifted our attention to substituted cyclohexanones, starting with 4-substitution, as we should only obtain diastereomers instead of regioisomers and diastereomers (using 2- or 3-substitution). Employment of a simple methyl substituent in **494** decreased the yield of the diazo-insertion only to a small extend (see table 2, entry 1) and gave a diastereomeric mixture of compound **495**/**496**. The stereochemistry was not assigned in any cases, as one stereocenter will be destroyed in the upcoming reduction step, thereby rendereing the stereochemistry inconsequential. Using a larger substiuent (**497**, entry 2) led to both stereoisomers **498**/**499** in good yield. When the even bigger 3-*tert*-butyl-cyclohexanone **427** was subjected to the diazo insertion conditions, we were able to identify the double insertion product **502** as the main product, along with both possible diastereomers (**500**/**501**) after monoinsertion. Changing the substitution pattern from all-carbon substituents to a *tert*-butyl-dimethysilyl-protected alcohol (**503**, entry 4) led to the formation of compounds **504**/**505** in good yield.

Table 2: Diazo insertion on 4-substituted cyclohexanones.

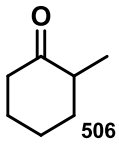
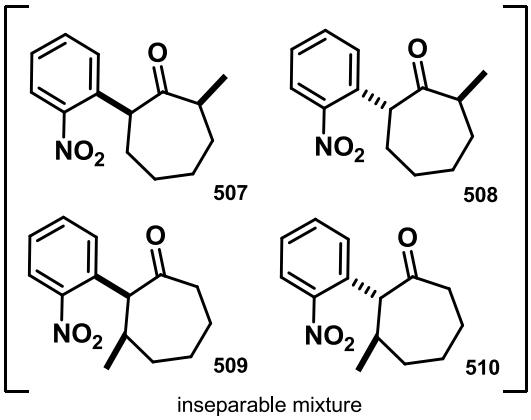
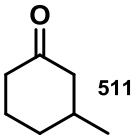
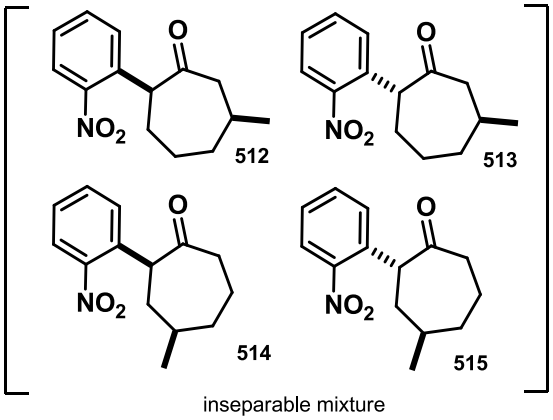
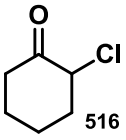
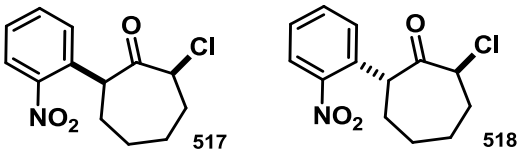
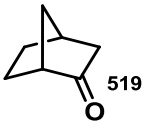
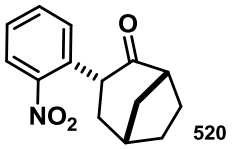
En-try[a]	Starting material	Products[b]	Yield
1	 494	 495  496	80
4	 497	 498  499	93
3	 427	 500  501  502	31/36
4	 503	 504  505	81

a=conditions: ketone at –78 °C in DCM, add 1.0 eq. $AlMe_3$, then add 3.0 eq. DMNB, warm to rt over 16 h. b=stereochemistry was not assigned for any compound.

When we shifted our focus to *ortho*/*para* substituted cyclohexanones, we had to deal with the formation of regioisomers. Employment of 2-methylcyclohexanone **506** (table 3, entry 1) led to the formation of the four possible compounds **507–510** in a very moderate yield, which could not be separated any further.[4.48] Using 3-methylcyclohexanone (**511**, entry 2) led to the formation of the four compounds **512–515**, which could not be separated any further. Again, the yield was only moderate, but roughly treefold compared to 2-methylcyclohexanone **506**.[4.48] When 2-chlorocyclohexanone **516** was used, the outcome changed impressively (entry 3, for an explanantion see below). The yield was shown to be 47%, and only the two diastereomers **517**/**518** were observed. Finally, employment of cyclic normethylcamphor **519** gave tricyclic **520** in acceptable yield (entry 4). The use of camphor

itself did not yield any desired reaction products (see figure 32 for a variety of unsuccessfull starting materials for the attempted indolization).

Table 3: Diazo insertion on 2- and 3-substituted cyclohexanones.

Entry[a]	Starting material	Productsb	Yield
1[c]	 506	 507 508 509 510 inseparable mixture	11
2[c]	 511	 512 513 514 515 inseparable mixture	33
3	 516	 517 518	47
4	 519	 520	55

a=conditions: ketone at –78 °C in DCM, add 1.0 eq. $AlMe_3$, then add 3.0 eq. DMNB, warm to rt over 16 h. b=stereochemistry was not assigned for any compound. c=see reference [3.1] for further details.

The improvement in yield for 2-chlorocyclohexanone **516** to give **517**/**518** compared to 2-methylcyclohexanone (**506**, yielding **507**–**510**) can be attributed to the more reactive orbital with which the reaction occurs (see figure 34). The $\pi^*_{C=O}$ orbital is usually employed for attack of a nucleophile onto a ketone moiety. With an adjacent heteroatom a new orbital is formed through orbital overlap of the σ^*_{C-Cl} orbital and the $\pi^*_{C=O}$ orbital. The newly formed empty orbital is lower in energy, therefore more likely to be attacked by a nucleophile.

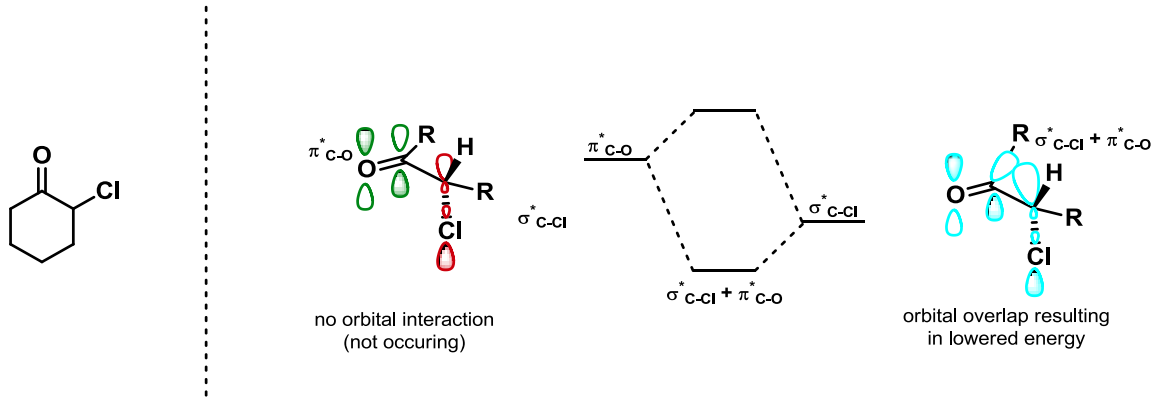


Figure 34: Explanation of the higher reactivity of 2-chlorocyclohexanone **516** compared to 2-methylcyclohexanone **506**.

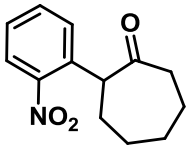
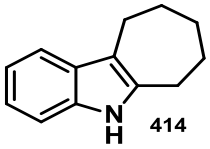
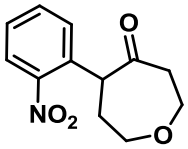
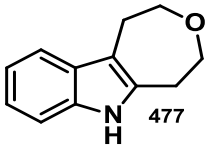
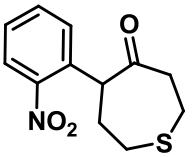
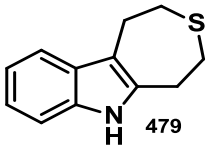
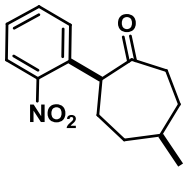
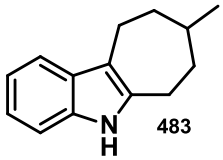
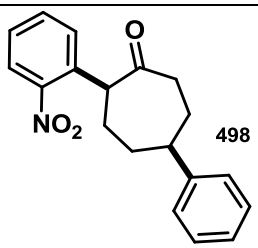
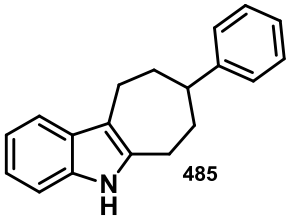
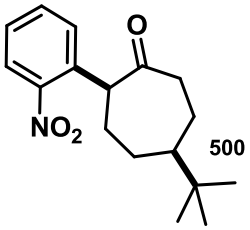
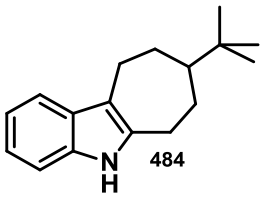
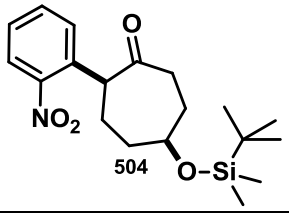
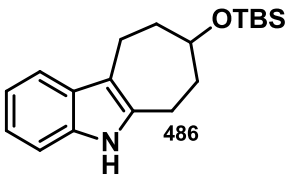
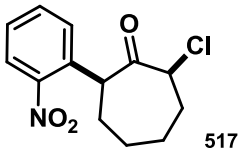
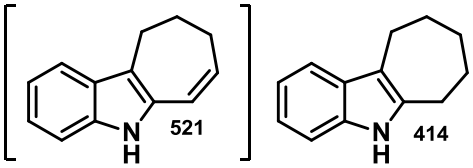
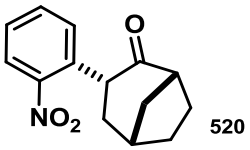
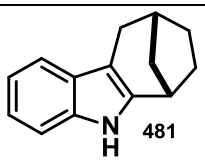
We then set out to investigate the cyclohepta[*b*]indole formation *via* reduction. The best reduction results were obtained using an excess of zinc in acetic acid as the solvent. Plain simple hexahydrocyclohepta[*b*]indole **414** can be readily obtained from compound **447** in a quantitative fashion (table 4, entry 1).

Compound **492** can be reduced in the same fashion, again yielding compound **477** quantitatively, thereby showing the tolerance of oxygen-substitution within the seven membered ring (entry 2). Reduction of sulfur containing compound **493** gave a diminished yield of indole **479**, which might be attributed to the possible removal of sulfur in the presence of complexing metals and hydrogen (entry 3).

The formation of 8-methylsubstituted cyclohepta[*b*]indole **483** could be achieved in great yield from starting compound **495** (entry 4).

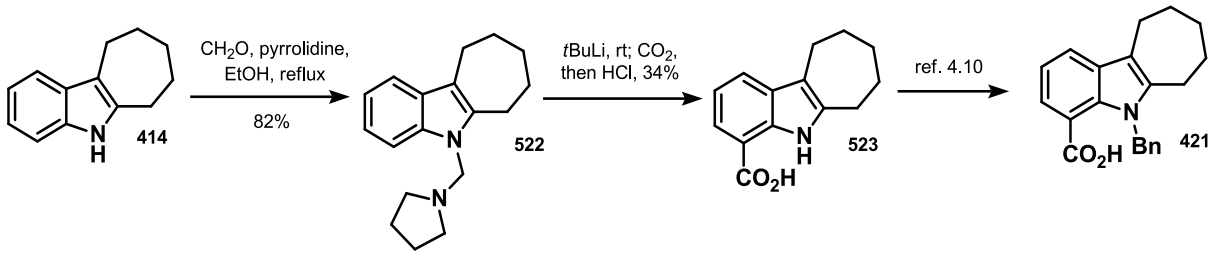
The formation of both 8-phenyl-substituted compound **485** from starting material **498** (entry 5) and 8-*tert*-butyl-substituted compound **484** from precursor **500** (entry 6) can be achieved in good yields. Surprisingly, the formation of 8-OTBS substituted polycycle **486** proceeded uneventfully without the removal of the protecting group from **504** (entry 7). This demonstrated nicely the mild reduction conditions for the necessary indole formation. Chloro-substituted compound **517** can be converted into plain compound **514** in good yield (entry 8). This reaction proceeds *via* the formation of unsaturated compound **521**, which is reduced further under the applied reduction conditions with prolonged reaction time. After the typical duration of the reduction (1.5 h), both compounds are usually isolated and cannot be separated. Entry 9 finally shows the formation of bridged cyclohepta[*b*]indole **481** arising from polycyclic **520** in good yield.

Table 4: Reductive cyclohepta[*b*]indole formation.

Entry[a]	Starting material[b]	Product	Yield
1	 447	 414	100
2	 492	 477	100
3	 493	 479	66
4	 495	 483	100
5	 498	 485	96
6	 500	 484	83
7	 504	 486	99
8	 517	 521 414	83
9	 520	 481	66

a=conditions: Zn, AcOH, 50 °C, 1.5 h. b=only one isomer depicted. In order to see which isomer was used, see the experimental part. The stereochemistry is not asigned.

To showcase the applicability of our developed methodology, we chose to demonstrate the formal synthesis of A FABP inhibitor **421** (see scheme 64).[4.10] In order to introduce the necessary carboxylic acid, we first installed an *ortho*-lithiation handle according to the procedure of Katritzky and co-workers.[4.49] This was easily achieved using formalin solution in the presence of pyrrolidine under refluxing conditions. Compound **522** can be obtained in this fashion in 82% yield. *Ortho*-lithiation was then achieved using *tert*-butyllithium at ambient temperature. Trapping of this Grignard-like reagent with CO_2 resulted in the formal synthesis of A FABP inhibitor **421.** The obtained compound **523** has been shown to be interconvertable into compound **421** *via* esterification, benzylation and saponification.



Scheme 64: Formal synthesis of A FABP inhibitor **421**.

Beyond We originally intended to further stretch the scope of this methodology to form 2-substituted indoles, using aldehydes as starting materials. This approach did not proceed fruitfull, a detailed account can be found in the master thesis of L. Dempwolff.[4.1] In order to spare future colleagues the effort of rerunning useless experiments a summary of unsucessfull insertion precursors is provided next.

Piperidones did not work in the diazo insertion reaction, neither with a methylated nitrogen (**524**) nor with more deactivated carbamate **525** (see figure 35). The only attempts using phosphorus substitution employed β-ketophosphonate **526**, which did not give any desired reaction products.

A variety of carbon/oxygen compounds did not undergo the desired reaction, due to conjugation of the keto-functionality (like **527**/**531**/**535**/**536**), due to steric congestion (**530**/**532**) or wrong ring size (**528**/**529**/**536**). In addition to that, further oxo-functionalities seem to be not tolerated in this reaction (**533**/**534**/**535**). The only examined lactone **537** did not undergo the desired reaction.

No failed attempt for the reduction to the corresponding indole has been observed.

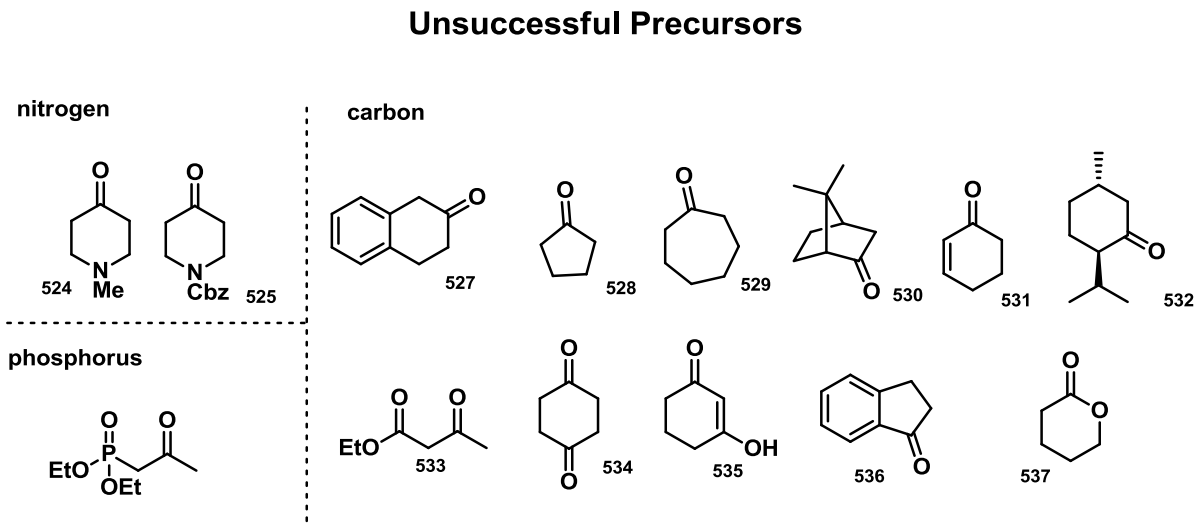


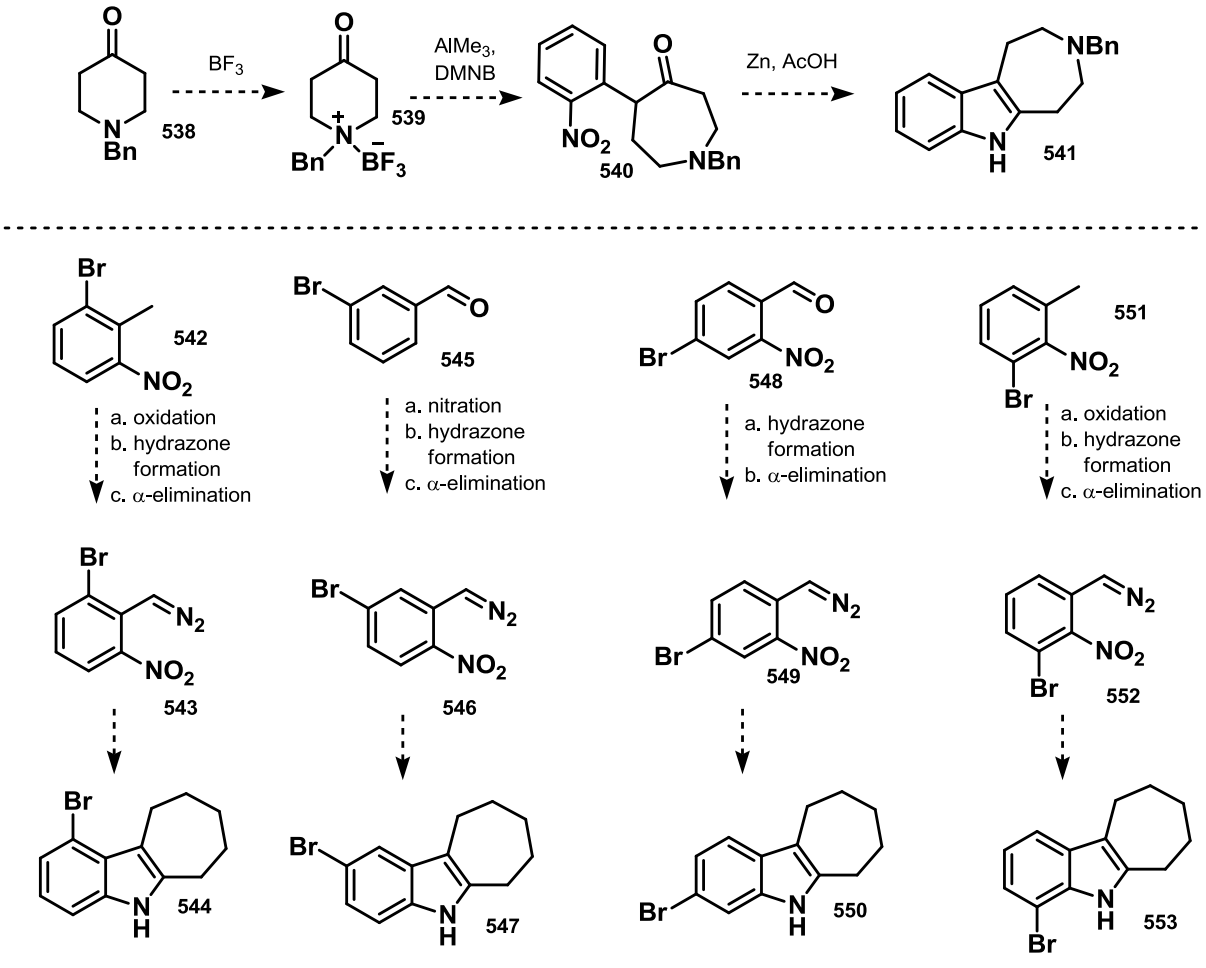
Figure 35: Unsuccessful precursors for the diazo-insertion reaction with DMNB **235**.

4.7 Summary and Outlook

In summary, we have developed a unique methodology for the synthesis of 8-substituted cyclohepta[*b*]indoles *via* diazo insertion with DMNB **235** and subsequent reduction. The scope of this reaction sequence includes the incooperation of heteroatoms at the 8-position (oxygen, sulfur), as well as aliphatic or aromatic moieties. In most cases both reactions are high yielding, and deliver fast access to previously unsynthesized molecules. The chemistry of DMNB **235** has been greatly expanded, a daunting endeavour, as DMNB is said to be an explosive compound and tends to react easily enough with itself. We furthermore succeeded in demonstrating the utility of our new methodology in the formal synthesis of A FABP inhibitor **421**. The scope of the reaction can be best described by being limited to 3-substituted cyclohexanones, if the yield is to be in an acceptable range. 2-Substituted hexanones yield only a small amount of product, with inseparable product mixtures, apart from the activating chloro-substituent. Cage structures can be generated as well using this methodology. The discussed methodology failed using nitrogen surrogates, which would be a very valuable addition to the substrate scope.

For future endeavours the implementation of other nitrogen surrogates is recommended. Because of the complexing nature of the nitrogen lone pair it has to be deactivated, probably by the formation of borate complex **539** from compound **538** (see scheme 65). Now the “real” Lewis acid trimethylaluminium can activate the carbonyl moiety and lead to successful diazo insertion to give **540**. Final reduction will lead to the incoporation of nitrogen to the substrate scope, yielding **541**. In order to increase the versatility of this reaction, the attachment of halides onto the to-be-formed indole core has to be achieved. Thereby

the substitution pattern can be greatly increased due to later cross coupling reactions. 1-bromo-2-(diazomethyl)-3-nitrobenzene (**543**) can probably be prepared from commercially available toluene derivative **542** upon oxidation[4.50] and the well established hydrazone formation/α-elimination sequence. Next in line, 4-bromo-2-(diazomethyl)-1-nitrobenzene (**546**) should be accessible from 3-bromobenzaldehyde **545** *via* nitration[4.51] and the aforementioned diazo-formation sequence. 4-bromo-1-(diazomethyl)-2-nitrobenzene (**549)** could be accessed from 4-bromo-2-nitrobenzaldehyde **548**, as this aldehyde is fairly inexpensive, *via* diazo formtion. Finally, 1-bromo-3-methyl-2-nitrobenzene (**551**) can be oxidized to the corresponding aldehyde, which should be convertible to 1-bromo-3-(diazomethyl)-2-nitrobenzene (**552**). With an access to those diazo compounds, we could obtain all the different bromo-substituted indoles **544**, **547**, **550** and **553**.



Scheme 65: Synthetic outlook towards a bigger substrate scope.

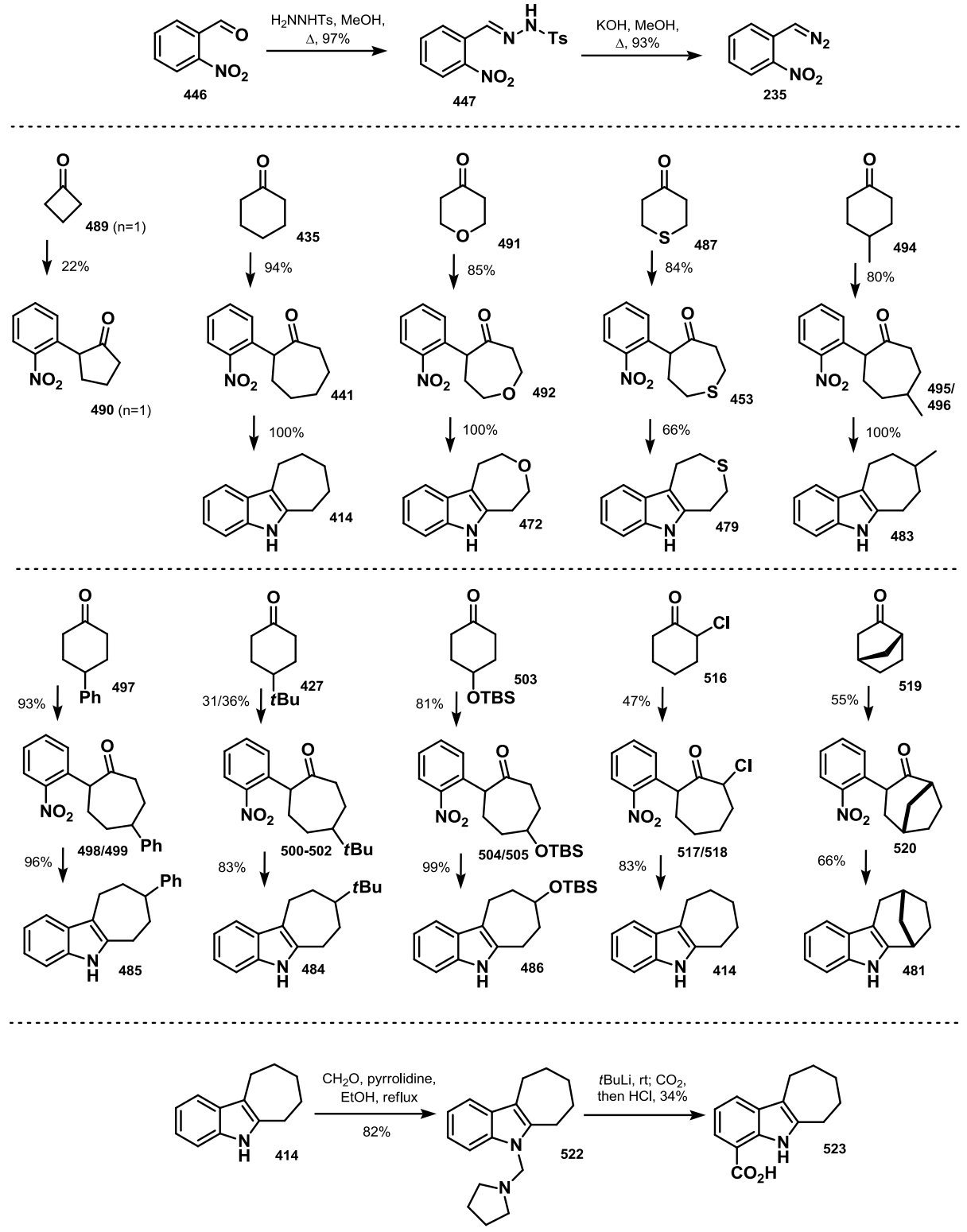
4.8 Experimentals

General

All reactions were performed under an inert atmosphere using Argon as the inert gas, using oven-dried glassware unless stated otherwise. Chemicals were used as bought from chemical suppliers. Solvents were used as bought from chemical suppliers or obtained from a dispensory system. THF was used dry after being distilled from Na/benzophenone or as bought from Acros Organics, 99,5% over molsieves, stabilized. DCM was used after distillation over CaH_2 or as bought from chemical suppliers. Acetonitrile was used as bought from Acros Organics 99.9% over molsieves. Acetone was used as bought from Acetone: VMR, technical grade. NEt_3 was used after distillation over CaH_2 or as bought from chemical suppliers. No difference in reactivities/yields was observed using different solvent sources. THF for Pd-catalyzed enolate coupling was used after sparging the solvent with argon for 30 minutes under ultrasonication. TLC was carried out using Macherey-Nagel, ALUGRAM Xtra SIL G/UV_{254}, Aluminium plates, silica 60. Silica gel-chromatography was carried out using Macherey-Nagel, Silica 60M, 0.04-0.083 mm mesh. Preparative thin layer chromatography was carried out using Macherey-Nagel, ADAMANT UV_{254}, Glass plates, silica 60. NMR-measurements were carried out using Bruker DPX 200 MHz, Bruker AV 400 MHz, Bruker DPX 400 MHz and Bruker DRX 500 MHz. All NMR-spectra are referenced to 7.26 ppm ($CDCl_3$, ^1H) and 77.16 ppm ($CDCl_3$, ^{13}C), 3.31 ppm (methanol-d_4, ^1H) and 49.00 ppm (methanol-d_4, ^{13}C) or 2.50 ppm (DMSO-d_6, ^1H) and 39.52 (DMSO-d_6, ^{13}C). IR measurements were carried out using Bruker Vector 22 or Shimadzu IRAffinity-1S. UPLC-MS Spectra were recorded using Waters QTOF-Premier (Waters Aquity Ultra Performance, electron spray ionization). HR-EI-MS were obtained using Micromass GCT. Optical rotations were measured using Perkin Elmer Polarimeter 341.

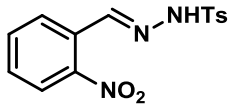
This project has been in part conducted within the Master Thesis of Lukas Dempwolff at the Leibniz University of Hanover under the supervision of the author of this thesis.[4.1]

Graphical Overview VI



DMNB-preparation

4-methyl-*N'*-(2-nitrobenzylidene)benzenesulfonohydrazide (**447**)

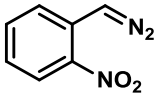


447

2-nitrobenzaldehyde **446** (10.63 g, 70 mmol, 1.0 equiv.) was dissolved in MeOH (120 mL) and *p*-toluenesulfonylhydrazide (13.75 g, 74 mmol, 1.1 equiv.) was added under stirring. The solution was heated to 60 °C for 30 minutes. The precipitate was filtered off, washed with MeOH and dried *in vacuo* to yield 21.8 g (97%) of **447** as a yellow powder.

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 10.91 (s, 1H), 8.28 (s, 1H), 8.02 (dd, *J*=8.2, 1.2 Hz, 1H), 7.91–7.69 (m, 4H), 7.68–7.55 (m, 1H), 7.42 (d, *J*=8.2 Hz, 2H), 2.36 (s, 3H) ppm. **^{13}C-NMR (100 MHz, DMSO-d_6):** δ = 147.8, 143.7, 142.3, 136.1, 133.8, 130.7, 129.8, 128.0, 127.8, 127.2, 124.6, 21.0 ppm. **IR (neat sample):** 3190, 1964, 1595, 1521, 1434, 1372, 1342, 1300, 1212, 1186, 1169, 1159, 1085, 1062, 931, 877, 861, 808 cm^{-1}.

1-(diazomethyl)-2-nitrobenzene (**235**)



235

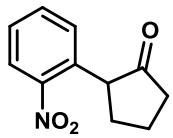
Potassium hydroxide (1.76 g, 31 mmol, 2.0 equiv.) was dissolved in MeOH (47 mL) and 4-methyl-*N*'-(2-nitrobenzylidene)benzenesulfonohydrazide **447** (5.00 g, 16 mmol, 1.0 equiv.) was added under stirring. The solution was heated to reflux for 30 minutes and then cooled to ambient temperature followed by dilution with ice and water. The solution was extracted with DCM, dried over $MgSO_4$ and concentrated *in vacuo* to afford 2.38 g (93%) of **235** as an orange oil. The product was always prepared freshly for subsequent reactions and was temporarily stored in the dark.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.20–8.16 (m, 1H), 7.58–7.50 (m, 1H), 7.14–7.05 (m, 2H), 6.55 (s, 1H) ppm. **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 134.0, 129.0, 127.1, 123.2 (2C), 47.2 ppm. **IR (neat sample):** 3130, 2056, 1603, 1562, 1508, 1479, 1436, 1366, 1331, 1304, 1263, 1202, 1163, 1132, 1069, 1045, 860, 822 cm^{-1}.

4.8.1 General procedure for diazo-insertion

The ketone was weighed out in an argon-sparged schlenk flask, followed by the addition of dichloromethane (0.5 mL) and cooling to –78 °C. Trimethylaluminium (2 M in toluene, 1 eq.) was added dropwise, a gas outlet was attached. The diazo compound **235** (3 eq.) was then added over the course of 2 h (0.5 eq. every 20 min.) by using a 1 M solution. The reaction was finished after the gas evolution ceased, but was usually carried out overnight. Addition of water quenched the reaction, extraction with diethyl ether and drying over $MgSO_4$ followed next. The solution was then concentrated *in vacuo* and purified *via* column chromatography.

2-(2-nitrophenyl)cyclopentan-1-one (**490**, n=1)

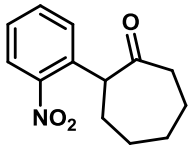


490, n=1

According to the general procedure using cyclobutanone (**489**, n=1) (96 mg, 100 µL, 1.37 mmol, 1 eq.) and yielding 32.0 mg (22%) of **490** after chromatography.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.03–7.99 (m, 1H), 7.61–7.56 (m, 1H), 7.46–7.40 (m, 1H), 7.31–7.27 (m, 1H), 3.91 (dd, *J*=11.8, 8.2 Hz, 2H), 2.63–2.52 (m, 1H), 2.52–2.47 (m, 1H), 2.46–2.35 (m, 1H), 2.29–2.14 (m, 2H), 2.09–1.95 (m, 1H) ppm. **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 215.6, 149.4, 133.7, 133.5, 131.7, 128.2, 125.5, 54.1, 38.0, 31.5, 21.1 ppm. **IR (neat sample**): 2928, 2858, 1701, 1520, 1347, 934, 853 cm^{-1}. **HRMS** (ESI, *m/z*): calc. for $[C_{11}H_{11}NO_3Na^+]$: 228.0637, found: 228.0637.

2-(2-nitrophenyl)cycloheptan-1-one (**441**)

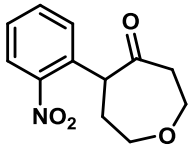


441

According to the general procedure using cyclohexanone **435** (97 mg, 100 µL, 99 µmol, 1 eq.) and yielding 223 mg (95%) of **441** after chromatography.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, *J*=8.2 Hz, 1H), 7.63 (t, *J*=7.2 Hz, 1H), 7.47 (d, *J*=7.3 Hz, 1H), 7.41 (t, *J*=7.8 Hz, 1H), 4.43 (d, *J*=10.8 Hz, 1H), 2.98–2.87 (m, 1H), 2.60 (ddd, *J*=16.7, 12.0 Hz, 1H), 2.10–1.98 (m, 5H), 1.88–1.78 (m, 1H), 1.63–1.57 (m, 1H), 1.40–1.30 (m, 1H) ppm. **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 211.6, 148.4, 136.6, 133.2, 131.0, 127.7, 124.6, 53.0, 43.9, 32.3, 30.3, 29.1, 23.5 ppm. **IR (neat sample):** 2934, 2858, 1698, 1525, 1347, 852 cm^{-1}. **R_f:** 0.38 (5:1 PE:EtOAc), **HRMS** (ESI, *m/z*): calc. for [$C_{13}H_{15}NO_3Na^+$]: 256.0950, found: 256.0950.

5-(2-nitrophenyl)oxepan-4-one (**492**)

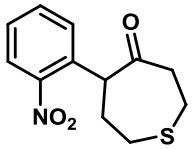


492

According to the general procedure using tetrahydro-4*H*-pyran-4-one **491** (105 mg, 97 µL, 105 µmol, 1 eq.) and yielding 210 mg (85%) of **492** after chromatography.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.01–7.94 (m, 1H), 7.67–7.60 (m, 1H), 7.46–7.40 (m, 2H), 4.66 (dd, *J*=11.9, 2.0 Hz, 1H), 4.25 (dt, *J*=12.6, 3.4 Hz, 1H), 4.19 (ddd, *J*=13.3, 5.0, 3.3 Hz, 1H), 3.93–3.80 (m, 1H), 3.77–3.65 (m, 1H), 3.02–2.83 (m, 2H), 2.42–2.26 (m, 1H), 2.05–1.91 (m, 1H) ppm. **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 208.2, 148.3, 135.4, 133.6, 130.7, 128.1, 125.0, 72.7, 66.6, 52.9, 45.8, 33.8 ppm. **IR (neat sample):** 2957, 2868, 1980, 1710, 1609, 1578, 1524, 1393, 1348, 1302, 1200, 1156, 1116, 1042, 994, 921, 895, 855, 821 cm^{-1}. **R_f:** 0.14 (5:1 PE:EtOAc), **HRMS** (ESI, *m/z*): calc. for [$C_{12}H_{13}NO_4Na^+$]: 258.0742, found: 258.074.

5-(2-nitrophenyl)thiepan-4-one (**493**)

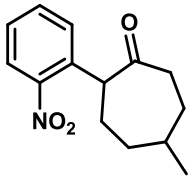


493

According to the general procedure using tetrahydro-4*H*-thiopyran-4-one **487** (118 mg, 1.00 mmol, 1 eq.) and yielding 215 mg (85%) of **493** after chromatography.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, *J*=8.2, 1H), 7.70–7.60 (m, 2H), 7.45–7.38 (m, 1H), 4.54–4.45 (m, 1H), 3.38 (dt, *J*=15.6, 3.7 Hz, 1H), 3.07–2.99 (m, 2H), 2.96–2.78 (m, 3H), 2.39–2.25 (m, 2H) ppm. **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 208.5, 148.2, 135.3, 133.3, 131.04, 127.9, 124.3, 50.7, 46.8, 36.4, 34.2, 27.0 ppm. **IR (neat sample):** 3791, 3630, 2918, 2187, 2051, 1963, 1711, 1608, 1578, 1524, 1427, 1350, 1185, 854 cm^{-1}. **R_f:** 0.43 (5:1 PE:EtOAc), **HRMS** (ESI, *m/z*): calc. for $[C_{12}H_{13}NO_3NaS^{+}]$: 274.0513, found: 274.0514.

5-methyl-2-(2-nitrophenyl)cycloheptan-1-one (**495**/**496**)



495/496

According to the general procedure using 4-methylcyclohexanone **494** (116 mg, 127 µL, 103 µmol, 1 eq.) and yielding 202 mg (80%) **495**/**496** after chromatography as a 1.7:1 (ds1:ds2) diastereomeric mixture.

Diastereomer 1:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.92 (dd, *J*=8.2, 1.4 Hz, 1H), 7.61 (td, *J*=7.5, 1.4 Hz, 1H), 7.45 (dd, *J*=7.9, 1.4 Hz, 1H), 7.40 (td, *J*=7.7, 1.4 Hz, 1H), 4.45 (dd, *J*=8.9, 3.8 Hz, 1H), 2.84–2.76 (m, 1H), 2.68–2.59 (m, 1H), 2.22–2.09 (m, 2H), 2.09–1.99 (m, 2H), 1.89–1.80 (m, 1H), 1.72–1.63 (m, 2H), 0.97 (d, *J*=7.2 Hz, 3H) ppm. **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 211.3, 148.9, 136.2, 133.3, 130.8, 127.7, 124.7, 52.8, 40.2, 35.4, 32.0, 30.0, 27.6, 18.6 ppm. **IR (neat sample):**

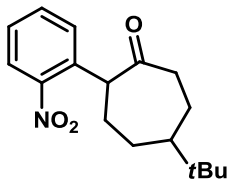
2953, 2926, 2870, 1705, 1609, 1578, 1524, 1456, 1348, 1163, 1150, 852 cm^{-1}. **R_f:** 0.59 (5:1 PE:EtOAc).

Diastereomer 2:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.93 (dd, *J*=8.0, 1.2 Hz, 1H), 7.61 (td, *J*=7.7, 1.4 Hz, 1H), 7.44–7.37 (m, 2H), 4.39–4.35 (m, 1H), 2.91–2.83 (m, 1H), 2.71–2.61 (m, 1H), 2.15−1.98 (m, 3H), 1.88–1.79 (m, 1H), 1.75–1.64 (m, 1H). 1.62–1.56 (m, 1H), 1.44–1.32 (m, 1H), 1.04 (d, *J*=6.8 Hz, 3H) ppm. **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 211.3, 148.3, 136.5, 133.2, 130.9, 127.6, 124.6, 53.4, 43.0, 39.0, 35.9, 31.7, 31.5, 24.3 ppm. **IR (neat sample):** 2949, 2924, 2868, 1701, 1609, 1578, 1522, 1454, 1346, 1165, 1149, 852 cm^{-1}. **R_f:** 0.54 (5:1 PE:EtOAc).

HRMS (mixture of diastereomers) (ESI, *m/z*): calc. for [$C_{14}H_{17}NO_3Na^+$] 270.1107, found: 270.1106.

5-(*tert*-butyl)-2-(2-nitrophenyl)cycloheptanone (**500**-**502**)



500/501

According to the general procedure using 4-*tert*-butylcyclohexanone **427** (154 mg, 100 µmol, 1 eq.) and yielding 89.7 mg (31%) of **500**/**501** in a 1.16:1 mixture of diastereomers (ds1:ds2) and 152.8 mg (36%) of double insertion product **502**.

First Diastereomer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.96–7.87 (m, 1H), 7.64–7.56 (m, 1H), 7.45–7.36 (m, 2H), 4.57 (t, *J*=6.2 Hz, 1H), 2.81–2.69 (m, 1H), 2.69–2.60 (m, 1H), 2.31–2.15 (m, 2H), 2.11–1.97 (m, 2H), 1.54–1.39 (m, 3H), 0.91 (s, 9H) ppm. **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 210.6, 149.7, 135.4, 132.9, 130.4, 127.7, 124.7, 51.9, 49.5, 33.8, 29.1, 27.6 (3C), 27.0, 25.7 ppm. **IR (neat sample):** 2955, 2866, 1707, 1609, 1578, 1522, 1479, 1443, 1396, 1346, 1302, 1234, 1213, 1109, 1088, 997, 962, 927, 903, 852 cm^{-1}. **R_f:** 0.52 (5:1 PE:EtOAc).

Second Diastereomer:

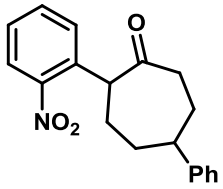
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.92 (dd, *J*=8.2, 1.4 Hz, 1H), 7.62 (td, *J*=7.7, 1.4 Hz, 1H), 7.48–7.44 (m, 1H), 7.42–7.37 (m, 1H), 4.43 (dd, *J*=11.6, 1.9 Hz, 1H), 2.99–2.89 (m, 1H), 2.55 (ddd, *J*=16.7, 12.1, 4.5 Hz, 1H), 2.23–1.94 (m, 4H), 1.67–1.55 (m, 1H), 1.44–1.32 (m, 1H), 1.12–1.03 (m, 1H), 0.92 (s, 9H) ppm. **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 211.7, 148.5, 136.5, 133.3, 130.9, 127.7, 124.6, 52.8, 51.2, 43.6, 33.9, 32.7, 31.4, 27.6, 25.2 ppm. **IR (neat sample):** 2957, 2868, 1707, 1609, 1578, 1526, 1478, 1449, 1366, 1346, 853 cm^{-1}. **R_f:** 0.50 (5:1 PE:EtOAc).

HRMS (mixture of diastereomers) (ESI, *m/z*): calc. for [$C_{17}H_{23}NO_3Na^+$] 312.1576, found: 312.1571.

Double insertion product (**502**):

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.84–7.78 (m, 4H), 7.55 (td, *J*=7.7, 1.3 Hz, 2H), 7.34 (td, *J*=7.8, 1.3 Hz, 2H), 4.91 (dd, *J*=10.7, 4.2 Hz, 2H), 2.36–2.26 (m, 2H), 2.13 (ddt, *J*=14.0, 9.4, 4.5 Hz, 2H), 1.95–1.85 (m, 2H), 1.67–1.59 (m, 1H), 1.57–1.47 (m, 2H), 0.94 (s, 9H) ppm. **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 213.2, 149.3, 134.8, 132.8, 130.6, 127.6, 124.3, 51.1, 45.1, 35.2, 34.9, 27.5, 26.6 ppm. **IR (neat sample):** 2951, 1868, 1714, 1607, 1578, 1520, 1477, 1445, 1346, 1265, 1070, 1051, 856 cm^{-1}. **R_f:** 0.46 (5:1 PE:EtOAc). **HRMS** (ESI, *m/z*): calc. for [$C_{24}H_{28}N_2O_5N^+$]: 447.1896, found: 447.1898.

2-(2-nitrophenyl)-5-phenylcycloheptanone (**498**/**499**)



498/499

According to the general procedure using 4-phenylcyclohexanone **497** (174 mg, 1.00 mmol, 1 eq.) and yielding 288 mg (93%) of **498**/**499** in a 2.1:1 diastereomeric mixture of ds1:ds2 after chromatography as a clear oil.

Diastereomer 1:

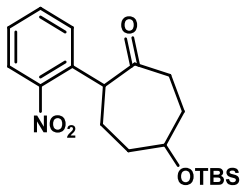
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.95 (dd, *J*=8.2, 1.4 Hz, 1H), 7.65–7.59 (m, 1H), 7.47–7.40 (m, 2H), 7.34–7.29 (m, 2H), 7.25–7.19 (m, 3H), 4.74 (t, *J*=5.8 Hz, 1H), 3.04 (tt, *J*=10.4, 3.8 Hz, 1H), 2.94 (ddd, *J*=12.9, 11.5, 3.2 Hz, 1H), 2.70 (ddd, *J*=13.0, 7.5, 2.7 Hz, 1H), 2.44–2.37 (m, 2H), 2.26-2.09 (m, 2H), 1.99–1.87 (m, 2H) ppm. **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 210.3, 149.7, 146.4, 135.2, 133.0, 130.4, 128.8, 128.7, 127.8, 126.9, 126.5, 124.8, 52.4, 46.3, 42.1, 33.4, 32.2, 29.1 ppm. **IR (neat sample):** 2930, 2860, 1705, 1609, 1522, 1493, 1450, 1348, 937, 891, 854 cm^{-1}. **R_f:** 0.45 (5:1 PE:EtOAc).

Diastereomer 2:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.96 (dd, *J*=8.1, 1.3 Hz, 1H), 7.64 (td, *J*=7.6, 1.4 Hz, 1H), 7.47 (dd, *J*=7.9, 1.4 Hz, 1H), 7.42 (ddd, *J*=8.3, 7.2, 1.4 Hz, 1H), 7.35–7.30 (m, 2H), 7.24–7.21 (m, 3H), 4.52 (dd, *J*=10.2, 2.8 Hz, 1H), 3.05–2.97 (m, 1H), 2.81 (ddd, *J*=16.9, 12.2, 4.5 Hz, 1H), 2.72–2.67 (m, 1H), 2.30–2.09 (m, 5H), 1.95–1.83 (m, 1H) ppm. **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 211.0, 147.8, 136.5, 133.4, 131.0, 128.8, 127.9, 126.5 (2C), 124.8, 53.5, 47.6, 43.3, 39.1, 32.1, 30.9 ppm. **IR (neat sample):** 2928, 2864, 1705, 1609, 1524, 1493, 1348, 930, 910, 854 cm^{-1}. **R_f:** 0.42 (5:1 PE:EtOAc).

HRMS (mixture of diastereomers) (ESI, *m/z*): calc. for [$C_{19}H_{19}NO_3Na^+$] 332.1263, found: 332.1264.

5-((*tert*-butyldimethylsilyl)oxy)-2-(2-nitrophenyl)cycloheptanone (**504**/**505**)



504/505

According to the general procedure using 4-(*tert*-butyldimethylsilyl)oxy)cyclohexanone **503** (228 mg, 1.00 mmol, 1 eq.) and yielding 294 mg (81%) of **504**/**505** in an undeterminable diastereomeric mixture (*via* crude NMR) after chromatography as a colourless oil.

Diastereomer 1:

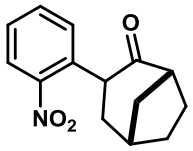
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.91 (dd, *J*=8.2, 1.2 Hz, 1H), 7.60 (td *J*=7.6, 1.4 Hz, 1H), 7.43 (dd, *J*=7.9, 1.4 Hz, 1H), 7.42–7.35 (m, 1H), 4.34–4.28 (m, 2H), 3.05–2.94 (m, 1H), 2.58 (dt, *J*=16.8, 4.3 Hz, 1H), 2.47–2.34 (m, 1H), 2.11–1.98 (m, 3H), 1.85–1.68 (m, 2H), 0.91 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H) ppm. **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 210.9, 148.5, 136.9, 133.2, 131.0, 127.6, 124.6, 67.6, 53.6, 38.0, 36.9, 30.2, 25.9, 25.6, 18.2, –4.7, –4.8 ppm. **IR (neat sample):** 2951, 2928, 1855, 1705, 1524, 1472, 1348, 1252, 1074, 1049, 974, 922, 837 cm^{-1}. **R_f:** 0.68 (5:1 PE:EtOAc).

Diastereomer 2:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.95 (dd, *J*=8.2, 1.4 Hz, 1H), 7.63-7.57 (m, 1H), 7.44-7.36 (m, 2H), 4.37 (dd, *J*=9.8, 3.0 Hz, 1H), 3.76 (tt, *J*=9.1, 3.4 Hz, 1H), 2.88 (ddd, *J*=16.3, 6.0, 3.9 Hz, 1H), 2.66-2.56 (m, 1H), 2.16-1.95 (m, 5H), 1.84–1.73 (m, 1H), 0.91 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H) ppm. **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 210.6, 148.6, 136.2, 133.4, 131.0, 127.9, 124.9, 73.0, 53.7, 39.3, 38.7, 33.2, 27.7, 26.0, 25.9, 18.3, –4.6 (2C) ppm. **IR (neat sample):** 2951, 2928, 2857, 1707, 1609, 1526, 1472, 1348, 1252, 1080, 1005, 930, 837 cm^{-1}. **R_f:** 0.57 (5:1 PE:EtOAc).

HRMS (mixture of diastereomers) (ESI, *m/z*): calc. for [$C_{19}H_{29}NO_4SiNa^+$]: 386.1774, found: 386.1770.

3-(2-nitrophenyl)bicyclo[3.2.1]octan-2-one (**520**)



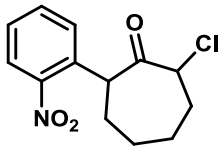
520

According to the general procedure using norcamphor **519** (100 mg, 1.00 mmol, 1 eq.) and yielding 121 mg (34%) of **520** after chromatography.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.00–7.94 (m, 1H), 7.62–7.54 (m, 1H), 7.45–7.37 (m, 1H), 7.30 (s, 1H), 4.25 (dd, *J*=11.6, 7.9 Hz, 1H), 2.91 (t, *J*=5.4 Hz, 1H), 2.69–2.54 (m, 1H), 2.29–2.19 (m, 1H), 2.15–2.04 (m, 3H), 2.02–1.86 (m, 4H) ppm. **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 210.0, 149.8,

134.0, 133.2, 131.9, 128.0, 125.2, 51.4, 48.0, 41.0, 38.2, 35.1, 28.4, 28.3 ppm. **IR (neat sample):** 2952, 2873, 2154, 1711, 1610, 1578, 1525, 1455, 1351, 1089, 850 cm^{-1}. **HRMS** (ESI, *m/z*): calc. for [$C_{14}H_{15}NO_3Na$+] 268.0949, found: 268.0950.

2-chloro-7-(2-nitrophenyl)cycloheptanone (**517**/**518**)



517/518

According to the general procedure using 2-chlorocyclohexanone **519** (133 mg, 114 µL, 1.00 mmol, 1 eq.) and yielding 126 mg (47%) of **517**/**518** in an undeterminable diastereomeric mixture (*via* crude NMR) after chromatography.

First diastereomer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.95–7.88 (m, 1H), 7.68–7.64 (m, 2H), 7.61–7.59 (m, 1H), 7.42 (ddd, *J*=8.3, 7.1, 1.6 Hz, 1H), 5.17 (t, *J*=4.3 Hz, 1H), 4.52 (dd, *J*=10.0, 3.8 Hz, 1H), 2.53–2.35 (m, 2H), 2.15–2.06 (m, 2H), 2.02 (d, *J*=4.44 Hz, 1H), 2.00–1.89 (m, 1H), 1.66–1.58 (m, 2H) ppm. **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 203.3, 148.3, 135.2, 133.5, 130.7, 128.1, 124.5, 65.7, 50.5, 33.9, 32.9, 29.2, 23.4 ppm. **IR (neat sample):** 2933, 2863, 1730, 1609, 1524, 1451, 1348, 952, 854 cm^{-1}. **R_f:** 0.46 (5:1 PE:EtOAc).

Second diastereomer:

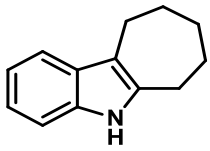
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.88 (dd, *J*=8.2, 1.4 Hz, 1H), 7.63–7.59 (m, 1H), 7.56 (td, *J*=7.9, 1.2 Hz, 1H), 7.42 (td, *J*=7.7, 1.7 Hz, 1H), 4.72 (dd, *J*=9.9, 3.8 Hz, 1H), 4.55 (dd, *J*=9.7, 4.6 Hz, 1H), 2.44–2.35 (m, 1H), 2.23–2.15 (m, 1H), 2.13–2.01 (m, 3H), 2.01–1.87 (m, 2H), 1.79–1.67 (m, 1H) ppm. **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 203.7, 148.8, 135.0, 133.1, 131.3, 128.1, 124.7, 63.8, 49.4, 34.5, 32.8, 29.0, 26.6 ppm. **IR (neat sample):** 2934, 2855, 1721, 1609, 1578, 1526, 1452, 1445, 1350, 1123, 937, 852 cm^{-1}. **R_f:** 0.40 (5:1 PE:EtOAc).

HRMS (mixture of diastereomers) (ESI, *m/z*): calc. for [$C_{13}H_{14}NO_3ClNa^+$]: 290.0555, found: 290.0557.

4.8.2 General procedure for the indole formation

The ketone was dissolved in concentrated acetic acid (0.1 M) in a schlenk flask, followed by the addition of zinc powder (25 eq.) and stirring at 50 °C for 1.5 h. The reaction was then diluted with diethyl ether and quenched upon the addition of sodium hydroxide solution (2 M) until basic conditions were achieved. After extraction with dichloromethane and drying over $MgSO_4$, the solution was then concentrated *in vacuo* and purified *via* column chromatography.

5,6,7,8,9,10-hexahydrocyclohepta[*b*]indole (**414**)

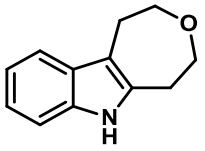


414

According to the general procedure, using **441** (46 mg, 20 µmol, 1 eq.) and quantitatively yielding 37.0 mg of **441** after chromatography.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.67 (br. s., 1H), 7.52–7.46 (m, 1H), 7.27 (d, *J*=8.7 Hz, 1H), 7.14–7.06 (m, 2H), 2.90–2.77 (m, 4H), 1.97–1.87 (m, 2H), 1.83–1.77 (m, 4H) ppm. **^{13}C-NMR (125 MHz, $CDCl_3$):** δ = 137.5, 134.4, 129.4, 120.7, 119.1, 117.8, 113.9, 110.3, 31.9, 29.7, 28.9, 27.7, 24.8 ppm. **IR (neat sample):** 2923, 2853, 1738, 1706, 1525, 1464, 1348, 1240, 1046, 849 cm^{-1}. **R_f:** 0.70 (5:1 PE:EtOAc). **HRMS** (ESI, *m/z*): calc. for [$C_{13}H_{15}N$+H] 186.1283, found: 186.1283.

1,4,5,6-tetrahydro-2H-oxepino[4,5-*b*]indole (**472**)

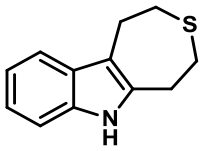


472

According to the general procedure, using **491** (80 mg, 34 µmol, 1 eq.) and quantitatively yielding 66.0 mg of **472** after chromatography.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.85 (br. s., 1H), 7.50 (d, *J*=7.5 Hz, 1H), 7.34–7.25 (m, 1H), 7.16 (quin, *J*=6.7 Hz, 2H), 4.06–3.94 (m, 4H), 3.09–2.94 (m, 4H) ppm. **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 135.6, 134.8, 129.0, 121.3, 119.4, 117.8, 112.4 (2C), 110.5, 73.1, 70.7, 32.3, 27.7 ppm. **IR (neat sample):** 3897, 3874, 3745, 3665, 3537, 3403, 3297, 3056, 2924, 2856, 1620, 1464, 1423, 1389, 1336, 1319, 1268, 1242, 1179, 1158, 1114, 1009, 922, 839 cm^{-1}. **HRMS** (ESI, *m/z*): calc. for [$C_{12}H_{13}NO$+H] 188.1075, found: 188.1079.

1,4,5,6-tetrahydro-2H-thiepino[4,5-*b*]indole (**479**)

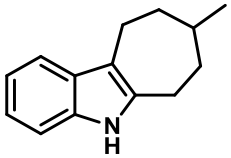


479

According to the general procedure, using **493** (88 mg, 35 µmol, 1 eq.) and yielding 47.1 mg (66%) of **479** after chromatography.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.71 (br. s., 1H), 7.53–7.46 (m, 1H), 7.32–7.24 (m, 1H), 7.20–7.08 (m, 2H), 3.40–3.13 (m, 4H), 2.98–2.74 (m, 4H) ppm. **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 135.9, 134.3, 129.4, 121.3, 119.5, 117.9, 112.9, 110.4, 34.1, 31.9, 30.0, 28.7 ppm. **IR (neat sample**): 3388, 3050, 2901, 1463, 1422, 1335, 1313, 1277, 1242, 1219, 1187, 1009, 885 cm^{-1}. **R_f:** 0.49 (5:1 PE:EtOAc). **HRMS** (ESI, *m/z*): calc. for [$C_{12}H_{13}NS$ +H]: 204.0847, found: 204.0848.

8-methyl-5,6,7,8,9,10-hexahydrocyclohepta[*b*]indole (**483**)

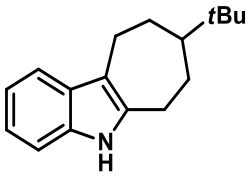


483

According to the general procedure, using the first diastereomer of **495**/**496** only (25.5 mg, 103 µmol, 1.0 eq.) and quantitatively yielding **483** as a white solid (20.5 mg) after chromatography.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.65 (br.s., 1H), 7.52–7.46 (m, 1H), 7.29–7.23 (m, 1H), 7.14–7.09 (m, 2H), 3.03 (ddd, *J*=15.5, 6.5, 2.6 Hz, 1H), 2.90–2.76 (m, 2H), 2.66–2.57 (m, 1H), 2.00–1.80 (m, 3H), 1.45–1.32 (m, 2H), 1.07 (d, *J*=6.8 Hz, 3H) ppm. **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 137.2, 134.3, 129.3, 120.7, 119.1, 117.7, 113.6, 110.3, 37.1, 36.5, 35.2, 27.6, 24.1, 22.9 ppm. **IR (neat sample):** 3402, 2947, 2909, 2872, 2841, 1464, 1431, 1335, 1260, 1190, 1150, 1009, 901 cm^{-1}. **R_f:** 0.76 (5:1 PE:EtOAc). **HRMS** (ESI, *m/z*): calc. for [$C_{14}H_{17}N$+H]: 200.1439, found: 200.1436.

8-(*tert*-butyl)-5,6,7,8,9,10-hexahydrocyclohepta[*b*]indole (**484**)

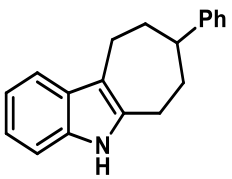


484

According to the general procedure, using both diastereomers of **500**/**501** (21.5 mg, 74.3 µmol, 1.0 eq.) and yielding 14.9 mg (83%) of **484** as a white solid after chromatography.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.66 (br. s., 1H), 7.51–7.46 (m, 1H), 7.28–7.23 (m, 1H), 7.13–7.05 (m, 2H), 3.13 (ddd, J=15.6, 5.9, 2.4 Hz, 1H), 2.96–2.87 (m, 1H), 2.82–2.71 (m, 1H), 2.58–2.48 (m, 1H), 2.23–2.10 (m, 2H), 1.43–1.27 (m, 3H), 0.95 (s, 9H) ppm. **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 137.0, 134.5, 129.3, 120.8, 119.1, 117.7, 113.3, 110.3, 52.8, 34.3, 29.7, 28.8, 28.4, 27.9 (3C), 24.3 ppm. **IR (neat sample):** 3389, 2949, 2916, 2859, 1464, 1335, 1262, 1190, 1153, 1007, 908 cm^{-1}. **R_f:** 0.82 (5:1 PE:EtOAc). **HRMS** (ESI, *m/z*): calc. for [$C_{17}H_{23}N$+H]: 242.1909, found: 242.1914.

8-phenyl-5,6,7,8,9,10-hexahydrocyclohepta[*b*]indole (**485**)

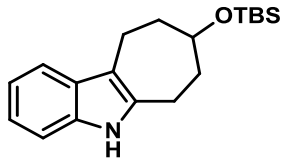


485

According to the general procedure, using only the first diastereomer of **498**/**499** (3.0 mg, 9.7 µmol, 1.0 eq.) and yielding 2.2 mg (96%) of **295** as a white solid after chromatography.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.76 (br.s., 1H), 7.54–7.46 (m, 1H), 7.34–7.28 (m, 3H), 7.24–7.17 (m, 3H), 7.15–7.06 (m, 2H), 3.19 (ddd, *J*=15.6, 5.6, 2.4 Hz, 1H), 3.07–2.96 (m, 1H), 2.95–2.84 (m, 2H), 2.71 (t, *J*=13.1 Hz, 1H), 2.23–2.08 (m, 2H), 1.92–1.74 (m, 2H) ppm. **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 149.5, 137.0, 134.3, 129.2, 128.7, 126.8, 126.1, 120.9, 119.3, 117.8, 113.5, 110.4, 50.1, 36.4, 35.1, 28.7, 24.0 ppm. **IR (neat sample):** 3402, 2920, 2851, 1493, 1464, 1335, 1258, 1234, 1153, 1011 cm^{-1}. **R_f:** 0.82 (5:1 PE:EtOAc). **HRMS** (EI, *m/z*): calc. for [$C_{19}H_{19}N$+]: 261.1517, found: 261.1518.

8-((*tert*-butyldimethylsilyl)oxy)-5,6,7,8,9,10-hexahydrocyclohepta[*b*]indole (**486**)

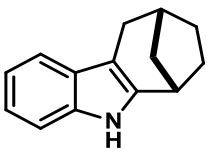


486

According to the general procedure, using both diastereomers of **504**/**505** (14.9 mg, 40.9 µmol, 1.0 eq.) and yielding 12.8 mg (99%) of **486** as a white solid after chromatopgraphy.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.70 (br.s, 1H), 7.50–7.41 (m, 1H), 7.28–7.24 (m, 1H), 7.13–7.05 (m, 2H), 4.13 (tt, *J*=7.7, 2.7 Hz, 1H), 3.11–2.98 (m, 2H), 2.61 (ddd, *J*=15.5, 8.8, 2.7 Hz, 2H), 1.99–1.90 (m, 2H), 1.90–1.80 (m, 2H), 0.93 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H) ppm. **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 137.0, 134.3, 129.2, 120.8, 119.2, 117.7, 113.4, 110.3, 73.0, 37.0, 35.7, 26.1 (3C), 23.3, 18.6, 18.4, -4.5 (2C) ppm. **IR (neat sample):** 3404, 2951, 2926, 2855, 1464, 1431, 1360, 1252, 1078, 1005, 947, 835 cm^{-1}. **R_f:** 0.84 (5:1 PE:EtOAc). **HRMS** (ESI, *m/z*): calc. for [$C_{19}H_{29}NOSi$+H]: 316.2097, found: 316.2093.

1,4,5,6-tetrahydro-2*H*-thiepino[4,5-*b*]indole (**481**)

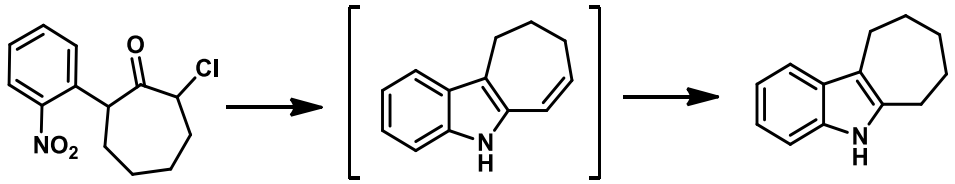


481

According to the general procedure, using **520** (50 mg, 20.0 µmol, 1.0 eq.) and yielding 25.2 mg (64%) of **481** after chromatography.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.84 (br. s., 1H), 7.64–7.57 (m, 1H), 7.50–7.42 (m, 1H), 7.31–7.22 (m, 2H), 3.23 (br. s., 1H), 3.17 (dd, *J*=15.2, 4.1 Hz, 1H), 2.90 (d, *J*=5.0 Hz, 1H), 2.75–2.68 (m, 1H), 2.05–1.97 (m, 1H), 1.95–1.90 (m, 3H), 1.82–1.77 (m, 1H), 2.02–1.91 (m, 1H) ppm. **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 141.6, 135.5, 128.4, 120.6, 119.3, 117.8, 110.8, 105.5, 37.1, 36.2, 35.5, 33.8, 31.5, 29.8 ppm. **IR (neat sample):** 3398, 3052, 2942, 2862, 2255, 2862, 2255, 2172, 2103, 1939, 1678, 1620, 1469, 1449, 1363, 1318, 1283, 1239, 1171, 1012 cm^{-1}. **HRMS** (EI, *m/z*): calc. for [$C_{14}H_{15}N$+]: 197.1204, found: 197.1206.

5,6,7,8,9,10-hexahydrocyclohepta[*b*]indole (**414**)



517/518 521 414

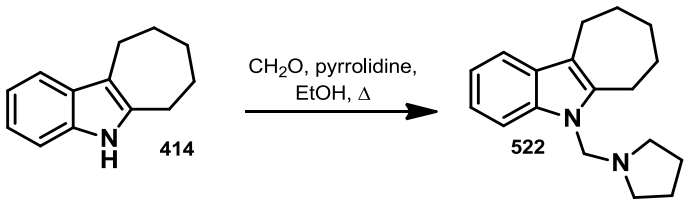
According to the general procedure, using **517/518** (2.6 mg, 9.71 µmol, 1 eq.) and yielding 1.5 mg (83%) of **414** after 16 hours reaction time. After 1.5 hours olefin **521** and reduced **414** can be obtained in an inseparable mixture.

NMR-Values for **521**:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.68 (br. s., 1H), 7.55–7.45 (m, 1H), 7.31–7.22 (m, 1H), 7.20–7.04 (m, 2H), 6.27 (d, *J*=11.4 Hz, 1H), 6.00–5.86 (m, 1H), 3.09–3.01 (m, 2H), 2.57 (q, *J*=5.1 Hz, 2H), 2.11–2.03 (m, 2H) ppm. **IR (neat sample):** 3405, 3053, 2917, 2839, 1971, 1620, 1464, 1334, 1247, 1168, 1010 cm^{-1}. **R_f:** 0.70 (5:1 PE:EtOAc). **HRMS** (ESI, *m/z*): calc. for [$C_{13}H_{13}N$+H]: 184.1126, found: 184.1126.

A FABP-inhibitor

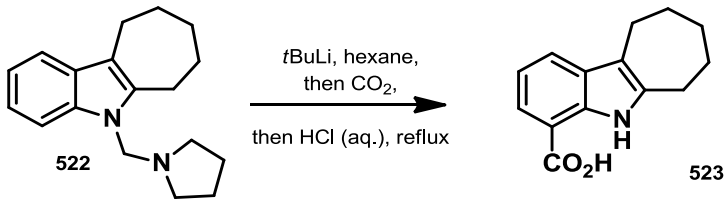
5-(pyrrolidin-1-ylmethyl)-5,6,7,8,9,10-hexahydrocyclohepta[*b*]indole (**522**)



Cyclohepta[*b*]indole **414** (300 mg, 1.62 mmol, 1.0 eq.) was put in a sealed tube and EtOH (4 mL), formaldehyde (0.5 mL of a 37% solution in water) and pyrrolidine (0.5 mL, 6.09 mmol, 3.75 eq.) were added. The mixture was heated to reflux for 16 hours. The solvent was then evaporated, and the remaining oil was purified *via* column chromatography using 5:1 PE:EtOAc as eluent. The desired compound **522** was obtained as a clear oil in 82% yield (355 mg).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.58–7.51 (m, 1H), 7.47–7.33 (m, 1H), 7.21–7.10 (m, 2H), 4.98 (s, 2H), 3.05–2.95 (m, 2H), 2.95–2.86 (m, 2H), 2.72–2.61 (m, 4H), 2.03–1.93 (m, 2H), 1.87–1.77 (m, 8H) ppm. **^{13}C-NMR (100 MHz, $CDCl_3$):** δ=139.7, 136.5, 128.0, 120.4, 118.9, 117.5, 114.2, 109.5, 61.0 51.3, 32.1, 28.4, 27.4, 26.7, 24.5, 23.6 ppm. **IR (neat sample):** 2916, 2843, 1464, 1344, 1314, 1234, 1180, 1134, 1012, 878, 820 cm^{-1}. **R_f:** 0.53 (5:1 PE:EtOAc). **HRMS** (ESI, *m/z*): calc. for [$C_{18}H_{23}N_2$+H]: 269.2018, found: 269.2020.

5,6,7,8,9,10-hexahydrocyclohepta[*b*]indole-4-carboxylic acid (**523**)

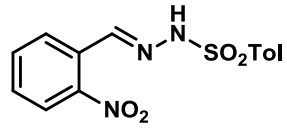


Amine **522** (197 mg, 734 µmol, 1.0 eq) was dispersed in hexane (15 mL), and the mixture was cooled to –78 °C, followed by the addition of *t*BuLi (0.58 mL of a 1.9 M solution in pentane, 1.5 eq.). The solution was allowed to warm to ambient temperature over 16 hours and was then cooled back to –78 °C. THF (1 mL) was then added, the cooling bad was removed and a stream of CO_2 was passed through the reaction. After 30 minutes 1 M HCl (6 mL) was added, and the mixture was heated to 85 °C for 30 minutes. EtOAc was then added, as well as solid

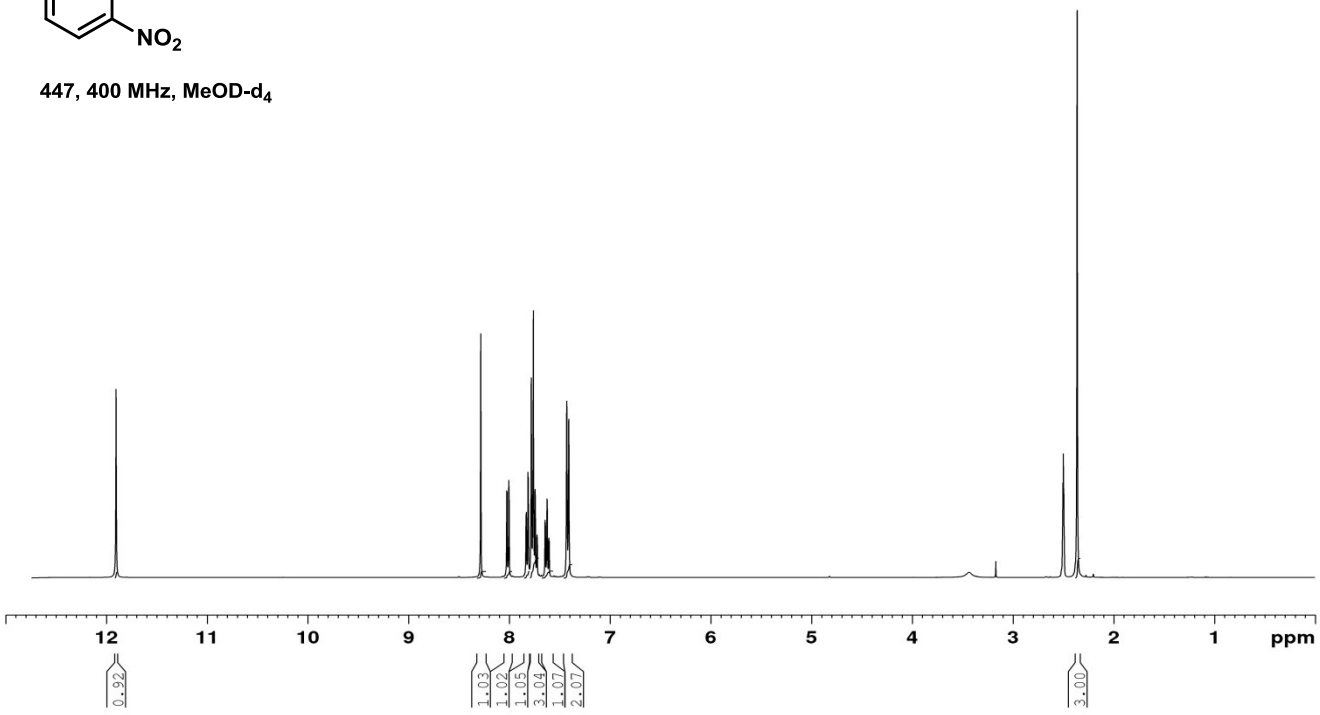
brine. The phases were separated, and the aqueous phase was extracted two more times with EtOAc. The combined organic layers were then washed with brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure. The remaining crude solid was the purified *via* flash colun chromatography using 1:1 PE:EtOAc to pure EtOAc to yield 57.3 mg (34%) of compound **523** as a white solid.

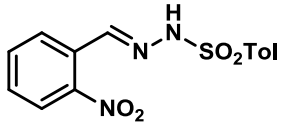
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.33 (br.s., 1H), 7.86 (dd, *J*=7.5, 0.9 Hz, 1H), 7.74 (d, *J*=7.7 Hz, 1H), 7.13 (t, *J*=7.7 Hz, 1H), 2.97–2.80 (m, 4 H), 2.00–1.78 (m, 6H) ppm. **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 171.7, 139.0, 134.7, 130.7, 124.3, 124.0, 118.5, 114.0, 110.5, 31.9, 29.8, 29.6, 28.8, 27.5, 24.8 ppm. **IR (neat sample):** 3455, 2920, 2849, 1672, 1614, 1572, 1464, 1441, 1368, 1331, 1306, 1258, 1229, 1200, 1150, 1061 cm^{-1}. **R_f:** 0.64 (EtOAc). **HRMS** (ESI, *m/z*): calcd. for $[C_{14}H_{15}NO_2+H]$: 230.1181; found: 230.1181, calcd. for $[C_{14}H_{15}NO_2-H]$: 228.1025; found: 228.1026.

4.9 Spectra

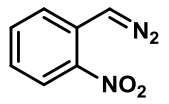


447, 400 MHz, MeOD-d_4

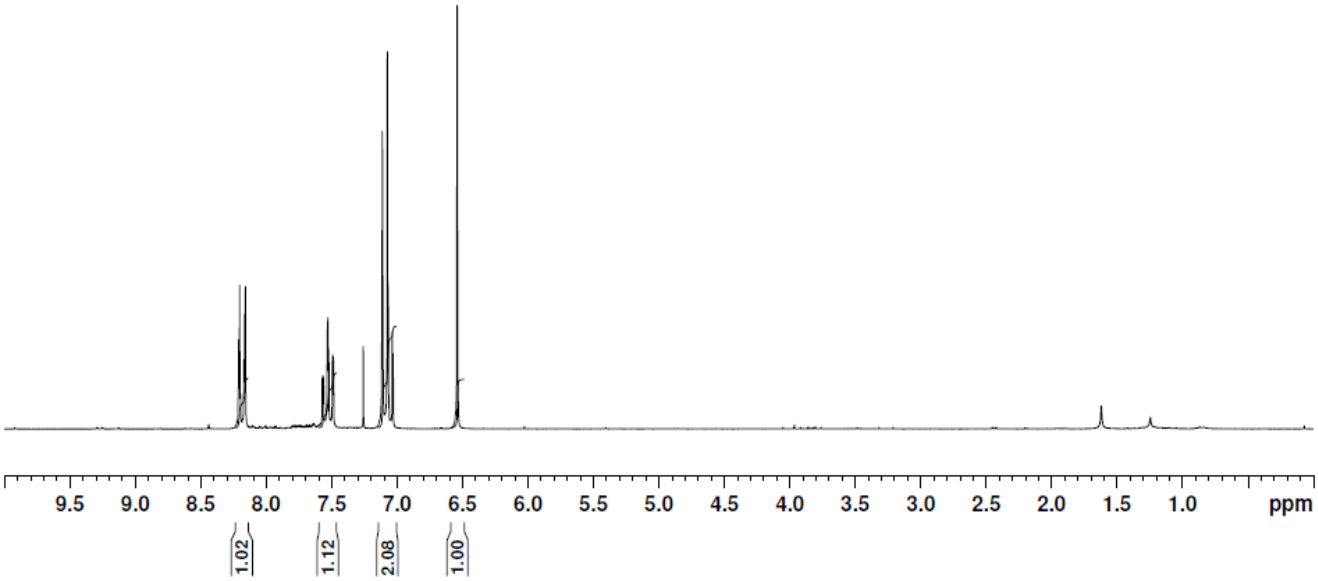


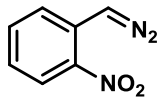


447, 100 MHz, MeOD-d_4

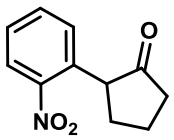


235, 400 MHz, $CDCl_3$

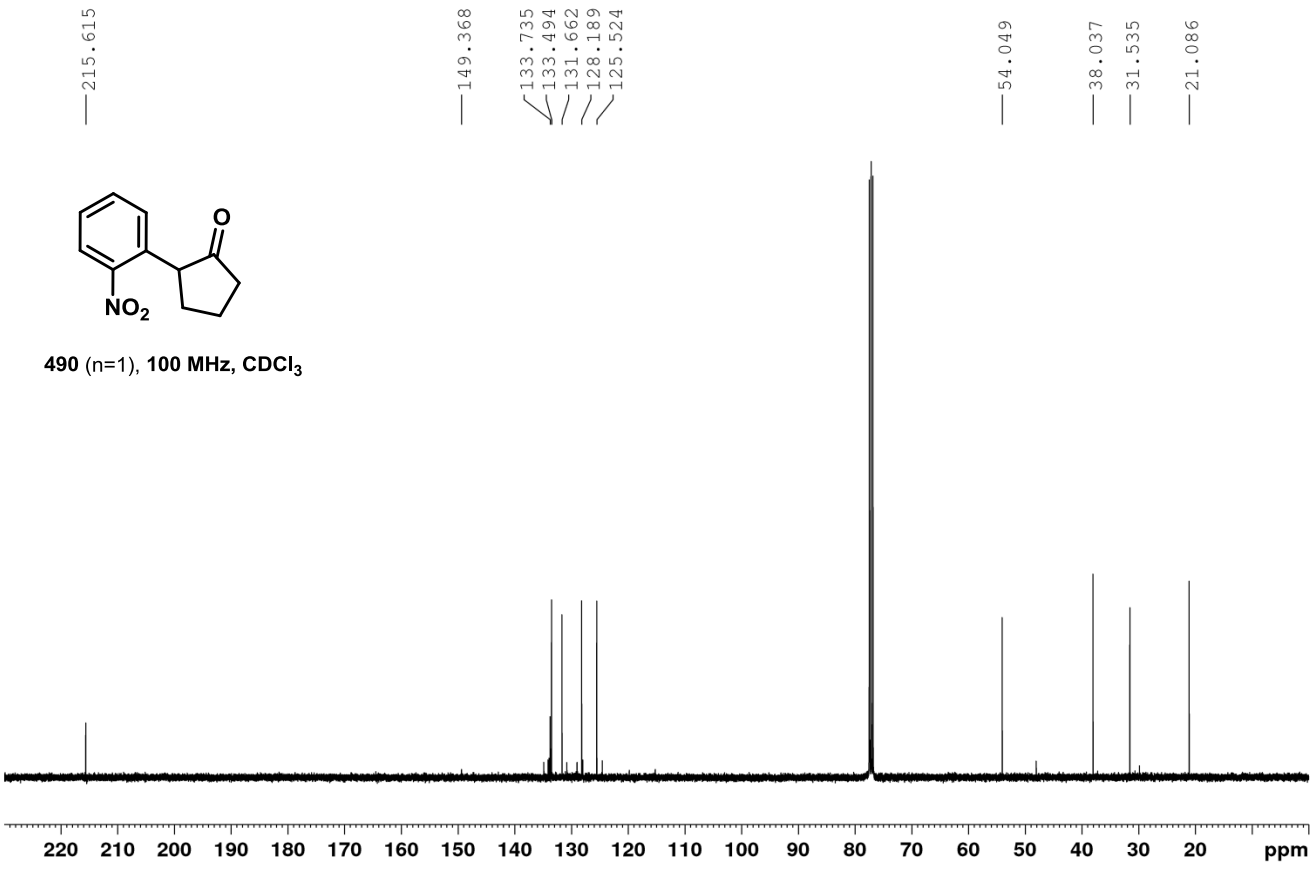




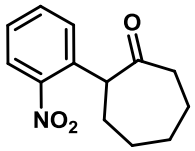
235, 100 MHz, $CDCl_3$



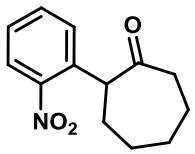
490 (n=1), **400 MHz, $CDCl_3$**



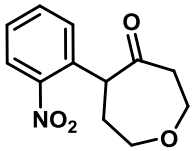
490 (n=1), **100 MHz, $CDCl_3$**



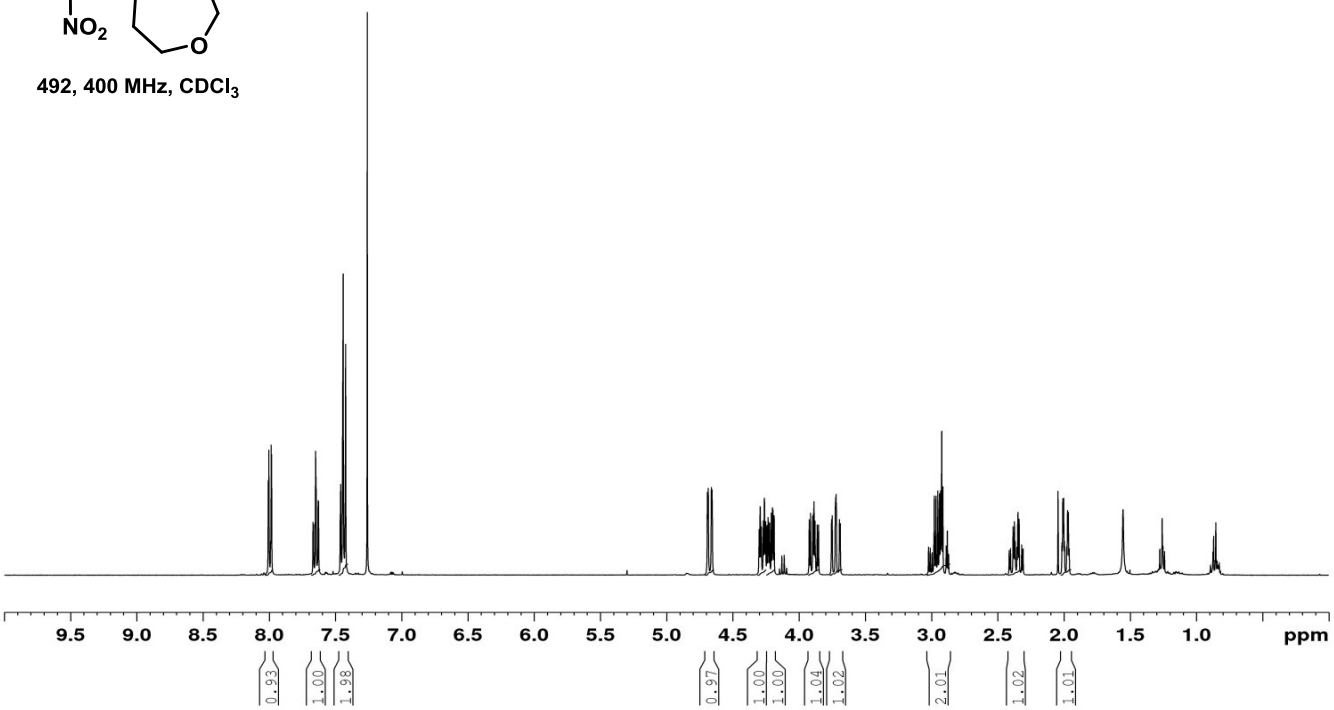
441, 400 MHz, $CDCl_3$

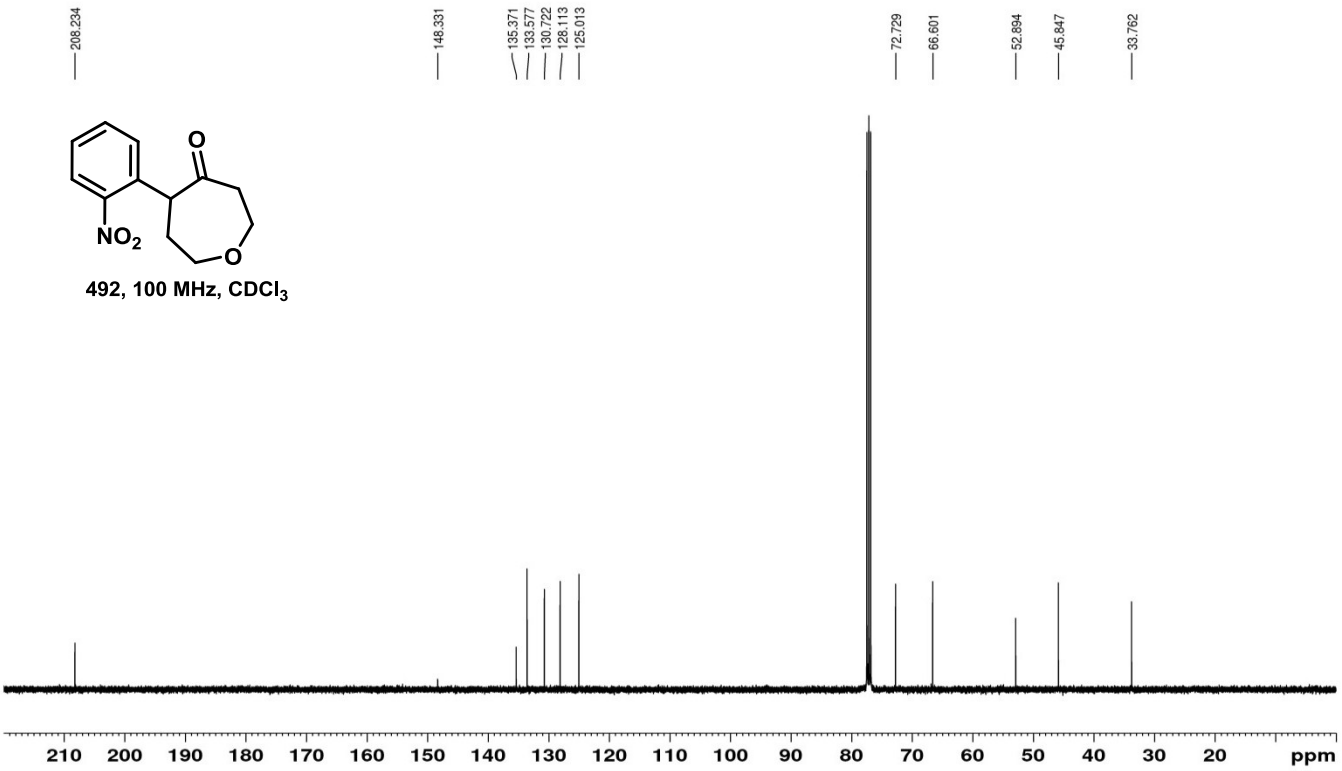


441, 100 MHz, $CDCl_3$

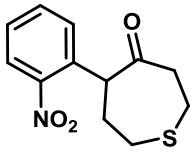


492, 400 MHz, $CDCl_3$

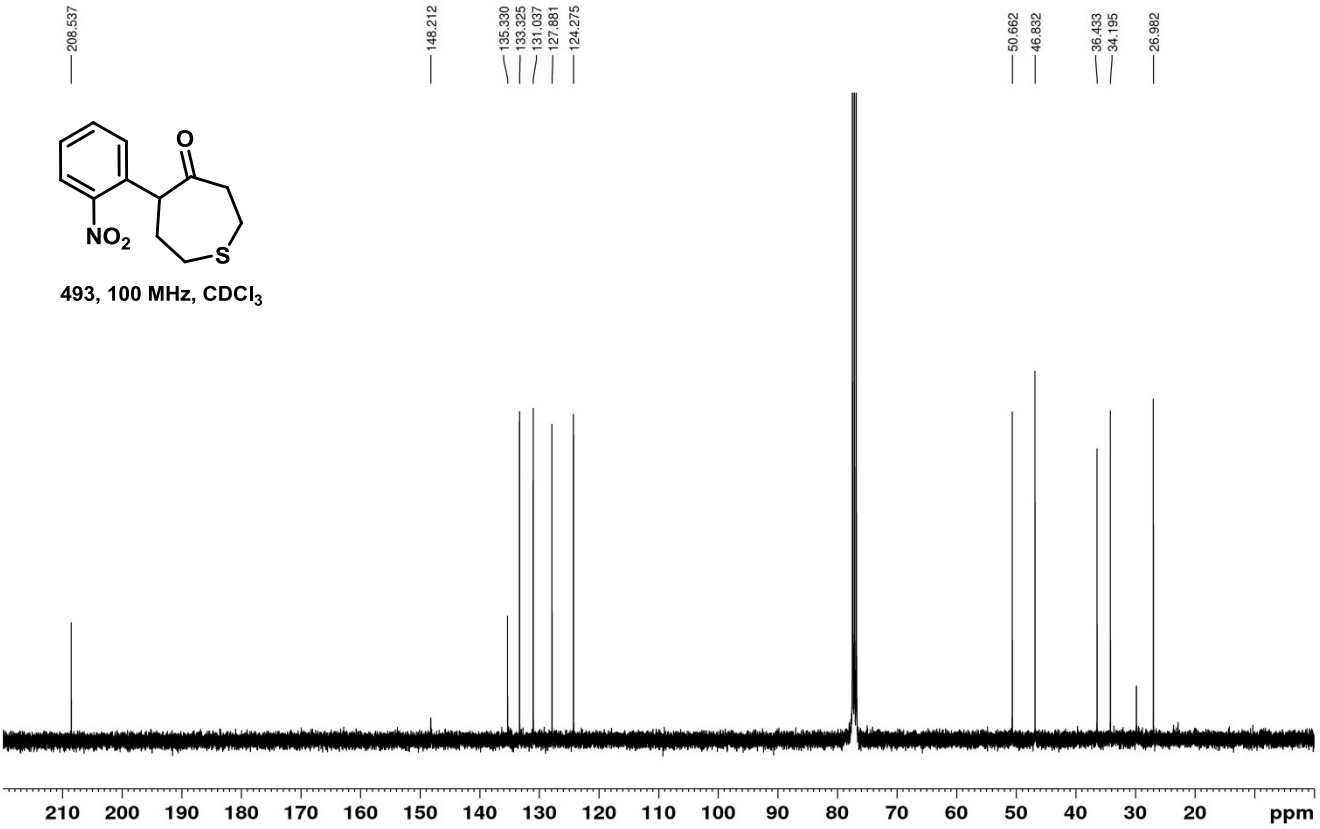




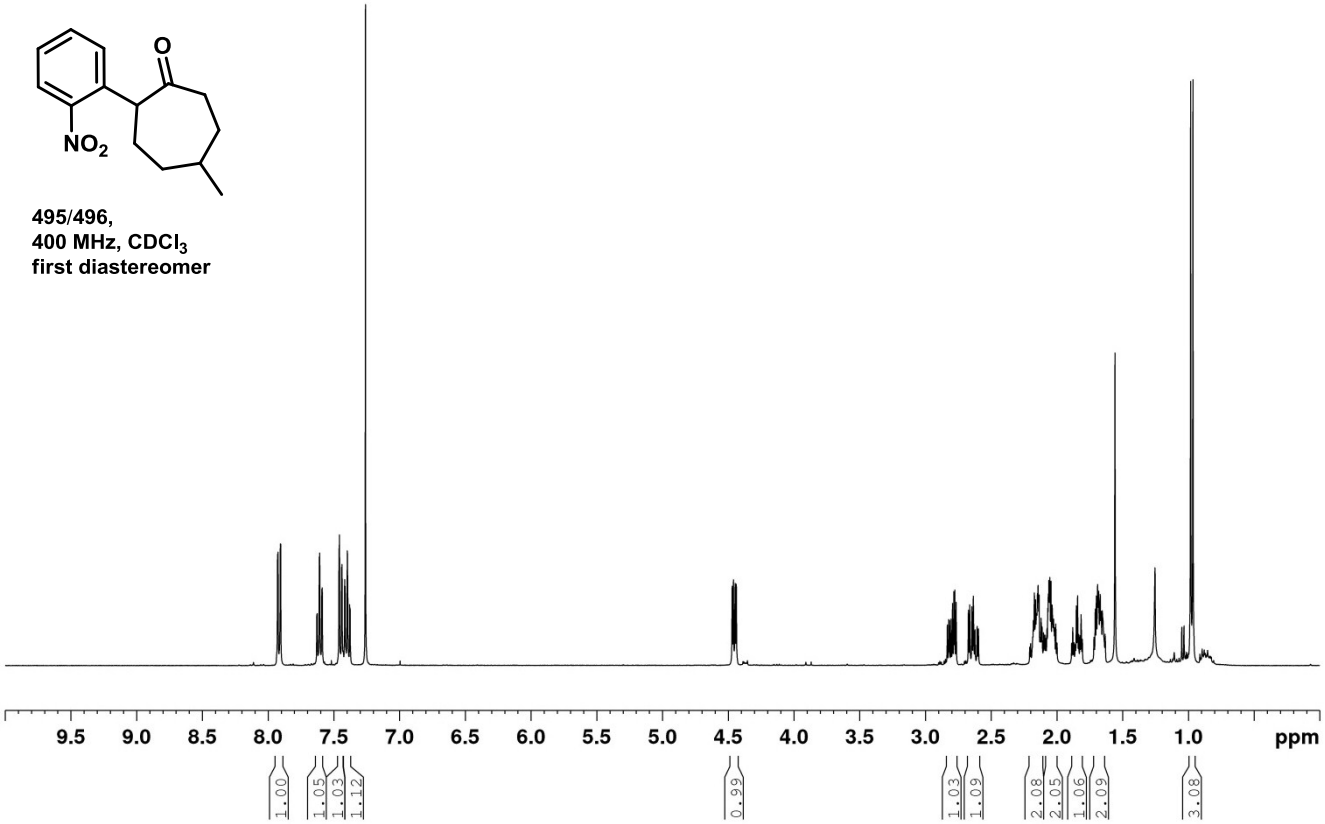
492, 100 MHz, $CDCl_3$



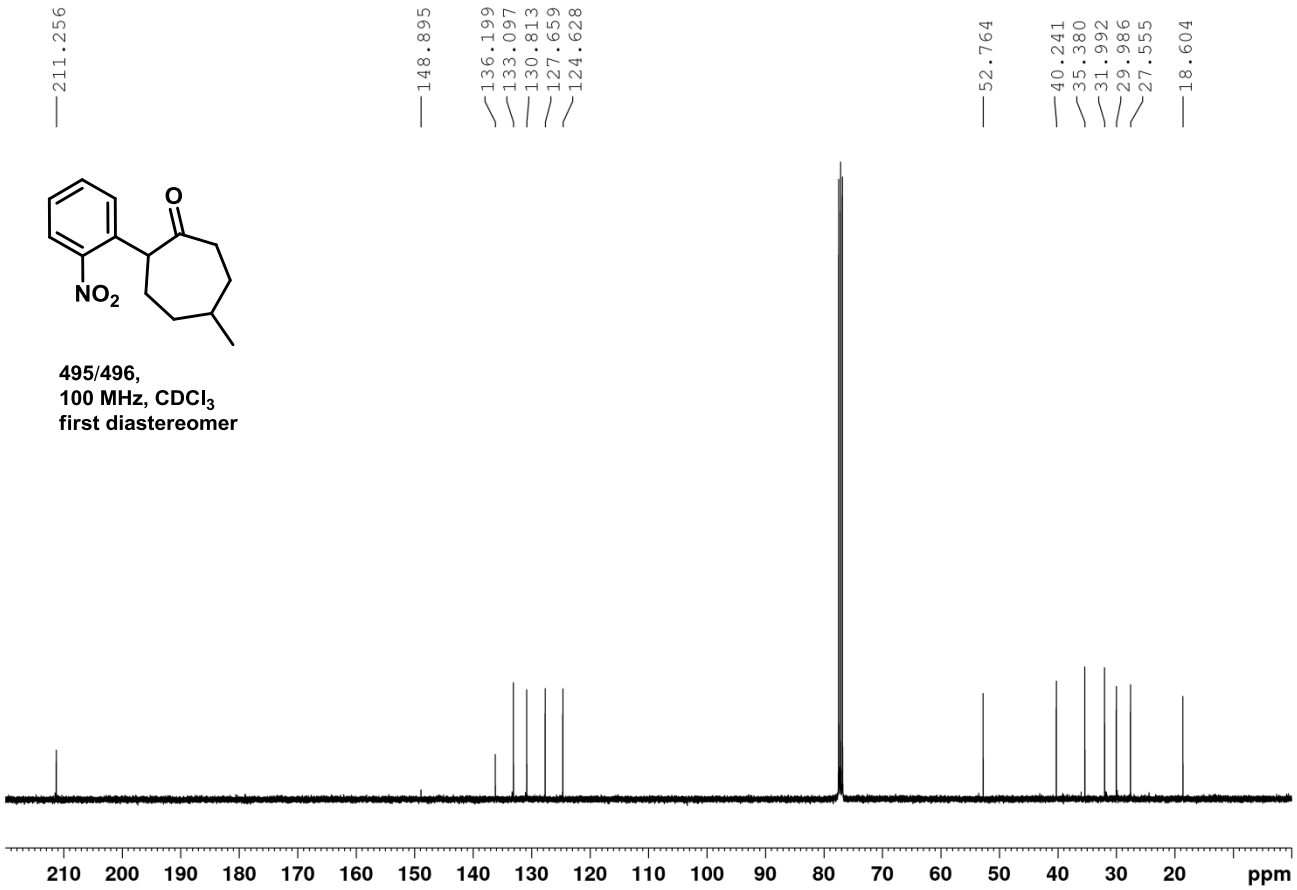
493, 400 MHz, $CDCl_3$



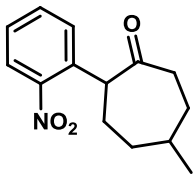
493, 100 MHz, $CDCl_3$



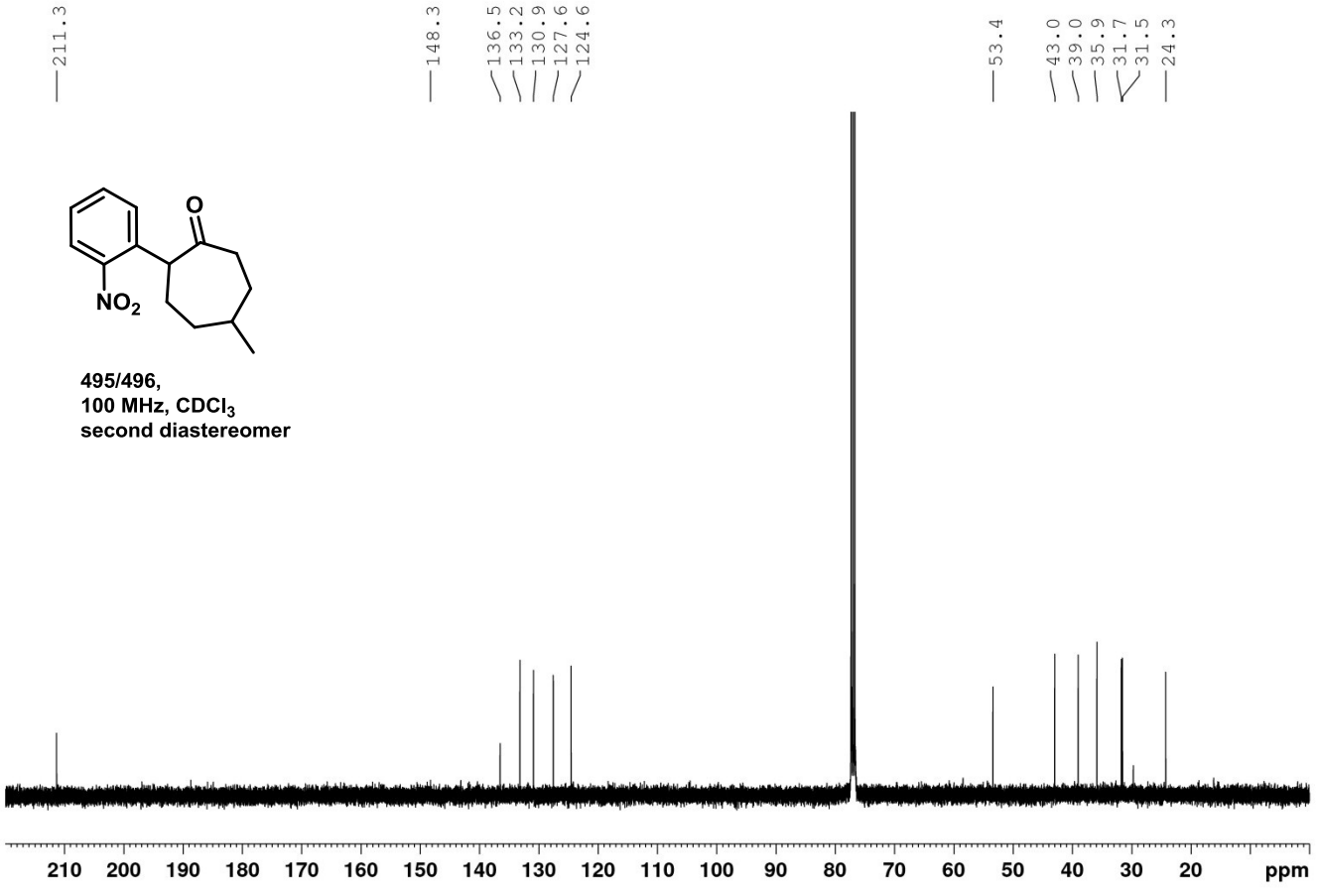
495/496,
400 MHz, $CDCl_3$
first diastereomer



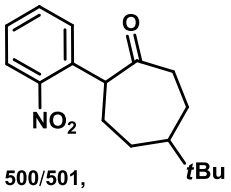
495/496,
100 MHz, $CDCl_3$
first diastereomer



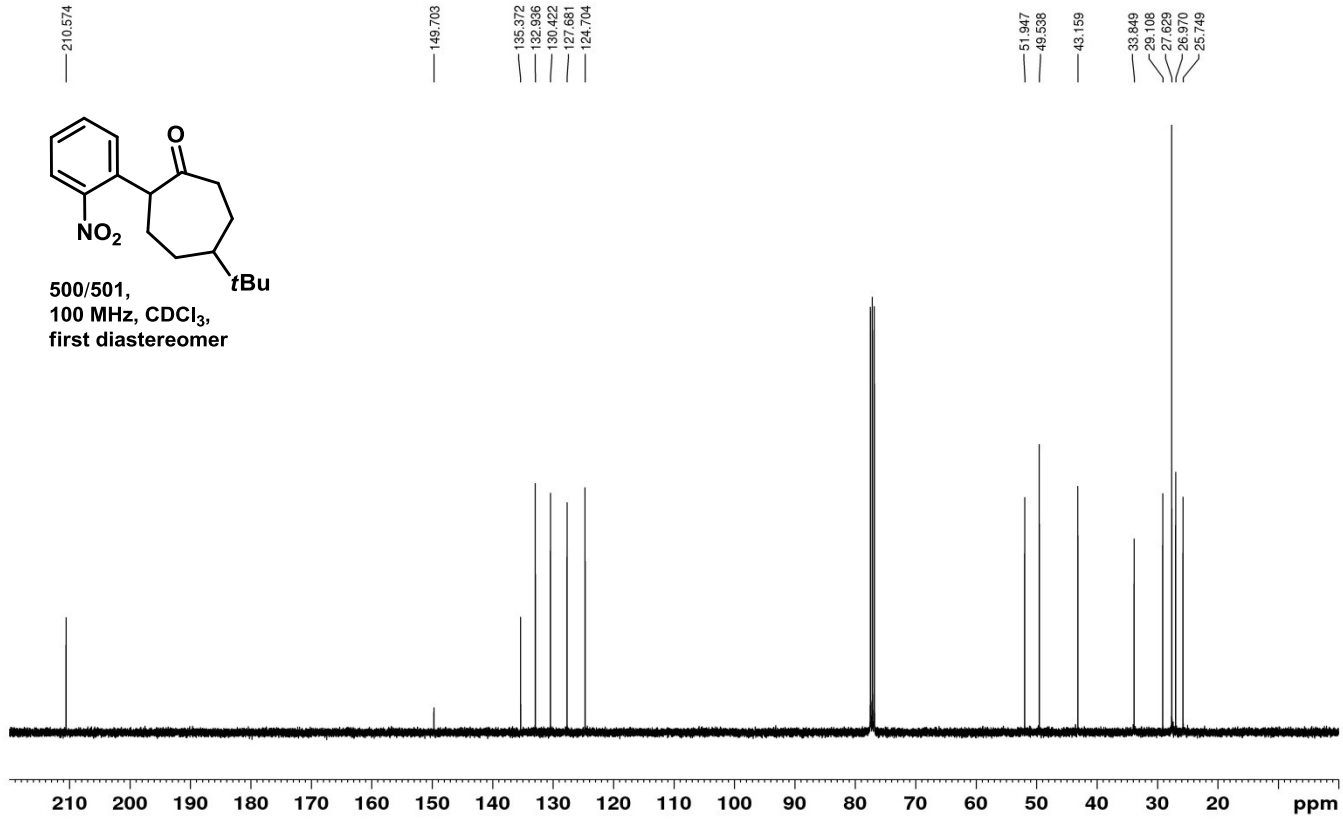
495/496,
400 MHz, $CDCl_3$
second diastereomer



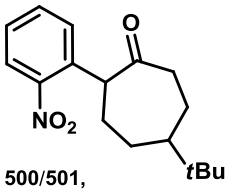
495/496,
100 MHz, $CDCl_3$
second diastereomer



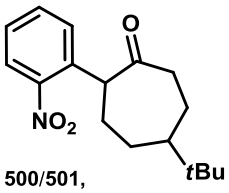
500/501,
400 MHz, $CDCl_3$,
first diastereomer



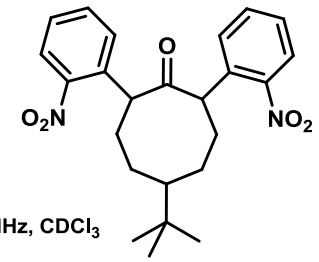
500/501,
100 MHz, $CDCl_3$,
first diastereomer



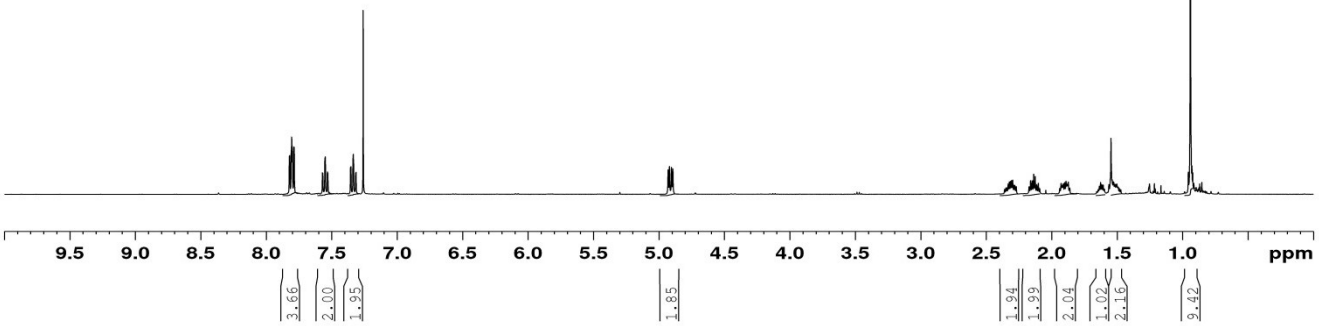
500/501,
400 MHz, $CDCl_3$,
second diastereomer

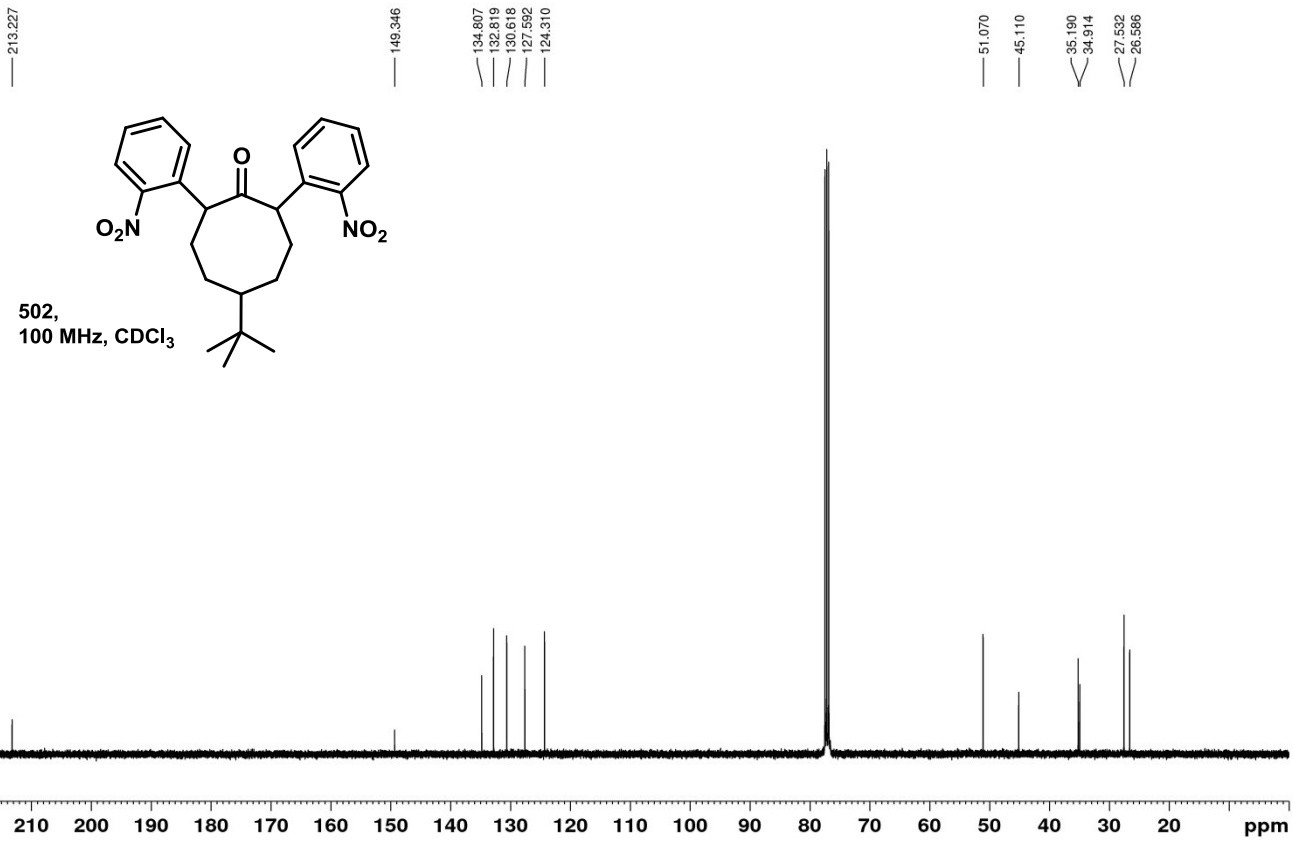


500/501,
100 MHz, $CDCl_3$,
second diastereomer

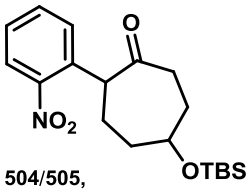


502,
400 MHz, $CDCl_3$

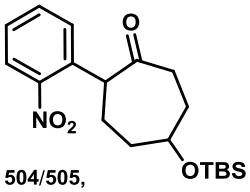




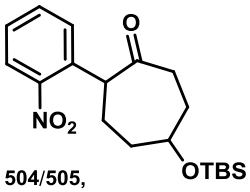
502,
100 MHz, $CDCl_3$



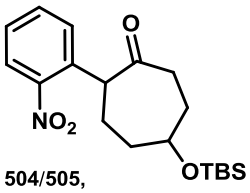
504/505,
400 MHz, $CDCl_3$,
first diastereomer



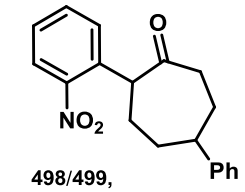
504/505,
100 MHz, $CDCl_3$,
first diastereomer



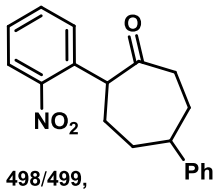
504/505,
400 MHz, $CDCl_3$,
second diastereomer



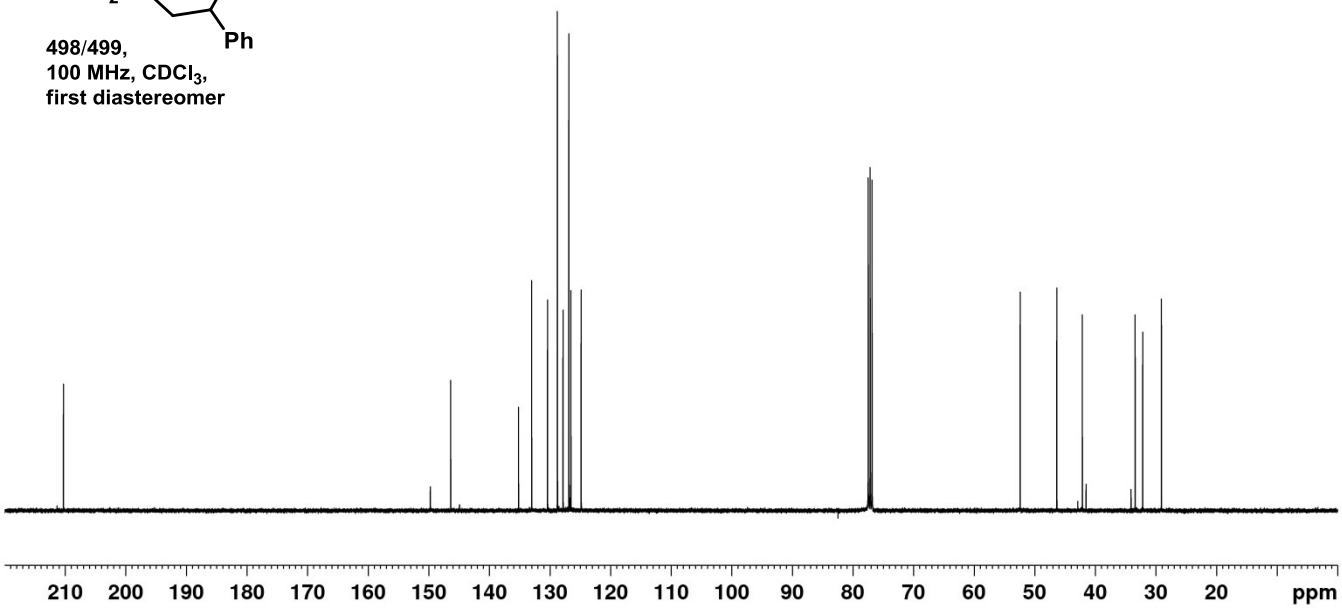
504/505,
100 MHz, $CDCl_3$,
second diastereomer

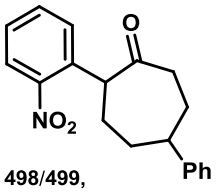


498/499,
400 MHz, $CDCl_3$,
first diastereomer

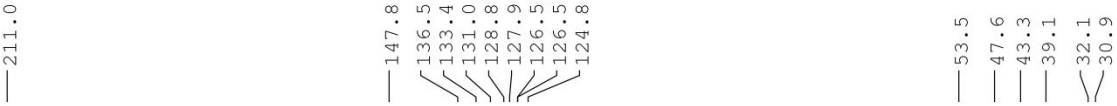


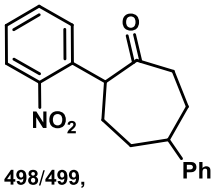
498/499,
100 MHz, $CDCl_3$,
first diastereomer



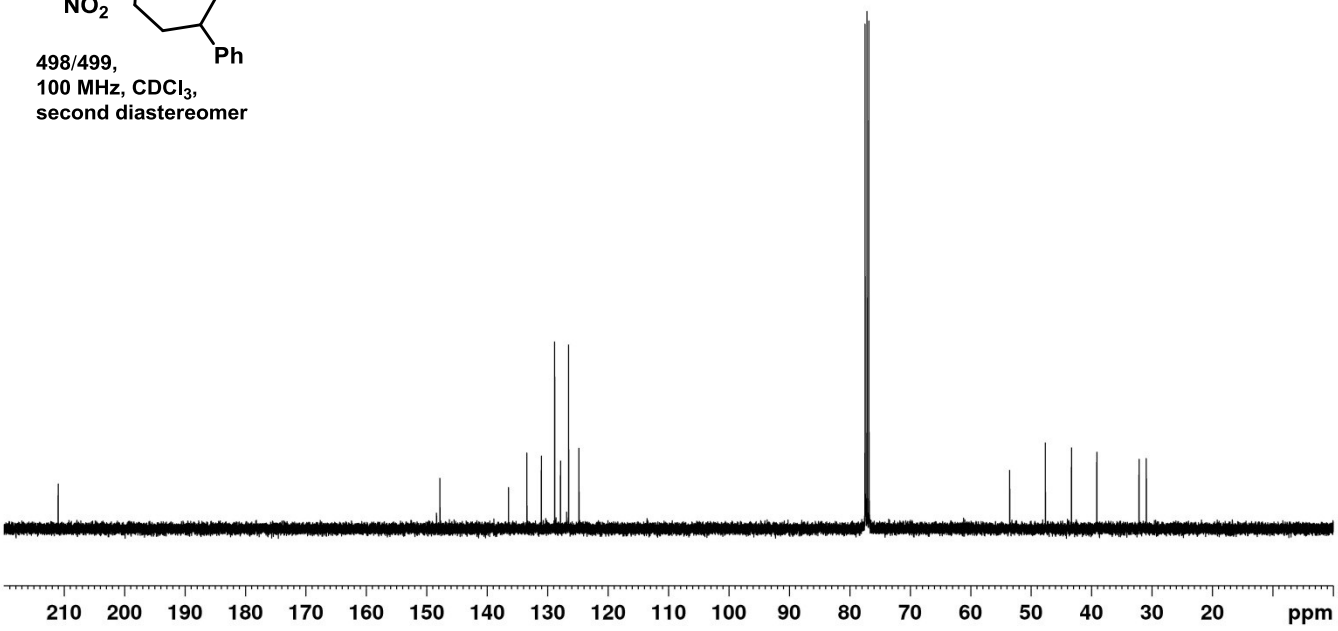


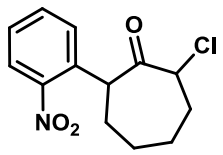
498/499,
400 MHz, $CDCl_3$,
second diastereomer



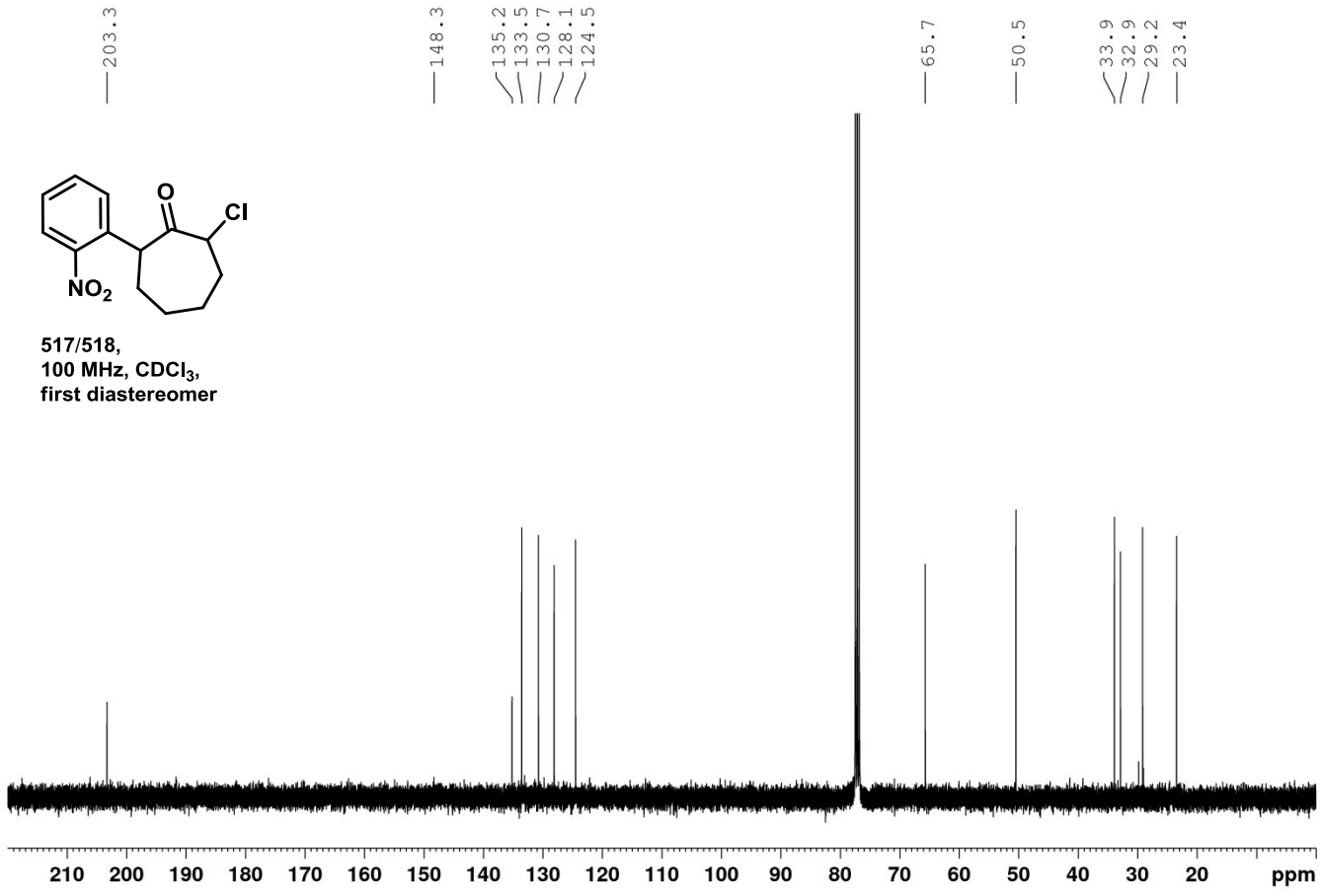


498/499,
100 MHz, $CDCl_3$,
second diastereomer

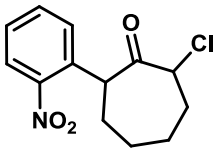




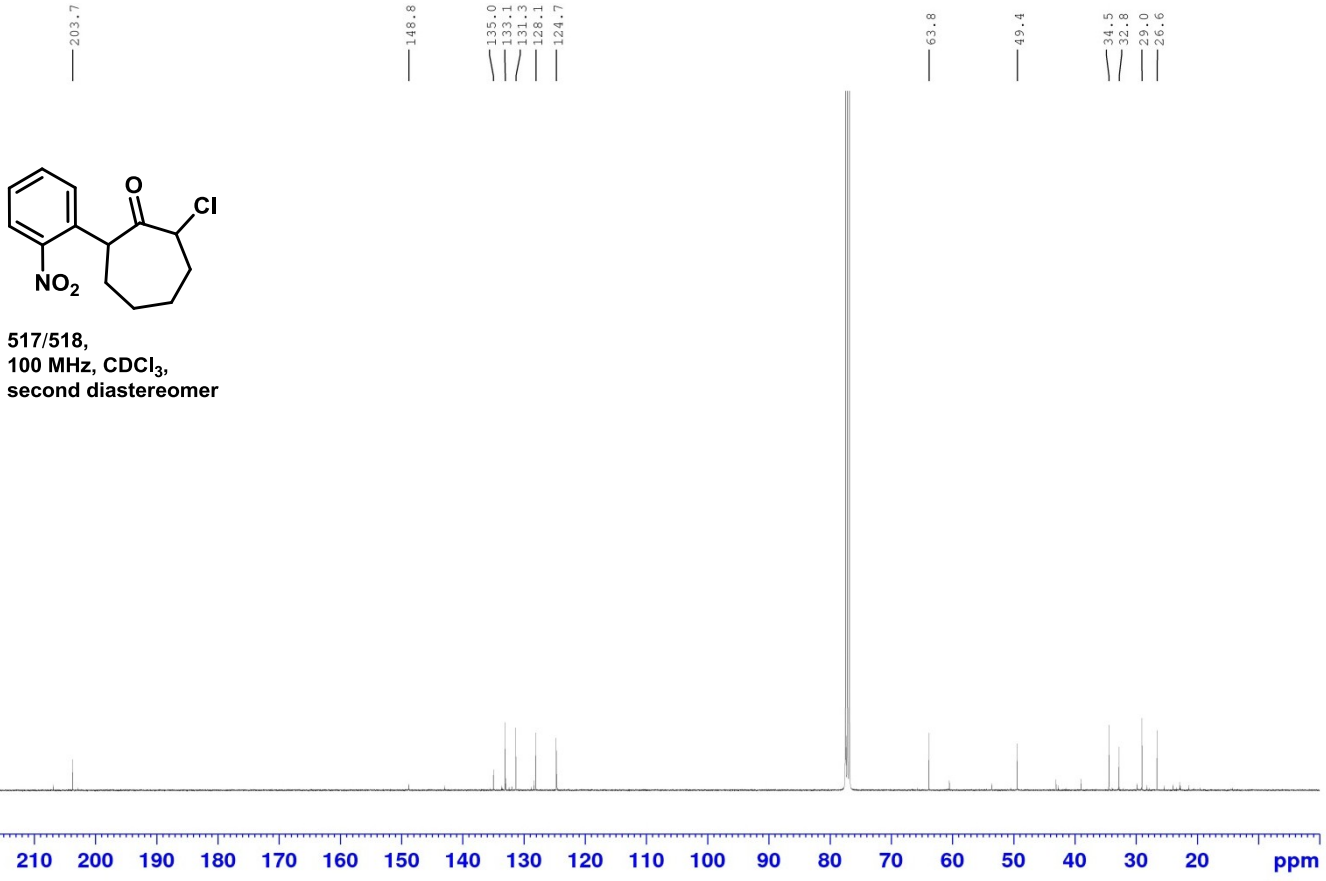
517/518,
400 MHz, $CDCl_3$,
first diastereomer



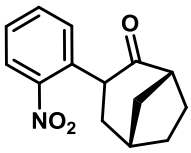
517/518,
100 MHz, $CDCl_3$,
first diastereomer



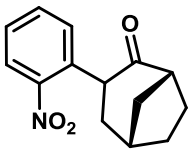
517/518,
400 MHz, $CDCl_3$,
second diastereomer



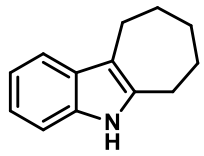
517/518,
100 MHz, $CDCl_3$,
second diastereomer



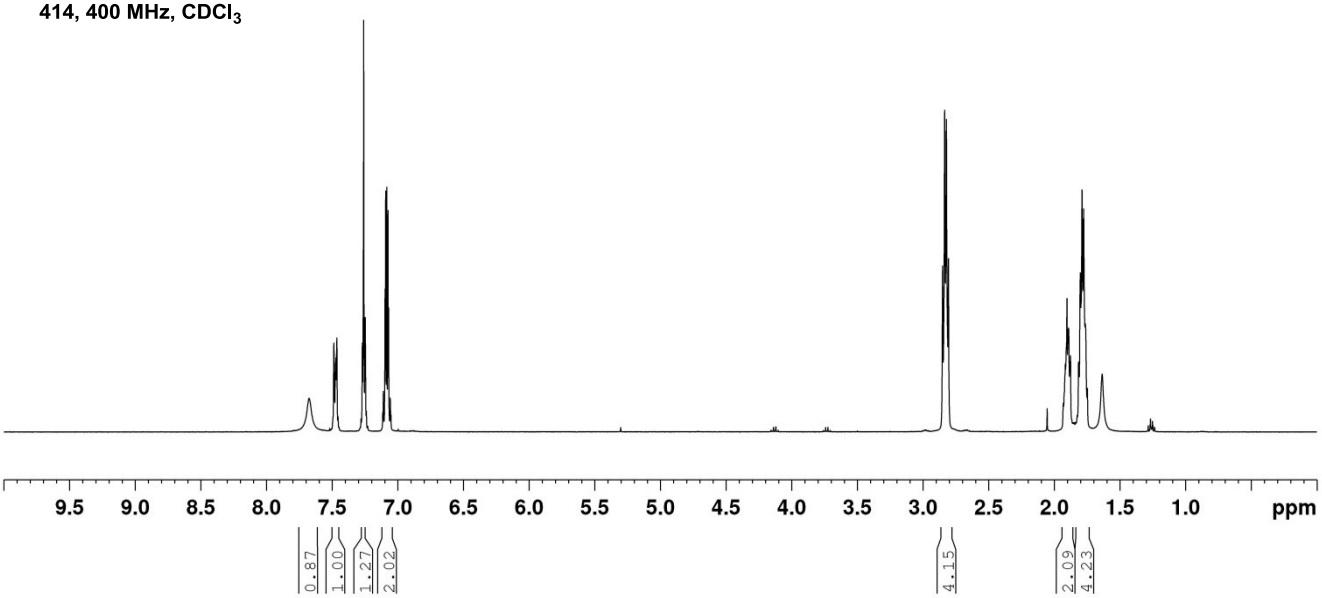
520,
400 MHz, $CDCl_3$

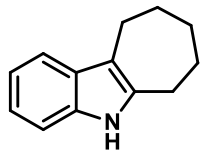


520,
100 MHz, $CDCl_3$

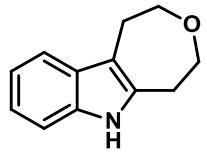


414, 400 MHz, $CDCl_3$

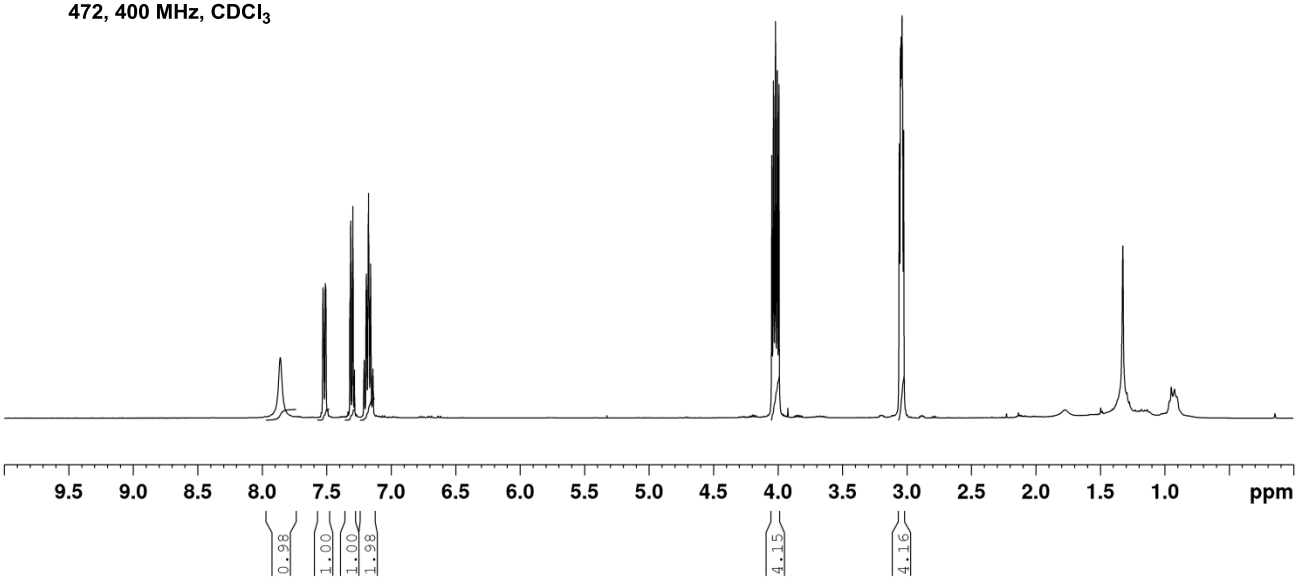


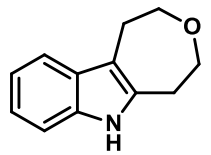


414, 100 MHz, $CDCl_3$

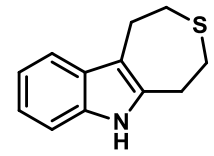


472, 400 MHz, $CDCl_3$

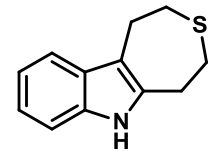




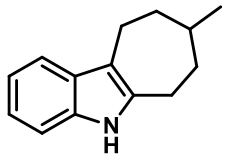
472, 100 MHz, $CDCl_3$



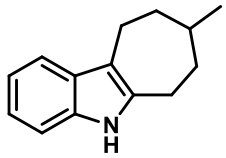
479, 400 MHz, $CDCl_3$



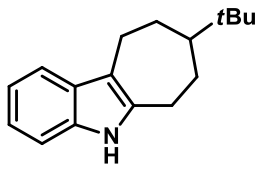
479, 100 MHz, $CDCl_3$



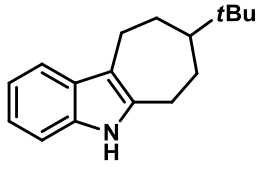
483, 400 MHz, $CDCl_3$



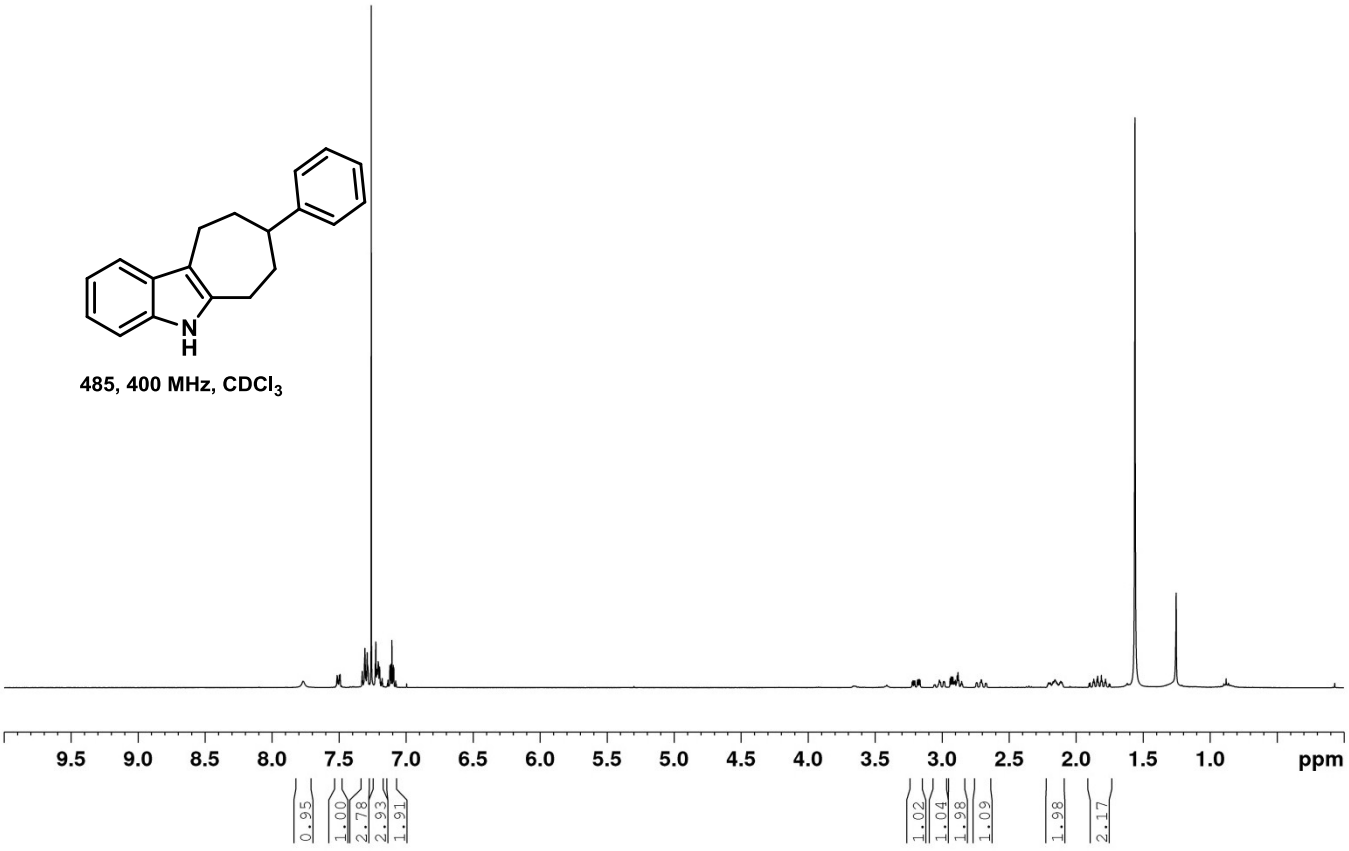
483, 100 MHz, $CDCl_3$



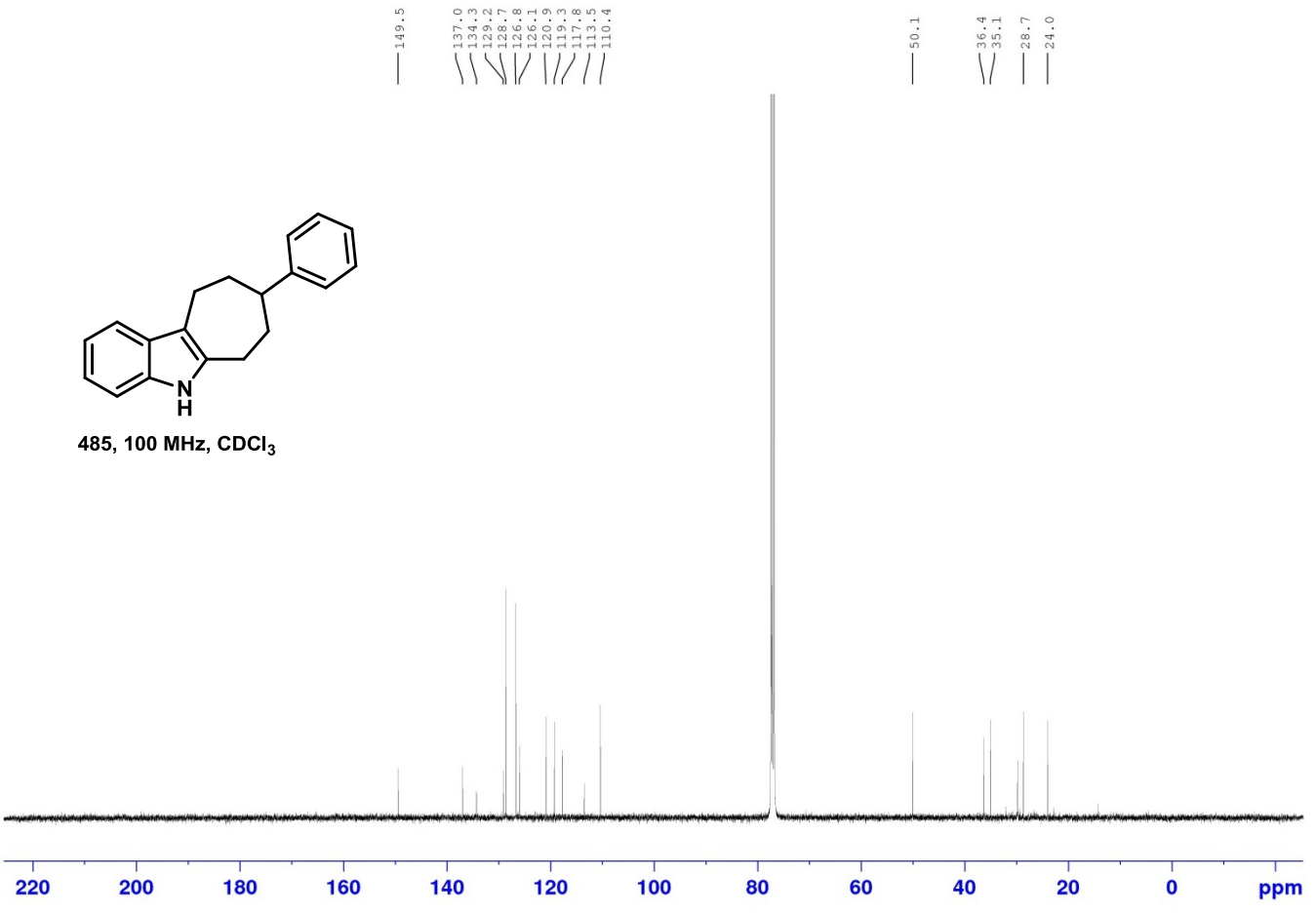
484, 400 MHz, $CDCl_3$



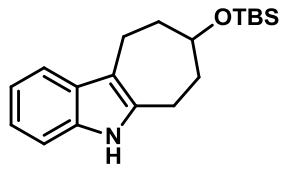
484, 100 MHz, $CDCl_3$



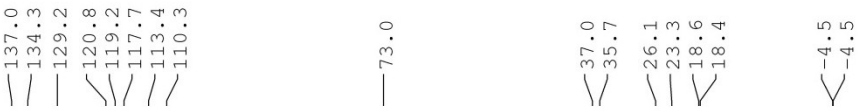
485, 400 MHz, $CDCl_3$

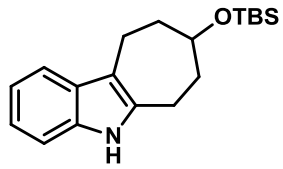


485, 100 MHz, $CDCl_3$

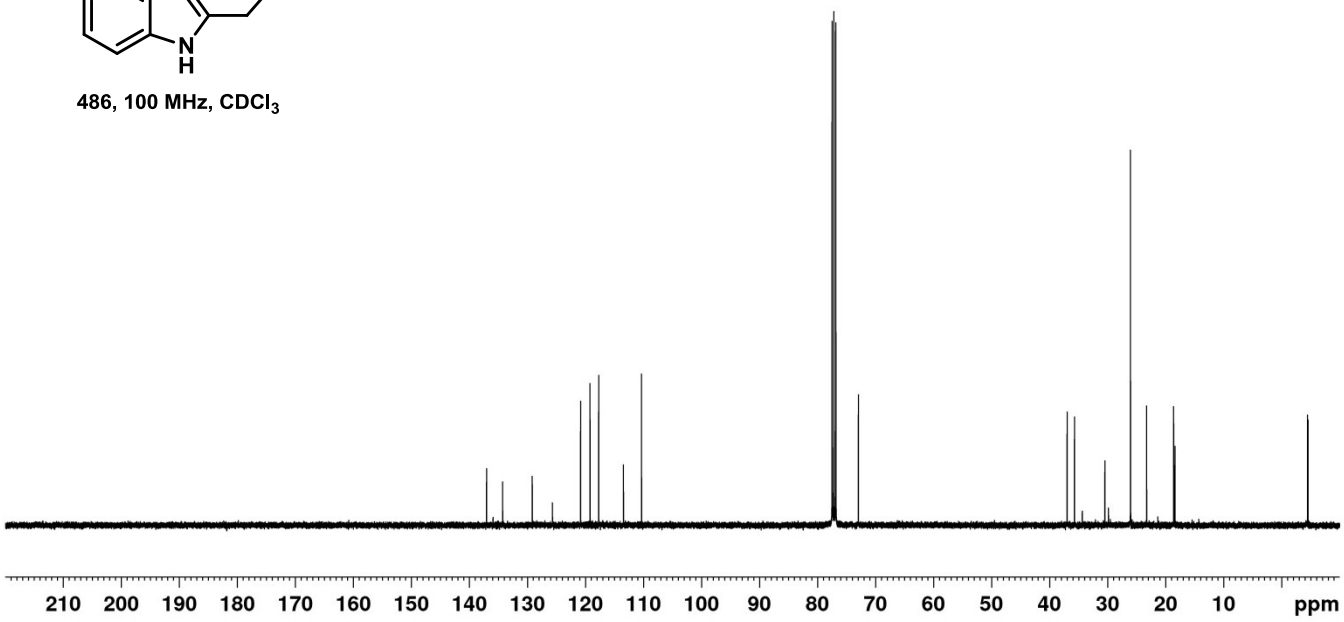


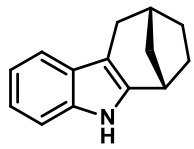
486, 400 MHz, $CDCl_3$



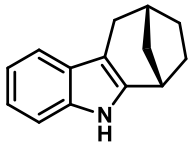


486, 100 MHz, $CDCl_3$

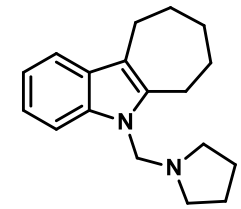




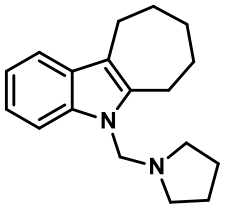
481, 400 MHz, $CDCl_3$



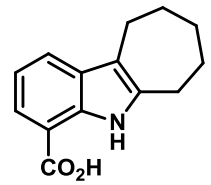
481, 100 MHz, $CDCl_3$



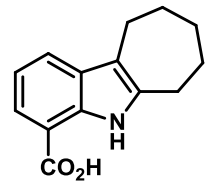
522, 400 MHz, $CDCl_3$



522, 100 MHz, $CDCl_3$



523, 400 MHz, $CDCl_3$



523, 100 MHz, $CDCl_3$

4.10 References

[4.1] L. Dempwolff, "*Development of a diazo-mediated indole synthesis*", Master Thesis at the Gottfried Wilhelm Leibniz Universität Hannover, **2015**

[4.2] J. R. Knox, J. Slobbe, *Tetrahedron Letters*, **1971**, *24*, 2149–2151.

[4.3] P. C. Riche, *Acta. Christ. B.* **1974**, *30*, 610–616.

[4.4] A. R. Carroll, E. Hyde, J. Smith, R. J. Quinn, G. Guymer, P. I. Forster, *J. Org. Chem.* **2005**, *70*, 1096–1099.

[4.5] Z.-J. Zhang, J. Yang, J. He, X.-D. Wu, L.-D. Shao, Y. Li, S.-X. Huang, R.-T. Li, Q.-S. Zhao, *Tetrahedron Letters*, **2014**, *55*, 6490–6494.

[4.6] M. Gorman, N. Neuss, N. J. Cone, *J. Am. Chem. Soc*. **1965**, *87*, 93–99.

[4.7] S. Serte, Y. Fu, Y. Zu, B. Rebacz, B. Konkimalla, P. K. Plinkert, A. Kramer, J. Gertsch, T. Efferth, *Biochemical Pharmacology*, **2011**, *81*, 723–735.

[4.8] H. Ishikawa, D. A. Colby, S. Seto, P. Va, A. Tam, K. Kakei, T. J. Rayl, I. Hwang, D. L. Boger, *J. Am. Chem. Soc.* **2009**, *131*, 4904–4916.

[4.9] A. D. Napper, J. Hixon, T. McDonagh, K. Keavey, J.-F. Pons, J. Barker, W. Yau, P. Amouzegh, A. Flegg, E. Hamelin, R. J. Thomas, M. Kates, S. Jones, M. A. Navia, J. O. Saunders, P. S. DiStefano, R. Curtis, *J. Med. Chem.* **2005**, *48*, 8045–8054.

[4.10] T. Barf, F. Lehmann, K. Hammer, S. Haile, E. Axen, C. Medina, J. Uppenberg, S. Svensson, L. Rondahl, T. Lundbäck, *Bioorganic & Medicinal Chemistry Letters*, **2009**, *19*, 1745–1748.

[4.11] G. Tuncman, E. Erbay, I. De Vivo, H. Campos, E. B. Rimm, G. S. Hotamisligil, *PNAS*, **2006**, *103*, 6970–6975.

[4.12] C. E. Holmquist, J. Roskamp, *J. Org. Chem*. **1989**, *54*, 3528–3560.

[4.13] C. E. Holmquist, J. Roskamp, *Tetrahedron. Lett.* **1992**, *33*, 1131–1134.

[4.14] K. Maruoka, A. B. Concepcion, H. Yamamoto, *Synthesis*, **1994**, 1283–1290.

[4.15] S. Yang, B. Hungerhoff, P. Metz, *Tetrahedron Lett.* **1998**, 2097–2098.

[4.16] D. C. Moebius, J. S. Kingsbury, *J. Am. Chem. Soc.* **2009**, *131*, 878–879.

[4.17] V. L. Rendina, D. C. Moebius, J. S. Kingsbury, *Org. Lett.* **2011**, *13*, 2004–2007.

[4.18] V. L. Rendina, H. Z. Kaplan, J. S. Kingsbury, *Synthesis*, **2012**, 686–693.

[4.19] T. Hashimoto, Y. Naganawa, K. Maruoka, *J. Am. Chem. Soc.* **2011**, *133*, 8834–8837.

[4.20] Y. Zhang, J. Wang, *Chem. Commun.* **2009**, 5350–5361.

[4.21] T. Iwama, V. B. Birman, S. A. Kozmin, V. H. Rawal, *Org Lett.* **1999**, *1*, 673–676.

[4.22] S. A. Kozmin, V. H. Rawal, *J. Am. Chem. Soc.* **1998**, *120*, 13523–13524.

[4.23] E. Merritt, B. Olofsson, *Synthesis*, **2011**, *4*, 517–538

[4.24] W. Ried, M. Ritz, *Liebigs Ann. Chem.* **1966**, *691*, 50–54.

[4.25] E. Ohtsuka, T. Wakabayashi, S. Tanaka, T. Tanaka, K. Oshie, A. Hasegawa, M. Ikehara, *Chem. Pharm. Bull.* **1981**, *29*, 318–324.

[4.26] C. C. Dudman, C. B. Reese, *Synthesis*, **1982**, 419–421.

[4.27] K. Tomioka, N. Iochikawa, K. Komatsu, *J. Am. Chem. Soc.* **1992**, *144*, 8045–8053.

[4.28] for a review see: D. F. Taber, P. K. Tirunahari, *Tetrahedron*, **2011**, *67*, 7195–7210.

[4.29] S. Gore, S. Baskaran, B. König, *Org. Lett*. **2012**, *14*, 4568–4571.

[4.30] Q. Nguyen, T. Nguyen, T. G. Driver, *J. Am. Chem. Soc.* **2013**, *135*, 620−623.

[4.31] K. G. Liu, A. J. Robichaud, J. R. Lo, J. F. Mattes, Y. Cai, *Org. Lett*. **2006**, *8*, 5769-5771.

[4.32] B.-Y. Lim, B.-E. Jung, C.-G. Cho, *Org. Lett*. **2014**, *16*, 4492−4495.

[4.33] P. Linnepe, A. M. Schmidt, P. Eilbracht, *Org. Biomol. Chem.* **2006**, *4*, 302–313.

[4.34] C. Min Wong, K. Q. Vuong, M. R. D. Gatus, C. Hua, M. Bhadbhade, B. A. Messerle, *Organometallics*, **2012**, *31*, 7500−7510.

[4.35] M. G. Banwell, B. D. Kelly, O. J. Kokas, D. W. Lupton, *Org. Lett*. **2003**, *5*, 2497–2500.

[4.36] G. Adam, J. Andrieux, M. Plat, *Tetrahedron*, **1985**, *41*, 399–407.

[4.37] P. J. Gritsch, E. Stempel, T. Gaich, *Org. Lett.* **2013**, *15*, 5472–5475.

[4.38] N. S. Dange, B.-C. Hong, C.-C. Lee, G.-H. Lee, *Org. Lett.* **2013**, *15*, 3914–3917.

[4.39] G. Mei, H. Yuan, Y. Gu, W. Chen, L. W. Chung, C.-C. Li, *Angew. Chem. Int. Ed.* **2014**, *53*, 11051–11055.

[4.40] A. Chakraborty, K. Goswami, A. Adiyala, S. Sinha, *Eur. J. Org. Chem.* **2013**, 7117–7127.

[4.41] K. Sun, S. Liu, P. M. Bec, T. G. Driver, *Angew. Chem. Int. Ed*. **2011**, *50*, 1702–1706.

[4.42] L. A. Aksanova, *Journal of Organic Chemistry USSR (English Translation)*, **1965**, *1*, 2254–2257.

[4.43] V. P. Arya, S. J. Shenoy, *Indian Journal of Chemistry*, **1972**, *10*, 815–819.

[4.44] G. S. Hotamisligil, R. S. Johnson, R. J. Distel, R. Ellis, V. E. Papaioannou, B. M. Spiegelman, *Science*, **1996**, *274*, 1377–1379.

[4.45] L. Makowski, J. B. Boord, K. Maeda, V. R. Babaev, K. T. Uysal, M. A. Morgan, R. A. Parker, J. Suttles, S. Fazio, G. S. Hotamisligil, M. F. Linton, *Nat. Med*. **2001**, *7*, 699–705.

[4.46] H. Hoberg, *Angew. Chem. Int. Ed.* **1966**, *5*, 513–514.

[4.47] H. Hoberg, *Liebigs Ann. Chem.* **1962**, *656*, 1–14.

[4.48] for experimentals for those reactions see reference 4.1

[4.49] A. R. Katritzky, G. W. Rewcastle, L. M. Vazquez de Miguel, *J. Org. Chem.* **1988**, *53*, 794–799.

[4.50] B. O. Ashburn, R. G. Carter, *Angew. Chem. Int. Ed*. **2006**, *45*, 6737–6741.

[4.51] C. L. Diedrich, D. Haase, J. Cristoffers, *Synthesis*, **2008**, *14*, 2199–2210.

[4.52] F. Bischoff, D. Berthelot, M. De Cleyn, G. Macdonald, G. Minne, D. Oehlrich, S. Pieters, M. Surkyn, A. A. Trabanco, G. Tresadern, S. Van Brandt, I. Velter, M. Zaja, H. Borghys, C. Masungi, M. Mercken, H. J. M. Gijsen, *J. Med. Chem.* **2012**, *55*, 9089−9106.

5 Summary and Outlook

I In the first project within this thesis, we were able to demonstrate the access towards four members of the *sarpagine* alkaloids in 15-16 steps in overall good yield. Our synthesis is carried out in an enantioselective, protecting group free fashion and targets multiple alkaloids *via* a late stage diversification strategy (see figure 36). As the key step we employed the 3-oxidopyridinium [5+2] cycloaddition of vinylbissulfoxide **196** and pyridinium ion **197**.

For *sarpagine* alkaloids bearing substitution at the indole core (like **8** or **9**) our synthesis is by far the shortest access. We should now be able to produce nearly all members of the 16-epi and the 16-regular subgroup of *sarpagine* alkaloids which have not suffered from dimerization or additional ring formation. This amounts to 48 of the 99 alkaloids isolated so far.

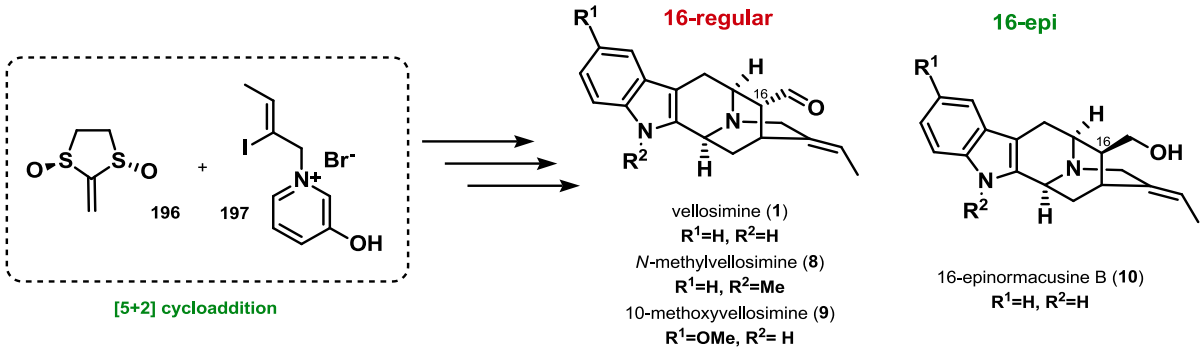


Figure 36: Summary of the *sarpagine* project.

The key synthetic challenges of vellosimine (**1**) and our synthetic solutions are summarized in figure 37. Vellosimine contains five contiguous stereocenters, four at carbon atoms and one being the N_b-nitrogen, as no inversion can occur with the nitrogen lone pair. Stereocenters 1 and 3 arise from the stereochemistry that is introduced during the asymmetric 3-oxidopyridinium [5+2] cycloaddition. Stereocenters 4 and 5 are generated during the Pd-catalyzed enolate coupling. Stereocenter 3 is generated during the Fischer indole synthesis at the very end of the synthesis, as the resulting aldehyde is stereoselectivly equilibrated to the desired stereochemistry. In the synthesis of 16-epinormacusine B (**10**) stereocenter 3 results from less steric interactions during the final hydroboration reaction.

The *sarpagine* skeleton in general contains two *cis*-quinolizidine systems, both of them are installed in our synthetic access during the Pd-catalyzed enolate coupling. Vellosimine's signature quinuclidine core is assembled in the same Pd-catalyzed reaction. The azabicyclo[3.3.1]nonane core is assembled through two key steps in the synthesis, the 3-oxidopyridinium [5+2] cycloaddition and the diazo ring expansion.

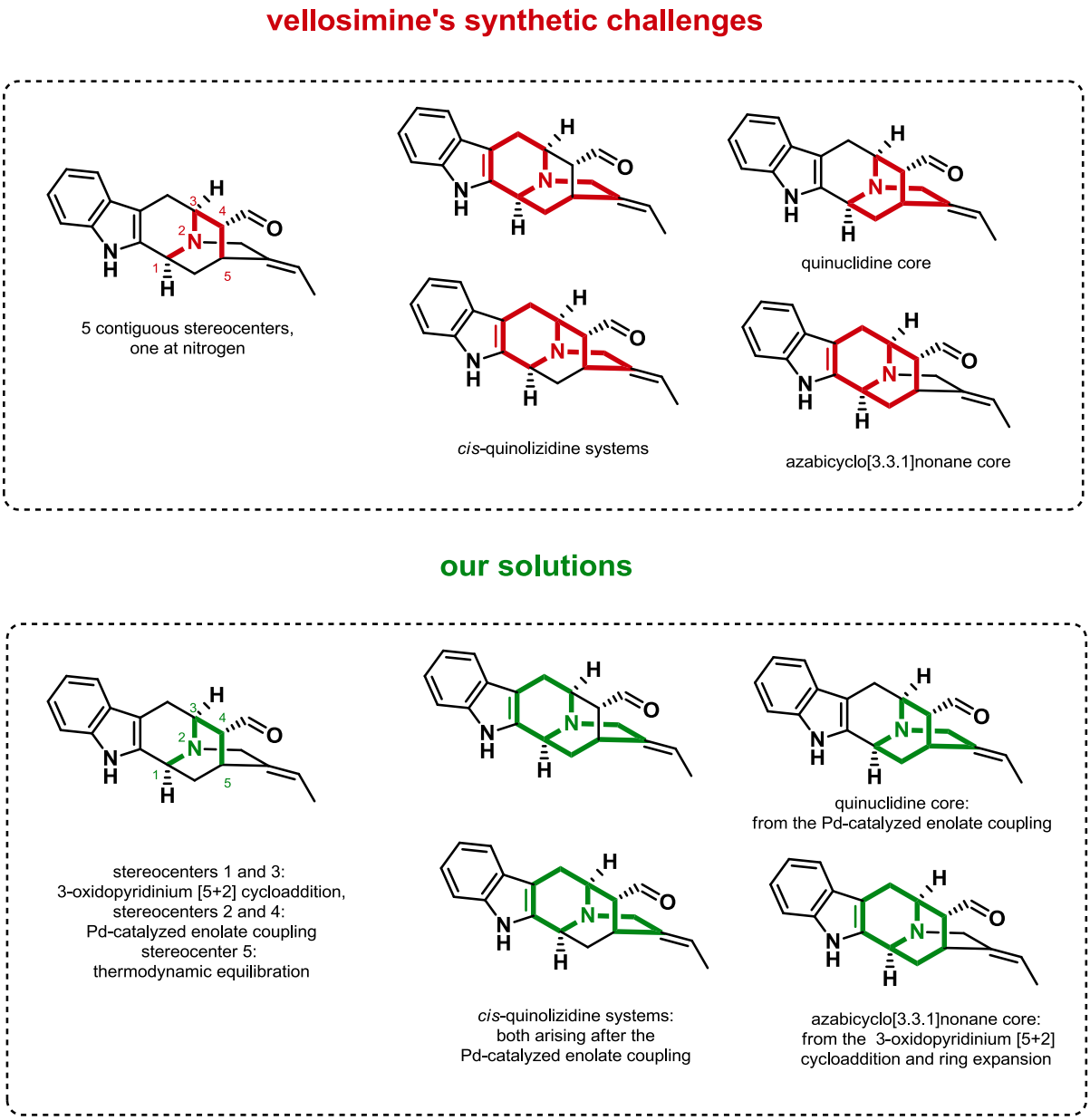


Figure 37: Key synthetic challenges of vellosimine (**1**) and our synthetic solutions.

Further progress within the *sarpagine* alkaloids will be achieved by the synthesis of dimers, which is currently investigated. Unnatural *sarpagine* alkaloids will be prepared using our late stage diversification strategy with unnatural phenylhydrazine derivatives and will be tested for their bioactivities (see scheme 33 for details). We can furthermore expand our synthetic strategy towards the peraksine subgroup of *sarpagine* alkaloids (see figure 21 for details).

II In the second project within this thesis, we have established an enantiodivergent, protecting group free access to the *stemona* alkaloid parvineostemonine (**2**). We are able to prepare each antipode of the natural product in only nine steps from known starting materi-

als. Our synthesis is carried out in an enantiodivergent, protecting group free fashion with the 3-oxidopyridinium [5+2] cycloaddition between vinylbissulfoxide **196** and pyridinium ion **371** as the key step.

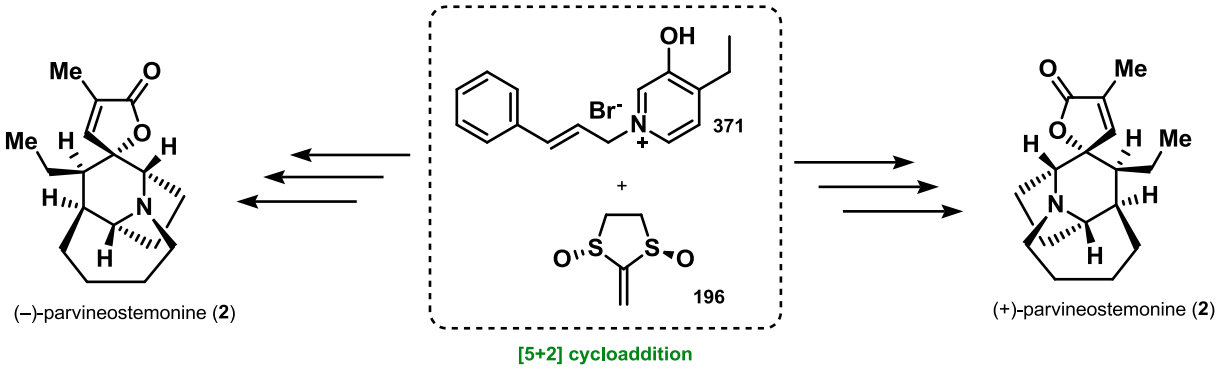


Figure 38: Summary of the parvineostemonine project.

The biggest challenge in the synthesis of parvineostemonine (**2**) is the central piperidine moiety which is substituted at every position, resulting in six contiguous stereocenters (see figure 39). We were able to install stereocenters 2 and 6 in a stereoselective fashion during the course of the 3-oxidopyridinium [5+2] cycloaddition. The conjugate addition of an allyl moiety from the opposite side as the C2 bridge results in the formation of stereocenter 5. Stereocenter 1 at the piperidine nitrogen is fixed after the ring closing metathesis to form the azepane ring. The α-stereocenter is installed *via* equilibration of this position and separation of the two diastereomers. Stereocenter 3 is installed in a stereoselective fashion during the Reformatzky based spirofuranone synthesis.

The azabicyclo[3.2.1]octane core is installed in the key 3-oxidopyridinium [5+2] cycloaddition enantioselectively.

The azabicyclo[4.3.1]decane substructure is assembled *via* a Michael addition and later ring closing metathesis to form the azepane moiety. The piperidine moiety in this substructure results from reduction of the starting material 3-hydroxypyridine.

Most *stemona* alkaloids bear a signature pyrrolo[1,2-*a*]azepane motife, which is assembled in our synthesis through a mixture of the 3-oxidopyridinium [5+2] cycloaddition, a Michael addition and later ring closing metathesis.

In the last steps of the synthesis, we installed the spirofuranone moiety of parvineostemonine (**2**) *via* a two step process consisting of a Reformatzky reaction and a rhodium-catalyzed double bond isomerization.

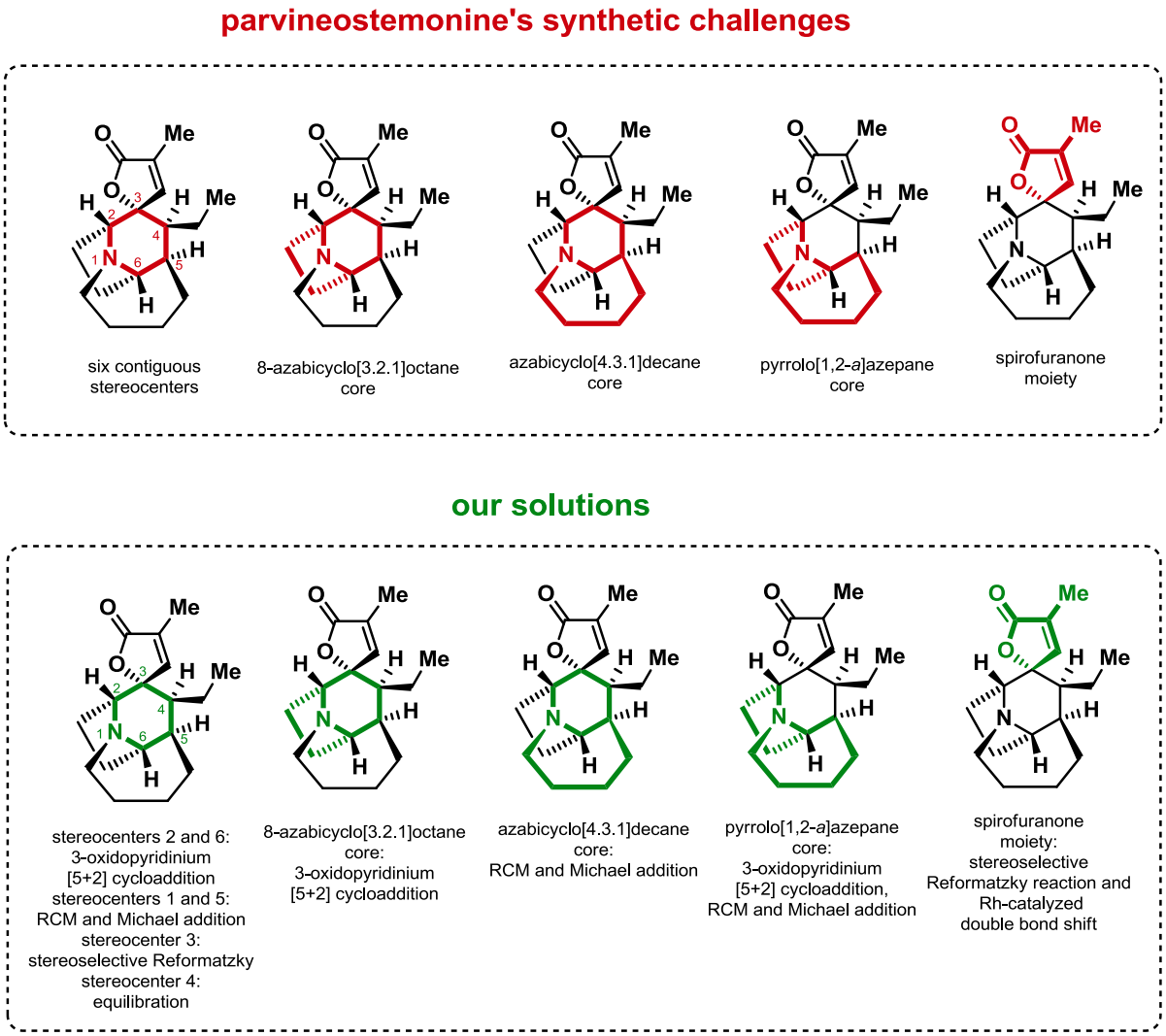


Figure 39: Key synthetic challenges of parvineostmonine (**2**) and our synthetic solutions.

As parvineostemonine (**2**) bears a unique skeleton within the *stemona* alkaloids, we will have to make slight alterations in oder to apply our synthetic concept towards further members of this alkaloid family.

Nearly one quarter of the *stemona* alkaloids include a substituted tropanone skeleton, which arises from the 3-oxidopyridinium [5+2] cycloaddition, and may therefore be synthetically accessible based on work in this thesis (see figure 32).

Our initial goal was to establish the common intermediate based total synthesis of several alkaloids from different natural product classes. We have achieved this aim by synthesizing four *sarpagine* alkaloids and one *stemona* alkaloid (see figure 40).

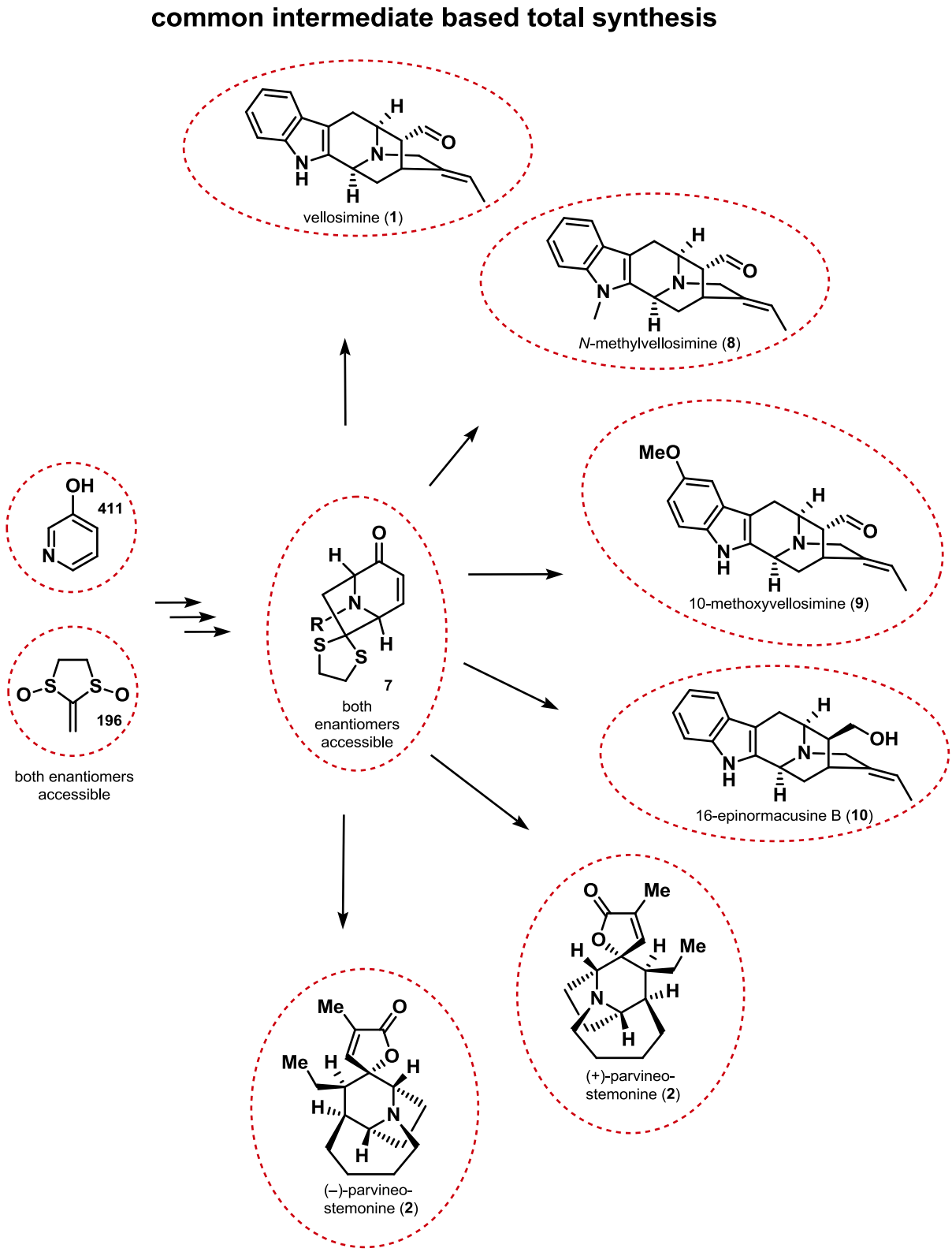


Figure 40: Summary of the synthetic achievements *via* a common intermediate.

As this synthetic endeavour is aimed at three different alkaloid classes in total, the synthetic access to the *alstonia* alkaloids remains an open challenge to future members of the Gaich group (see figure 41). First synthetic attempts have already been carried out, but are not part of this thesis.

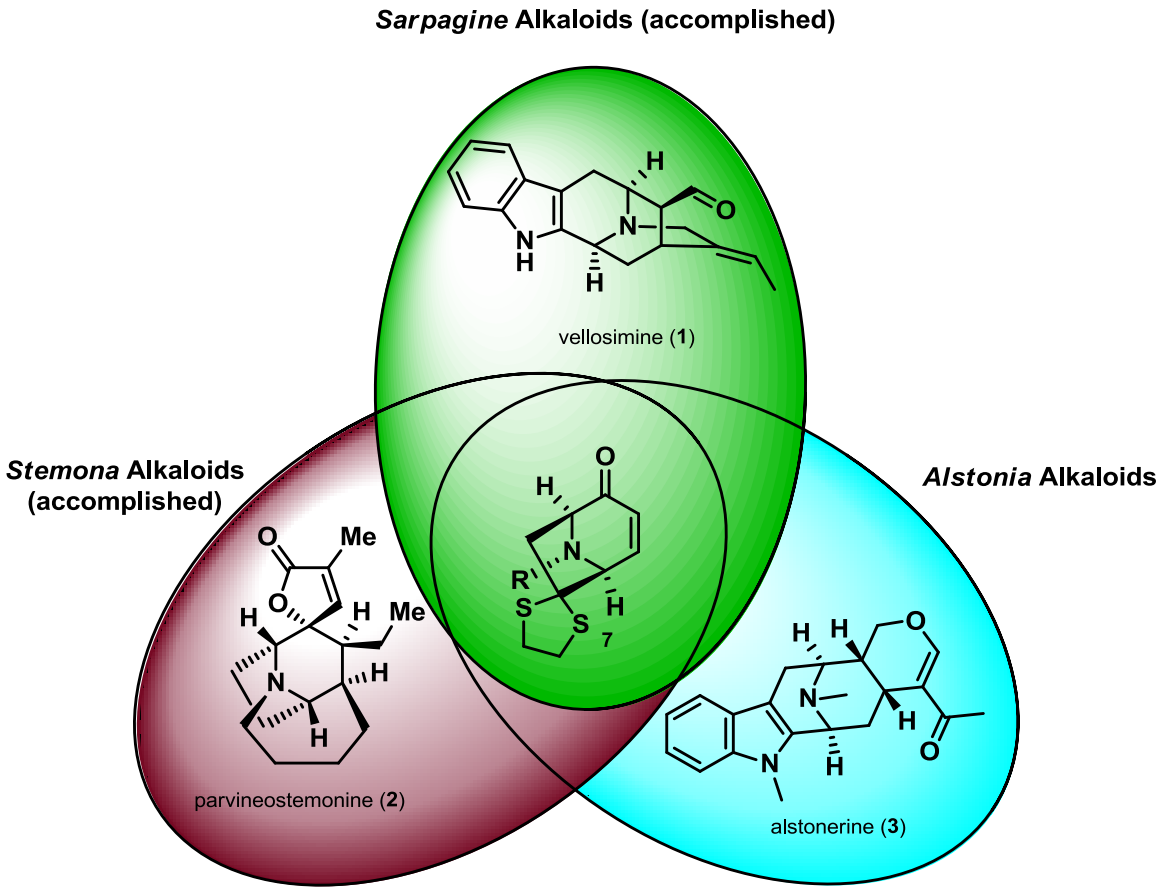


Figure 41: Synthetic concept and the common intermediate.

III In the third project we were able to demonstrate a new access to the hexahydro-cyclohepta[*b*]indole skeleton. The substrate scope includes heteroaromtic substitution at C8, as well as aliphatic and aromatic substituents. As several of the newly accessed compounds have never been synthesized previously, we have enlarged the variety of available substituted cyclohepta[*b*]indoles to a good extend.

So far, we have found nine examples of the diazo mediated ring expansion using DMNB **235** with yields ranging from 47-100% (see figure 42). The subsequent reduction step has been demonstrated to work efficiently with nine examples as well, with yields ranging from 66-100%.

To showcase the versatility of the developed indolization strategy, the formal synthesis of A FABP inhibitor **421** was carried out. Future work will be directed at the introduction of substituents at the indole core, which will greatly increase the utility of our reaction due to later cross coupling. This project demonstrates the creative influence of total synthesis towards other areas of organic chemistry, as it was initially developed to overcome a synthetic problem arising during the *sarpagine* project.

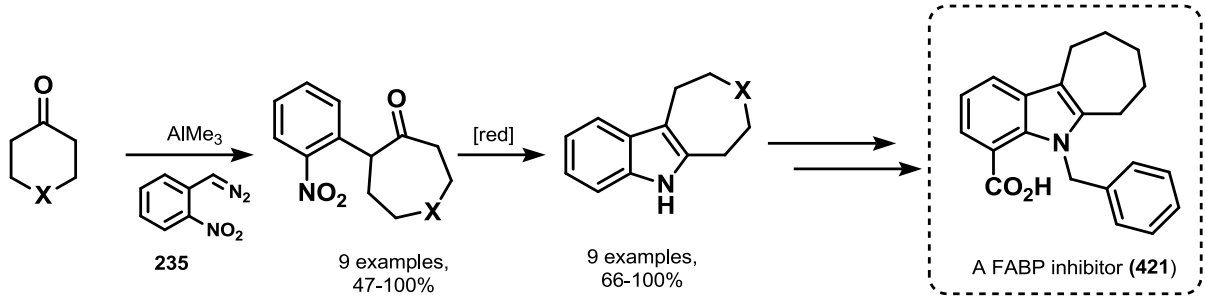


Figure 42: Summary of the DMNB project.

6 List of Schemes

7 List of Figures

8 List of Tables

9 List of Abbreviations

A FABP	adipocyte fatty acid binding proteins (A FABP, FABP4 or aP2)
Ac	acetyl
acac	acetylacetonate
ACN	1,1’-Azobis-1-cyclohexanenitrile
BINOL	1,1'-bi-2-naphthol
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Cbz	carboxybenzyl
CoA	coenzyme A
CPU	carboxypeptidase U
DCC	*N,N*'-dicyclohexylcarbodiimide
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMAPP	dimethylallyl pyrophosphate
DMDO	dimethyldioxirane
DME	dimethoxyethane
DMF	dimethyl formamide
DMNB	1-(diazomethyl)-2-nitrobenzene
DMP	Dess-Martin periodinane
DMS	dimethylsuldide
DMSO	dimethyl sulfoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
Et	ethyl

G II	Grubbs second generation catalyst
HMPA	hexamethylphosphoramide
IPP	isopentenyl pyrophosphate
KHMDS	potassium bis(trimethylsilyl)amide
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
L-selectride	lithium tri-*sec*-butyl(hydrido)borate
MAD	methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide)
*m*CPBA	*meta*-chloroperoxybenzoic acid
MeCN	acetonitrile
MptpB	*mycobacterium tuberculosis* protein tyrosine phosphatase B
MTC	medullary thyroid carcinoma
NaHMDS	sodium bis(trimethylsilyl)amide
NMR	nuclear magnetic resonance
NOeSY	Nuclear Overhauser effect spectroscopy
PE	petrol ether
Ph	phenyl
PPTS	pyridinium *p*-toluenesulfonate
RaNi	Raney nickel
RCM	ring closing metathesis
rfx	reflux
SIRT	sirtuin
sm	structural motif
TBAF	tetra-*n*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl

*t*Bu	*tert*-butyl
Tf	triflate
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMEDA	tetramethylethylenediamine
TMS	trimethyl silyl
Tp	hydridotris(pyrazolyl)borate
Ts	tosyl
TS	transition state

10 Acknowledgements

Prof. Dr. Tanja Gaich, for the possibility of letting me work on whatever I fancied most. I repay trust with results.

Prof. Dr. Markus Kalesse, for being the second examiner and inviting me to play soccer in Otze with free barbecue afterwards. And for welcoming me in his working group for three months.

Prof. Dr. Jürgen Caro and Prof. Dr. Siegfried Blechert for completing the examination board.

Magnus Pfaffenbach for the long companionship. I remember whale watching in the Bay area as well as our last time on the soccer pitch, separated by nearly three years. 235 for life.

Erik Stempel for the friendship and the help with apple computers over the years. Right now I hear you whistling completely off tune to a piano song.

Darius, Kostja, Christian, Phillip, Ruben and Birte for the support and the nice group activities over the years.

Lukas Dempwollf for the incredible amount of work on the DMNB project. It has been a pleasure to have you in our lab, I learned several interesting facts about the internet. Plus, you provided the laboratory anthem.

Timo Hoffmann for additional experiments towards the synthesis of 16-epinormacusine B.

The finnish motivation wizard for her help during the last days in lab.

The working group of Prof. Dr. Kalesse for countless breaks and beers.

Dr. Maria Moreno for the translational help with Spanish manuscripts.

Prof. Dr. Barry M. Trost, for accepting me into his group at a very early stage of my academic career and letting me experience a deep insight into organic chemistry within one of the world's leading working groups.

Dr. Maxim Osipov, for providing me with a total synthetic skill set, that lacked close to nothing.

Sergej, Thea, Dawid and Franzi for the Wednesday lunch club. Which transformed wednesday into the best day of the week.

The inorganic institute for welcoming me into their soccer team for the last six years. Which made Wednesday the best day ever. Each week.

My family for supporting me over the previous eight years. You valued my education more than spending. A lot to be repaid.

Inga. My very own lady luck.

11 CV

C V

03/2013 - 09/2015	**Ph. D. student** Gottfried-Wilhelm-Leibniz Universität Hannover, Prof. Dr. Tanja Gaich (now at Universität Konstanz)
06/2012 - 02/2013	**Master Course Medicinal- and Natural Product Chemistry** Gottfried-Wilhelm-Leibniz Universität Hannover 2 Semester, Graduation with Distinction, Overall Grade 1.0
10/2011 - 06/2012	**Internationale Studenten Austausch Partnerschaft (DAAD)** Stanford University, California, USA Prof. Dr. Barry M. Trost, 9 Month
04/2011 - 09/2011	**Master Course Medicinal- and Natural Product Chemistry** Gottfried-Wilhelm-Leibniz Universität Hannover 2 Semester
10/2007 - 01/2011	**Bachelor Course Chemistry** Gottfried-Wilhelm-Leibniz Universität Hannover 6 Semester, Graduation with Overall Grade 2.0