Studies towards the total synthesis of dichomine

Dissertation submitted for the degree of
Doctor of Natural Science
(Dr. rer. nat.)

Presented by

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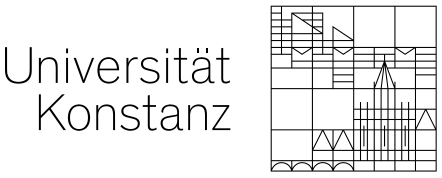
At the



Faculty of Science

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Date of oral examination: 17.10.2016
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Abstract:

This Ph.D. thesis describes the synthetic efforts towards the total synthesis of dichomine and the total syntheses of the related *iboga* alkaloids cleavamine, dihydrocleavamine, velbanamine, isovelbanamine, 20*S*-hydroxy-1,2-dehydro-pseudoaspidospermidine and 20*R*-1,2-dehydro-pseudoaspidospermidine.

Dichomine was discovered by Verpoorte and coworkers in 1983 as part of a program to screen natural products as potential therapeutic agents. It was isolated from the leaves and fruits of *Tabernaemontana dichotoma* and a little bit later from the leaves and twigs of *Tabernaemontana eglandulosa*. Dichomine is an indole alkaloid of the ibogan class and exhibits a hypotensive- and strong muscle relaxant activity.

The envisioned synthetic strategy to synthesize the unique bicyclo[5.3.2]dodecane framework of dichomine is based on an oxidative biomimetic ring-closing reaction from a heterocyclic 9-membered ring. The key step for the formation of this macrocyclic compound is a Witkop photocyclization. Due to this strategy it is also possible to address the related natural products velbanamine, isovelbanamine, cleavamine and dihydrocleavamine. In this thesis, four different approaches were investigated to prepare a suitable Witkop precursor. However, only the last strategy provided the desired compound, which subsequently could be cyclized to the 9-membered lactam. Further experimental investigations yielded in the synthesis of cleavamine and its analogs. Moreover, a novel retro-biomimetic oxidation approach of isovelbanamine and dihydrocleavamine provides a concise access to the alkaloids 20*S*-hydroxy-1,2-dehydro-pseudoaspidospermidine and 20*R*-1,2-dehydro-pseudoaspidospermidine respectively. Unfortunately, the envisioned biomimetic transformation to dichomine could not be realized.

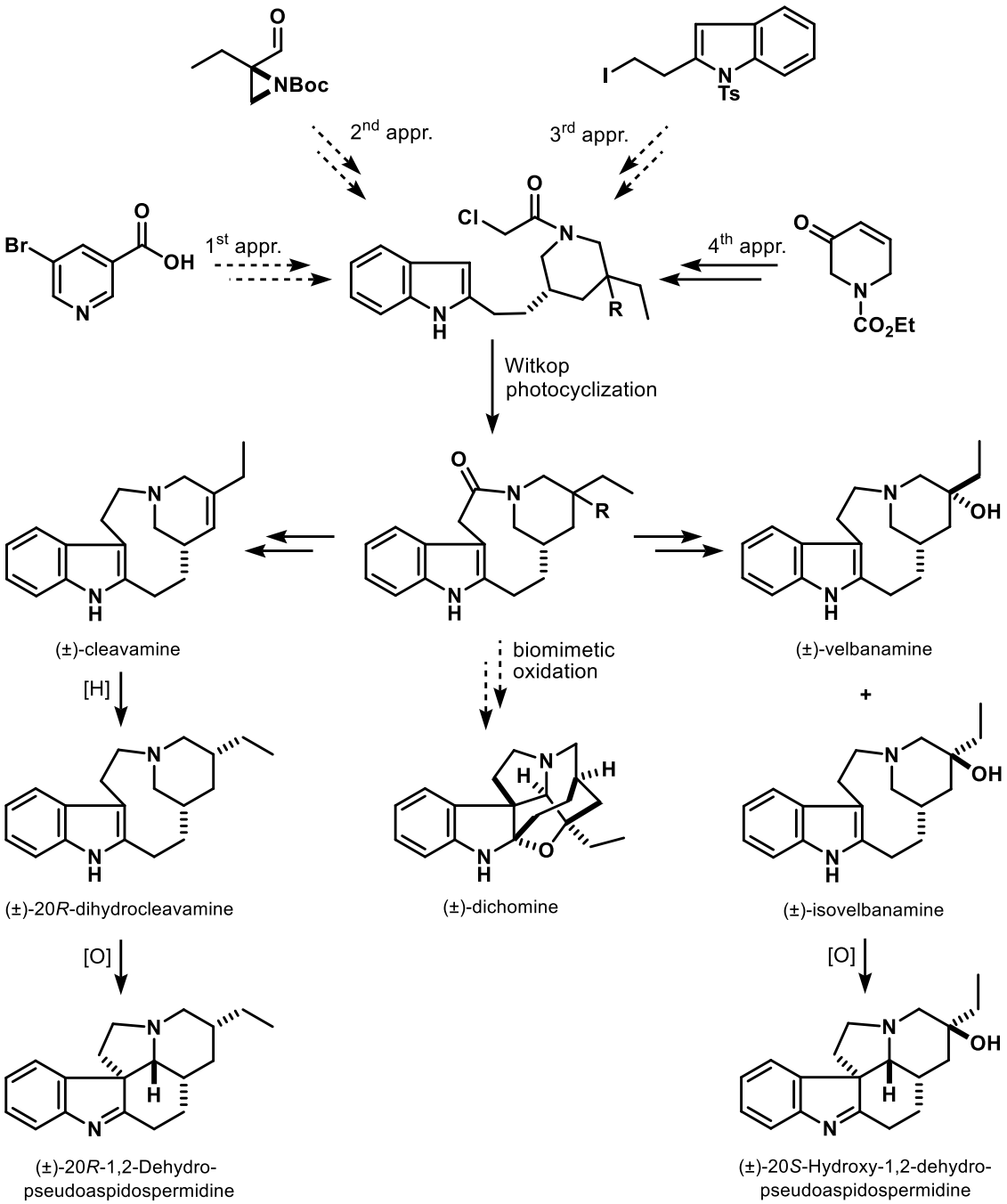
Zusammenfassung

Die vorliegende Doktorarbeit beschreibt die synthetischen Studien zur Totalsynthese von Dichomine und die Totalsynthese der verwandten *Iboga* Alkaloide Cleavamine, Dihydrocleavamine, Velbanamine, Isovelbanamine, 20*S*-Hydroxy-1,2-dehydro-pseudoaspidospermidine und 20*R*-1,2-Dehydro-pseudoaspidospermidine.

Dichomine wurde von Verpoorte und dessen Mitarbeiter im Zuge eines Programms zur Identifikation von Naturstoffen mit physiologisch positiver Wirkung im Jahr 1983 entdeckt. Dabei wurde diese Verbindung zuerst aus den Blättern und Früchten von *Tabernaemontana dichotoma* und ein wenig später auch aus den Blättern und Zweigen von *Tabernaemontana eglandulosa* isoliert. Dichomine zählt zu den Indolalkaloiden der Ibogan Klasse und weißt eine hypotensive- und stark muskelrelaxierende Wirkung auf.

Die Synthesestrategie zur Darstellung des Bicyclo[5.3.2]dodecane-Systems von Dichomine basiert auf einer biomimetischen oxidativen Ringschlussreaktion eines heterocyclischen 9-gliedrigen Rings. Der Schlüsselschritt zur Synthese dieses makrozyklischen Bausteins ist eine Witkop-Photozyklisierung. Anhand dieser Vorgehensweise ist es auch möglich die beiden verwandten Naturstoffe Velbanamine, Isovelbanamine, Cleavamine und Dihydrocleavamine darzustellen. In Rahmen dieser Arbeit wurden vier verschiedene Syntheseansätze verfolgt um einen passenden Witkop-Vorläufer zu generieren. Dabei führte lediglich die letzte Synthesestrategie zur gewünschten Verbindung, welche anschließend zum 9-gliedrigen Lactam zyklisiert werden konnte. Weiterführende Experimente ermöglichten die Synthese von Cleavamine und dessen Analoga. Darüber hinaus ermöglicht eine neuartige, retro-biomimetische Oxidation von Isovelbanamine und Dihydrocleavamine den Zugang zu den Alkaloiden 20*S*-Hydroxy-1,2-dehydro-pseudoaspidospermidine beziehungsweise 20*R*-1,2-Dehydro-pseudoaspidospermidine. Unglücklicherweise konnte die angestrebte biomimetische Umwandlung zu Dichomine nicht durchgeführt werden.

Graphical Abstract



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List of Abbreviations

Ac	acetyl
acac	acetylacetone
ATR	attenuated total reflection
Bn	benzyl
Boc	*t*-butoxycarbonyl
Bu (*n*Bu)	butyl
Cbz	carboxybenzyl
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N´*-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL	diisobutylaluminum hydride
DIC	*N,N´*-diisopropylcarbodiimide
DIPEA	diisopropylethylamine
DMAP	*N,N*-4-dimethylaminopyridine
DME	dimethoxyethane
DMF	*N,N*-dimethylformamide
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
dppf	1,1´-*bis*(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
dr	diastereomeric ratio
ee	enantiomeric excess
EDC-HCl	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
EE	ethyl acetate
Enz	enzyme
Et	ethyl
FGI	functional group interconversion
Glc	glucosyl
H.E.	Hantzsch ester
HRMS	high resolution mass spectrometry
Im	imidazole

IR	infrared spectroscopy
KHMDS	potassium *bis*(trimethylsilyl)amide
LDA	lithium diisopropylamide
LHMDS	lithium *bis*(trimethylsilyl)amide
*m*CPBA	*meta* chloroperbenzoic acid
Me	methyl
Ms	mesyl (methansulfonyl)
MS	mass spectrometry
MVK	methyl vinyl ketone
NaHMDS	sodium *bis*(trimethylsilyl)amide
NMO	*N*-methylmorpholine oxide
NMR	nuclear magnetic resonance
PET	photon-induced electron transfer
Ph	phenyl
PhthNH	phthalimide
PIDA	phenyliodonium diacetate
PPA	polyphosphonic acid
py.	pyridine
Red-Al	sodium bis(2-methoxyethoxy)aluminumhydride
r.t.	room temperature
SAM	*S*-adenosylmethionine
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n*-butylammonium iodide
TBHP	*tert*-butylhydroperoxide
TBS	*t*-dibutyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoracetic acid
TFAA	trifluoracetic anhydride
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMS	trimethylsilyl
Tr	trityl
p-Ts	*p*-toluenesulfonyl

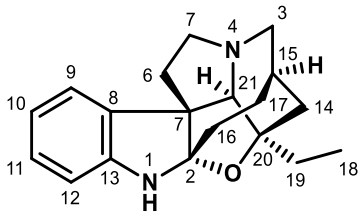
1. Introduction

Tabernaemontana dichotoma is a small tree native to India and Sri Lanka (Figure 1). In Sri Lanka it is the only species of the genus *Tabernaemontana* and it is known there as *divi kaduru*.

Figure 1: *Tabernaemontana dichotoma*

The rootbark and stembark of this medicinal plant are used in traditional medicine for healing wounds caused by snake bites and the bites of centipedes.[1,2] Moreover, aqueous and ethanol extracts of these parts of the plant revealed during a antimicrobial screening a strong activity against Gram-positive and Gram-negative bacteria as well as yeast and fungus.[3] The tender leaves are part of a medicine to soften carbuncles. Furthermore, a combination of the bark and leaves is said to have cathartic effects and acts as a purgative. The seeds seemed to possess a narcotic effect, which produces delirium and other similar symptoms. The fruits of this plant are deadly poisonous and therefore are called “the forbidden fruit of Eden” or “Eve´s apple”.[4] Due to that property this fruit is frequently used in Sri Lanka by girls who face the birth of an undesired child to commit suicide. Death occurs within a few hours by eating only a single fruit of this plant. Nevertheless, the petroleum ether extracts of the fruits have revealed a CNS depressant and hypotensive activity, whereas the methanolic extracts have shown antitumor activity.[5]

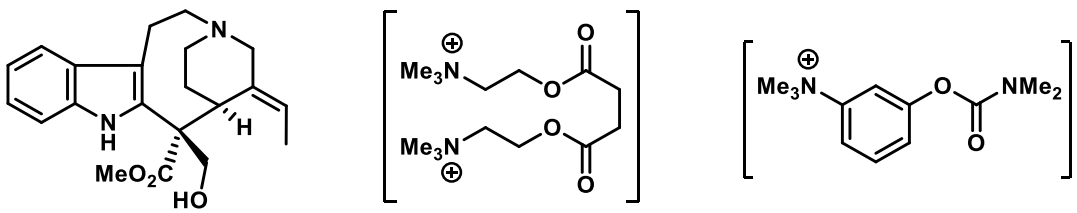
As a part of this screening process in the year 1983, dichomine (**1**) was discovered by Verpoorte and coworkers (Figure 2).[6] This natural compound was isolated from the leaves and fruits of *Tabernaemontana dichotoma*.[7] Therefore, 40 kg of fresh fruits were macerated in a 4% aqueous acetic acid solution. Further extraction and filtration processes provided a dry tertiary alkaloid fraction of 30 g, which contained approximately 8 mg of the new alkaloid. Moreover, during the identification process this compound was also isolated from the leaves and twigs of *Tabernaemontana eglandulosa* in smaller amounts.[8]



dichomine (**1**)

Figure 2: Structure of dichomine (**1**) and carbon atom numbering.

Dichomine (**1**) is an indole alkaloid, which exhibits a hypotensive and strong muscle relaxant activity and belongs to the ibogan class. *In vivo* rat experiments have shown that this natural product was seven times more potent than stemmadenine (**2**) and 1 μg of dichomine gave the same response as 0.14 μg succinylcholine (**3**)[9], which is a potent muscle relaxant (Figure 3). It is also remarkable that the neuromuscular blocking effect of this compound was not influenced by neostigmine (**4**). Furthermore, at a concentration of 14 μg/ml dichomine lowers the amplitude of contractions of the stimulated rat diaphragm-phrenic nerve preparation by 50%. A concentration of 28 μg/ml caused complete blockage of the contractions.[10] Based on these properties this natural product could be interesting for the development of new narcotics in medicine.



stemmadenine (**2**) succinylcholine (**3**) neostigmine (**4**)

Figure 3: Structures of stemmadenine (**2**), succinylcholine (**3**) and neostigmine (**4**).

As depicted in Figure 2, dichomine (**1**) possesses 6 rings in total, which can be divided into an indoline moiety and the saturated tetracyclic framework. These two parts are annulated to each other *via* the C-2, C-7 carbon bond, whereas the carbon at the C-2 position contains a *N,O*-ketal functionality. Furthermore, the adjacent carbon atom at the C-7 position is a quaternary carbon center and demands therefore special attention in the retrosynthetic analysis. Unusual about this tetracyclic structure is the C-16, C-17 methylene carbon chain generating a unique heterocyclic[4.3.2]system. The two heterocycles in this bridged system are the piperidine ring and the tetrahydrofuran ring. The pyrrolidine ring, which includes the carbon atoms C-6 and C-7, is the last part of the tetracyclic scaffold in this compound. It is also noteworthy that this molecule possesses five stereogenic centers with an unknown absolute configuration. It is also worth mentioning that so far no total synthesis of this compound was achieved.

In summary, the low abundance, the biological properties, the unprecedented hexacyclic structure, the lack of a synthetic access and the unknown absolute configuration makes this natural product an utmost attractive target for total synthesis.

2. Related indole alkaloids isolated from the genus *Tabernaemontana*

Several phytochemical investigations of many different species revealed that the genus *Tabernaemontana* contains mainly indole alkaloids of the *corynanthe*, *iboga* and *aspidosperma* families and dimeric alkaloids, which are a combination of these classes.[11,12] Based on the published research studies of the species *Tabernaemontana dichotoma* it can be concluded that this plant is a typical representative of the genus. This chapter gives a short overview about these indole alkaloid classes and some of their isolated representatives.

2.1. The corynanthe class

Figure 4 shows some members of the *corynanthe* class. One of the best known natural products of this family is geissoschizine (**5**). Further important members are reserpiline (**6**) and yohimbine (**7**). Common to those metabolites is the quinolizidine sub structure, which is annulated to the indole moiety. Within this structure motif the stereochemistry at the C-3 position requires special attention. In the case of geissoschizine (**5**) and

yohimbine (**7**) this stereocenter has an (*S*)-configuration and in the case of reserpiline (**6**) an (*R*)-configuration. A further structural feature in case of reserpiline and its related alkaloids is the additional annulated dihydropyrane ring at the quinolizidine moiety. Yohimbine possesses an additionally carbon ring at the same position, which is typically annulated to the quinolizidine structure in a *trans* fashion. Akuammidine (**8**) belongs to the class of *corynanthe* alkaloids, but it is also a representative of the *sarpagine* alkaloids. A special structural feature of this compound is the quinuclidine moiety, which is connected to the indole functionality *via* a 6-membered ring.

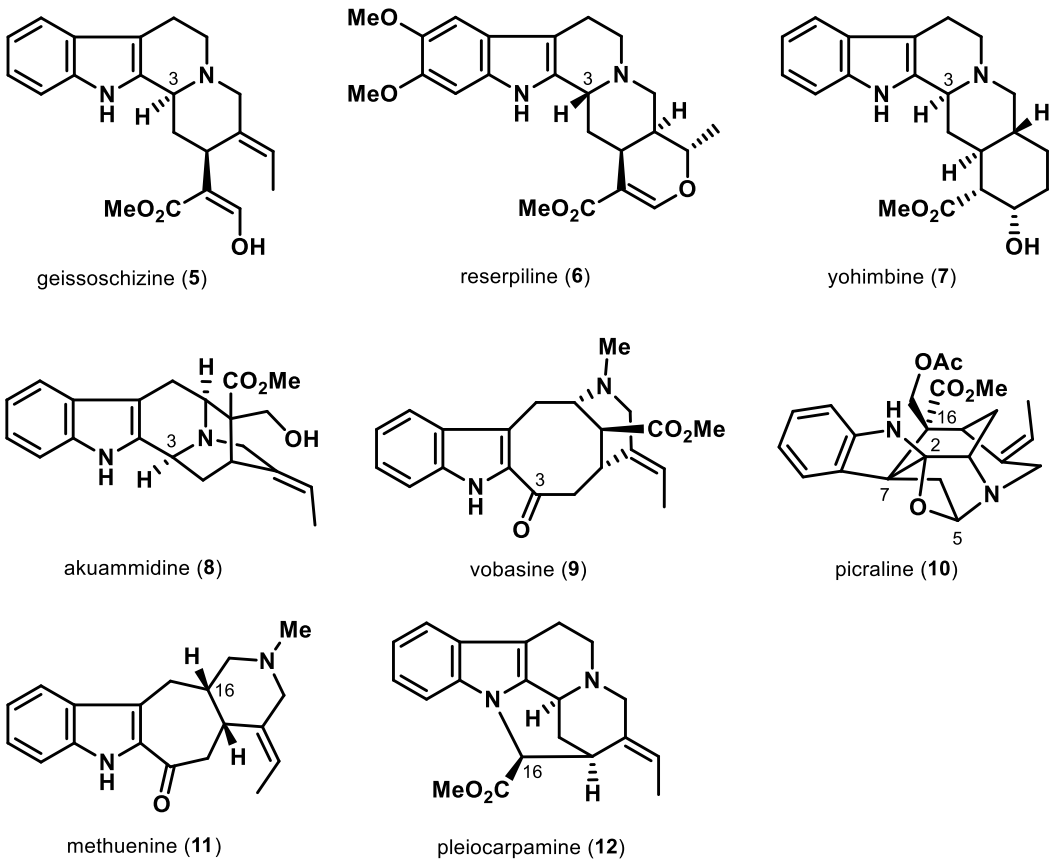


Figure 4: Representative members of the *corynanthe* class of alkaloids.

The next member of this family is vobasine (**9**). Remarkably about this metabolite is the 8-membered carbocycle, which could be obtained from an *N*-methylated derivative of akuammidine (**8**) *via* an oxidative cleavage of the C-3 carbon-nitrogen bond. A further complex representative of the *corynanthe* class is picraline (**10**). Noteworthy about this structure is the C-7, C-16 carbon bond generating the bicyclo[3.3.1]system. Moreover, the higher oxidation state of the C-2 and C-5 carbon atom enables the formation of an oxygen bridge, which is a part of two *N,O*-acetal functionalities at the same time. A much less structurally complex metabolite is methuenine (**11**). This

subclass contains a 6,7-membered annulated ring system next to the indole, whereas the stereochemistry at the C-16 carbon can arise in both configurations. The last depicted representative in this class is pleiocarpamine (**12**). It possesses an (*S*)-configured quinolizidine system similar to geissoschizine or yohimbine, which is annulated to the indole core. A special feature of this framework is the connection between the C-16 carbon atom and the indole nitrogen. This additional bond results in the generation of a quite complex bicyclo[3.3.1]scaffold.

2.2. The aspidosperma class

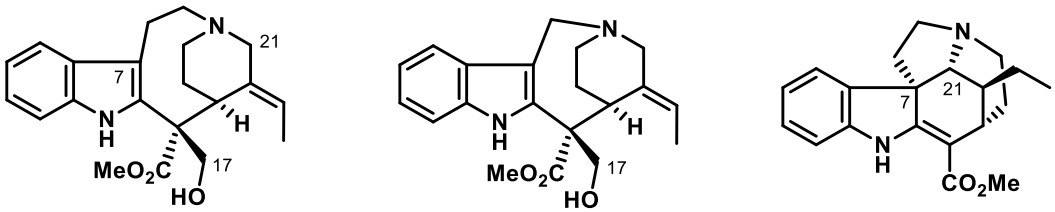
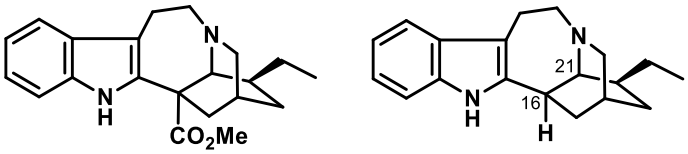


Figure 5: Representative members of the *aspidosperma* class of alkaloids.

As depicted in Figure 5, the natural products isolated from *tabernaemontana* plants so far only incorporate three different scaffolds of this alkaloid class. The framework of stemmadenine (**2**) consists of an indole moiety and a bicyclo[5.2.2] system. The structure of vallesamine (**13**) is closely related to stemmadenine. The only difference between this two compounds is the missing carbon atom in the bicyclic structure, which results in a bicyclo[4.2.2]system. In the case of tubotaiwine (**14**), an additional carbon bond between C-7 and C-21 generates an annulated 5,6-membered ring system from the 9-membered macrocycle. Moreover, this all-carbon 6-membered ring is part of a bicyclo[3.3.1]scaffold, which is annulated to the reduced indole system. It is also noteworthy that the C-17 carbon, which contains the hydroxyl functionality in the case of stemmadenine or vallesamine is absent.

2.3. The iboga class

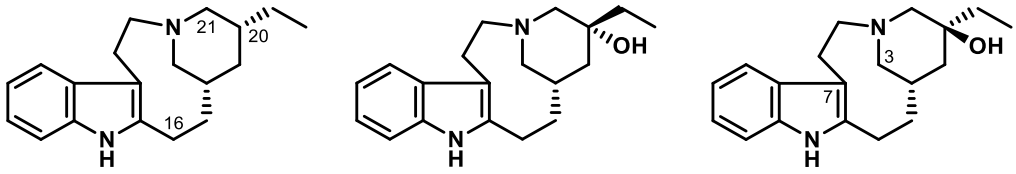


coronaridine (**15**) ibogamine (**16**)

Figure 6: Representative members of the *iboga* class of alkaloids, part 1.

Many of the indole alkaloids isolated from *tabernaemontana* belong to the *iboga* class. Hence, in the following figures several representatives are shown for each structure subtype. Moreover, most of this natural products such like coronaridine (**15**) are related to the ibogamine framework. A special feature of this subclass is the azabicyclo[2.2.2]framework, which is annulated *via* a 7-membered ring to the indole core (Figure 6).

The next three representatives are shown in Figure 7 and belong to the cleavamine type. Remarkably about this scaffold is the bicyclo[6.3.1]system, which could be generated from the ibogamine skeleton by a formal cleavage of the C-16, C-21 carbon bond.



20*R*-dihydrocleavamine (**17**) (-)-velbanamine (**18**) (+)-isovelbanamine (**19**)

Figure 7: Representative members of the *iboga* class of alkaloids, part 2.

A further subclass of the *iboga* family are the pseudotabernosines (Figure 8). In principle, the scaffold of 20*S*-hydroxy-1,2-dehydro-pseudoaspidospermidine (**20**) could be obtained by a formal oxidative carbon bond formation between the C-3 and C-7 carbon of isovelbanamine (**19**). This additional bond generates an annulated 5,6-membered ring system from the 9-membered macrocycle. The presence of a methyl ester at the C-16 carbon atom results in an isomerization of the indolenine double bond to a more stable vinylogous carbamate functionality in both 20*R*-pandoline (**22**) and 20*S*-pseudovincadifformine (**23**).

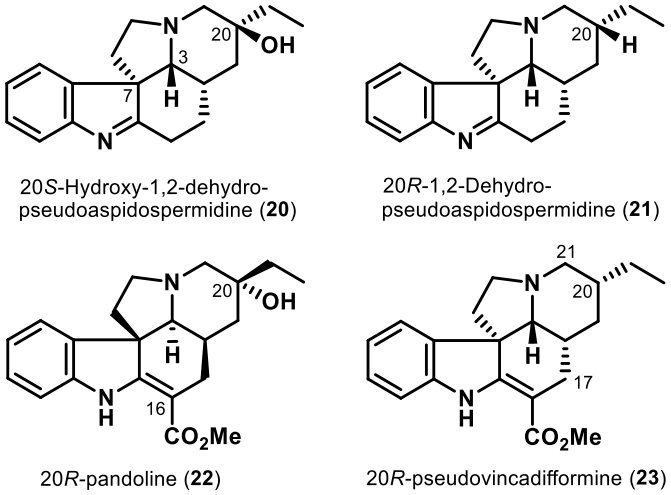


Figure 8: Representative members of the *iboga* class of alkaloids, part 3.

Two further different frameworks also belonging to the *iboga* class are depicted in Figure 9. In the case of pandine (**24**) the carbon bond between the C-17 and C-21 carbon generates a quite uncommon azabicyclo[2.2.1]structural motif. It is also noteworthy that a formal cleavage of that bond would result in the formation of 20-*epi*-pandoline.

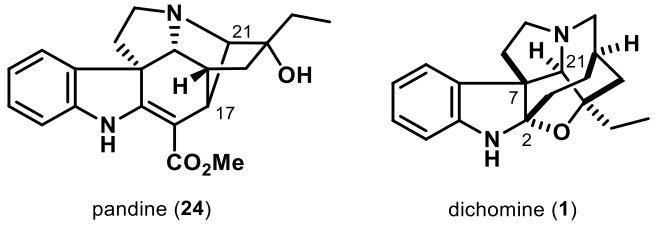
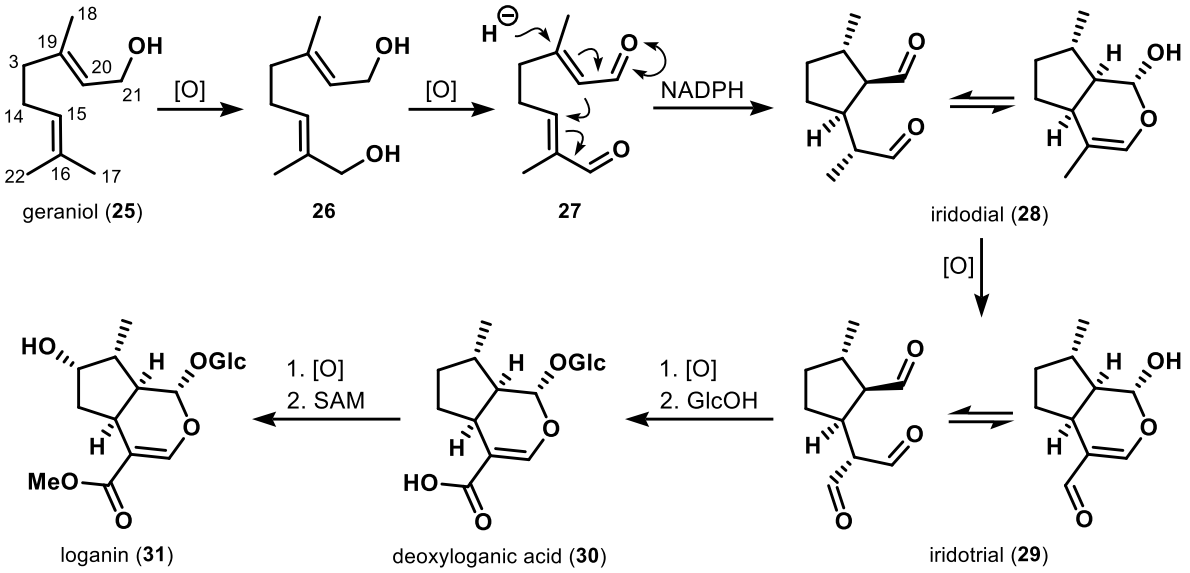


Figure 9: Representative members of the *iboga* class of alkaloids, part 4.

However, the second representative of an unconventional carbon skeleton in the *iboga* class is dichomine (**1**). Remarkably about this compound is the heterocyclic[4.3.2]system, which is generated *via* an uncommon carbon bond formation between C-7 and C-21. Experimental work from Verpoorte *et al.* showed, that a cleavage of the oxygen carbon bond at the C-2 position resulted in a spontaneous fragmentation of the C-7 C-21 carbon bond.[6] Due to these results it can be concluded that this oxygen carbon bond plays a crucial role with respect to the stability of this cage structure. Furthermore, it is also noteworthy that a reductive cleavage of the C-7, C-21 carbon bond furnishes the natural product velbanamine (**18**).

2.4. Biosynthesis

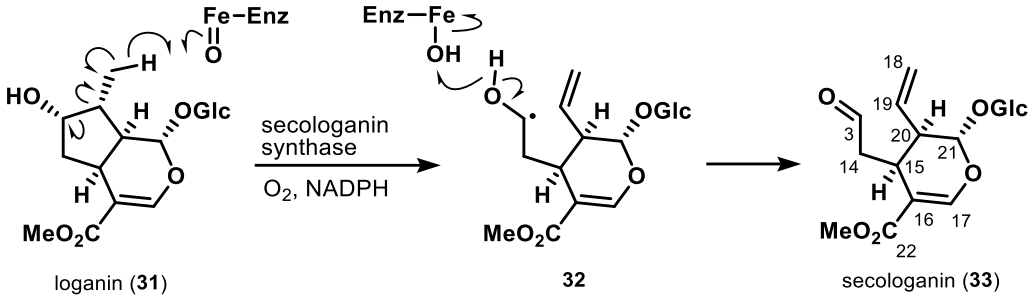
All of the previously depicted indole alkaloids of the *corynanthe*, *aspidosperma* and *iboga* class belong to the monoterpenoid indole alkaloids in biosynthetic terms. Consequently, all of these natural products are synthesized starting from the monoterpenoid secologanin (**33**) and the amino acid derivative tryptamine. The biosynthesis of secologanin starts with an oxidation of geraniol (**25**) to diol (**26**) (Scheme 1). Further oxidation of the allylic alcohols provides intermediate **27**. A subsequent NADPH-mediated reduction at C-19 generates an enol intermediate, attacking the adjacent α,β-unsaturated aldehyde to form iridodial (**28**). This structure is in equilibrium with its bicyclic hemiacetal. This compound is further oxidized at the C-22 carbon to yield iridotiral (**29**). Furthermore, a selective oxidation of the aldehyde to the carboxylate followed by a glycosylation reaction with glucose affords deoxyloganic acid (**30**). Oxidation of the C-3 position and a subsequent SAM mediated esterification of the carboxylic acid provides loganin (**31**).



Scheme 1: Biosynthesis of loganin (**31**).

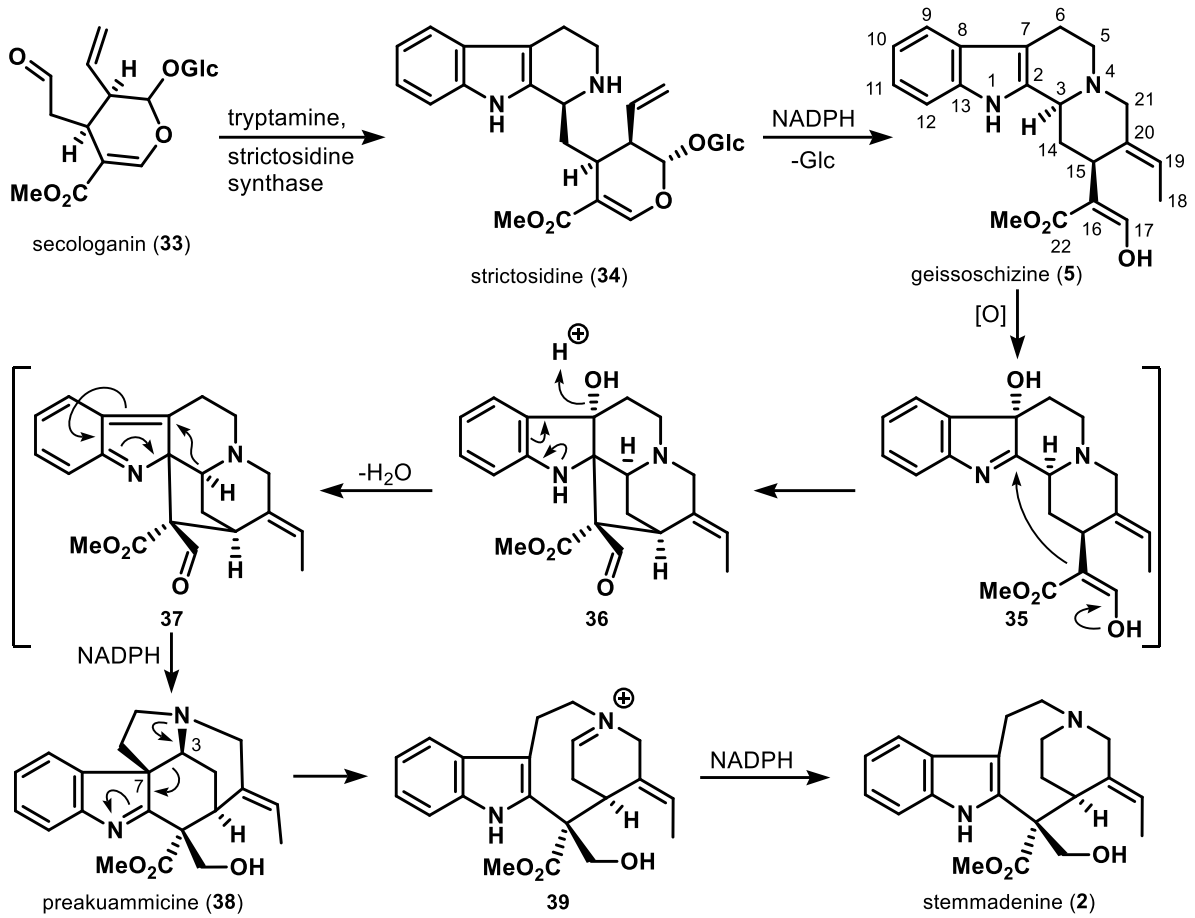
In the next step an oxidative carbon bond cleavage between C-3 and C-19 occurs. This reaction is catalyzed by an enzyme called secologanin synthase belonging to the cytochrome P450 monooxygenases. A plausible mechanism of this reaction is proposed in Scheme 2. In the first step a homolytic C-H abstraction at position C-18 provides a primary radical. A following recombination of this radical with the vicinal electron of the C-3, C-19 carbon bond furnishes the double bond and simultaneously

initiates the fragmentation of the 5-membered ring. The resulting radical at the C-3 carbon atom is quenched by a subsequent homolytic cleavage of the oxygen hydrogen bond to yield secologanin (**33**).[13]



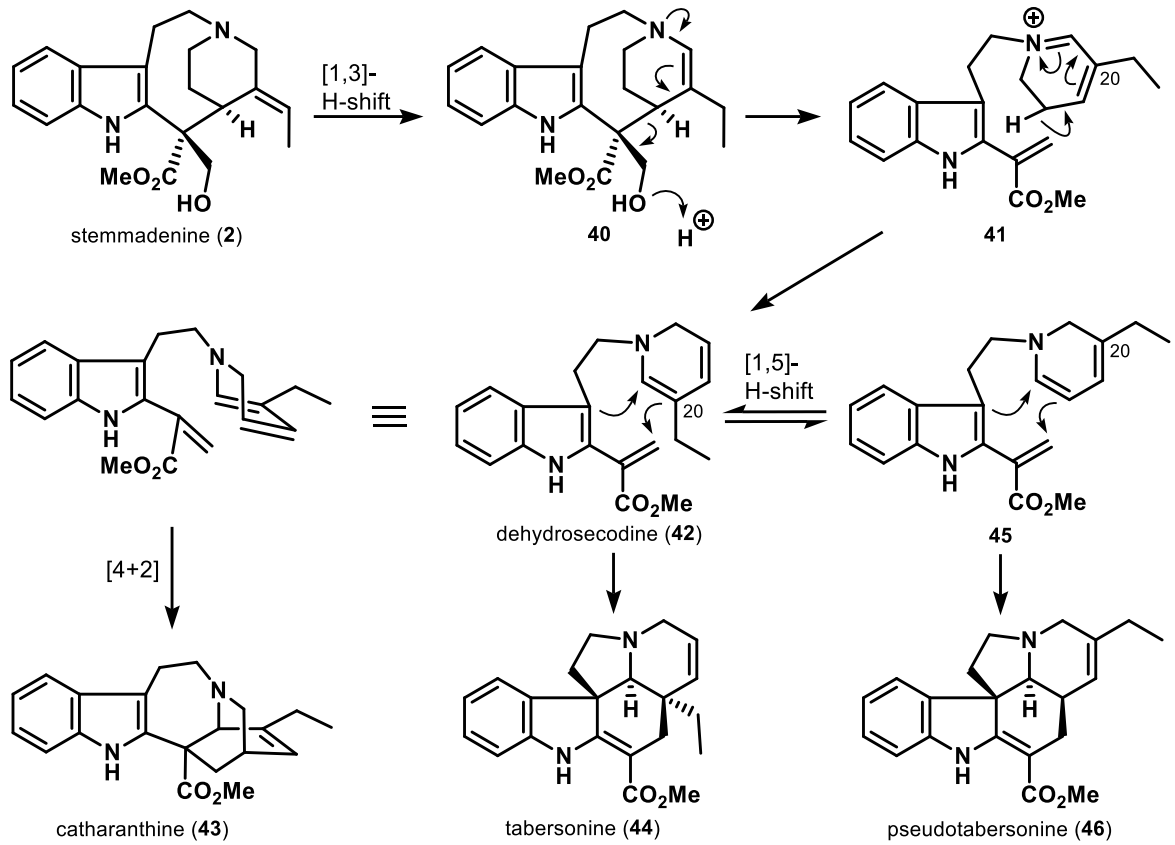
Scheme 2: Proposed mechanism towards secologanin (**33**).

It is also noteworthy that the biosynthesis of secologanin is quite untypical with respect to the absence of any phosphorylated intermediates. Therefore, also the carbocationic cyclization reactions or rearrangements, which are typical for this natural product class are missing.



Scheme 3: Proposed biosynthesis of stemmadenine (**2**).

Next, a strictosidine synthase catalyzed condensation between secologanin (**33**) and tryptamine generates the tetrahydro-β-carboline system of strictosidine (**34**) (Scheme 3). Subsequent cleavage of the glycoside allows the opening of the hemiacetal to a reactive aldehyde condensing with the amine moiety to provide a quaternary iminium ion. In the next step, an allylic isomerization of the terminal double bond towards the iminium ion followed by a reduction of this cationic species with NADPH yields geissoschizine (**5**).[14] At this point, it is also noteworthy that the biosynthetic generation of preakuammicine (**38**) from geissoschizine is not fully elucidated. However, a proposed mechanism for this transformation is depicted in Scheme 3. Oxidation of the indole moiety affords indolenine (**35**), which is attacked by the vinylogous carbonate to yield intermediate **36**. Dehydration under acidic conditions leads to compound **37**, which rearomatizes under C-3 to C-7 bond migration. Finally, a reduction of the aldehyde to the alcohol with NADPH provides preakuammicine (**38**). In the next step, a fragmentation reaction at the C-3, C-7 bond occurs with concomitant reduction of the iminium ion in intermediate **39** with NADPH to yield stemmadenine (**2**).[15]



Scheme 4: Proposed biosynthesis of *aspidosperma* and *iboga* alkaloids.

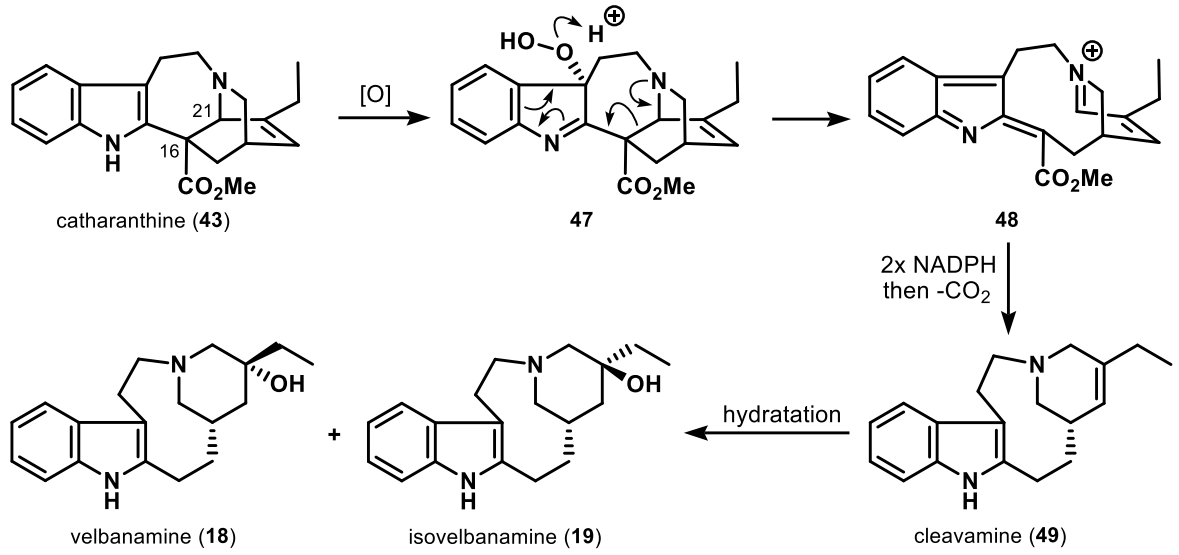
As depicted in Scheme 4, the biosynthetic transformation to dehydrosecodine (**42**) is probably initiated by a double bond of migration of stemmadenine (**2**) to form enamine intermediate **40**. Subsequent loss of water under acid conditions, induced by a fragmentation reaction of the enamine, forms iminium ion **41**. Thereafter, tautomerization of the iminium species provides dehydrosecodine (**42**).[16] In principle, this compound could undergo two different Diels-Alder reaction. In the first case, the indole enamine in combination with the α,β-unsaturated ester could act as a diene and the enamine of the dihydropyridine ring as dienophile. On the other hand, the dihydropyridine ring provides the diene and the α,β-unsaturated ester represents the dienophile. A closer look at the reaction partners in the first case reveals a diene, which possesses an electron donating- and an electron withdrawing group. This kind of dienes proved to be quite unreactive in Diels-Alder reactions. The relatively high sterically demand, which is caused by the ethyl side chain has to be considered as well. Due to these facts, a stepwise cycloaddition towards tabersonine (**44**) starting with a nucleophilic attack of the enamine to the α,β-unsaturated ester followed by a subsequent attack of the indole enamine at the resulting iminium ion seems to be more plausible.

An analysis of the reaction participants in the second case reveals an electronrich dihydropyridine diene and an electronpoor dienophile in the unsaturated ester moiety, combined with the less sterically demand of this alignment. Based on this observations, a Diels-Alder reaction to catharanthine (**43**) appears to be very reasonable, but a stepwise mechanism like in the first case cannot be strictly excluded.

Pseudotabersonine (**46**) is generated like tabersonine (**44**) by the same stepwise cycloaddition reaction of intermediate **45**. This compound could be obtained *via* a [1,5] proton shift from dehydrosecodine (**42**). Remarkably about compound **45** is the lack of a Diels-Alder product, which could be explained based on the previous considerations, by a higher sterically demand of the dihydropyridine diene during the transition state. Moreover, this observation supports the theory of a stepwise mechanism in the biosynthesis of tabersonine and pseudotabersonine just as well as the occurrence of a Diels-Alder reaction in the case of catharanthine.[17]

Further biosynthetic derivatization of catharanthine (**43**) proceeds *via* a peroxidase enzyme, which is catalyzed by the oxidation of the indole moiety to intermediate **47** (Scheme 5).[18] Subsequently the carbon bond between C-16 and C-21 is cleaved under

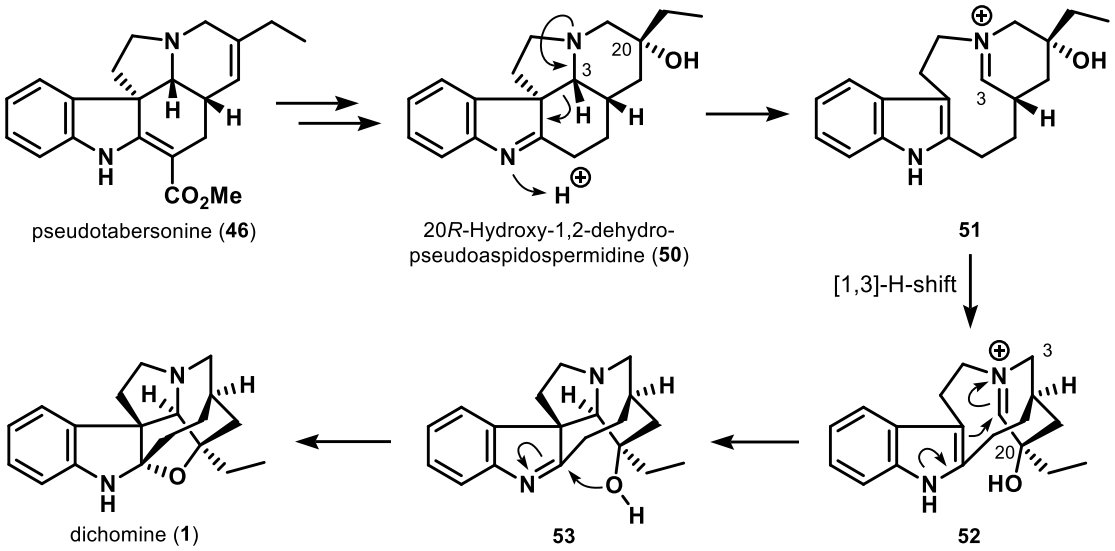
release of hydrogen peroxide to generate iminium ion **48**. This rather unstable compound possesses two highly nucleophilic positions at C-16 and C-21, which in case of the biosynthesis of cleavamine (**49**) and their analogs are probably reduced with two equivalents of NADPH. It is also worth mentioning that iminium ion **48** is the reactive species in the biosynthesis of vinblastine and vincristine. Saponification of the ester moiety followed by decarboxylation of the carboxylic acid affords cleavamine (**49**). Furthermore, a formal addition of water to the C-15, C-20 double bond provides the two epimers velbanamine (**18**) and isovelbanamine (**19**).



Scheme 5: Proposed biosynthesis of *iboga* alkaloids.

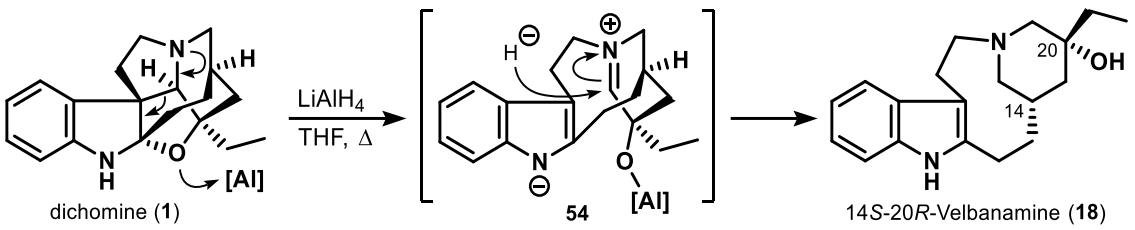
As depicted in Scheme 6, the biosynthetic proposal of dichomine (**1**) leads back to 20*R*-Hydroxy-1,2-dehydro-pseudoaspidospermidine (**50**), which is a biosynthetic derivative of pseudotabersonine (**46**).[6]

The transformation towards dichomine (**1**) is initiated by an acid-promoted activation of the indolenine nitrogen resulting in a cleavage of the C-3, C-7 carbon bond to give iminium ion **51**. Then, a transposition of the double bond from the C-3 carbon to the adjacent C-21 carbon *via* a [1,3] hydrogen shift to intermediate **52** occurs. Afterwards, an attack of the enamine to the iminium ion establishes the C-7, C-21 carbon bond and therefore the pyrrolidine moiety. The resulting indolenine is subsequently trapped by the proximal alkoxide to generate the remaining tetrahydrofuran ring of dichomine (**1**).



Scheme 6: Proposed biosynthesis of dichomine (**1**).

To confirm this biosynthetic proposal and to determine the molecular structure, Verpoorte and coworkers treated dichomine with lithium aluminum hydride to reduce the *N,O*-ketal functionality (Scheme 7). Instead of the expected reduction product they could only isolate the natural product 14*S*, 20*R*-velbanamine (**18**). An explanation for this experimental outcome could be a prevenient Lewis acid-mediated fragmentation reaction of the C-7, C-21 carbon bond, which resulted in the formation of intermediate **54**. A subsequent reduction of the iminium ion finally provides velbanamine (**18**).



Scheme 7: Reduction of dichomine (**1**).

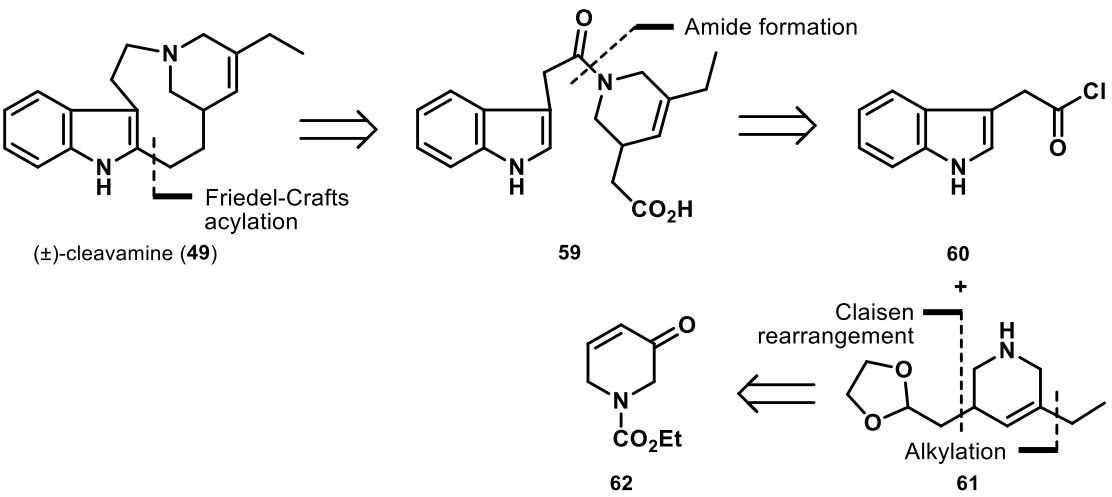
The similarity of intermediate **52** in the biosynthetic proposal compared to intermediate **54**, which is generated during the reduction process, encouraged Verpoorte to formulate this biosynthetic proposal. Moreover, this proposal would also explain why they could only isolate the 20*S*-Hydroxy-1,2-dehydro-pseudoaspidospermidine (**20**) from *Tabernaemontana dichotoma* and not the 20*R* epimer of this compound.

3. Previous synthetic work on related *iboga* alkaloids

Up to date no total synthesis of dichomine (**1**) has been reported. Hence, this chapter gives an overview about total syntheses of related *iboga* alkaloids deserving some special attention with respect to our retrosynthesis. Moreover, due to the use of an uncommon Witkop photocyclization as a key step in our synthesis, the last part of this section deals with some aspects of this reaction.

3.1. Total synthesis of (±)-cleavamine by Hanaoka *et al.* 1981

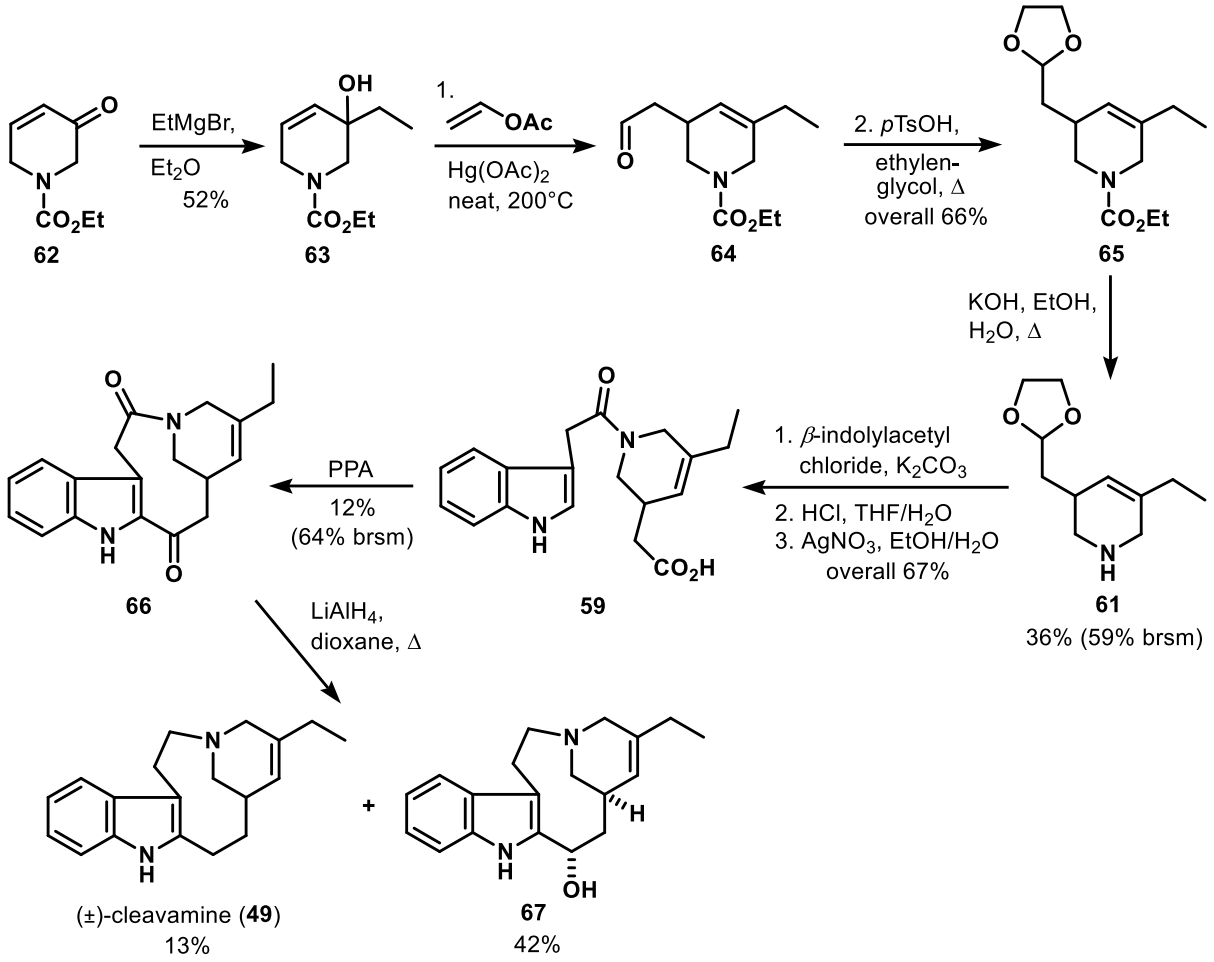
Hanaokas synthesis is based on a late stage Friedel-Crafts acylation to install the 9-membered macrocycle (Scheme 8).[19,20] The precursor for this cyclization reaction is prepared *via* a condensation reaction between β-indolylacetyl chloride (**60**) and tetrahydropyridine **61**. The ethyl side chain at the tetrahydropyridine core is installed by an addition of a Grignard reagent at ketone **62**. A mercury-mediated Claisen rearrangement with vinyl acetate of the allylic alcohol generates the second side chain and the desired double bond alignment in compound **61**.



Scheme 8: Retrosynthetic analysis of Hanaoka´s approach to (±)-cleavamine (**49**).

As depicted in Scheme 9, the synthesis starts with a nucleophilic addition of ethyl magnesium bromide to the ketone moiety of literature known dihydropyridone **62**.[21,22] A subsequent mercury-mediated Claisen rearrangement with vinyl acetate affords aldehyde **64**.[23] Protection of the aldehyde with ethylene glycol yields acetal **65**. Furthermore, cleavage of the ethyl carbamate with potassium hydroxide under reflux

gives the free amine **61**, albeit without full conversion of the starting material. In the next step an amide formation reaction with β-indolylacetyl chloride[24] and tetrahydropyridine **61** is performed. Subsequent cleavage of the acetal moiety with aqueous hydrochloric acid followed by an oxidation of the released aldehyde with silver nitrate furnishes the cyclization precursor **59**. The cyclization is accomplished by the use of polyphosphoric acid in chloroform under reflux and provides diketo compound **66** together with unreacted starting material. Finally, a reduction of the benzylic ketone and the amide with lithium aluminum hydride provides the desired natural product **49** along with the 16*S*-hydroxy cleavamine **67**.

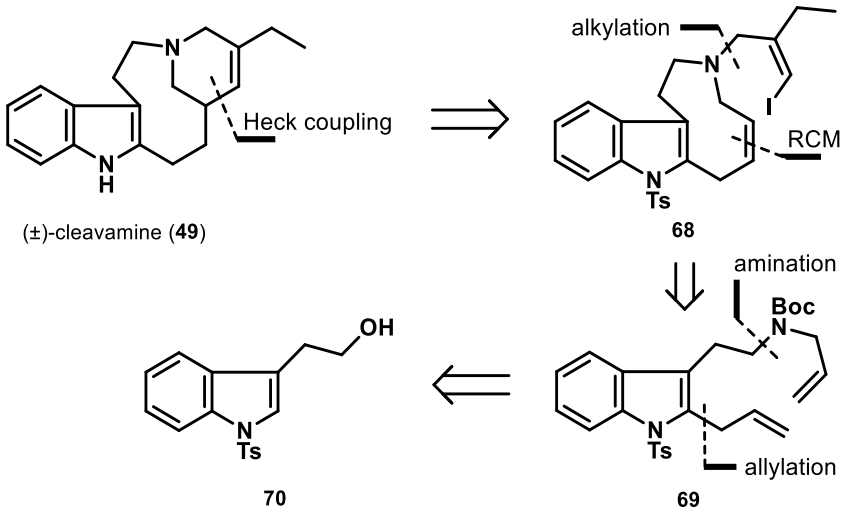


Scheme 9: Hanaoka´s total synthesis of (±)-cleavamine (**49**).

In summary, the racemic total synthesis of cleavamine by Hanaoka and coworkers has been reported with an approx. overall yield of 1% in 9 steps starting from literature known dihydropyridone **62**. Key steps of the synthesis are the mercury-mediated Claisen rearrangement to establish the tetrahydropyridine core and the Friedel-Crafts macrocyclization to generate the 9-membered lactam.

3.2. Total synthesis of (±)-cleavamine by Bennasar *et al.* 2011

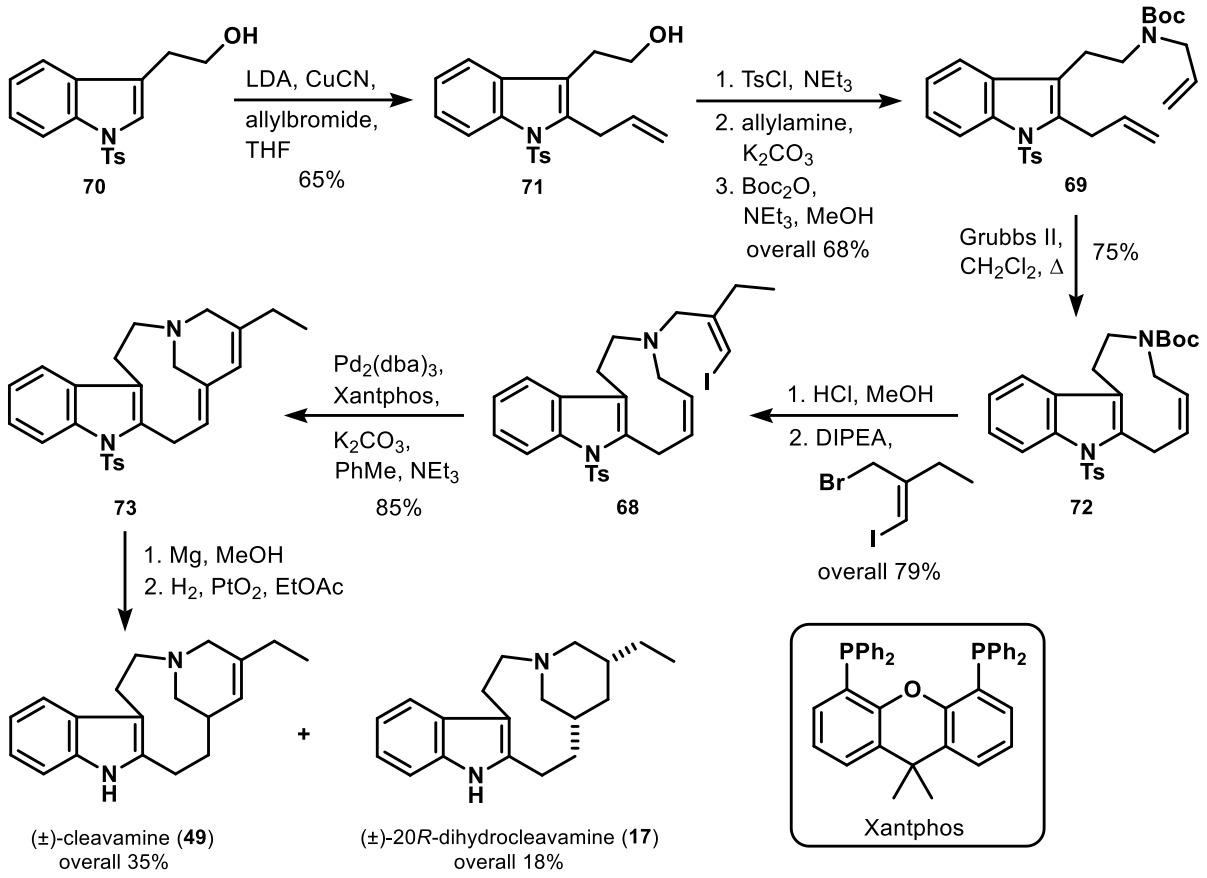
In contrast to other reported total syntheses of the cleavamine class, Bennasar and coworkers envisioned a late stage introduction of the tetrahydropyridine ring *via* a Heck coupling (Scheme 10).[25] The second key step in this synthesis deals with a ring-closing metathesis to generate the 9-membered macrocycle. Further strategic disconnections are the installation of the vinyl iodine at the secondary amine and the introduction of the amine by the use of allylamine. The second required double bond for the RCM reaction in compound **69** is established *via* an allylation reaction at the indole C-2 position. Due to this considerations, the starting material for this synthesis is the protected tryptophol **70**.[26]



Scheme 10: Retrosynthetic approach of Bennasar and coworkers.

However, compound **70** is deprotonated with an excess of LDA in the presence of copper cyanide to generate an organocopper species, which is further subjected to allyl bromide to obtain indole **71**. Transformation of the primary alcohol into a leaving group by the use of tosyl chloride followed by a substitution of the resulting tosylate with allyl amine yields the secondary amine. A subsequent protection of the amine with Boc_2O provides intermediate **69**. In the next step, the ring-closing metathesis is performed with the Grubbs 2nd generation catalyst in refluxing methylene chloride to generate the 9-membered ring. Afterwards, a cleavage of the Boc group using hydrochloric acid in methanol followed by an alkylation at the secondary amine with (*Z*)-3-bromo-2-ethyl-1-iodopropene[27] affords tertiary amine **68**. A Heck coupling reaction using Xantphos as a ligand for the palladium catalyst in combination with a

1:1 mixture of toluene and triethylamine affords the remaining 6-membered ring. In the next step, the tosyl group at the indole moiety is cleaved under reductive conditions by the use of magnesium in methanol. A following hydrogenation with Adam´s catalyst in ethyl acetate provides the partially reduced natural product (±)-cleavamine (**49**) and the fully reduced 20*R*-dihydrocleavamine (**17**) as a side product.

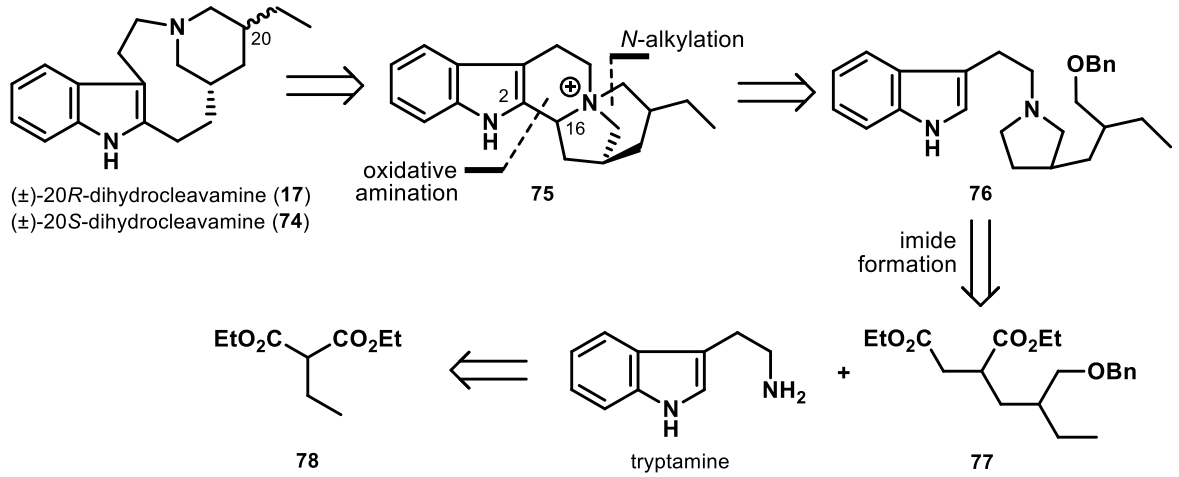


Scheme 11: Bennasar´s total synthesis of (±)-cleavamine (**49**) and (±)-dihydrocleavamine (**17**).

In a nutshell, the total synthesis of (±)-cleavamine (**49**) and (±)-dihydrocleavamine (**17**) is accomplished in 10 steps with an overall yield of 8% and 4% from literature known starting material **70**. Key steps of the synthesis are the RCM reaction to generate the 9-membered macrocycle and the Heck reaction providing the tetrahydropyridine motif.

3.3. Total syntheses of (±)-dihydrocleavamines by Kutney *et al.* 1970

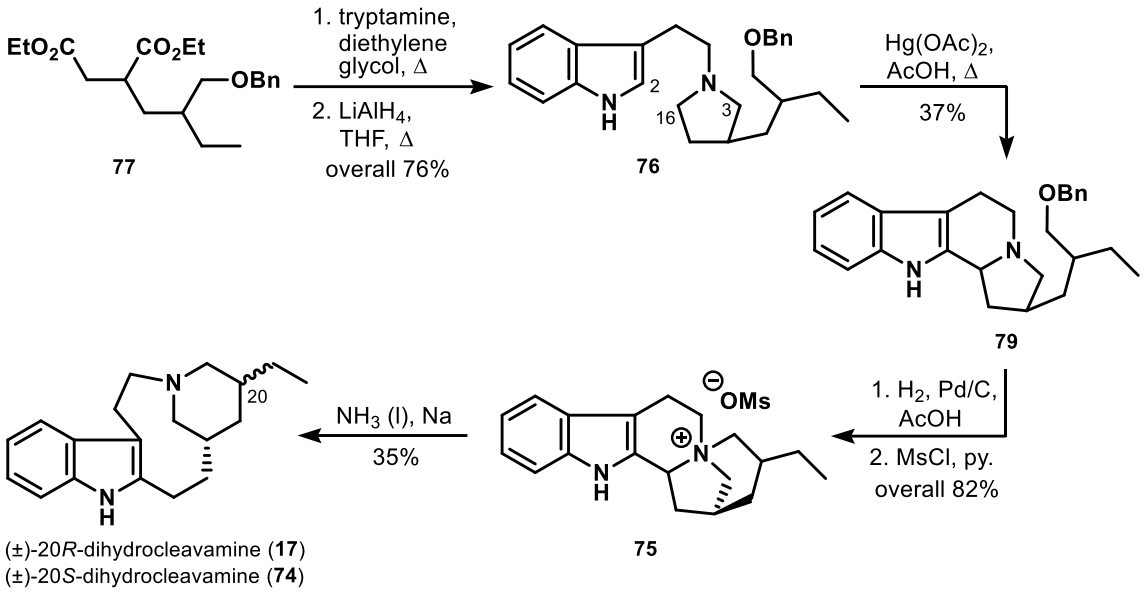
Kutney and coworkers envisioned a reductive fragmentation of the C-16 carbon nitrogen bond in compound **75** to obtain the 9-membered macrocycle (Scheme 12).[28] The required ammonium ion for this reaction is provided *via* a simple *N*-alkylation reaction between the tertiary amine and the adjacent mesyl alcohol of **76**. A further key step in their retrosynthetic analysis is the mercury-mediated oxidative amination reaction to generate the desired C-2, C-16 carbon bond. Furthermore, a doubled condensation reaction between tryptamine and the diester **77** provides the imide, which is reduced in a following step to establish the pyrrolidine motif. The diester compound **77** is available in 7 steps from diethyl malonate derivative **78**.[29,30,31]



Scheme 12: Kutney´s retrosynthetic analysis of (±)-dihydrocleavamines.

The first step in this synthesis is the doubled condensation reaction between tryptamine and the two ethyl ester moieties of compound **77** to provide a 5-membered imide. A following reduction using lithium aluminum hydride in refluxing THF affords the fully reduced tertiary amine **76** (Scheme 13). In the next step, the oxidative amination to generate tetra cycle **79** is initiated by treatment of compound **76** with mercury acetate in hot glacial acetic acid.[32] It is also noteworthy that this reaction does not proceed in a selective manner and therefore cyclization between the C-2 and C-3 carbon atom occurred as a major side product. Nevertheless, cleavage of the benzyl group by the use of hydrogen under palladium catalysis yields the primary alcohol. Conversion of the alcohol into the mesylate with methanesulfonyl chloride in pyridine results in a spontaneous generation of the quaternary ammonium salt **75**. Finally,

reduction of intermediate **75** under Birch conditions yields the desired natural products (±)-20*S*- and 20*R*-dihydrocleavamine.[33]



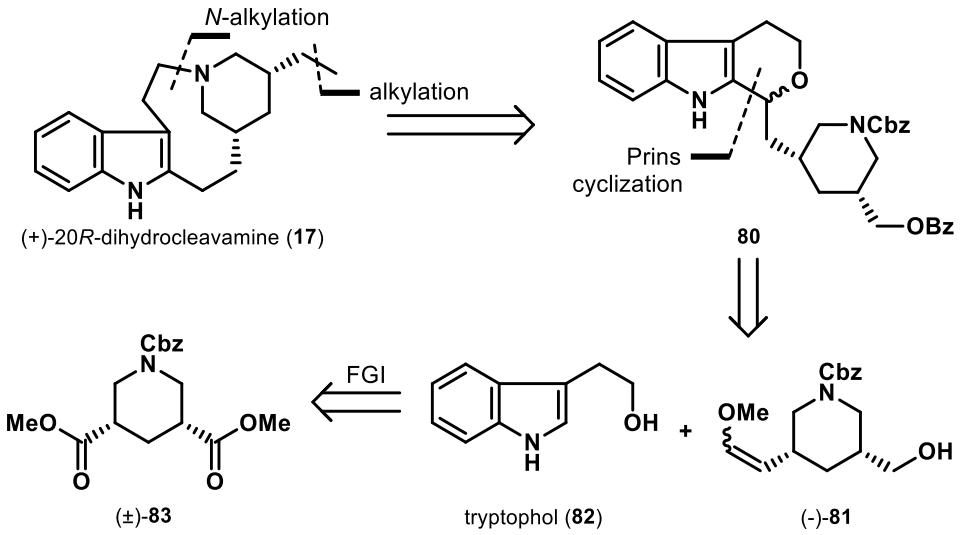
Scheme 13: Kutney´s total synthesis of (±)-dihydrocleavamines.

In summary, the total synthesis of 20*S*- and 20*R*-dihydrocleavamine is accomplished in 6 steps with a combined overall yield of 8% starting from diester **77**. Key steps of the synthesis are the late stage reductive fragmentation to obtain the 9-membered macrocycle and the mercury-mediated oxidative amination.

3.4. Total synthesis of (+)-dihydrocleavamine by Lesma *et al.* 2000

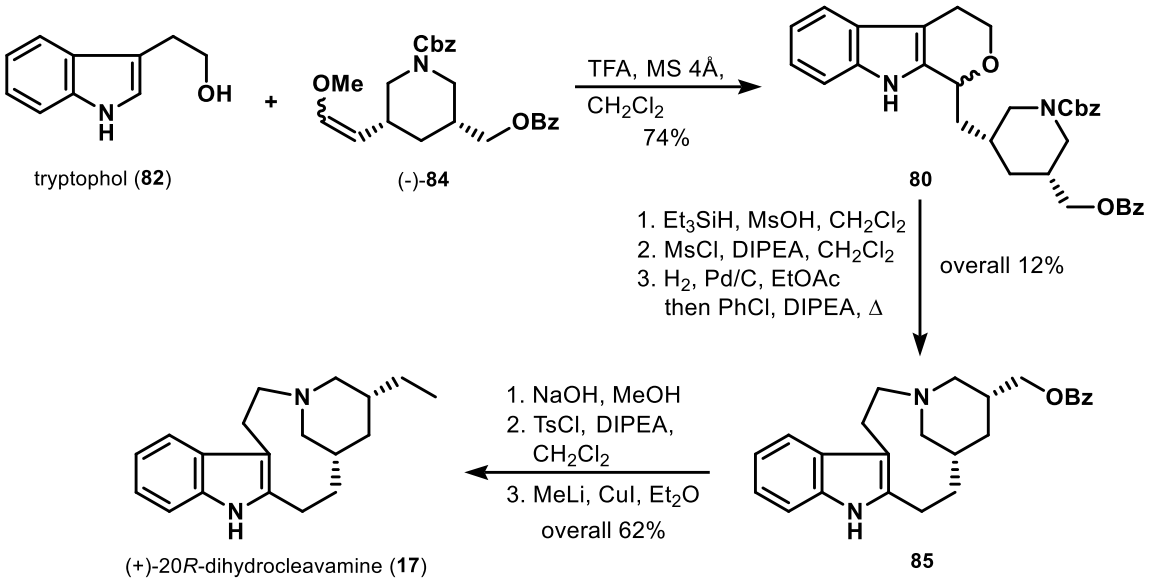
Lesma and coworkers developed an enantioselective synthesis of dihydrocleavamine starting form chiral piperidine derivative **81** (Scheme 14).[34] This building block is accessible in 7 steps from the *meso* diester **83**.[35] Desymmetrization of this compound is achieved *via* a side-selective enzymatic saponification reaction. The indole moiety is installed by the use of a Prins cyclization reaction between tryptophol (**82**) and enolether **84**. Moreover, a subsequent cleavage of the dihydropyran ring at the ether junction provides the primary alcohol, which is substituted some steps later by the piperidine nitrogen to generate the 9-membered macrocycle. Remarkably about Lesma´s approach, in contrast to other macrocyclization strategies, is the envisioned ring-closing reaction *via* the C-3 side chain of the indole moiety. However, a final

copper mediated elongation to the ethyl side chain provides the natural compound dihydrocleavamine (**17**).



Scheme 14: Lesma´s retrosynthetic analysis of (+)-dihydrocleavamine (**17**).

As depicted in Scheme 15, a trifluoroacetic acid-catalyzed Prins reaction between tryptophol (**82**) and piperidine **84** provides intermediate **80** in a 1:1 mixture of diastereomers. A following reductive cleavage of the dihydropyran by the use of triethylsilane in combination with methansulfonic acid provides the primary alcohol.[36]



Scheme 15: Lesma´s total synthesis of (+)-20*R*-dihydrocleavamine (**17**).

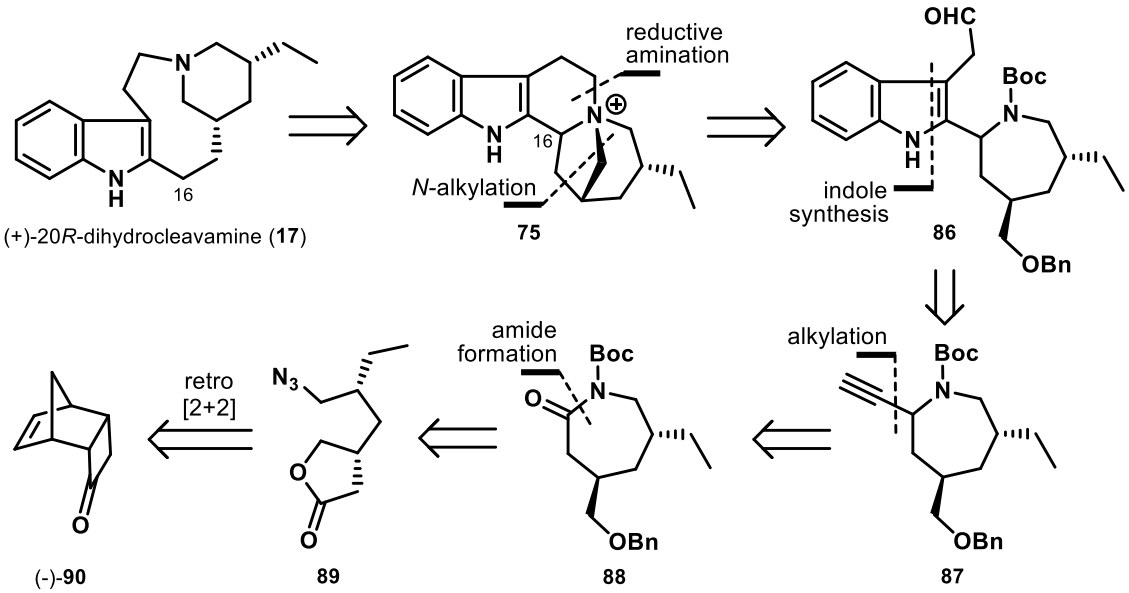
Further steps are the conversion of the primary alcohol into a leaving group by the use of mesyl chloride with Hünigs base and the hydrogenolytic cleavage of the carbamate

to the secondary amine. Subsequent heating of this compound initiates the *N*-alkylation reaction to form 9-membered macrocycle **85**, albeit in poor yields. Saponification of the ester moiety with sodium hydroxide followed by treatment of the resulting alcohol with tosyl chloride affords the tosylate. Finally, a copper mediated substitution with methyl lithium yields the desired product (+)-dihydrocleavamine (**17**).

Lemar and coworkers reported an enantioselective synthesis of dihydrocleavamine in 7 steps with an overall yield of 6% starting from optically active compound **84**. Key steps in the synthesis are the Brønsted acid-mediated Prins cyclization and the *N*-alkylation at the piperidine ring *via* the C-3 side chain of the indole moiety to obtain the 9-membered macrocycle.

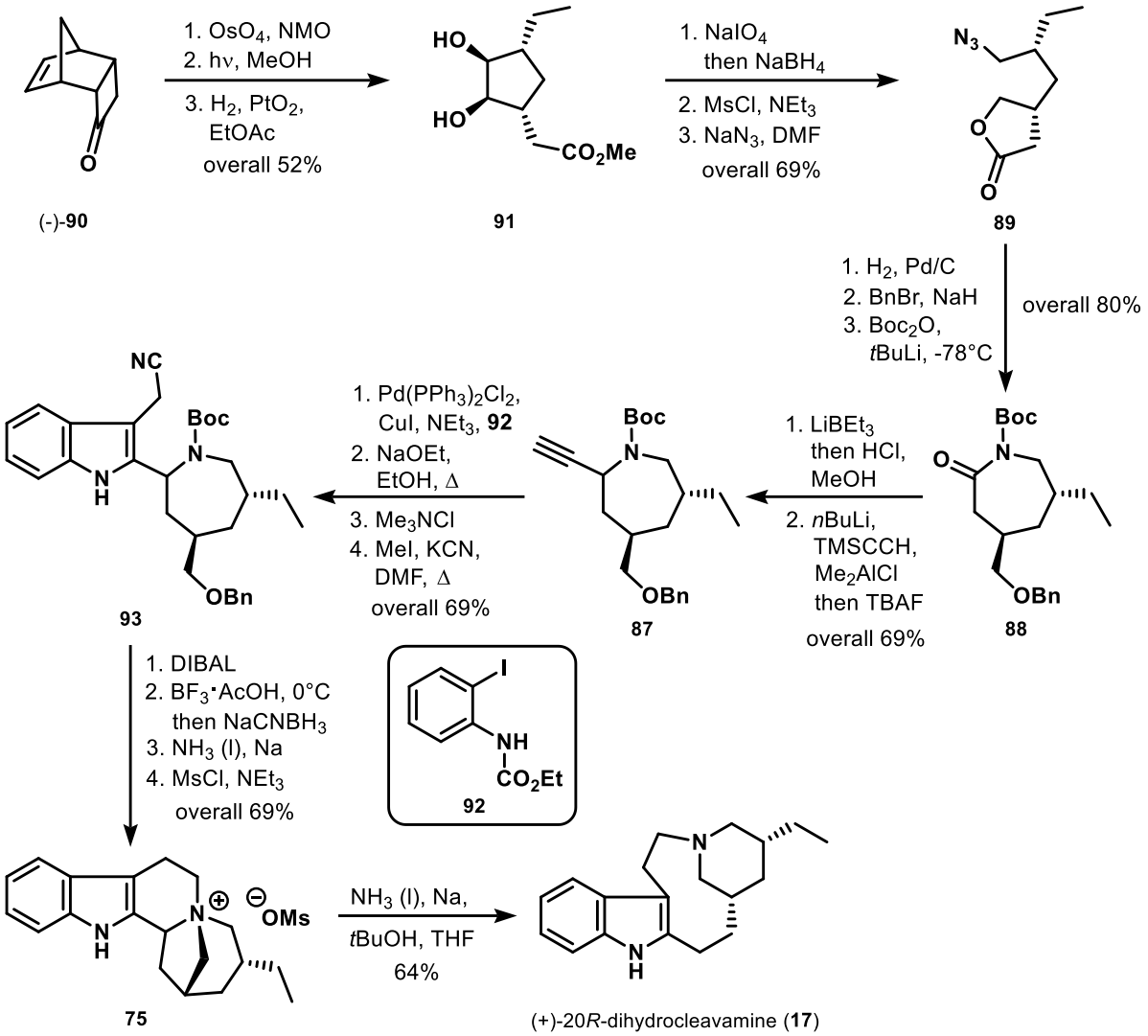
3.5. Total synthesis of (+)-dihydrocleavamine by Ogasawara *et al.* 2001

Ogasawara´s approach to establish the 9-membered ring is based on the reductive fragmentation methodology, which was investigated by Kutney and coworkers in their synthesis of (±)-dihydrocleavamine (**17**).[28,37] Furthermore, the construction of the quaternary ammonium salt **75** is based on the same *N*-alkylation strategy. Nevertheless, the 6-membered ring is installed by a reductive amination between the secondary amine and the adjacent aldehyde.



Scheme 16: Retrosynthetic approach of Ogasawara *et al.* towards (+)-20*R*-dihydrocleavamine (**17**).

The indole moiety is synthesized by the use of a Sonogashira coupling and cyclization protocol, which was developed by Yamanaka and coworkers.[38] Moreover, introduction of the alkyne is achieved *via* nucleophilic addition onto an acyliminium species. The caprolactam key structural motif is generated by utilizing a lactamization reaction between the *in situ* generated amine from the primary azide **89** and the adjacent γ-lactone. Further functional group interconversions and a photoinduced [2+2] cycloreversion reaction lead back to chiral bicycle **90**. This optically active starting material is accessible in 5 steps from cyclopentadiene.[39,40]



Scheme 17: Ogasawara´s total synthesis of (+)-20*R*-dihydrocleavamine (**17**).

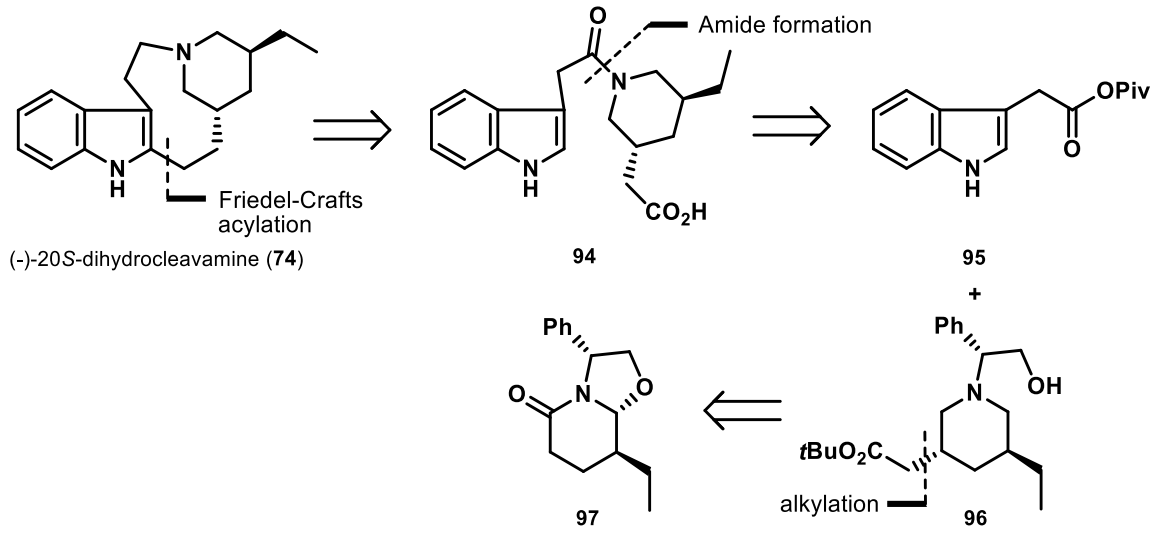
The first step in the synthesis is a stereospecific dihydroxylation of the double bond in bicycle **90** with osmium tetroxide (Scheme 17). Irradiation of the resulting diol in methanol in a Pyrex vessel initiates the cycloreversion reaction of the cyclobutanone ring.[41] It is also noteworthy that the *in situ* generated ketene is trapped with methanol

to afford the methyl ester. A subsequent reduction of the double bond by the use of hydrogen and palladium on charcoal provides compound **91**. The next step is a periodate cleavage of the diol followed by a sodium borohydride reduction of the resulting aldehydes to the corresponding alcohols. Thereby, the alcohol next to the ester moiety cyclizes to form a γ-lactone. The remaining primary alcohol is mesylated and substituted with sodium azide to give intermediate **89**. Catalytic reduction of the azide in methanol accompanied by ammonia results in the generation of the desired caprolactam.[42] Furthermore, benzyl protection of the alcohol followed by an imide formation with Boc_2O provides compound **88**. In the next step, the imide is reduced with super hydride and treated subsequently with a methanolic hydrogen chloride solution to obtain the acyloxy aminal.[43] A following Lewis acid-promoted substitution reaction with TMS protected acetylide establishes the alkyne moiety in a 1:1 mixture of diastereomers.[44] Cleavage of the TMS group with TBAF generates the terminal alkyne **87**. A Sonogashira coupling of alkyne **87** and aromatic compound **92** yields the disubstituted alkyne, which is subjected in a following step to sodium ethoxide in ethanol to initiate the indole formation moiety and the cleavage of the ethyl carbamate. Treatment of the free indole with Eschenmoser´s salt leads to the formation of a tertiary amine, which is converted afterwards into the ammonium salt with methyl iodide to perform a nucleophilic substitution with potassium cyanide to intermediate **93**. In the next step, the cyanide moiety is reduced with DIBAL to an aldehyde. Deprotection of the amine with boron trifluoride acetic acid complex followed by a reductive amination between the secondary amine and the aldehyde under the use of sodium cyanoborohydride affords the 6-membered ring. Reductive cleavage of the benzyl ether under Birch conditions and subsequent treatment of the resulting alcohol with mesyl chloride yields spontaneously the quaternary ammonium salt **75**. A further Birch reduction performs the fragmentation reaction to furnish the final product (+)-20*R*-dihydrocleavamine (**17**).

Ogasawara reported the total synthesis of (+)-20*R*-dihydrocleavamine in 20 steps with an overall yield of 6% starting from optically active bicycle **90**. Key step of the synthesis, similar to Kutney´s approach, is the reductive fragmentation reaction of an ammonium salt. Further key steps are the reductive amination to generate the 6-membered ring and the alkynation of an acyliminium species of compound **88** providing the introduction of the indole moiety later in the synthesis.

3.6. Total synthesis of (-)-20*S*-dihydrocleavamine by Bosh *et al.* 2003

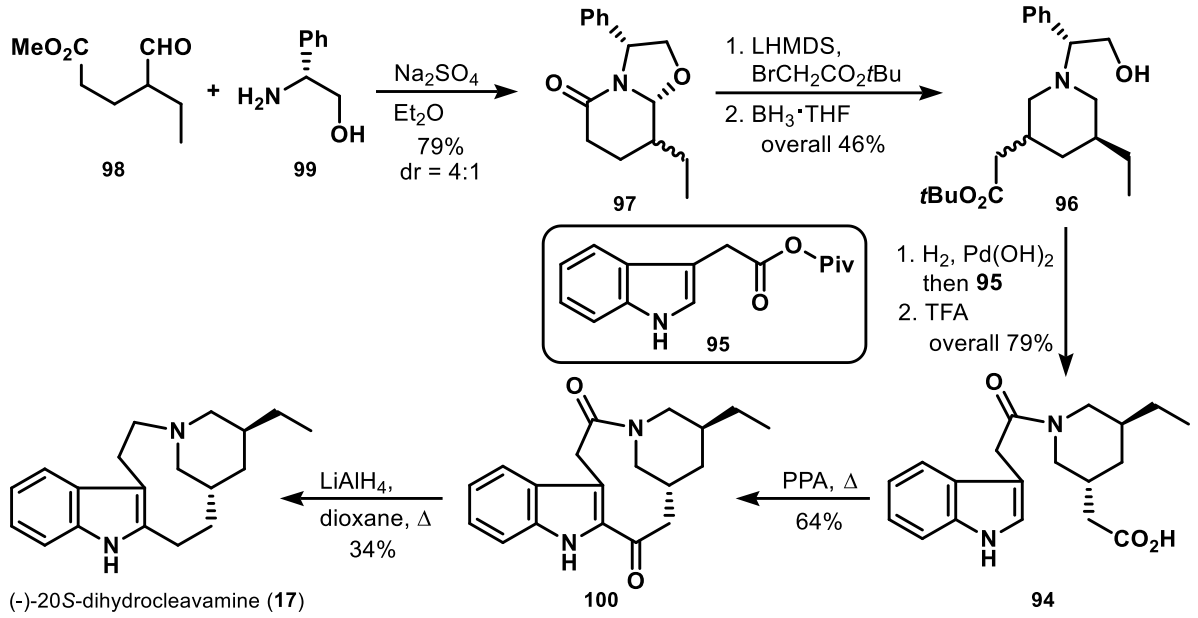
The retrosynthetic strategy of Bosh and coworkers is based on the use of optically active starting material **97** (Scheme 18).[45,46] Moreover, the remaining second side chain is introduced *via* an alkylation reaction. A subsequent condensation reaction between the mixed anhydride of indoleacetate **95** and piperidine derivative **96** provides intermediate **94**. To complete the synthesis of this natural product, Bosh utilizes the same Friedel-Crafts macrocyclization approach as Hanaoka and coworkers.[19]



Scheme 18: Retrosynthetic approach of Bosh and coworkers towards (-)-20*S*-dihydrocleavamine (**74**).

Cylcocondensation of racemic aldehyde **98** with (*R*)-phenylglycinol (**99**) under neutral reaction conditions provides enantiopure bicycle **97** in a 4:1 mixture of diastereomers in favor of the *trans* substituted product (Scheme 19).[47] It is also noteworthy that a treatment of the crude mixture with acidic conditions results in a reversed diastereomeric distribution of 3:7 in favor of the *cis* compound with an overall yield of 60%. The alkylation reaction between the lithium enolate of the *trans* product **97** and *tert*-butyl bromoacetate furnishes the second side chain in an almost 1:1 ratio of *cis/trans* diastereomers. In the next step, the use of borane enables the simultaneous reduction of the lactam and the *N,O*-ketal to obtain piperidine **96**. Cleavage of the benzyl moiety of *trans*-**96** with Perlman´s catalyst in the presence of mixed anhydride **95** and pivalic acid results in a direct condensation of the two building blocks.[48] A subsequent saponification in trifluoroacetic acid provides carboxylic acid **94**. The cyclization reaction is effected by the use of polyphosphoric acid under reflux to obtain

macrocyclic compound **100** in good yield. Simultaneous reduction of the lactam and the ketone with lithium aluminum hydride gives the natural product (-)-20*S*-dihydrocleavamine (**17**).

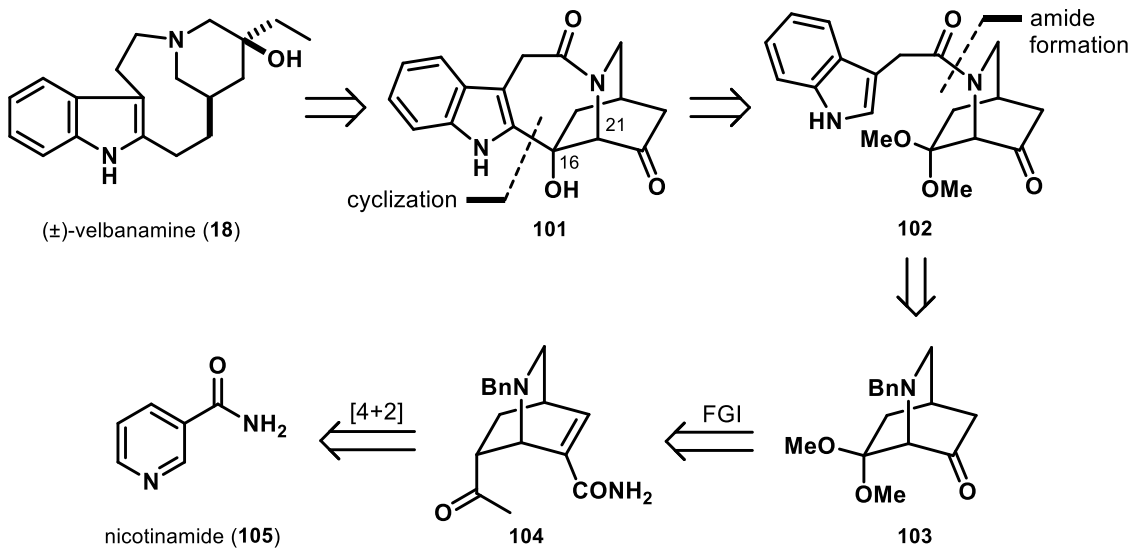


Scheme 19: Bosh´s total synthesis of (-)-20*S*-dihydrocleavamine (**74**).

In summary, Bosh and coworkers presented a quite concise enantioselective total synthesis of dihydrocleavamine in 7 steps with an overall yield of approx. 3% starting from racemic aldehyde **98**. The main strategy of this synthesis is based on the use of chiral lactam **97** providing a rapid access to the desired 3,5-disubstituted piperidine structural motif. A slight drawback of this synthetic approach is the poor side selectivity during the introduction of the second alkyl substituent.

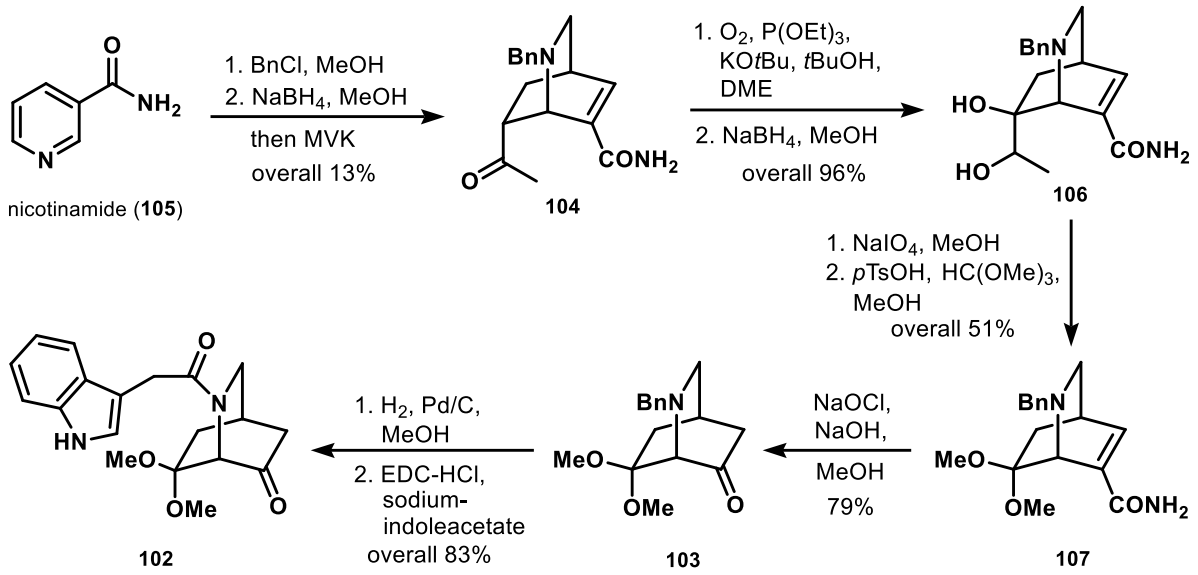
3.7. Total synthesis of (±)-velbanamine by Büchi *et al.* 1968

Büchi´s retrosynthetic strategy to generate the 9-membered ring is based on a C-16, C-21 carbon bond disconnection, which is accomplished by a retro-aldol reaction of compound **101** (Scheme 20).[49,50] A further key step in the synthesis is an acid-promoted nucleophilic attack of the indole to the methyl ketal to provide the caprolactam. The indole moiety is introduced *via* a simple condensation reaction between the secondary amine of azabicycle **103** and indoleacetate. Further functional group interconversions lead back to bicycle **104**, which can be prepared in two steps through a Diels-Alder reaction from nicotinamide (**105**).



Scheme 20: Retrosynthetic approach of Büchi and coworkers towards (±)-velbanamine (**18**).

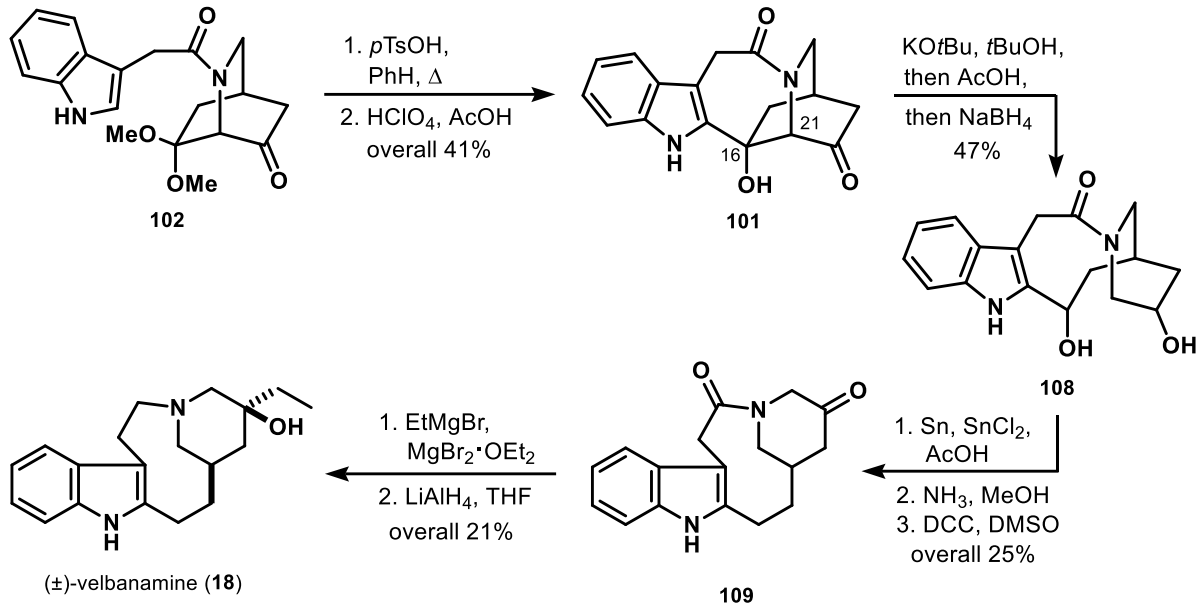
As depicted in Scheme 21, Büchi´s synthesis starts with the generation of the pyridinium salt of nicotinamide (**105**) by the use of benzyl chloride. Reduction of that salt with sodium borohydride provides the corresponding diene, which is then treated with methyl vinyl ketone to perform a Diels-Alder reaction to give bicycle **104**.[51]



Scheme 21: Büchi´s synthesis of compound **102**.

In the next step, a hydroxyl functionality is installed in α-position to the ketone by the use of oxygen and triethyl phosphite.[52] The ketone is then reduced with sodium borohydride to obtain diol **106**. Cleavage of the diol with sodium periodate followed by protection of the ketone with trimethyl orthoformate under acidic conditions affords

ketal **107**. Conversion of the unsaturated amide to ketone **103** is accomplished by the use of Weerman´s protocol.[53] Next steps are the reductive cleavage of the benzyl group by the use of hydrogen with palladium on charcoal and the condensation reaction of the crude product with sodium indole acetate in the presence of EDC hydrochloride to provide amide **102**.[54]



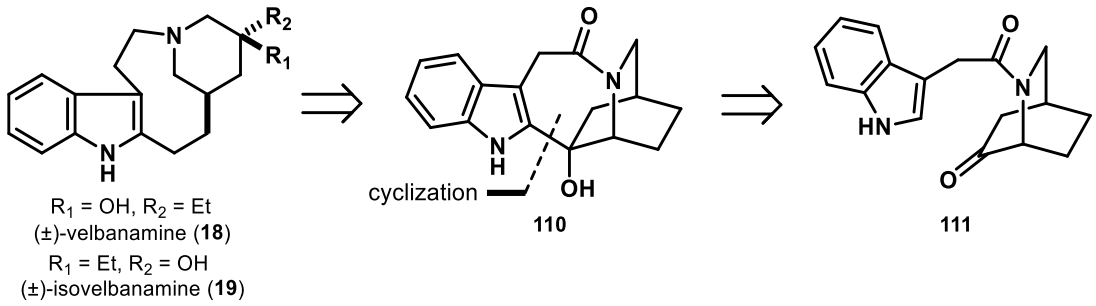
Scheme 22: Büchi´s total synthesis of (±)-velbanamine (**18**).

Treatment of this compound with *p*-toluenesulfonic acid in refluxing benzene yields the cyclized product, which is subsequently treated with perchloric acid to substitute the methoxide with a hydroxyl moiety to give intermediate **101** (Scheme 22). This substitution can be explained by a temporal cleavage of the C-16, C-21 carbon bond *via* a retro-aldol, aldol mechanism. The 9-membered ring is generated by the use of potassium *tert*-butoxide in *tert*-butanol. After acidic buffering with acetic acid, the crude diketo compound is reduced with sodium borohydride to obtain dialcohol **108**. Further reduction of the benzylic alcohol is accomplished using tin in combination with tin chloride in acetic acid.[55] Unfortunately, under these reaction conditions the remaining alcohol at the piperidine ring is partly acetylated. Therefore, the crude product mixture is treated with a methanol/ammonia solution to exclusively yield the desired alcohol. A subsequent oxidation of the alcohol under Pfitzner-Moffat conditions provides ketone **109**.[56] Finally, a nucleophilic addition of ethylmagnesium bromide to the ketone followed by reduction of the lactam with lithium aluminum hydride furnishes the natural product (±)-velbanamine (**18**).

Büchi and coworkers presented the first total synthesis of velbanamine in 17 steps with an overall yield of 0.04% starting from commercially available nicotinamide (**105**). Key steps in the synthesis are the Diels-Alder reaction to generate the bicyclic structure as well as the fragmentation reaction *via* a retro-aldol reaction. Worth mentioning is also the acid-promoted cyclization reaction to establish the caprolactam derivative **101**.

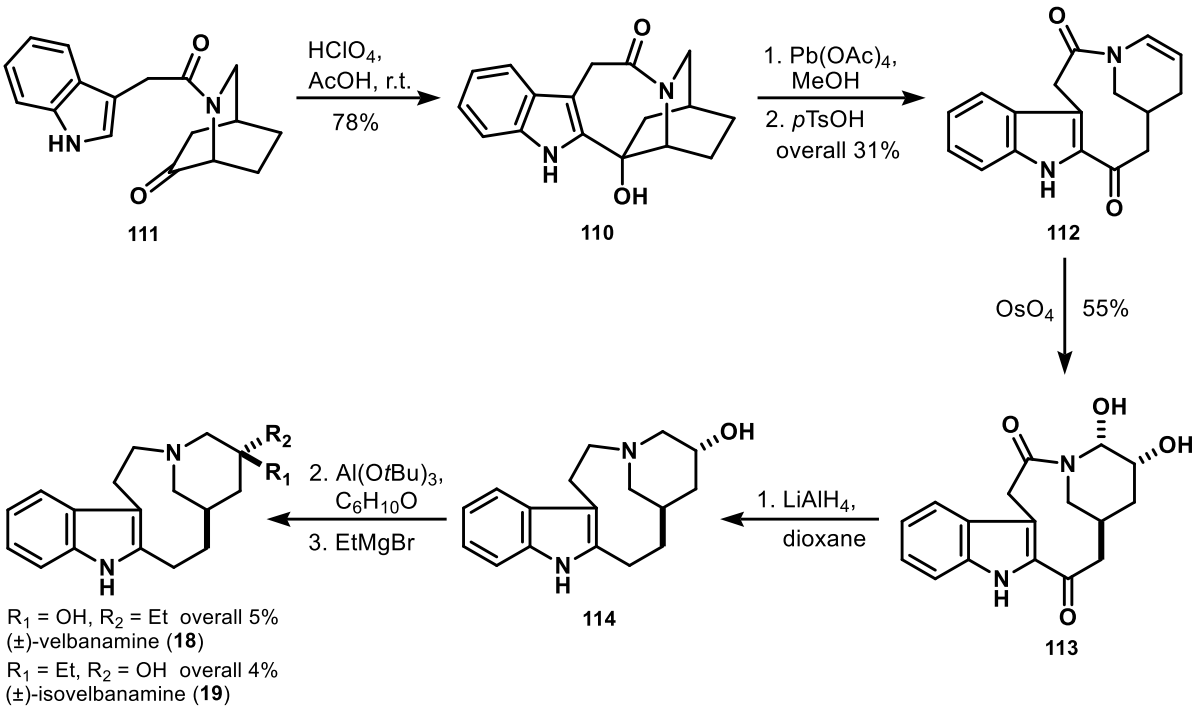
3.8. Total synthesis of velbanamine and isovelbanamine by Narisada *et al.* 1971

Narisada´s strategy to establish the macrocycle is quite similar to the approach of Büchi and coworkers (Scheme 23). In contrast to Büchi, Narisada utilizes a lead tetraacetate-mediated oxidative cleavage of the C-16, C-21 carbon bond to generate the 9-membered ring. Moreover, the preparation of the fragmentation precursor **110** is based on the same cyclization methodology.[57]



Scheme 23: Narisada´s retrosynthetic analysis of (±)-velbanamine (**18**) and (±)-isovelbanamine (**19**).

The synthesis of Narisada and coworkers starts with a nucleophilic attack of the indole to the adjacent carbonyl under strong acidic conditions to provide lactam **110** (Scheme 24).[58] An oxidative cleavage of the carbon bond by the use of lead tetraacetate provides the acylal, which is treated subsequently with *p*-toluenesulfonic acid to obtain intermediate **112**. Dihydroxylation of the acyl enamine with osmium tetroxide gives compound **113**. In the next step, a simultaneous reduction of three different moieties with lithium aluminum hydride yields alcohol **114**. A subsequent Oppenauer oxidation of the alcohol moiety by the use of aluminum *tert*-butoxide and cyclohexanone as oxidation reagent generates the ketone, which is then subjected to ethylmagnesium bromide to afford the two natural products (±)-velbanamine (**18**) and (±)-isovelbanamine (**19**) in a 1:1 mixture.

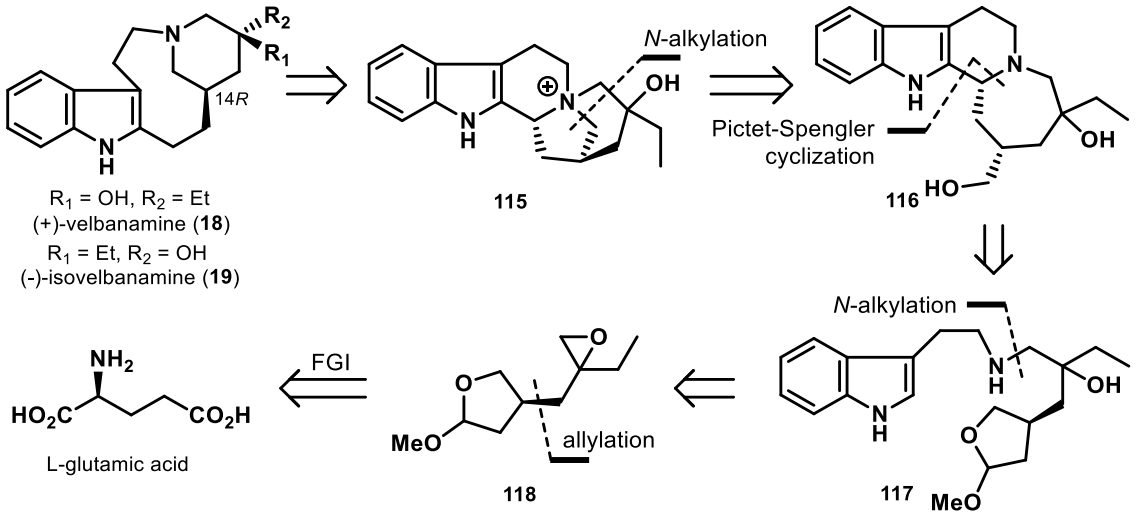


Scheme 24: Narisada´s total synthesis of (±)-velbanamine (**18**) and (±)-isovelbanamine (**19**).

In summary, the total synthesis of velbanamine and isovelbanamine is accomplished in 7 steps in a combined overall yield of 1.2% starting from azabicyle **111**. Key steps of the synthesis are the acid-mediated lactamization reaction to get access to the 7-membered ring and the oxidative carbon bond cleavage by the use of lead tetraacetate to generate the macrocyclic system.

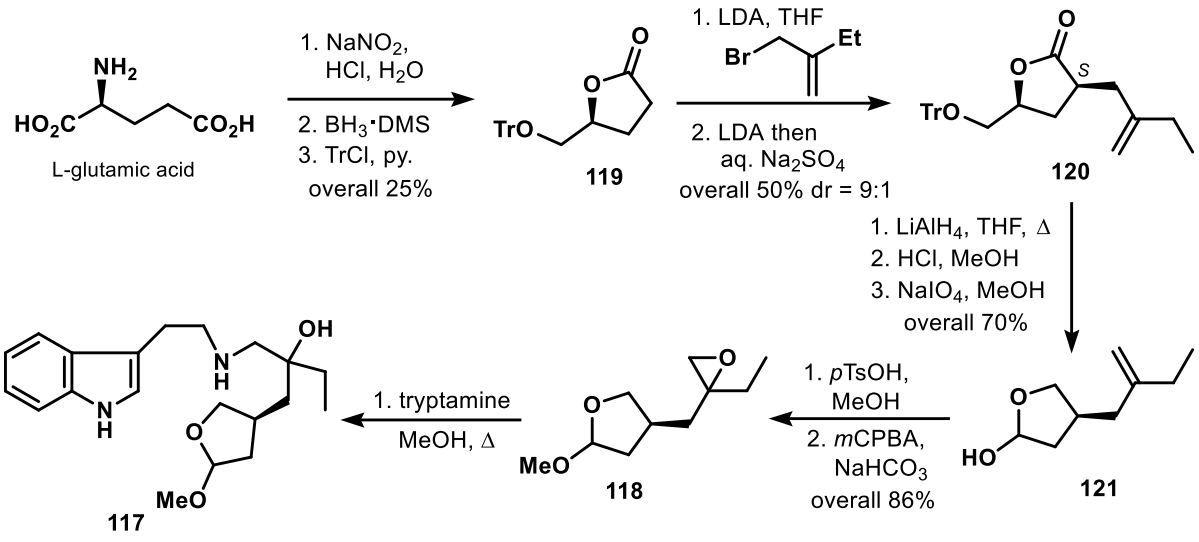
3.9. Total synthesis of (+)-velbanamine, (-)-isovelbanamine and (+)-cleavamine by Takano *et al.* 1982

As depicted in Scheme 25, also Takano´s retrosynthesis is based on the known late stage reductive fragmentation reaction to generate the 9-membered macrocycle.[59,60] The synthesis of the ammonium salt *via* an *N*-alkylation is carried out using the procedure developed by Kutney *et al*.[28] The 6- and 7-membered ring of compound **116** are prepared in a single step by the use of a Pictet-Spengler reaction. The required precursor **117** for this reaction is obtained from epoxide **118** and tryptamine *via* a nucleophilic epoxide-opening reaction. Building block **118** is available in a few steps from natural occurring L-glutamic acid.



Scheme 25: Retrosynthetic analysis of Takano and coworkers.

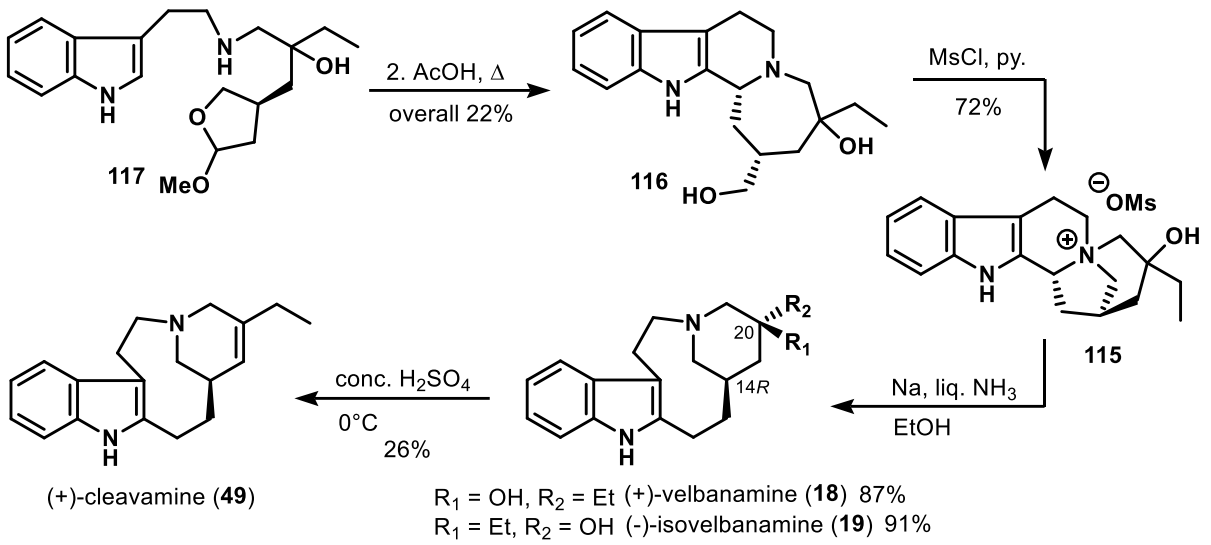
The first steps in the synthesis deals with the preparation of the already known chiral γ-lactone **119** (Scheme 26).[61] Enolization of the lactone with lithium diisopropylamine and a subsequent addition of ethylallyl bromide furnishes the allylated product with an undesired (*R*)-configuration. Subsequent deprotonation under the same reaction conditions followed by the addition of an aqueous solution of sodium sulfate preferentially provides the desired (*S*)-configuration of the allyl side chain in a 9:1 ratio.



Scheme 26: Synthesis of the cyclization precursor **117**.

It is worth mentioning that this alkylation/protonation strategy enables Takano and coworkers to synthesize both antipodes of the desired natural product. However, reduction of the lactone with lithium aluminum hydride yields the diol. Deprotection of the trityl ether with a methanolic solution of hydrochloric acid followed by glycol

cleavage of the resulting vicinal diol provides hemiacetal **121**. Next steps are the conversion of the hemiacetal to the acetal under acidic conditions in methanol and epoxidation of the double bond with *m*CPBA to afford intermediate **118**. The epoxide is opened with tryptamine from the less hindered side to give compound **117**. A subsequent treatment of this intermediate with glacial acetic acid under reflux initiates the acetal-opening and therefore the Pictet-Spengler reaction to form tetracycle **116** (Scheme 27). The ammonium salt is generated by mesylation of the primary alcohol. A following reductive fragmentation with sodium in liquid ammonia in the presence of ethanol yields the two natural products (+)-velbanamine (**18**) and (-)-isovelbanamine (**19**). Moreover, a dehydratization of this product mixture with concentrated sulfuric acid at 0 °C furnishes (+)-cleavamine (**49**) in low yields.[62]

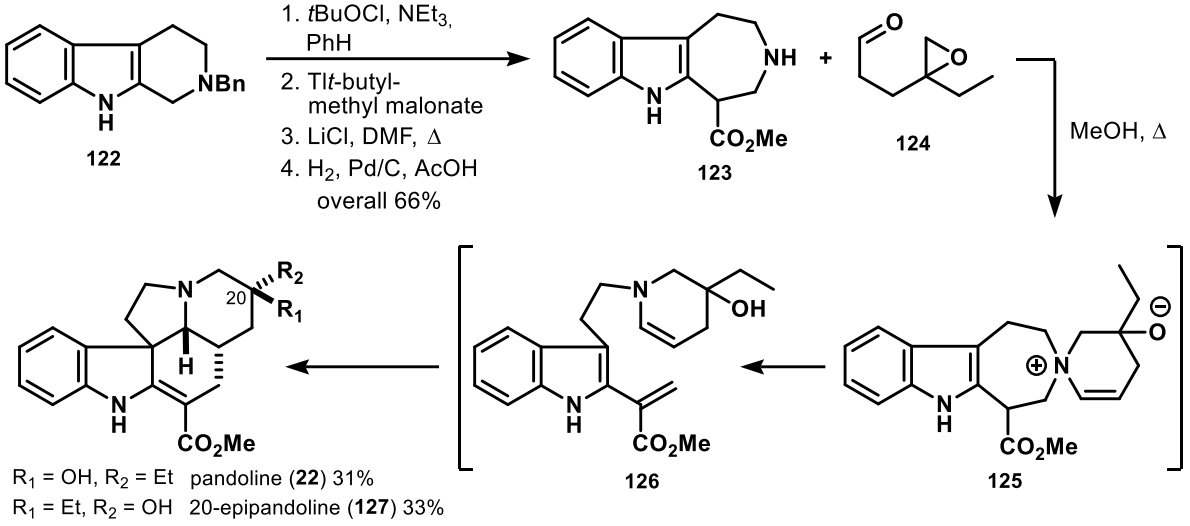


Scheme 27: Takano´s total synthesis of velbanamine (**18**), isovelbanamine (**19**) and cleavamine (**49**).

In a nutshell, the enantioselective total synthesis of velbanamine and isovelbanamine has been reported in 14 steps with an overall yield of 1% from L-glutamic acid. Key steps of the synthesis are the already established reductive fragmentation of the ammonium salt and the Pictet-Spengler cyclization of compound **117** to generate the 6,7-membered ring system. It is also noteworthy that the use of the chiral starting material and the stereoselective introduction of the (*R*)- or (*S*)-configuration at the allyl side chain in compound **120** facilitates an enantiodivergent synthesis. This group also published a racemic total synthesis of these alkaloids which is not discussed in this thesis due to the similarity of the retrosynthetic strategy.[63]

3.10. Total synthesis of (±)-pandoline by Kuehne *et al.* 1980

As depicted in Scheme 28, Kuehne and coworkers developed a very concise total synthesis of pandoline (**22**) and epipandoline (**127**).[64] Starting material of this synthesis is compound **122**, which could be prepared in three steps from tryptamine.[65] In the first step, an oxidation of the indole with *tert*-butyl hypochloride afford a chloroindolenine moiety. Then, a nucleophilic attack of thallium *tert*-butyl-methyl malonate at the imine functionality initiates a rearrangement cascade resulting in the formation of the azepane. Subsequent decarboxylation of the *tert*-butyl ester under Krapcho conditions followed by a cleavage of the benzyl group by the use of hydrogen and palladium on charcoal affords compound **123**. Subjection of the secondary amine to aldehyde **124**[66,67] provides ionic intermediate **125** *via* a condensation reaction and a subsequent nucleophilic epoxide-opening. A following deprotonation in α-position to the ester results in a fragmentation of the azepane to give tricycle **126**. Finally, a biomimetic nucleophilic attack of the enamine to the α,β-unsaturated ester followed by a subsequent attack of the indole enamine to the resulting iminium ion provides the two natural products pandoline (**22**) and epipandoline (**127**) in a 1:1 mixture of diastereomers.



Scheme 28: Kuehne´ total synthesis of pandoline (**22**) and 20-epipandoline (**127**).

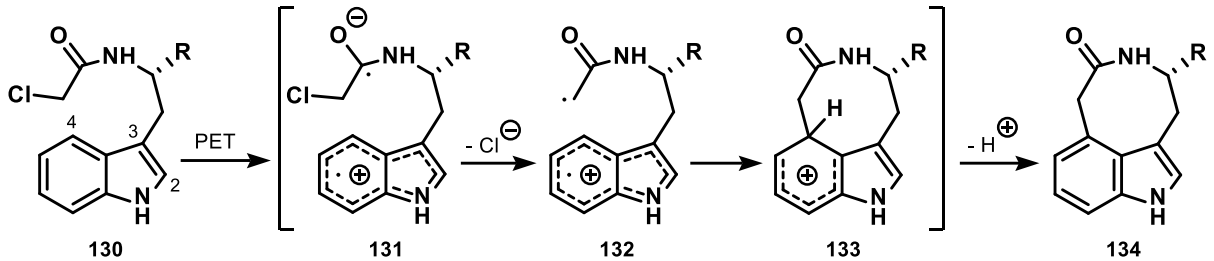
Kuehne and coworkers were able to accomplish a racemic total synthesis of pandoline and epipandoline in 5 steps with a combined overall yield of 42% starting from building

block **122**. Key step in the synthesis is the cascade reaction towards the final products, which is initiated by a condensation reaction between amine **123** and aldehyde **124**.

3.11. Previous synthetic work on related alkaloid scaffolds using the Witkop photocyclization as a key step[68]

Historically, the Witkop cyclization is the result of an attempted photoreduction of *N*-chloroacetyl-tryptophan, which results in a cyclization at the indole 4-position.[69] Since its discovery in 1966, the most important application is the direct formation of medium-sized lactams across indole heterocycles.[70] The reaction has been studied mostly on hydroxy and methoxy substituted aromatic systems with regard to the reaction mechanism and steric factors influencing the reaction behavior. The Witkop cyclization requires electronrich aromatic rings, which are able to adequately stabilize a radical cation intermediate. Product yields are modest, but the ability to afford medium-sized lactams, including some very strained molecular frameworks has proven to be of great interest in natural product synthesis.

The widely accepted mechanism of the Witkop cyclization involves an intramolecular photon-induced electron transfer (PET) from the excited state of the indole chromophore to the chlorocarbonyl moiety, generating intermediate **131** (Scheme 29). Loss of a chloride anion leads to diradical cation **132**, which undergoes cyclization with the aromatic ring yielding cation **133**. The final step is rearomatization to indole system **134** by loss of a proton.



Scheme 29: Accepted mechanism of the Witkop reaction

The Witkop transformation displays a high degree of regioselectivity. Depending on the substitution pattern of the substrate, two different products are mainly obtained. An indole moiety substituted at the C-2 position will form the C-C-bond at the C-3 position to give the 2, 3-annulated product. In contrast, an indole system substituted at the C-3

position reacts at the C-4 position to deliver a 3, 4-bridged indole as major, and the 2, 3-annulated product as a minor product (Figure 10). This thesis exclusively focuses on 2-substituted indoles.

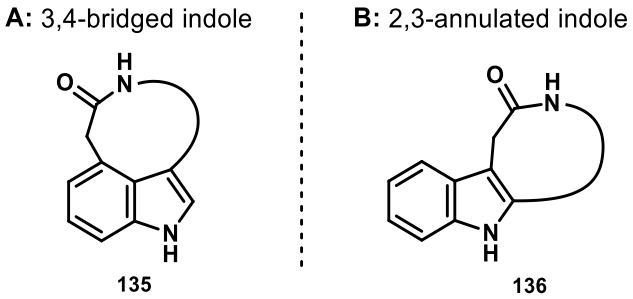
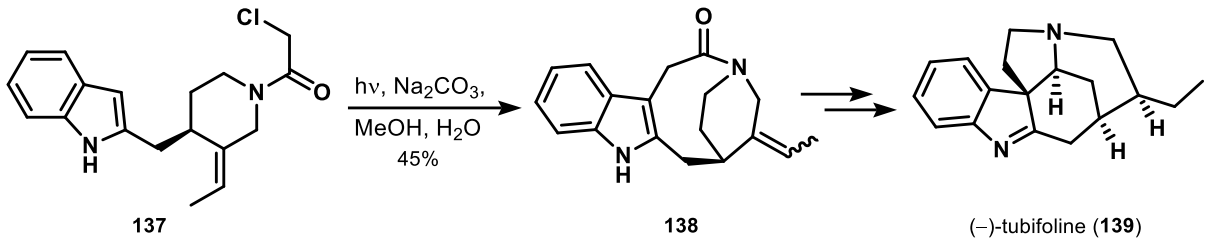


Figure 10: Substitution pattern of the Witkop reaction

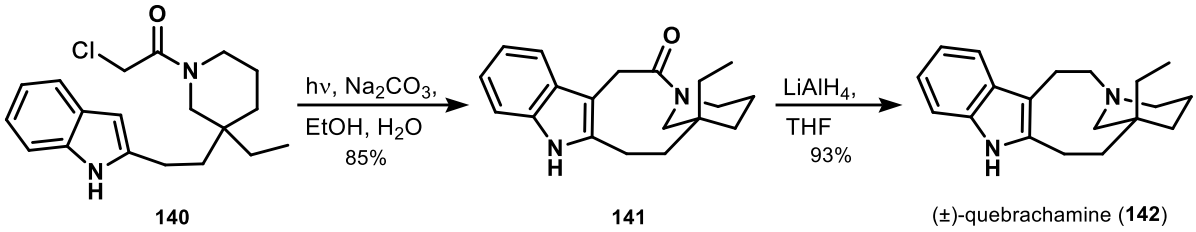
Bosch and co-workers applied the Witkop cyclization to their enantioselective synthesis of the *strychnos* alkaloid (-)-tubifoline (**139**), as depicted in Scheme 30.[71] The yield of this reaction was 45%, accompanied by double bond isomerization (approximately *E*/*Z* = 3:1). In comparison with other examples from literature this result is remarkable with respect to reaction time, as it was completed in only 15 minutes. When additional substituents were introduced on the piperidine ring, the reaction time prolonged to 9 hours and yields dropped to 15%.[72] Reduction of the double bond to an ethyl group and subsequent irradiation resulted in 20% yield of cyclized product.[73] Most likely, compound **137** containing the ethylene group adopts a conformation where the two reaction centers are brought into close proximity and therefore leads to increased yields.



Scheme 30: Photocyclization of compound **137** towards Bosch´s total synthesis of (-)-tubifoline (**139**).

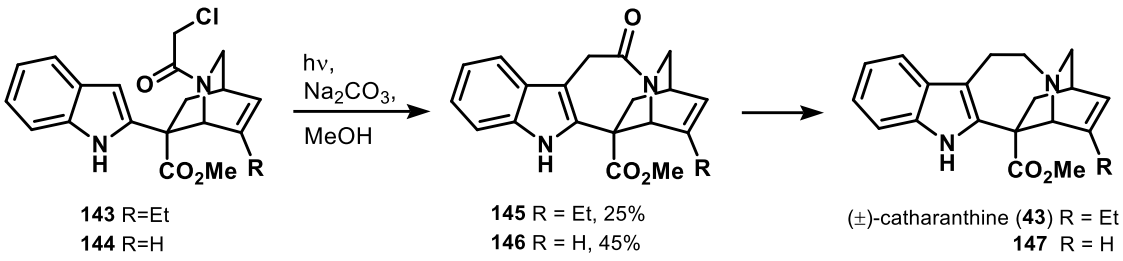
The total synthesis of (±)-quebrachamine (**142**) by Pagenkopf and Bajtos comprises an example for a high yielding photocyclization process (Scheme 31).[74] The reaction proceeded smoothly in aqueous ethanol in the presence of sodium carbonate and delivered the product in 85% yield. In comparison to results of similar Witkop

cyclizations, this yield is exceptionally high. The 9-membered transition state enables a more facile alignment of the reacting carbon atoms, which results in a less strained ring than in the previous shown example, thus facilitating the reaction. The final product is then obtained in one single step by reduction of the lactam with lithium aluminum hydride.



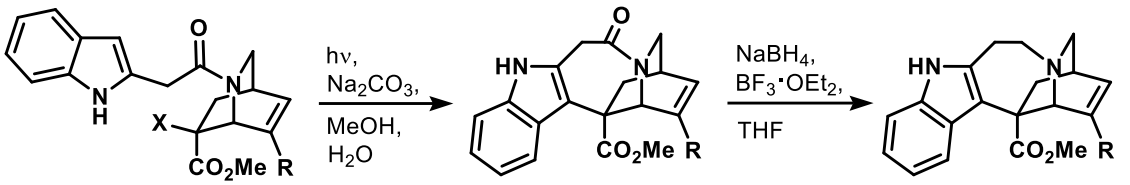
Scheme 31: Pagenkopf´s total synthesis of (±)-quebrachamine (**142**).

Sundberg *et al.* exhaustively investigated the efficiency of cyclization for different chain lengths at the C-3 indole position.[75,76] Furthermore, they employed the Witkop cyclization in the synthesis of catharanthine (**43**) and its regioisomeric analogs **153** and **154**.[77] The indole moiety is inversely incorporated into the natural product as compared to its analogs (Scheme 32).[78] Photocyclization of **143** lead to the ring closed product **145** in 25% yield, commencing in a formal total synthesis of (±)-catharanthine. Irradiation of chloroacetic amide **144**, lacking the ethyl side chain at the quinuclidine moiety, delivered **146** under the same conditions in 45% yield.



Scheme 32: Photocyclization studies towards the total synthesis of catharanthine (**43**).

The inverted indole substitution pattern required a α-chloro ester instead of an amide in the photocyclization reaction and turned out to be one of the few examples where the substrate is not a α-chloroamide (Scheme 33). Photocyclization gave the desired product **151** and **152** in 20-25% and 23% yield, respectively. The corresponding bromo-analogue **150** did not improve the yield.



148 X = Cl, R = H
149 X = Cl, R = Et
150 X = Br, R = H

151 R = H 20 - 25%
152 R = Et 23%

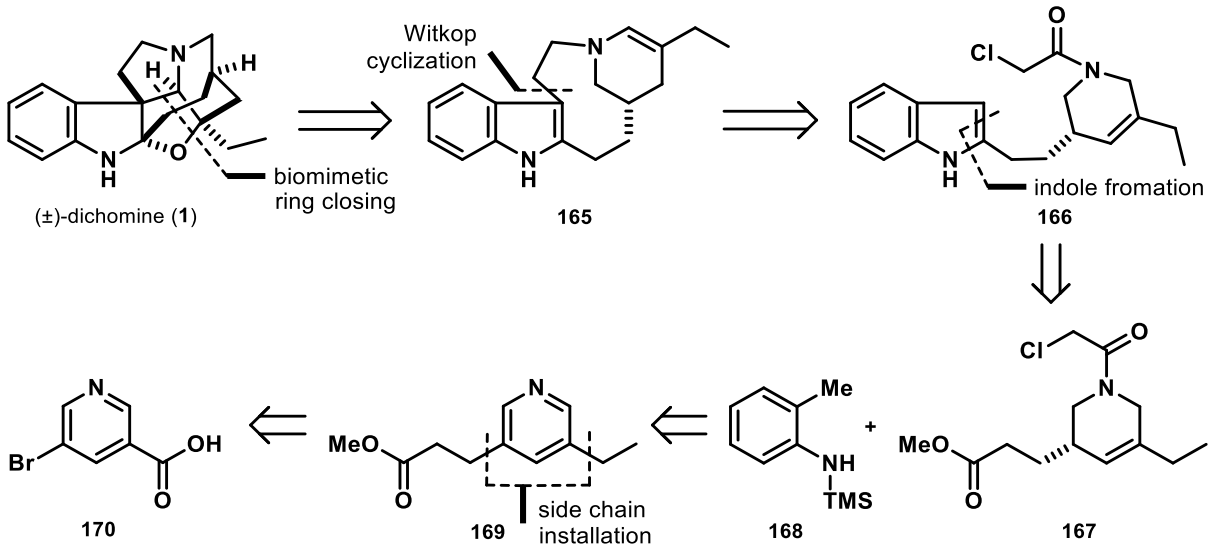
(±)-catharanthine analogs
153 R = H 93%
154 R = Et 93%

Scheme 33: Photocyclization of α-chloro esters to obtain regioisomeric catharanthine analogs.

In summary, the average yields for the Witkop cyclization range from 25 to 45%. High yields tend to be rare for this reaction, although certain examples have been reported. Nevertheless, this reaction provides a short and direct access to complex polycyclic structures, and is therefore of high synthetic value, since substrates for this reaction are in general easy to synthesize. Alternative strategies are most often more laborious, require multi-step sequences, and finally the overall yield may be lower than what is obtained *via* the Witkop cyclization. Therefore, this methodology is a viable synthetic tool for the synthesis of indole containing natural products.

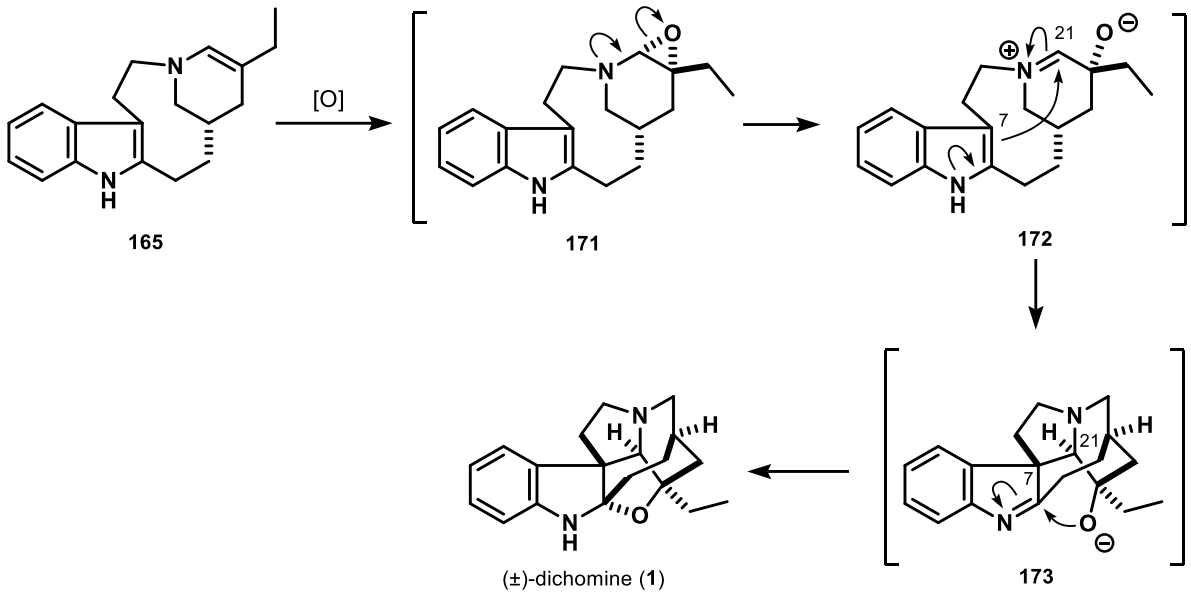
4. Results and Discussion

4.1. Retrosynthetic analysis



Scheme 34: Retrosynthetic analysis of (±)-dichomine (**1**)

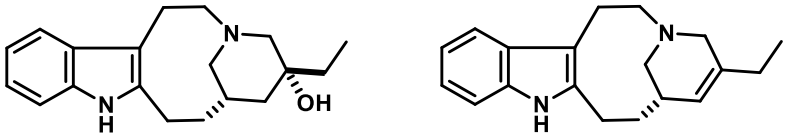
The retrosynthesis of dichomine is based on an oxidative biomimetic ring-closing reaction contracting the 9-membered macrocycle *via* a cascade reaction to the desired bicyclo[5.3.2]dodecane system (Scheme 34). A plausible mechanism for this transformation is depicted in Scheme 35.



Scheme 35: Proposed mechanism of the envisioned biomimetic ring-closing reaction.

This cascade reaction should be initiated *via* a chemoselective epoxidation of the tetrahydropyridine enamine **165** to generate epoxide **171**, which spontaneously decomposes to intermediate **172**. A following attack of the indole enamine to the iminium ion forms the C-7, C-21 carbon bond. The resulting indolenine is subsequently trapped by the proximal alkoxide to generate the remaining tetrahydrofuran ring of dichomine (**1**).

A further key step in the retrosynthesis is the Witkop photocyclization. This reaction should guarantee a facile and rapid access to the desired 9-membered ring. Moreover, due to this strategy it is also able to address the related natural products velbanamine (**18**) and cleavamine (**49**) (Figure 11).



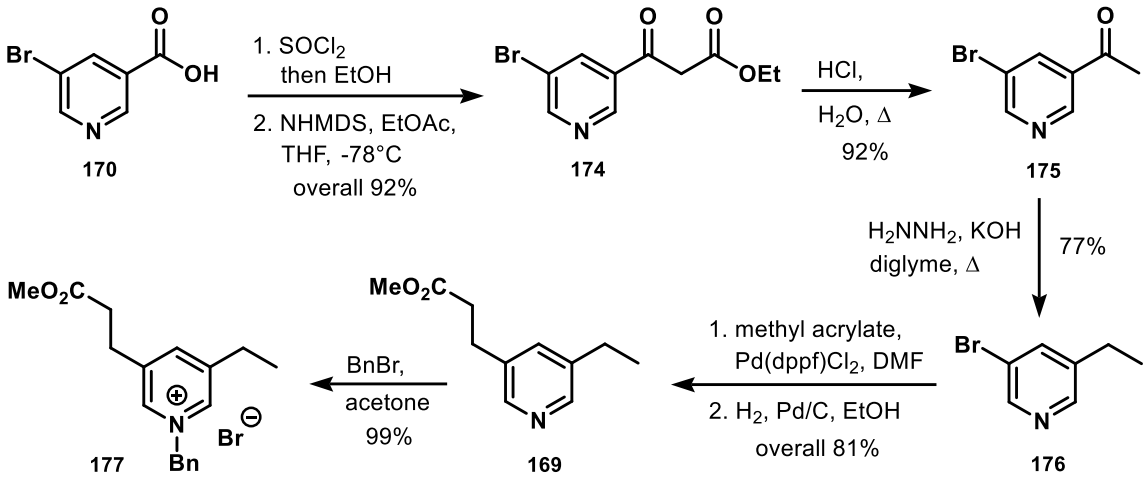
(±)-velbanamine (**18**) (±)-cleavamine (**49**)

Figure 11: Structure of velbanamine (**18**) and cleavamine (**49**).

The indole moiety in compound **166** should be synthesized *via* a condensation reaction between tetrahydropyridine **167** and aromatic compound **168**.[79,80] The building block **167** could be generated by a hydride reduction from the pyridinium salt of intermediate **169**. Furthermore, the substituted pyridine **169** is accessible in a few steps from commercially available 5-bromonicotinic acid (**170**).

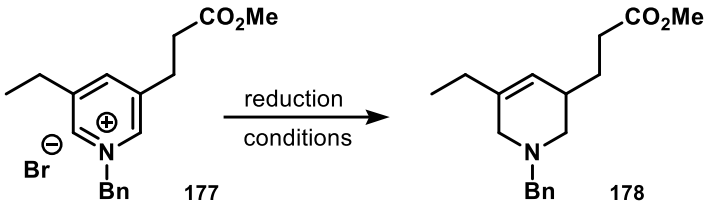
4.2. First approach towards dichomine

The first step in the synthesis was the literature known esterification of commercially available 5-bromonicotinic acid (**170**) with thionyl chloride and ethanol (Scheme 36).[81] A following Claisen condensation by the use of ethyl acetate and NaHMDS provided the β-keto ester **174**. Decarboxylation of the ester in aqueous hydrochloric acid and reduction of the resulting ketone **175** under Wolff-Kishner conditions yielded pyridine **176**.[82,83] Further steps were a Heck reaction with methyl acrylate and a reduction of the α,β-unsaturated ester with hydrogen and Palladium on charcoal to compound **169**. Treatment of this pyridine with benzyl bromide afforded the pyridinium salt **177** in very good yields.



Scheme 36: Synthesis of pyridine **169** and pyridinium salt **177**.

In the next step, a reduction of the pyridinium salt **177** to obtain tetrahydropyridine **178** was attempted (Scheme 37). Therefore, several reducing agents were tested, but unfortunately, none of them gave the desired product (Table 1). Reduction with sodium borohydride at r.t. furnished no reaction and an elevation of the reaction temperature commenced in decomposition of the starting material (Entry 1, 2). The same is true by the use of other reduction agents like lithium borohydride, DIBAL or super hydride (Entry 3-5).



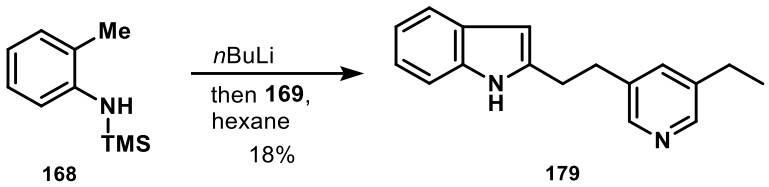
Scheme 37: Attempted reduction of pyridinium salt **177** to obtain tetrahydropyridine **178**.

Table 1: Conditions for the reduction of pyridinium salt **178**.

Entry	Reagents	Solvent	Temp.	Result
1	$NaBH_4$	MeOH	r.t.	no reaction
2	$NaBH_4$	MeOH	reflux	decomposition
3	$LiBH_4$	THF	0 °C	decomposition
4	DIBAL	THF	-78 to r.t.	decomposition
5	$LiHBEt_3$	THF	-78 to 0 °C	decomposition

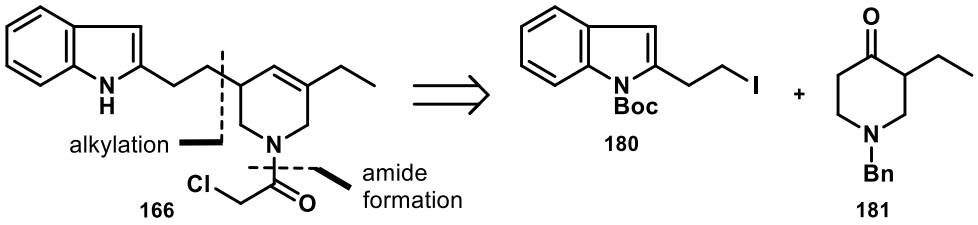
At that time, also the capability of the indole formation reaction with pyridine **169** was tested (Scheme 38). Hence, treatment of aromatic compound **168** with two equivalents of *n*BuLi followed by an addition of pyridine **179** gave the desired product, albeit in poor

yields. It is also noteworthy that even after several optimization attempts it was not possible to improve the yields.



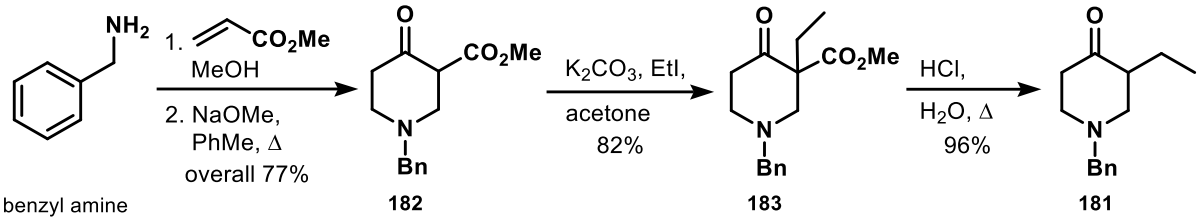
Scheme 38: Test reaction for the synthesis of indole **179**.

Due to these disappointing results, the indole formation strategy as well as the reduction of the pyridinium salt has to be reconsidered. To overcome these problems a new C-C bond disconnection to obtain compound **166** was envisioned. As depicted in Scheme 39, Witkop precursor **166** should be synthesized by an alkylation reaction between indole **180** and piperidone **181**. Subsequent transformations should convert the ketone into the double bond and the tertiary amine into the α-chloro amide.



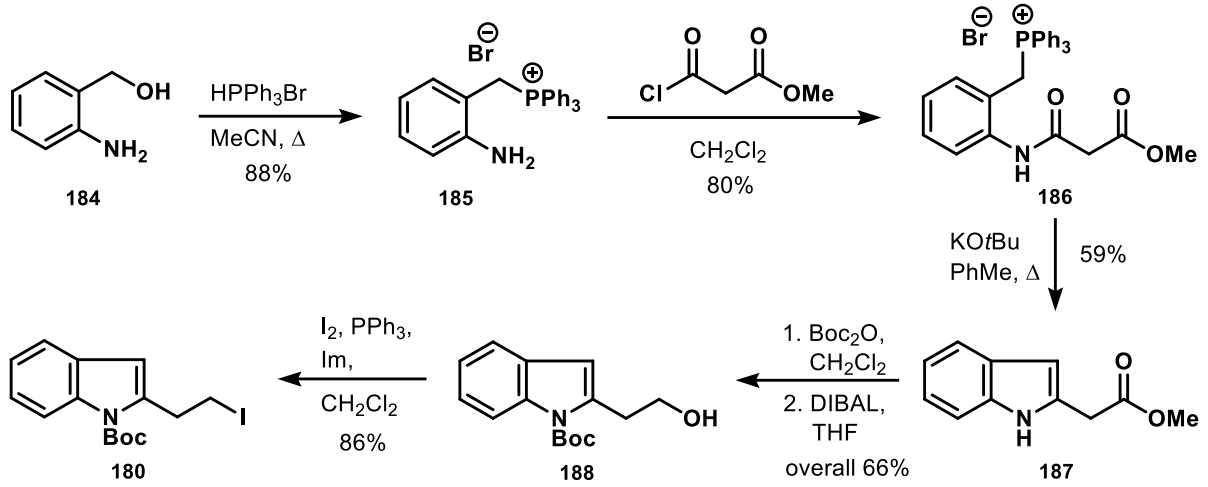
Scheme 39: Alternative retrosynthetic approach to compound **166**.

The synthesis of piperidone **181** started with a literature known two step procedure from benzyl amine and methyl acrylate (Scheme 40).[84] In the first step, a doubled Michael addition of the amine to the α,β-unsaturated ester provided the tertiary benzyl amine. A following Dieckman condensation by the use of sodium methoxide afforded the β-keto ester **182**.



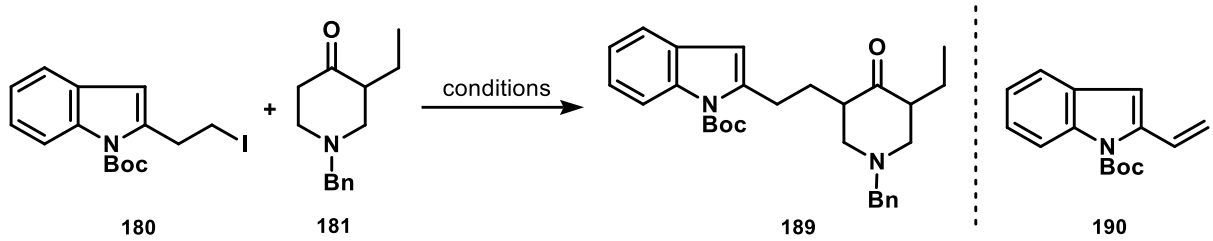
Scheme 40: Synthesis of piperidone building block **181**.

Alkylation with ethyl iodide and potassium carbonate provided intermediate **183**, which was decarboxylated under acidic conditions to the desired piperidone **181**.[85]



Scheme 41: Synthesis of the indole fragment **180**.

The indole building block **180** could be obtained by a literature known procedure from commercially available *o*-aminobenzyl alcohol **184** (Scheme 41).[86] Thereby, the benzyl alcohol is converted into the Wittig salt **185** with triphenylphosphonium bromide. Addition of methyl malonyl chloride provided amide **186**. A subsequent intramolecular Wittig olefination using potassium *tert*-butoxide as a base gave indole **187**. Boc protection of the free indole followed by a DIBAL reduction of the methyl ester in THF afforded alcohol **188**. Finally, an Appel reaction with iodine generated the desired building block **180**.



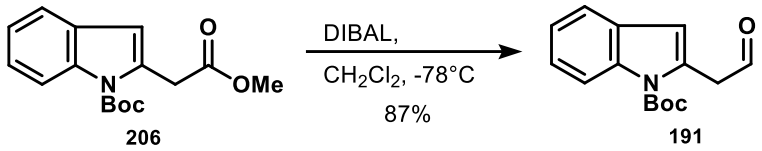
Scheme 42: Alkylation attempts between compound **180** and **181**.

Table 2: Conditions for the alkylation attempts between compound **180** and **181**.

Entry	Base	Solvent	Temp.	Results
1	LDA	THF	-78 to -20 °C	**190** + recov. **181**
2	LHMDS	THF	-78 to 0 °C	**190** + recov. **181**
3	NaHMDS	THF	-78 to 0 °C	**190** + recov. **181**
4	NaHMDS	Et_2O	-78 to 0 °C	**190** + recov. **181**

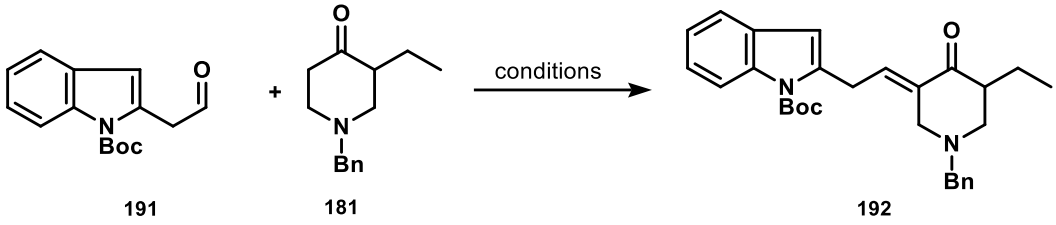
With the building blocks **180** and **181** in hands, several alkylation conditions were performed (Scheme 42). As shown in

Table **2**, all of the used bases generally resulted in decomposition of the indole fragment and the formation of elimination product **190** in small amounts. Remarkably about this reaction was also the reisolation of keto compound **181**. Due to these experimental results, the leaving group at the indole moiety was replaced by a more electrophilic aldehyde functionality. This was accomplished *via* a reduction of methyl ester **206** with one equivalent of DIBAL in methylene chloride at -78 °C (Scheme 43).



Scheme 43: Synthesis of the indole aldehyde **191**.

Subsequent aldol reaction experiments with aldehyde **191** and compound **181** were documented in Table 3 (Scheme 44). Unfortunately, none of the attempted reaction conditions gave any product formation (Entry 1-4). Moreover, also an additional activation of the aldehyde moiety with boron trifluoride led to decomposition (Entry 5). It is also noteworthy that aldehyde **191** decomposed under these reaction conditions, whereas compound **181** could be re-isolated in 30-40% yields.

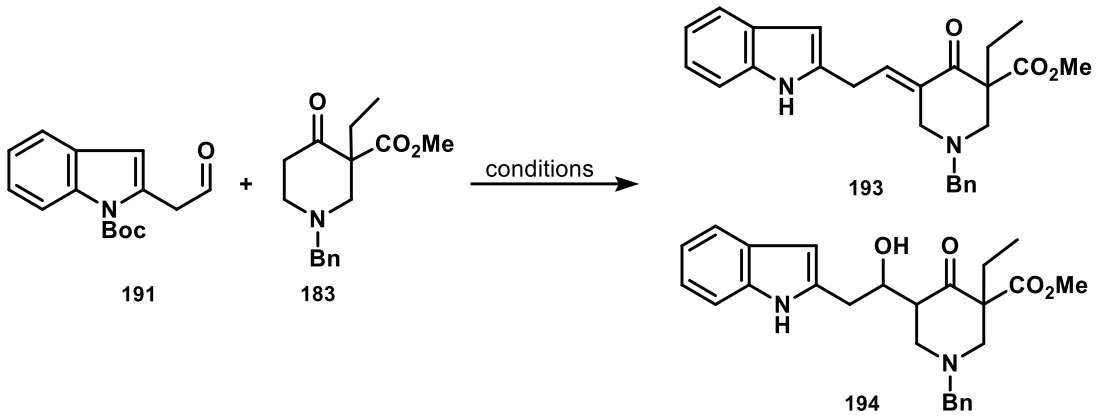


Scheme 44: Attempted aldol condensation reaction between compound **191** and **181**.

Table 3: Conditions for the aldol condensation reaction between compound **191** and **181**.

Entry	Reagents	Solvent	Temp.	Results
1	LDA	THF	-78 to -20 °C	decomp. **191** + recov. **181**
2	LHMDS	THF	-78 to 0 °C	decomp. **191** + recov. **181**
3	NaHMDS	THF	-78 to 0 °C	decomp. **191** + recov. **181**
4	NaHMDS	Et_2O	-78 to 0 °C	decomp. **191** + recov. **181**
5	NaHMDS, BF_3•OEt_2	THF	-78 °C	decomp. **191** + recov. **181**

Parallel to these experiments, further aldol reactions between piperidone **183** and aldehyde **191** were examined (Scheme 45, Table 4). Enolization of the ketone with LDA at -78 °C followed by addition of the aldehyde provided the aldol condensation product **193** in 29% yield without the Boc group at the indole moiety (Entry 1). In contrast, the use of LHMDS only resulted in decomposition of the aldehyde building block **191** and re-isolation of piperidone **183**. Using NaHMDS as base again furnished product **193** in a range of 15-39% yield (Entry 3). The Lewis acid supported aldol reaction with boron trifluoride and NaHMDS provided the aldol product **194** without a Boc protected indole. The use of KHMDS afforded only decomposition of both starting materials. Moreover, using potassium *tert*-butoxide as base provided also the aldol product **194**, albeit in poor yields (Entry 6).



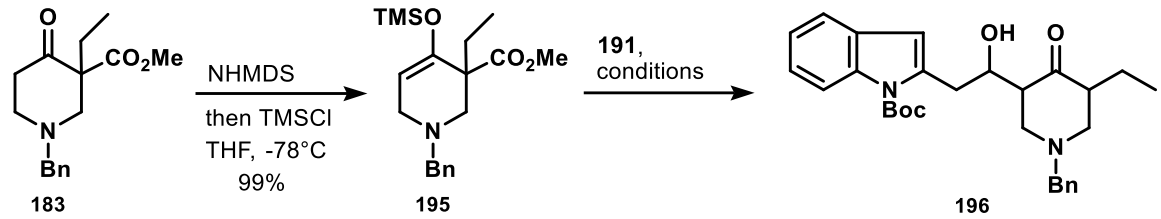
Scheme 45: Attempted aldol reactions between compound **181** and **183**.

Table 4: Conditions for the aldol reactions between compound **181** and **183**.

Entry	Reagents	Solvent	Temp.	Results
1	LDA	THF	-78 °C to r.t.	29% **193**
2	LHMDS	THF	-78 °C	Decomp. **191** + recov. **183**
3	NaHMDS	THF	-78 °C	15-39% **193**
4	NaHMDS, BF_3•OEt_2	THF	-78 to -25 °C	31% **194**
5	KHMDS	THF	-78 °C to r.t.	Decomp.
6	KO*t*Bu	THF	-78°C	24% **194**

However, additional enolization experiments with indole aldehyde **191** revealed remarkably acidic protons next to the aldehyde. Even sodium bicarbonate in THF at room temperature was able to enolize the aldehyde. Unfortunately, this behavior resulted in self-condensation and decomposition. Due to these observations it was decided to investigate in some Lewis acid driven aldol reactions. Hence, enolization of

piperidone **183** with NaHMDS at -78 °C followed by addition of TMSCl provided the silyl enolether **195** in excellent yields (Scheme 46).



Scheme 46: Lewis acid mediated aldol reaction approach to compound **110**.

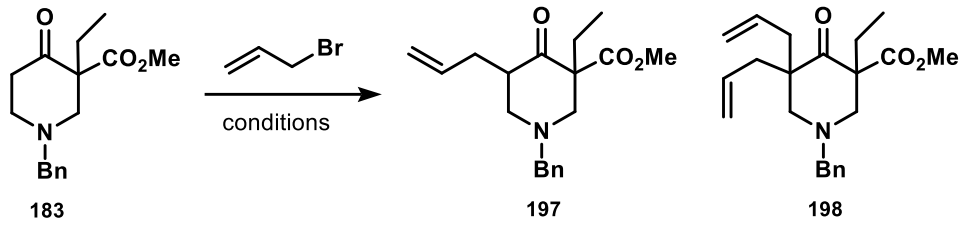
Table 5: Conditions for the Lewis acid mediated aldol reaction approach to compound **110**.

Entry	Reagents	Solvent	Temp.	Results
1	$TiCl_4$	CH_2Cl_2	-78 °C	decomp. **191** + recov. **183**
2	$TiCl_4$	THF	-78 °C to r.t.	decomp. **191** + recov. **183**
3	$BF_3 \bullet OEt_2$	CH_2Cl_2	-78 to -40 °C	decomp. **191** + recov. **183**
4	$BF_3 \bullet OEt_2$	THF	-78 °C to r.t.	decomposition
5	$Sc(OTf)_3$	CH_2Cl_2	-78 °C	decomposition
6	TMSOTf	CH_2Cl_2	-78 °C	decomposition

Unfortunately, treatment of the silyl enolether **195** in the presence of aldehyde **191** under various Lewis acid conditions proved to be unsuccessful (Table 5). For example the use of titanium tetrachloride or boron trifluoride at low reaction temperatures provided only decomposition of the aldehyde **191** and the cleaved silyl enolether product **183**. An increase of the reaction temperature to -40 °C or room temperature furnished the same results (Entry 2, 3). Moreover, the use of boron trifluoride in THF at ambient temperature revealed total decomposition of both starting materials (Entry 4). The same is true if $Sc(OTf)_3$ and TMSOTf were used as Lewis acids (Entry 5, 6).

Due to the incapability of the indole building blocks **180** and **191** with respect to an aldol or alkylation reaction, other suitable electrophiles like allyl bromide were examined. Therefore, several allylation reactions with allyl bromide and piperidone **183** were attempted (Scheme 47, Table 6). Enolization of the ketone with LDA or NaHMDS followed by an addition of allyl bromide at -78 °C gave only poor yields of the desired product (Entry 1, 2). The use of sodium hydride in refluxing THF afforded only 28% yield of product **197** in a 1:1 mixture of diastereomers. Moreover, using potassium *tert*-butoxide as a base at -78 °C generated the products **197** and **198** in a 1:1 mixture (Entry 4). An increase of the reaction temperature to 0 °C improved the yield of the

desired product **197** to 30%. A further warming to room temperature raised the yield of **197** to 62% accompanied by 38% of the double allylated product **198**. Unfortunately, during the scale up process (gram scale) the yield of the mono allylation product **197** decreased to 30%. It is also noteworthy that the use of only one equivalent of allyl bromide had no influence to the product ratio.

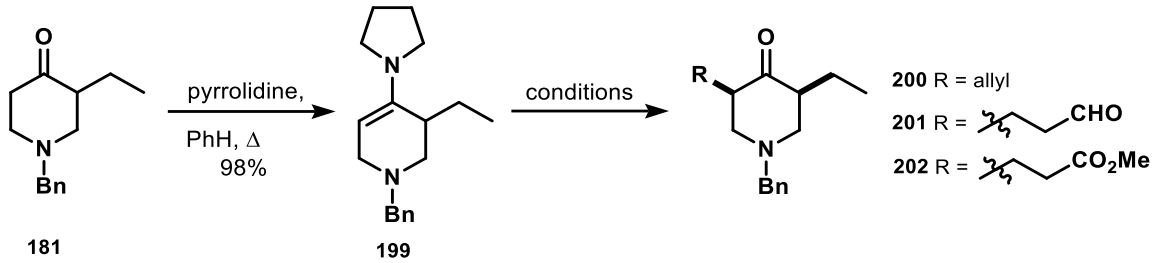


Scheme 47: Allylation attempts of piperidone **183** with allyl bromide.

Table 6: Conditions for the allylation attempts of piperidone **183** with allyl bromide.

Entry	Reagents	Solvent	Temp.	Results
1	LDA	THF	-78 °C	18% **197**
2	NaHMDS	THF	-78 °C	13% **197**
3	NaH	THF	reflux	28% **197**
4	KO*t*Bu	THF	-78 °C	21% **197** + 19% **198**
5	KO*t*Bu	THF	0 °C	30% **197** + 13% **198**
6	KO*t*Bu	THF	r.t.	30-62% **197** + 14-38% **198**

The poor yields of this allylation attempts led to the assumption that the pyridones **181** and **183** are quite weak nucleophiles. Therefore, an enamine-mediated alkylation strategy, which should enhance the nucleophilic properties of compound **181** was envisioned. Based on this considerations, piperidone **181** was treated with pyrrolidine under Dean-Stark conditions to provide the rather unstable enamine **199** in excellent yields (Scheme 48). It is also noteworthy that attempts to form an enamine of piperidone **183** with pyrrolidine or morpholine were unsuccessful. As documented in Table 7, treatment of freshly prepared enamine **199** with allyl bromide provided yields in the range of 16-39% of the desired product **200** (Entry 1). The use of indole aldehyde **191** as electrophile resulted in decomposition of the starting materials. In contrast to other Michael addition attempts, the reaction with acrolein proceeded at -78 °C, although in poor yields.



Scheme 48: Enamine mediated side chain installation attempts.

Table 7: Conditions for the enamine mediated side chain installation attempts.

Entry	Substrate	Solvent	Temp.	Results
1	AllylBr	MeCN	reflux	16-39% **200**
2	**191**	MeCN	reflux	decomposition
3	Acrolein	MeCN	-78 °C	18% **201**
4	Methyl acrylate	MeCN	reflux	15-27% **202**, 75% (brsm)
5	Acrylonitrile	MeCN	reflux	no reaction
6	Methyl propiolate	MeCN	reflux	decomposition

The addition to methyl acrylate proceeded in refluxing acetonitrile and provided the desired product in 15-27% yield (Entry 4). Further addition attempts using acrylonitrile and methyl propiolate as Michael acceptors were unproductive (Entry 5, 6). It is also worth mentioning that all alkylation reactions provided only the thermodynamically more stable *cis*-substituted product.

4.2.1. Conclusions of the first synthetic approach

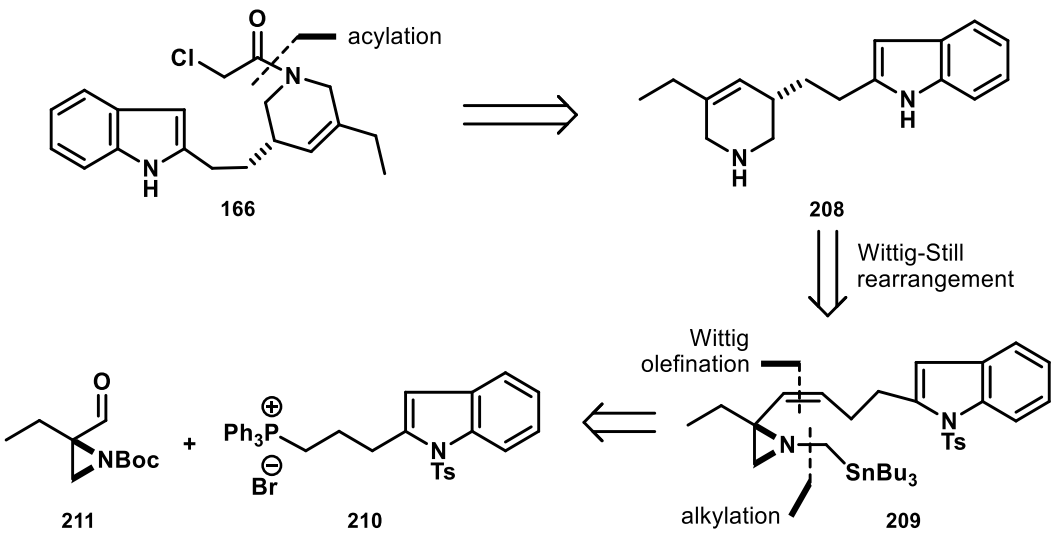
The first part of this approach dealt with the synthesis of pyridine derivative **169**. This was accomplished in 6 steps starting from commercially available 5-bromo nicotinic acid (**170**) (Scheme 36). Furthermore, it was possible to install the indole moiety at compound **169**, albeit only in poor yields (Scheme 38). The major drawback in this early approach were the unsuccessful reduction attempts of the pyridinium core **177** to the desired tetrahydropyridine moiety **178** (Scheme 37).

Based on these results, an alternative strategy to generate the tetrahydropyridine and the indole moiety has to be considered. Therefore, a new C-C bond disconnection to obtain compound **166** form the two building blocks **180** and **181** was envisioned. The synthesis of these fragments could be accomplished in 6 steps for the indole compound **180** and in 4 steps for the piperidone **181**, respectively. However, the intended C-C bond formation with indole **180** or other electrophiles proved to be very

difficult. Albeit some of the tested conditions provided the desired product, none of the obtained yields were satisfying. Due to these fruitless side chain installation approaches it was decided to skip this strategy as well.

4.3. Second approach towards dichomine

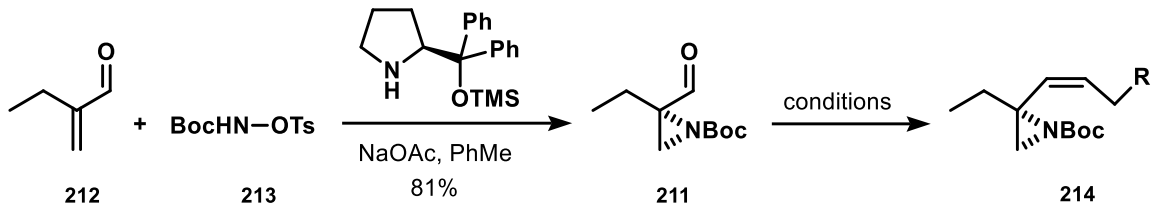
Herein, a totally different retrosynthetic strategy to obtain Witkop precursor **166** was developed (Scheme 49). This approach is based on a [2,3]-Wittig-Still rearrangement of aziridine **209**.[87,88] The required building block **209** for this key transformation should be synthesized *via* a Wittig olefination between phosphonium salt **210** and aldehyde **211**. A following deprotection- alkylation sequence at the aziridine nitrogen should establish the tributyltin side chain.



Scheme 49: New retrosynthetic analysis towards building block **166**.

As depicted in Scheme 50, the first target in this approach was the generation of aldehyde **211**. This was accomplished in one step by a literature known procedure starting from α-ethyl acrolein (**212**) and hydroxylamine derivative **213** in the presence of the Hayashi-Jørgenson catalyst.[89] At that point, several test reactions to examine the capability of this aldehyde in a Wittig reaction were performed. In contrast to some related substrates in literature, compound **211** proved to be an unsuitable starting material for this kind of a Wittig olefination.[90] Regardless which bases or non-stabilized Wittig salts were tested, none of them provided the desired product (Table 8). It is also

noteworthy that the starting material did not react at -78 °C and started to decompose during the warm up process.

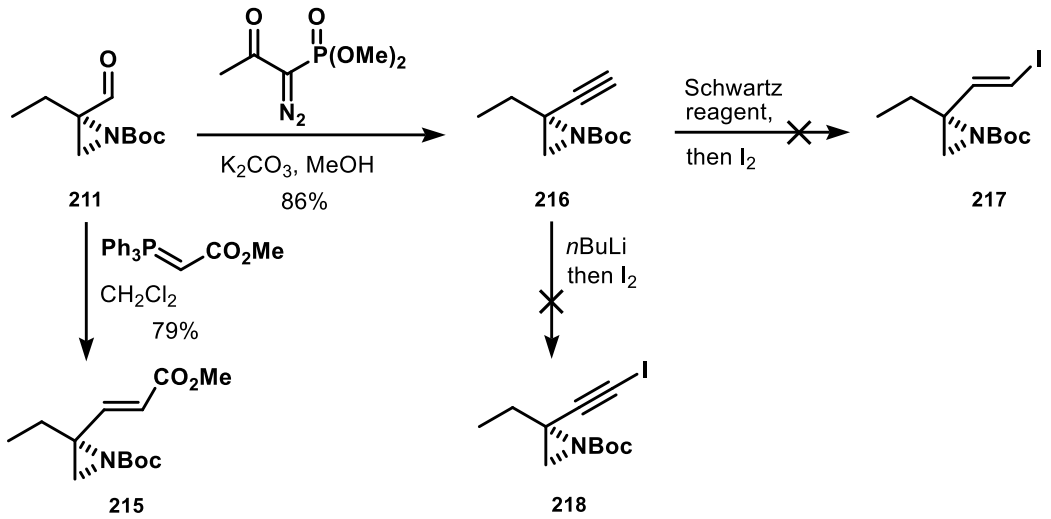


Scheme 50: Synthesis of aldehyde **211** and Wittig olefination attempts towards compound **214**.

Table 8: Condition for the Wittig olefination attempts towards compound **214**.

Entry	Wittig Salts	Base	Solvent	Temp.	Results
1	$EtPPh_3Br$	NaHMDS	THF	-78 °C to r.t.	decomposition
2	$EtPPh_3Br$	NaHMDS	Toluene	-78 °C to r.t.	decomposition
3	$EtPPh_3Br$	KHMDS	THF	-78 °C to r.t.	decomposition
4	$BrPPh_3(CH_2)_3OTIPS$	NaHMDS	THF	-78 °C to r.t.	decomposition
5	$BrPPh_3(CH_2)_3OTIPS$	KHMDS	THF	-78 °C to r.t.	decomposition

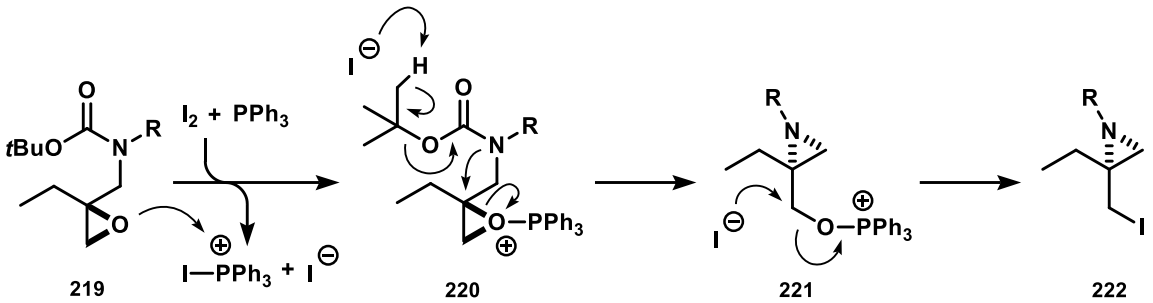
Furthermore, the addition of other nucleophilic reagents like vinylmagnesium bromide or vinylzinc chloride were also unsuccessful. Even the reduction with sodium borohydride to obtain the primary alcohol could not be achieved. An explanation for the instability of this compound could be an attack of the nucleophile at the less hindered side of the electron poor aziridine moiety. Therefore, several attempts to cleave the Boc group were tested, but unfortunately all of them led to decomposition.



Scheme 51: Several transformation attempts of aldehyde **211**.

On the other hand, an olefination reaction between aldehyde **211** and the methyl acetate Wittig reagent gave the desired product **215** (Scheme 51). However, reduction attempts at the ester moiety of this compound with DIBAL furnished only decomposition of the starting material. Experiments to cleave the Boc group provided the same results. Based on this experimental outcome, a Bestmann-Ohira reaction to install an alkyne moiety instead of a double bond were performed. This transformation proceeded smoothly and gave the volatile alkyne **216** in good yields. Unfortunately, a transformation of the alkyne into a vinyliodine functionality utilizing the Schwartz reagent and a subsequent electrophilic substitution of the vinylzirconium species with iodine was unsuccessful. Furthermore, the installation of an iodine at the alkyne moiety *via* deprotonation with *n*BuLi and subsequent quenching of the resulting anion with iodine did not furnished the desired product. It is also noteworthy that a deprotection of aziridine **216** with trifluoroacetic acid in methylene chloride was possible, albeit in poor yields.

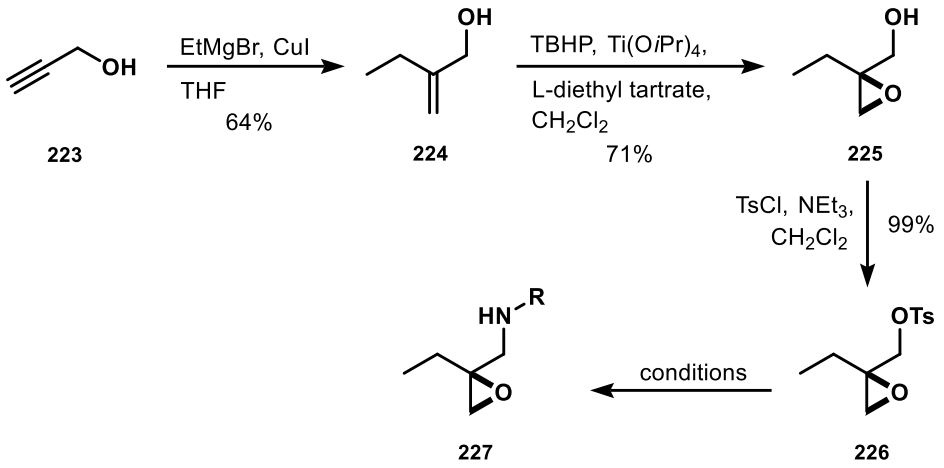
Due to the incapability of building block **211** relating to further derivatizations it was decided to establish a new synthetic approach to obtain aziridine **209**. Thereby, the aziridine moiety should be generated *via* an unprecedented structure specific double Appel reaction from epoxide **219** (Scheme 52). In this reaction the *in situ* generated triphenylphosphonium iodide activates the epoxide, whereas the released iodine simultaneously cleaves the Boc group. Then, the secondary amine performs a nucleophilic substitution in α-position to generate the aziridine. A following second substitution of the remaining iodine at the oxygen carbon generates the desired product **222**. Finally a Kornblum oxidation of the primary iodine should afford the required aldehyde for the Wittig olefination.



Scheme 52: Mechanistic consideration for a structure specific double Appel reaction.

A promising starting material, which should enable a rapid access to compound **219** was the literature known epoxide **225**. This epoxide could be obtained in two steps

from commercially available propargylic alcohol (**223**) (Scheme 53). Hence, the first step was a copper-mediated regioselective addition at the triple bond to provide allylic alcohol **224**.[91] A following Sharpless epoxidation with *tert*-butyl hydroperoxide and L-diethyl tartrate afforded epoxide **225**.[92] A subsequent conversion of the alcohol into the sulfonic ester by the use of tosyl chloride and triethylamine gave compound **226**. At that point several primary amines were tested to perform a substitution reaction at the tosylated alcohol (Table 9). Unfortunately, the substitution attempt with *tert*-butyl glycin ester and potassium carbonate in methanol gave no conversion of the starting material (Entry 1). A change of the solvent to DMF resulted in decomposition of the starting material. Also the use of sodium phthalimide as a nitrogen source was unsuccessful. On the other hand, using benzylamine in combination with pyridine as base resulted in product formation, albeit in 36% yields (Entry 4). Further substitution experiments with tributylstannylmethanamine in the present of pyridine or triethylamine did not proceed either (Entry 5, 6).

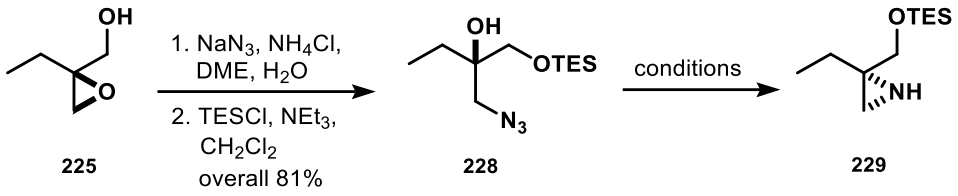


Scheme 53: Synthesis of epoxide **226** and substitution attempts to obtain amine **227**.

Table 9: Conditions for the substitution attempts to amine **227**.

Entry	Reagent	Base	Solvent	Temp.	Results
1	$NH_2CH_2CO_2tBu$	K_2CO_3	MeOH	60 °C	no reaction
2	$NH_2CH_2CO_2tBu$	K_2CO_3	DMF	60 °C	decomposition
3	PhthNH	NaH	DMF	r.t.	decomposition
4	$BnNH_2$	py.	DMF	65 °C	36%; R = Bn
5	$NH_2CH_2SnBu_3$	py.	DMF	65 °C	decomposition
6	$NH_2CH_2SnBu_3$	NEt_3	DMF	70 °C	decomposition

Due to the poor yields of the substitution reaction, an alternative literature known procedure to synthesize aziridines from α-hydroxy azides with triphenylphosphine was envisioned (Scheme 54).[93] Therefore, the epoxide **225** was opened with sodium azide in the presence of ammonium chloride in a dimethoxyethane water mixture to the diol. In the next step, the primary alcohol was protected with TESCl and triethylamine to obtain compound **228**. With the protected precursor in hands, several aziridine formation conditions were tested (Table 10). Treatment of azide **228** with triphenylphosphine at room temperature gave no reaction. An elevation of the reaction temperature to reflux resulted in decomposition. Also the addition of molecular sieves, which should enhance the reaction, did not provide any product. Furthermore, even the use of the more reactive tributylphosphine could not afford aziridine **299**.

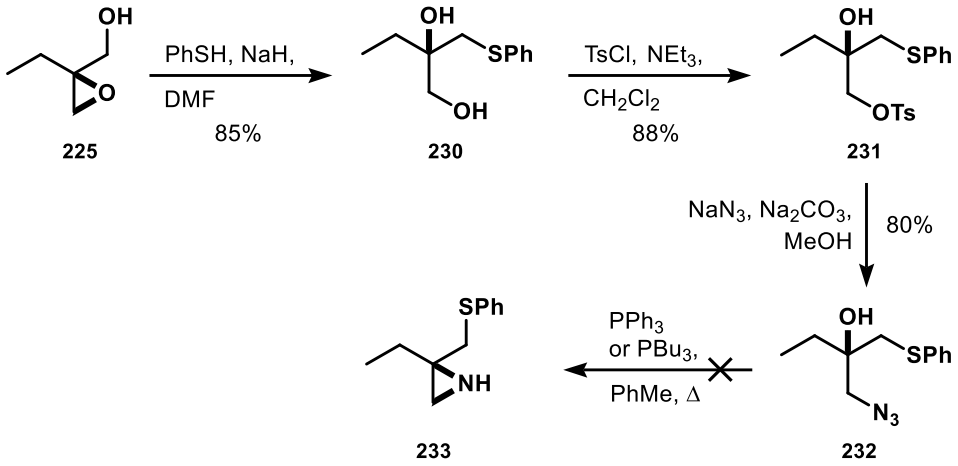


Scheme 54: Synthesis of azide **228** and attempts to generate aziridine **229**.

Table 10: Conditions for the Staudinger mediated aziridine formation.

Entry	Reagent	Additives	Solvent	Temp.	Results
1	PPh_3	none	PhMe	reflux	decomposition
2	PPh_3	MS 3Å	PhMe	100 °C	decomposition
3	$P(n\text{Bu})_3$	none	PhMe	r.t. to 50 °C	decomposition

An explanation for the unsuccessful formation of the aziridine could rely on the steric hindrance of the tertiary alcohol during the substitution reaction. Moreover, also the primary alcohol seems to have an unfavorable electronic influence to the reaction. With this in mind, an alternative functionality, which is able to enhance the substitution reaction has to be considered. Due to the known reaction enhancement of a participation group in a substitution reaction, an installation of a sulfur functionality was envisioned. This soft, nucleophilic and rather small sulfide moiety should accelerate the aziridine formation. Furthermore, it is possible to convert this functional group into an aldehyde moiety *via* a Pummerer oxidation protocol to perform a subsequent Wittig olefination.



Scheme 55: Synthesis of aziridine **232** and attempts to synthesize aziridine **229**.

However, the sulfide moiety was introduced as depicted in Scheme 55 *via* a nucleophilic epoxide-opening reaction with thiophenol and sodium hydride in DMF. A following regioselective tosylation of the primary alcohol with tosyl chloride and triethylamine provided compound **231**. The azide **232** was synthesized by a substitution reaction with sodium azide and the use of sodium carbonate as a base. Accurate reaction monitoring revealed that this reaction proceeds in two steps. In the first step the tertiary alcohol eliminates the tosyl group to generate an epoxide intermediate. This ether is opened subsequently from the less hindered side by a nucleophilic attack of sodium azide to from the desired product. In the next step, the azide **232** was treated with triphenylphosphine or tributylphosphine in toluene under several reaction conditions, but unfortunately, in all cases only small amounts of the primary amine could be detected.

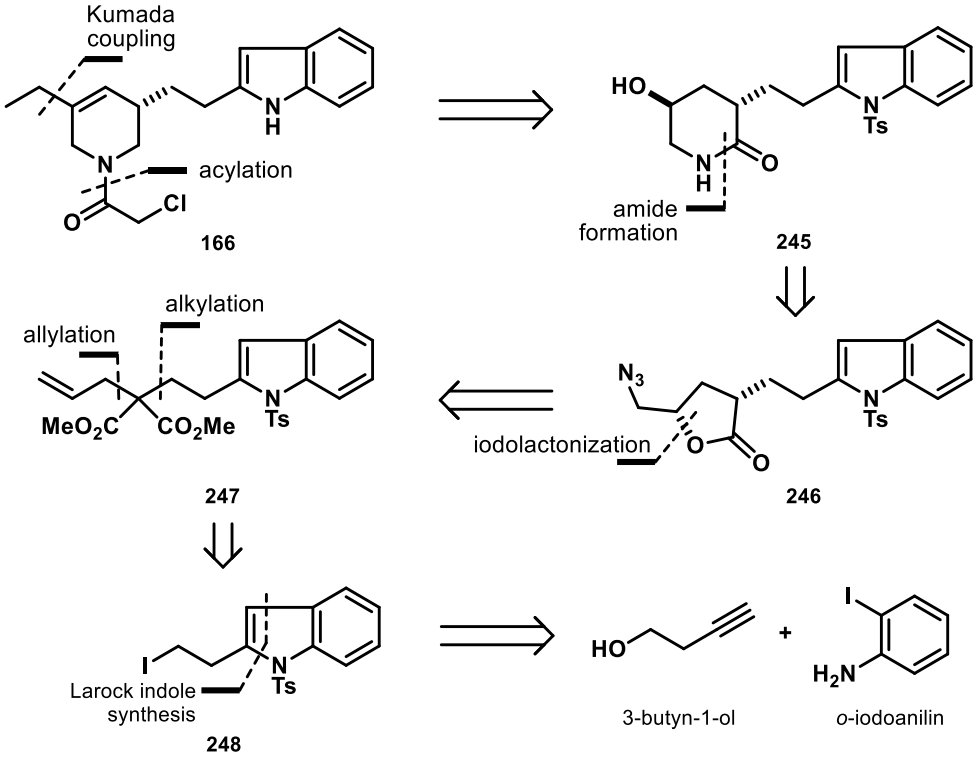
4.3.1. Conclusions of the second synthetic approach

The key step in this approach dealt with a [2,3]-Wittig-Still rearrangement of aziridine **209** to obtain the desired tetrahydropyridine **208**. This intermediate should be generated *via* a Wittig olefination from aziridine **211** and indole **210**. Therefore, the first challenging task was the synthesis of the aziridine fragment. However, it was possible to synthesize this building block without any problems, but unfortunately a further derivatization of this compound proved to be very difficult (Scheme 50). Due to this experimental outcome, it was decided to generate the aziridine functionality from epoxide **225** *via* several functional group interconversions. Thereby, the nitrogen should be installed by a nucleophilic substitution reaction at compound **226**.

Unfortunately, this reaction proceeded only with benzylamine in poor yields. Based on these disappointing results, an alternative Staudinger-mediated aziridine formation approach form α-hydroxy azide **228** was envisioned. This compound was synthesized in two steps of epoxide **225** (Scheme 54). However, a conversion of azide **228** into the desired aziridine **229** was probably due to steric demands of the tertiary alcohol not possible. Therefore, the primary alcohol of azide **228** was converted in several steps into a thioether, which should enhance the aziridine formation reaction by a participation group effect. Nevertheless, this thioether functionality could not facilitate the desired reaction. Due to these difficulties it was decided to abandon this approach.

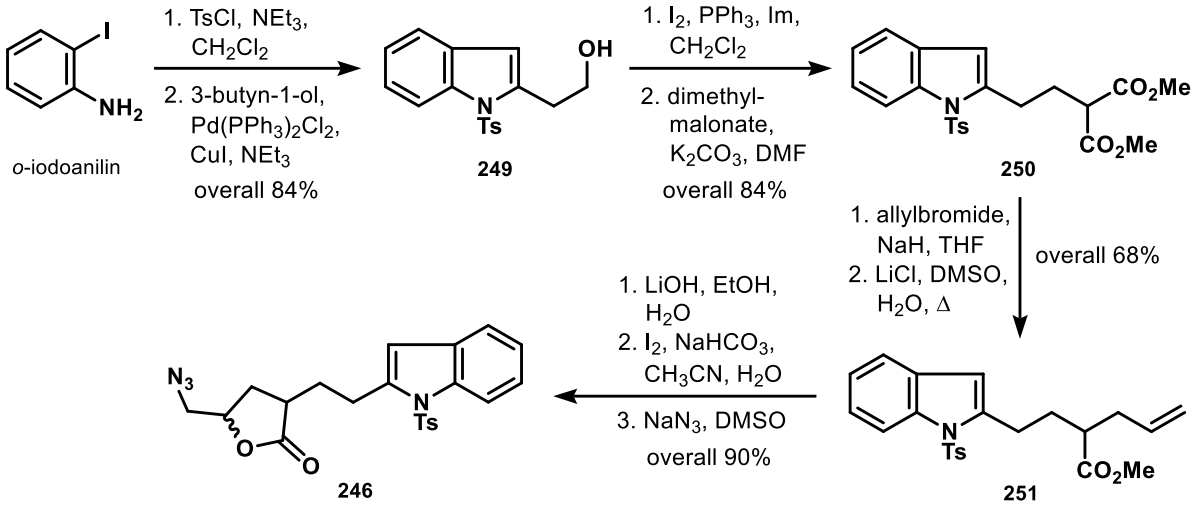
4.4. Third approach towards dichomine

Based on these disappointing results, an alternative approach to get access to the desired Witkop precursor **166** was envisioned. As depicted in Scheme 56 the ethyl side chain should be installed by the use of a Kumada coupling reaction between ethylmagnesium bromide and the corresponding enol triflate.



Scheme 56: Third retrosynthetic analysis towards Witkop precursor **166**.

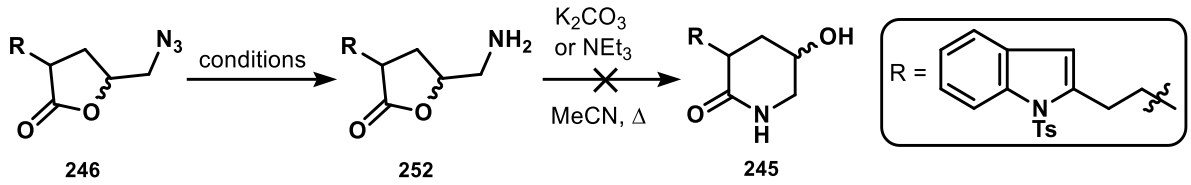
The required piperidon key structural motif for this retrosynthesis should be synthesized *via* a lactamization reaction between the *in situ* generated amine from the primary azide and the adjacent γ-lactone in intermediate **246**. This key transformation is based on a literature known reaction to generate 5-hydroxy-2-oxopiperidine systems.[94,95] However, building block **246** could be generated from compound **247** by an iodolactonization and a subsequent substitution of the primary iodine with sodium azide. An alkylation reaction with dimethyl malonate and intermediate **248** should establish the malonate unit, which could be further allylated to compound **247**. The indole **248** is accessible *via* a Larock indole formation reaction from *o*-iodoaniline and 3-Butyn-1-ol.



Scheme 57: Synthesis of azide compound **246**.

The first three steps in the synthesis are literature known and starting from commercially available *o*-iodoaniline.[96] Tosylation of the amine with tosyl chloride and triethylamine followed by a Larock indole synthesis with 3-butyn-1-ol provided intermediate **249** (Scheme 57). Conversion of the primary alcohol into the iodine was accomplished under Appel conditions. A substitution of the iodine with dimethylmalonate by the use of potassium carbonate in DMF afforded diester **250**. The required allyl functionality at the malonate carbon atom was introduced *via* a second nucleophilic substitution with allyl bromide and sodium hydride. A following Krapcho decarboxylation reaction by the use of lithium chloride in wet dimethyl sulfoxide provided compound **251**. Saponification with lithium hydroxide in ethanol gave the carboxylic acid, which was used in the next step to perform the iodolactonization

reaction to generate the γ-lactone. A subsequent substitution reaction of the iodine with sodium azide afforded product **246**.

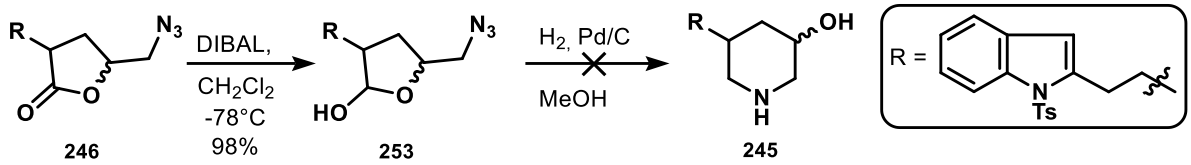


Scheme 58: Attempts to perform the ring-opening, ring-closing reaction.

Table 11: Conditions for the ring-opening, ring-closing reaction.

Entry	Reagent	Additives	Solvent	Temp.	Results
1	PPh_3	none	THF/H_2O	r.t.	20% **145**
2	H_2	Pd/C	MeOH	r.t.	78% **145**

With product **246** in hands, several lactamization conditions were examined. First triphenylphosphine was used to transform the azide into an amine, which spontaneously should perform the desired ring-opening, ring-closing reaction. Unfortunately, only the primary amine **252** was isolated in poor yields (Scheme 58, Table 11). The use of hydrogen with palladium on charcoal furnished the same results. However, even a subsequent treatment of the free amine with potassium carbonate or triethylamine in refluxing acetonitrile did not provided the desired lactam. Responsible for this unprecedented lactamization reaction is probably a major flexibility decrease of the 5-membered ring, which is caused by the additional substituent.



Scheme 59: Synthesis of compound **245** *via* reductive amination.

Based on this results, it was decided to reduce the lactone to become a more flexible lactol moiety. A subsequent reductive amination between the lactol and the *in situ* prepared primary amine should afford the required piperidine system. Therefore, the lactone **246** was treated with DIBAL at -78 °C in methylene chloride to afford lactol **253** (Scheme 59). However, a consecutive reduction of the azide by the use of hydrogen with palladium on charcoal gave a complex mixture of multiple unidentified products.

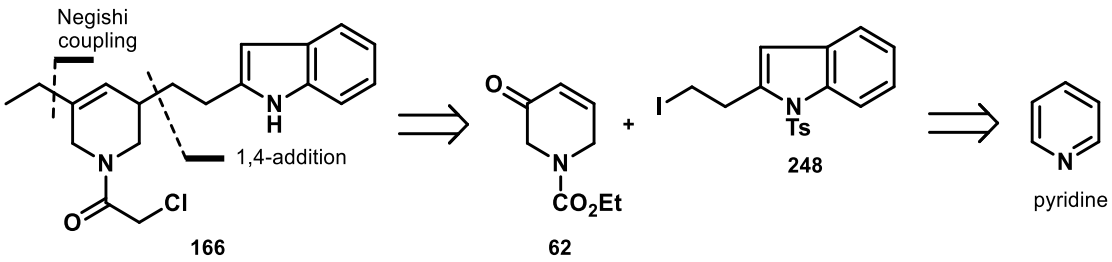
4.4.1. Conclusions of the third synthetic approach

The strategy in this approach focused on the synthesis of the piperidine core *via* an intramolecular ring-opening, ring-closing reaction between the *in situ* generated amine and the γ-lactone. According to this proposal, the literature known indole **248** should guarantee a concise access to this structural motif. After several attempts, it was possible to synthesize the desired lactone **246** in 6 steps from the adopted indole **248** with an overall yield of 51%. Unfortunately, even after extensive experimental research it was not feasible to perform the envisioned lactamization reaction. Furthermore, also the reductive amination approach proved to be unsuccessful.

Nevertheless, this approach revealed that double substituted γ-lactones do not undergo a ring-opening, ring-closing reaction to generate 5-hydroxy-2-oxopiperidine systems. An explanation for this lack of reactivity probably relies on could be the less flexibility of the lactone system due to the higher substitution pattern of the lactone. With that in mind, this approach appeared to be quite unattractive. Therefore, no further attempts to overcome these problems were performed.

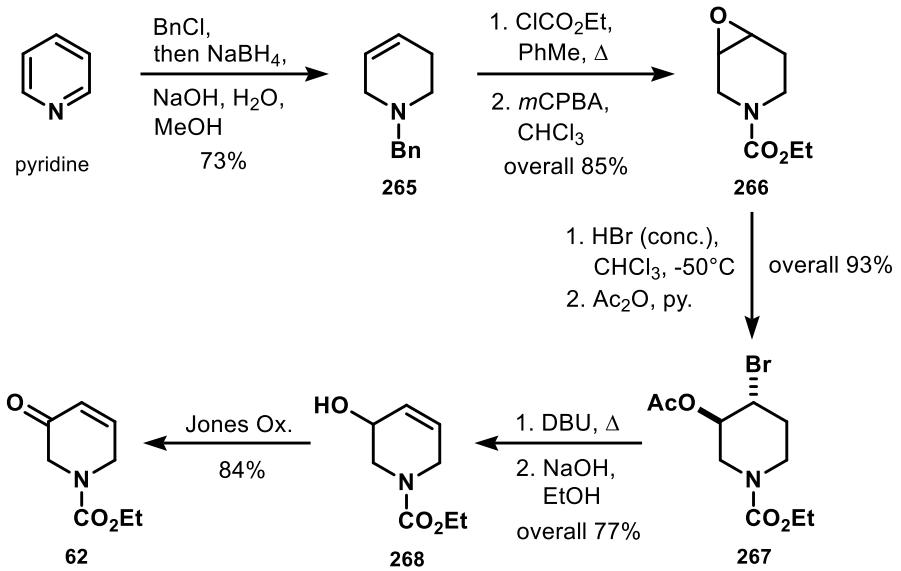
4.5. Fourth approach towards dichomine

Due to the failed reduction attempts of pyridinium salt **177** in the first approach as well as the unsuccessful piperidone syntheses in the first and third approach, it was decided to perform a 1,4-addition with the already synthesized primary iodine **248** and dihydropyridone **62** (Scheme 60). Thereby, the *in situ* generated enol should be triflated and used in a Negishi coupling reaction to introduce the required ethyl side chain. It is also noteworthy that the required Michael acceptor is literature known and could be synthesized in 7 steps from pyridine.[97]



Scheme 60: Fourth retrosynthetic approach towards Witkop precursor **166**.

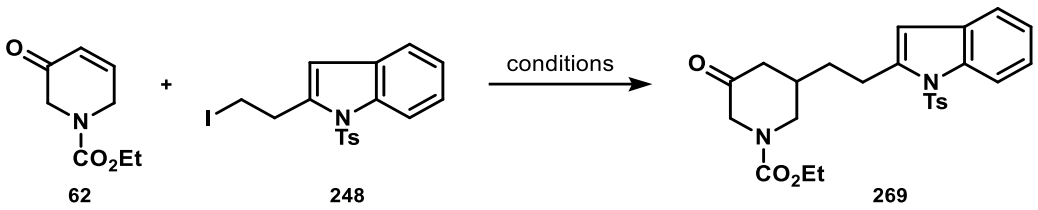
The first task in this approach was the synthesis of dihydropyridone **62** (Scheme 61). Therefore, the pyridine was treated with benzyl chloride to obtain *N*-benzylpyridinium chloride. A subsequent reduction with sodium borohydride and sodium hydroxide in a solvent mixture of methanol and water furnished tetrahydropyridine **265**.[98] Installation of the carbamate by treatment of the tertiary amine with ethyl chloroformate followed by an epoxidation of the double bond with *m*CPBA provided compound **266**. In the next step, the epoxide was opened in a regiospecific manner with concentrated hydrobromic acid in chloroform. The resulting alcohol was protected with acetic anhydride in pyridine to provide intermediate **267**. Elimination of the bromine with DBU under elevated temperature and cleavage of the acetate group with sodium hydroxide in ethanol gave allyl alcohol **268**. A following Jones oxidation provided the rather unstable dihydropiperidone **62** in good yields. It is also noteworthy that an oxidation under Swern conditions is also feasible, but the subsequent required purification by column chromatography was according to the instability of this product not possible. Moreover, due to this decomposition tendency, compound **62** was always freshly prepared for the following reactions to achieve higher and reproducible yields.



Scheme 61: Synthesis of dihydropyridon **62**.

With starting material **62** in hands, several conditions to perform a 1,4-addition with iodine **248** were examined (Scheme 62, Table 12). In the first attempt, the Grignard reagent was generated by the treatment of iodine **248** with magnesium and a copper bromide dimethyl sulfide complex was used to mediate the desired Michael addition. But unfortunately, under these reaction conditions only the protonated equivalent of

compound **248** could be isolated. Using *n*BuLi under the same conditions again provided the protonated equivalent together with the unreacted iodine **248**. Based on this result, *t*BuLi was used to guarantee a quantitatively halogen metal exchange. However, treatment of iodine **248** with *t*BuLi followed by addition of the starting material **62** in the presence of copper bromide dimethyl sulfide complex resulted in total decomposition of both compounds.



Scheme 62: Attempts to perform the 1,4-addition to obtain compound **269**.

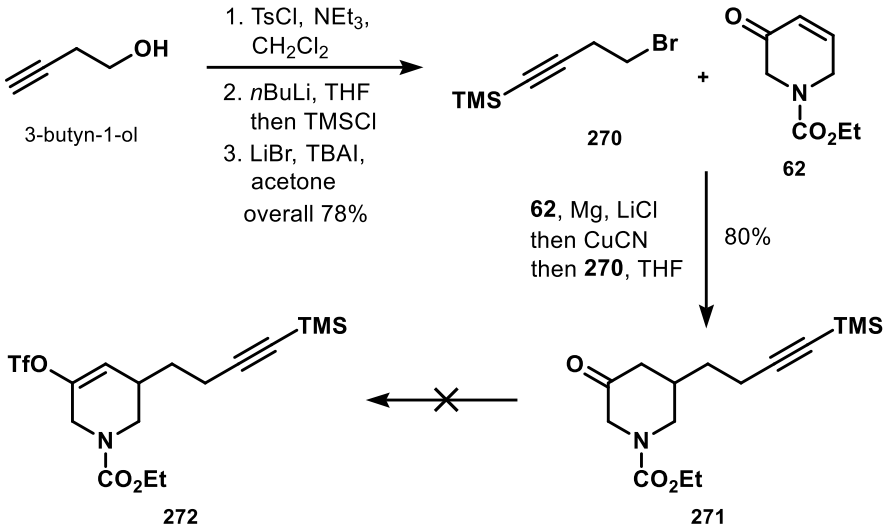
Table 12: Conditions for the 1,4-addition towards compound **269**.

Entry	Reagent	Additives	Solvent	Temp.	Results
1	Mg	CuBr•DMS	THF	-78 °C	protonation of **248**
2	*n*BuLi	CuBr•DMS	THF	-78 °C	protonation of **248** + SM
3	*t*BuLi	CuBr•DMS	THF	-78 °C	decomposition

Due to the remarkable weak nucleophilicity of the organometallic compound, several control experiments were accomplished. In these test reactions the organometallic reagent of compound **248** were added to a variety of electrophiles like acetyl chloride, acetone or cyclohexanone. In general, all experiments provided small amounts of the expected addition products in 10-20% yield together with lots of the already known undesired protonated side product.

Based on these results, iodide **248** proved to be an unsuitable building block for this reaction. Hence, a comparable nucleophile to iodide **248**, which is also applicable in a 1,4-addition has to be found. Moreover, this reagent should also guarantee a concise access to the indole moiety. After some literature research, the bromide **270** supposed to be an appropriate reagent (Scheme 63). This compound could be synthesized in three steps quite easily from commercially available 3-Butyn-1-ol.[99] The first step converted the primary alcohol into the sulfonic ester by the use of tosyl chloride and triethylamine. Deprotonation of the alkyne proton with *n*BuLi followed by addition of TMSCl established the TMS protecting group. A Finkelstein reaction with lithium

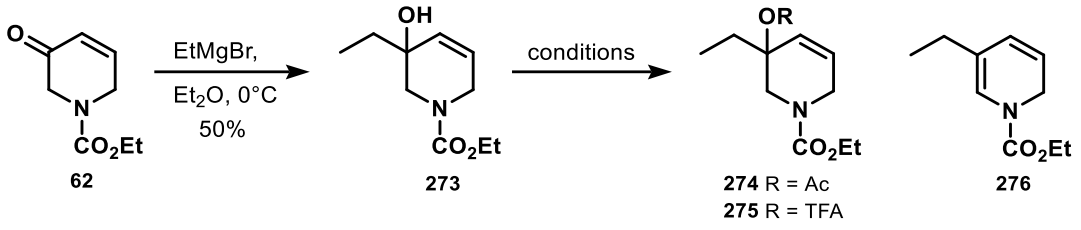
bromide and catalytic amounts of tetrabutylammonium iodide in acetone provided the desired bromide **270**.



Scheme 63: Synthesis of compound **271** *via* 1,4-addition.

After extensive experimental screening, it was possible to perform a Michael addition between the corresponding Grignard reagent of alkyne **270** and dihydropyridone **62** in excellent yields. Nevertheless, an *in situ* trapping of the occurring enol under different reaction conditions was not possible. Furthermore, even a subsequent treatment of ketone **271** with several strong bases like LDA, KHMDS or NaHMDS followed by an addition of different triflation reagent like Comin´s reagent, $PhNTf_2$ or Tf_2O yielded only in decomposition.

Parallel to the Michael addition approach, the feasibility of a $S_N2´$ displacement at allylic compound **273** was examined. Therefore, dihydropyridone **62** was subjected to ethylmagnesium bromide in diethyl ether at 0 °C to provide the tertiary allylic alcohol **273** (Scheme 64).[100] As documented in Table 13 several attempts were performed to convert the tertiary alcohol into a proper leaving group for a $S_N2´$ displacement.

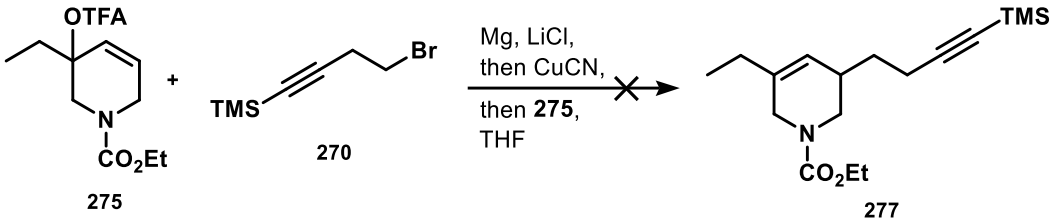


Scheme 64: Synthesis of allylic compound **273** and attempts to transform the allylic alcohol.

Table 13: Conditions for the derivatization attempts of the allylic alcohol.

Entry	Reagent	Base	Solvent	Temp.	Results
1	MsCl	2,6-lutidine	CH_2Cl_2	0 °C	83% **276**
2	TsCl	NEt_3	CH_2Cl_2	reflux	no reaction
3	Boc_2O	DMAP	CH_2Cl_2	r.t.	no reaction
4	CbzCl	NEt_3	CH_2Cl_2	reflux	no reaction
5	$ClCO_2Me$	py.	CH_2Cl_2	reflux	no reaction
6	AcCl	NEt_3	CH_2Cl_2	reflux	62% **276**
7	AcCl	py.	CH_2Cl_2	r.t.	33% **274**
8	TFAA	none	CH_2Cl_2	r.t.	80% **275**
9	ClAcCl	py.	CH_2Cl_2	r.t.	65% **276**

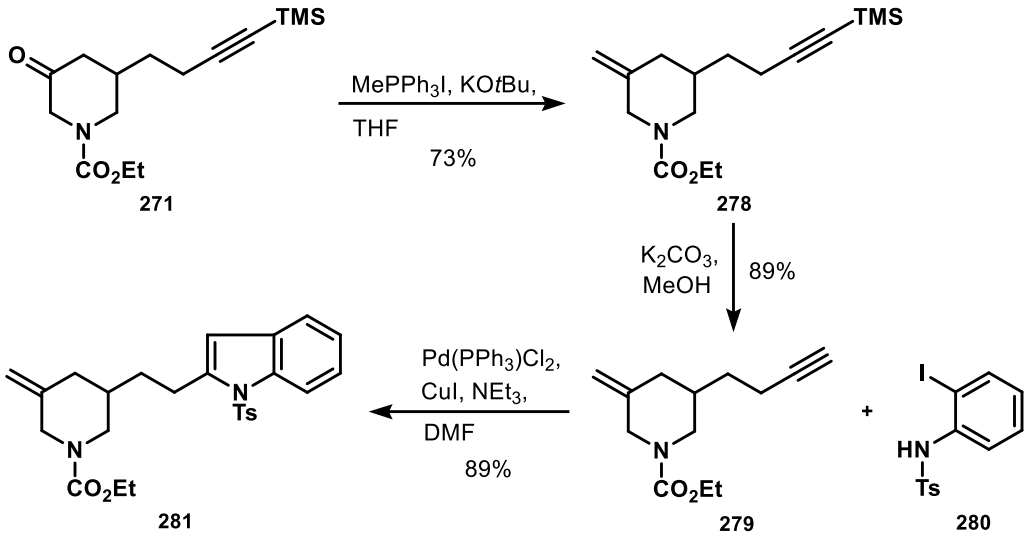
Treatment of compound **273** with mesyl chloride resulted in a direct elimination of the allylic alcohol to dihydropyridine **276**. Moreover, acetylation with acetyl chloride in combination with triethylamine under reflux, or the use of chloroacetyl chloride with pyridine again provided the elimination product **276** (Entry 6, 9). The use of pyridine as base together with acetyl chloride provided the desired product **274**, albeit in poor yields (Entry 7). On the other hand, subjecting the starting material to tosyl chloride afforded even under reflux no reaction (Entry 2). The same is true for all attempts to install a carbonate group (Entry 3-5). Only the use of trifluoroacetic acid under non-basic conditions furnished the fairly stable product **275** in good yields (Entry 8). It is also noteworthy that due to this instability issue a purification of this compound by column chromatography was not possible.



Scheme 65: Attempted substitution reaction towards compound **277**.

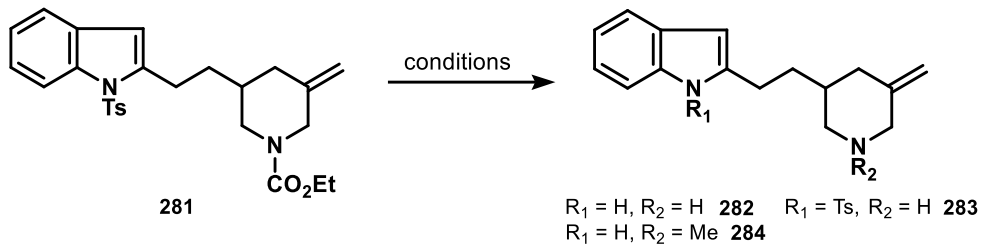
With intermediate **275** in hands, several reaction conditions to perform a $S_N2´$ reaction were tested (Scheme 65). Unfortunately, all attempts to synthesize the desired compound **277** resulted in decomposition of both starting materials. Responsible for this experimental outcome is probably the unstable allylic trifluoroacetate moiety of starting material **275**.

Due to these disappointing results, it was decided to proceed the synthesis with the Michael addition product **271**. At that point, a conversion of the carbonyl moiety into a double bond seemed to be a promising approach for a rapid access to the desired Witkop precursor. In the first place an *exo* double bond should be installed to overcome problems with *E/Z* isomers. Therefore, ketone **271** was treated with methyltriphenylphosphonium bromide in combination with potassium *tert*-butoxide to obtain the compound **278** (Scheme 66). Subsequent cleavage of the TMS group with potassium carbonate in methanol provided the alkyne **279**. A following Larock indole synthesis with aryl iodide **280** generated the required heterocyclic product **281**.



Scheme 66: Synthetic sequence towards compound **281**.

In the next step, both protecting groups should be cleaved by a one-step procedure (Scheme 67). Therefore, several reaction conditions were examined to solve this unprecedented problem (Table 14). In a first attempt, compound **281** was treated with MeLi at -40 °C to provide exclusively the piperidine unprotected product **283** in moderate yields.[101]

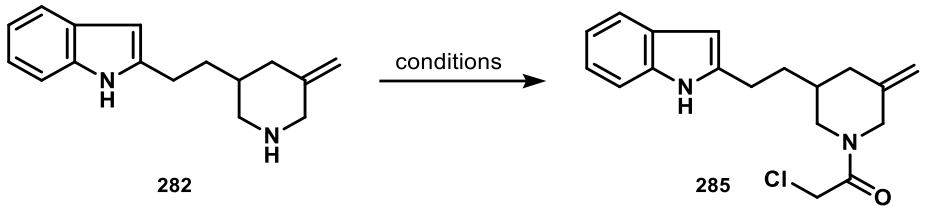


Scheme 67: One-step deprotection attempts to obtain compound **204**.

Table 14: Conditions for the one-step deprotection attempts.

Entry	Reagent	Solvent	Temp.	Results
1	MeLi	THF	-40 °C	46% **283**
2	HBr	AcOH	reflux	decomposition
3	KO*t*Bu	MeOH	r.t.	no reaction
4	$LiAlH_4$	THF	r.t.	45% **284**
5	DIBAL	THF	r.t.	no reaction
6	Red-Al	THF	r.t.	85% **284**
7	KOH	EtOH	reflux	no reaction
8	hydrazine, KOH	ethylene glycol	140 °C	95% **204**

Cleavage of the protecting groups under acidic conditions resulted in decomposition of the starting material. On the other hand, treatment of compound **281** with strong bases under moderate temperatures gave no reaction (Entry 3, 7). Furthermore, deprotection attempts with reducing agents such like lithium aluminum hydride or Red-Al furnished only the tertiary amine **284** (Entry 4, 6). Curiously, the use of DIBAL provided even at room temperature no conversion of the starting material. Finally, the simultaneous cleavage of both protecting groups could be achieved by the use of hydrazine hydrate together with potassium hydroxide in hot ethylene glycol.[102] It is also noteworthy that the cleavage of the tosyl group at the indole moiety occurred even under ambient temperatures.



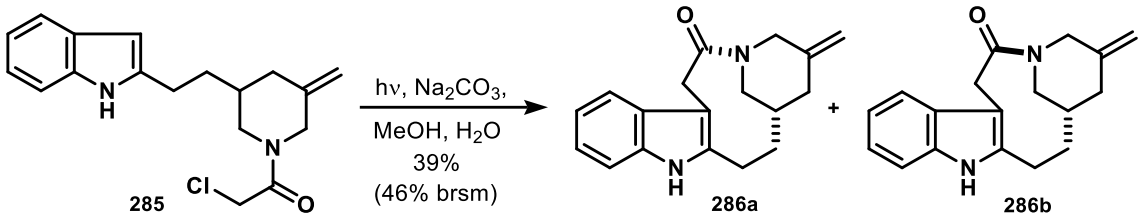
Scheme 68: Acylation attempts towards α-chloro lactam **285**.

Table 15: Conditions for the acylation reactions.

Entry	Reagent	Base	Solvent	Temp.	Results
1	ClAcCl	py.	CH_2Cl_2	0 °C	decomposition
2	ClAcOH	DIC, DMAP	CH_2Cl_2	r.t.	44%
3	$(ClAc)_2O$	NEt_3, DMAP	CH_2Cl_2	0 °C	61%
4	$(ClAc)_2O$	NEt_3	CH_2Cl_2	0 °C	79%

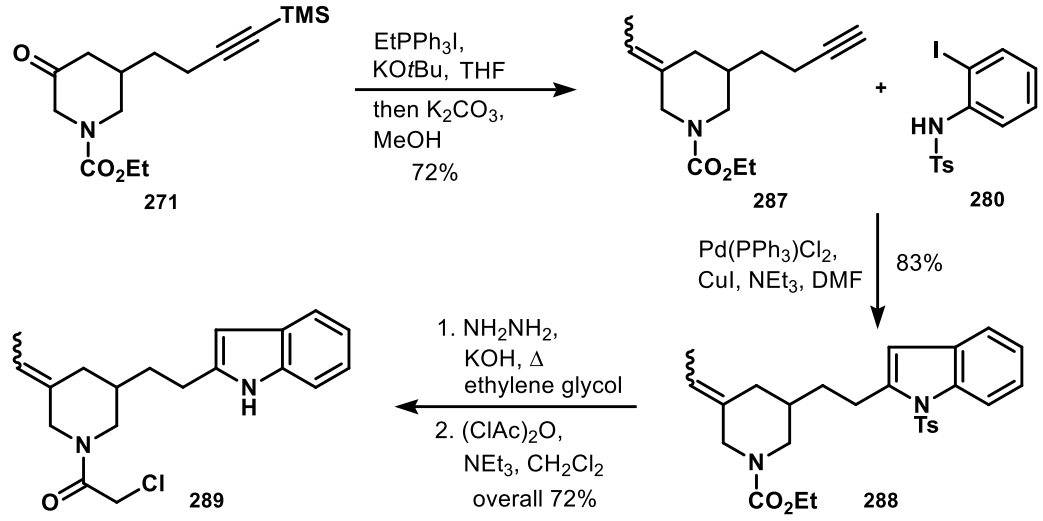
At that point the amine group had to be acylated to provide the required α-chloro lactam **285** for the Witkop reaction (Scheme 68). Treatment of the secondary amine **282** with

chloroacetyl chloride and pyridine resulted in decomposition of the starting material (Table 15). The use of the less reactive chloroacetic acid in combination with diisopropyl carbodiimid gave the desired product in moderate yields (Entry 2). Moreover, the use of chloroacetic anhydride with triethylamine and DMAP provided compound **285** in good yields. It is also noteworthy that under the same reaction conditions without using DMAP improved the yield to 79%.



Scheme 69: Synthesis of the macrolactams **286** by utilizing a Witkop photocyclization.

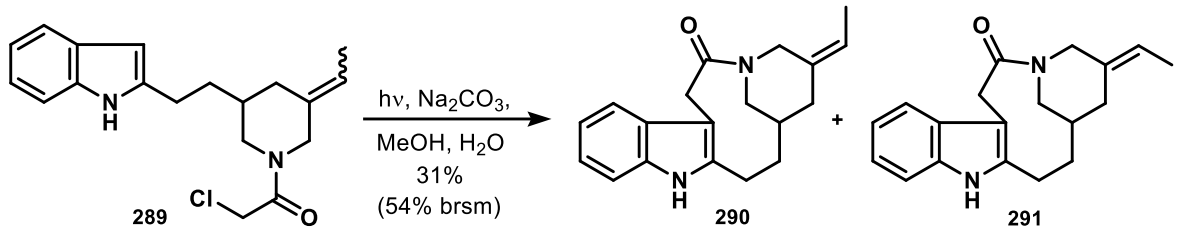
With compound **285** in hands, the Witkop reaction was performed (Scheme 69). After extensive experimental research, irradiation of the starting material with sodium carbonate in a 2:1 mixture of methanol and water proved to be the best conditions and provided the desired product **286** in a 1:1 mixture of conformational stable rotamers together with unreacted starting material. It is also noteworthy that a prolonged reaction time resulted in a decrease of product yield and decomposition of starting material.



Scheme 70: Synthetic route towards Witkop precursor **289**.

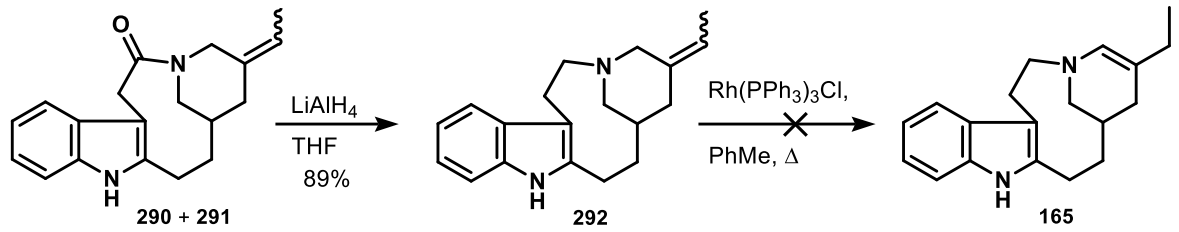
With the established synthetic route in hands, the preparation of compound **289** possessing the required ethyl side chain was initiated (Scheme 70). Therefore,

treatment of ketone **271** with ethyltriphenylphosphonium bromide and potassium *tert*-butoxide resulted in an inseparable 1:2 mixture of *E*/*Z* double bond isomers. Subsequent cleavage of the TMS group with potassium carbonate in methanol provided alkyne **287**. The following Larock indole synthesis furnished intermediate **288**. Cleavage of the two protecting groups with hydrazine and potassium hydroxide followed by an amide formation with chloroacetic anhydride afforded compound **289**.



Scheme 71: Witkop photocyclization of compound **289** to generate macrocycles **290** and **291**.

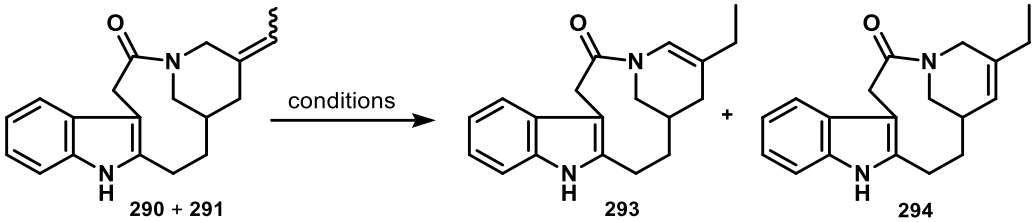
Also the Witkop photocyclization proceeded under the same reaction conditions and provided the two separable double bond isomers **290** and **291** in acceptable yields (Scheme 71). It is also noteworthy that the *E*/*Z* ratio of the double bond was not affected under these conditions. Moreover, in contrast to the photocyclization products of compound **285**, no conformational stable isomers of macrocycles **290** and **291** could be detected.



Scheme 72: Further steps to synthesize the biomimetic precursor **165**.

The next major task in the total synthesis of dichomine is the preparation of the biomimetic precursor **165**. This should be accomplished, as depicted in Scheme 72, in two steps *via* a reduction of the lactam to the tertiary amine and a following isomerization of the double bond to prepare the enamine. However, a reduction of both isomers by the use of lithium aluminum hydride in THF afforded the rather unstable tertiary amines **292**. Unfortunately, a subsequent isomerization attempt of the double bond to obtain enamine **165** by the use of the Wilkinson´s catalyst[103] resulted in

decomposition of the starting material. Due to the quite unstable amines **292** and a publication of Portier and coworkers, which reported about the instability of structurally related enamines, no further isomerization attempts were performed.[104]



Scheme 73: Isomerization attempts towards acyl enamine **293**.

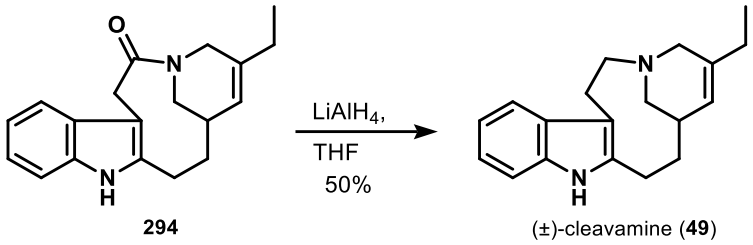
Table 16: Conditions for the isomerization attempts towards acyl enamine **293**.

Entry	Catalyst/Reagent	Solvent	Temp.	Results
1	$Rh(PPh_3)_3Cl$	EtOH	reflux	no reaction
2	$RhCl_3$	EtOH	reflux	no reaction
3	$HRh(CO)(PPh_3)_3$	xylene	reflux	no reaction
4	$PdCl_2$	toluene	reflux	no reaction
5	$Pd(OAc)_2$, dppp	DMF	reflux	no reaction
6	$Pd(PPh_3)_4$	AcOH	reflux	no reaction
7	NaI, TMSCl	CH_3CN	r.t.	decomposition
8	*p*TsOH	toluene	reflux	decomposition
9	Pd/C, H_2	EtOAc	r.t.	18% **293** + 35% **294**
10	Pd/C	MeOH	reflux	no reaction
11	$Pd(OH)_2$/C, H_2	EtOAc	r.t.	18% **293** + 29% **294**
12	$Rh(PPh_3)_3Cl$, H_2	CH_2Cl_2	r.t.	no reaction
13	PtO_2, H_2	EtOAc	r.t.	90% hydrated product

To overcome this instability issue, it was decided to isomerize the double bond one step earlier to obtain the acyl enamine **293** (Scheme 73). As shown in Table 16, the use of Wilkinson´s catalyst was without success. Also other rhodium complexes like rhodium chloride or $HRh(CO)(PPh_3)_3$ did not provide any product (Entry 2, 3).[103] Moreover, the use of palladium chloride in refluxing toluene gave no reaction. The use of palladium acetate and dppp as ligand in refluxing DMF was without any response (Entry 5).[105] Using tetrakis (triphenylphosphine) palladium in refluxing acetic acid led to decomposition of the catalyst and unreacted starting material. Furthermore, the use of sodium iodide and TMSCl in acetonitrile afforded just decomposition of the lactams.[106] The same is true for *p*TsOH in refluxing toluene. Surprisingly, the double

bond migrated under reductive conditions by the use of palladium on charcoal and hydrogen to the desired acyl enamine **293** and the tetrahydropyridine **294** in a 1:2 product mixture. It is also noteworthy that no migration occurs under absence of hydrogen (Entry 10). Furthermore, the use of Pearlman´s catalyst under hydrogen atmosphere provided also the two double bond isomers in comparable yields (Entry 11). In contrast to Wilkinson´s catalyst, which did not react under a reductive environment. The use of Adam´s catalyst under hydrogen atmosphere in ethyl acetate furnished the hydrated ethyl side chain in a 1:1 mixture of inseparable diastereomers (Entry 13).

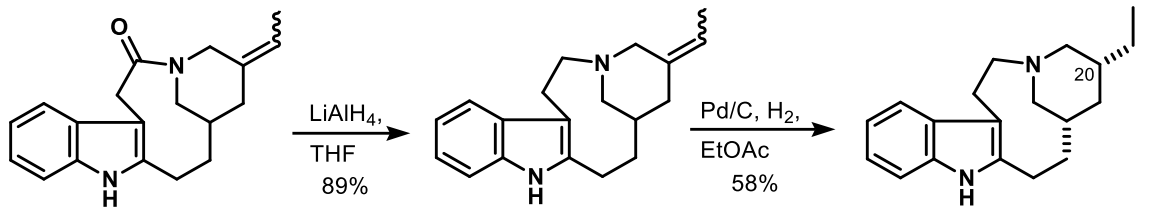
Due to the poor yields in the isomerization reaction, no further derivatization attempts to provide enamine **293** were undertaken. Nevertheless, the main product of that isomerization was treated with lithium aluminum hydride in THF to provide the natural product (±)-cleavamine (**49**) (Scheme 74).



294 (±)-cleavamine (**49**)

Scheme 74: Reduction of lactam **294** to obtain (±)-cleavamine (**49**)

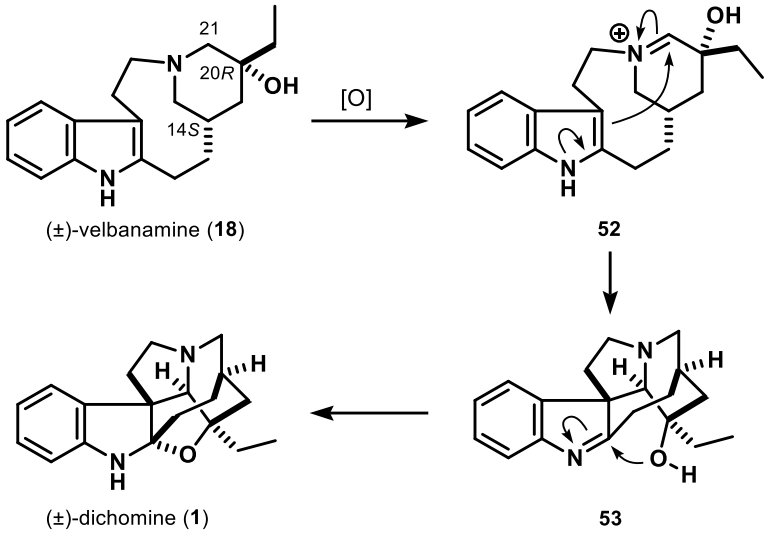
At that time, also the synthesis of (±)-dihydrocleavamine (**17**) was accomplished. Therefore, lactams **290** and **291** were reduced with lithium aluminum hydride to the amines **292**. A following substrate controlled side selective hydrogenation of the double bond with palladium on charcoal under hydrogen atmosphere provided exclusively (±)-20*R*-dihydrocleavamine (**17**).



290 + **291** **292** (±)-20*R*-dihydrocleavamine (**17**)

Scheme 75: Synthesis of (±)-20*R*-dihydrocleavamine (**17**) *via* reduction of amines **292**.

Due to the instability of amines **292** and the unfavorable results by the isomerization of compound **292**, an alternative retrosynthetic approach towards dichomine was envisioned. This strategy is based on a retro-biomimetic oxidation approach starting from the natural product velbanamine (**18**). As depicted in Scheme 76, the tertiary amine is oxidized at the C-21 position to generate the iminium ion, which is spontaneously attacked by the indole enamine to provide intermediate **53**. In a subsequent step, the resulting indolenine is trapped by the tertiary alcohol to generate the *N,O*-ketal functionality to dichomine (**1**).

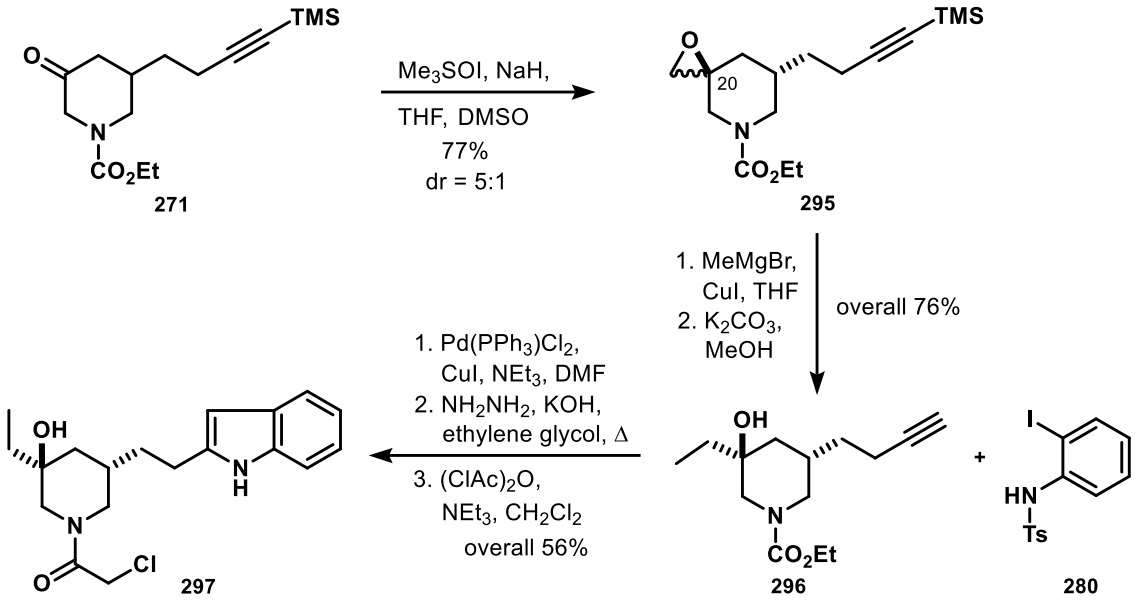


Scheme 76: Alternative retro-biomimetic oxidation approach towards (±)-dichomine (**1**).

It is also mentionable that this reaction could only proceed with the (20*R*,14*S*)-relative stereochemistry, which is present in velbanamine (**18**). Because in case of the (20*S*,14*S*)-configuration, the alcohol is not able to attack the indolenine in the last step of the cascade reaction.

According to this new strategy, it was necessary to introduce a tertiary alcohol at the C-20 position instead of the double bond. Unfortunately, the direct alkylation of ketone **271** with ethylmagnesium bromide or other metalorganics was not possible. Therefore, ketone **271** was alkylated with trimethylsulfoxonium iodine in combination with sodium hydride to provide epoxide **295** in a 5:1 mixture of diastereomers in favor of the (20*S*)-product (Scheme 77). At that point it was quite difficult to determine the stereochemical outcome of the epoxide. However, it was decided to verify first of all the synthetic route towards the Witkop precursor. The stereochemistry of the alcohol should be determined later on. Hence, the major diastereomer of compound **295** was

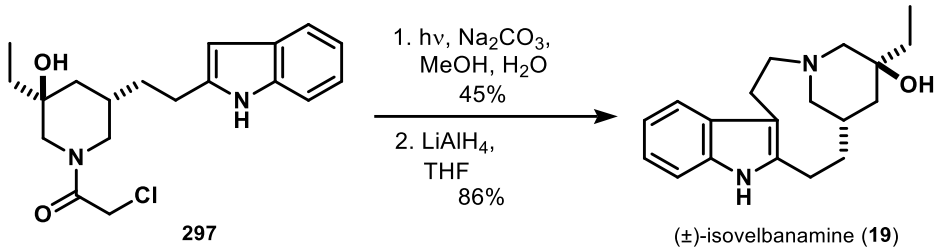
opened with methylmagnesium bromide under copper catalysis at -40 °C to install the ethyl side chain. It is also noteworthy that the epoxide opening of the (20*R*)-isomer required a higher reaction temperature of -20 °C. Subsequent cleavage of the TMS group using potassium carbonate in methanol provided alkyne **296**. Next, a Larock indole synthesis with aromatic compound **280** furnished the indole moiety. Also the cleavage of both protecting groups under the established conditions followed by an amide formation of the piperidine amine with chloroacetic anhydride and triethylamine proceeded in good yields.



Scheme 77: Corey Chaykovsky approach to epoxide **295** and synthesis of Witkop precursor **297**.

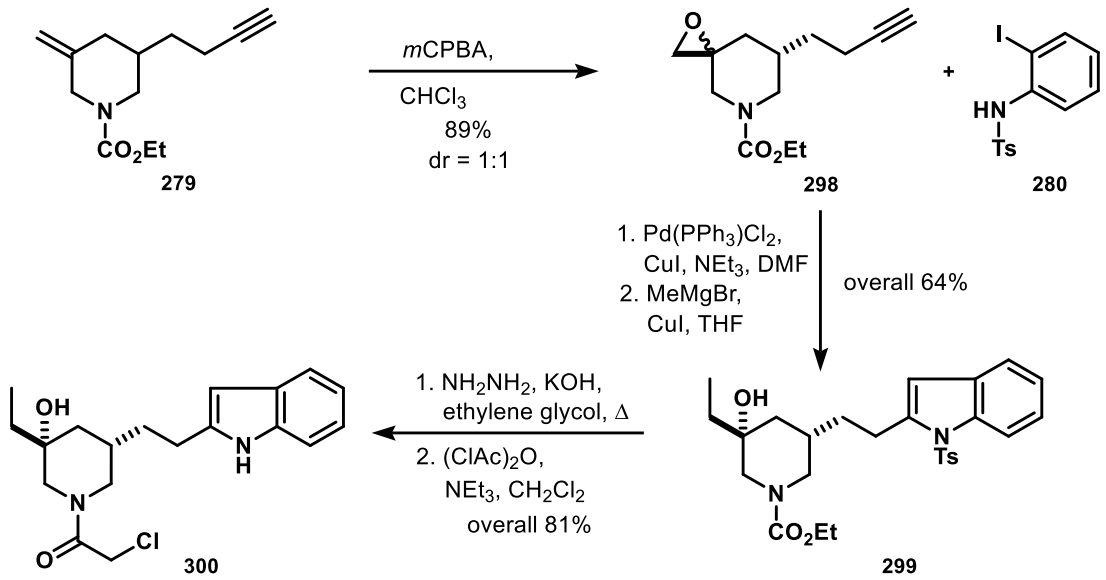
After some optimization attempts, the Witkop photocyclization was performed in a 3:2 mixture of methanol and water in a remarkable yield of 45% (Scheme 78). It is also noteworthy that the whole starting material was consumed and no additional side products occurred. A reason for this yield improvement is probably the missing double bond, which could be also a potential reactant under these conditions. Furthermore, due to the better solubility of the starting material it was able to increase the amount of water in the reaction mixture, which proved to be stabilizing for the reaction. However, reduction of the amide with lithium aluminum hydride under elevated temperatures afforded (±)-isovelbanamine (**19**). The formation of this natural product was furthermore the ultimate experimental proof for the (20*S*)-configuration of the major epoxide after the Corey Chaykovsky reaction. As mentioned earlier in this approach, according to the (*S*)-stereochemistry at the C-20 position, the desired oxidation

cascade to dichomine could not be performed. At that point it is also noteworthy that several elimination attempts of the tertiary alcohol, which would consequently provide the natural product (±)-cleavamine (**49**) by the use of methanesulfonyl chloride in combination with triethylamine or even the Burgess reagent[107] were fruitless.



Scheme 78: Remaining steps from compound **297** to (±)-isovelbanamine (**19**).

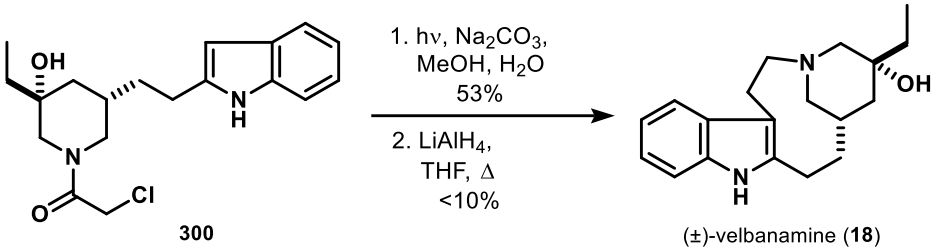
Nevertheless, based on the preferential (20*S*)-configuration in the Corey Chaykovsky reaction, a new approach to obtain the desired (20*R*)-alcohol was envisioned. After several attempts, the epoxidation of compound **279** with *m*CPBA provided the most convenient diastereomeric ratio of a 1:1 distribution (Scheme 79).



Scheme 79: Epoxidation approach to compound **298** and synthesis of Witkop precursor **300**.

A Larock indole synthesis with (20*R*)-**298** and aryl iodide **280** followed by a copper-mediated epoxide-opening with methylmagnesium bromide to introduce the ethyl side chain yielded compound **298**. Similar to the previously observed epoxide-opening reaction of compound **295**, the epoxide with the (*R*)-stereochemistry requires a higher reaction temperature than the (*S*)-configured. Further steps are the

simultaneous cleavage of both protecting groups and the subsequent amide formation with chloroacetic anhydride to intermediate **300**. Using the same reaction conditions as in the cyclization reaction of the (20*S*)-isomer, compound **300** cyclized in pleasant 53% yield (Scheme 80). With the literature known macrocycle in hands, the reported reduction of the lactam to the tertiary amine was performed by the use of lithium aluminum hydride in refluxing THF.[108] Unfortunately, even after several attempts it was not possible to obtain more than 10% yield.



Scheme 80: Remaining steps from compound **300** to (±)-velbanamine (**18**).

According to this disappointing result, alternative reduction attempts to obtain velbanamine (**18**) were performed. A selection of some key experiments are documented in Table 17. Reduction with *in situ* generated aluminum hydride at low temperature resulted in decomposition of the starting material (Entry 1). Moreover, the use of magnesium bromide as Lewis acid did not improve the yield. Using lithium chloride as Lewis acid in combination with lithium aluminum hydride provided the desired compound **18** in 30% yield (Entry 3). It is also noteworthy that the use of DIBAL at 0 °C resulted in product formation, albeit in poor yields. On the other hand, a Lewis acid supported reduction by using a mixture of DIBAL and titanium isopropoxide at room temperature gave no reaction and an increase of the reaction temperature to 50 °C resulted in decomposition (Entry 5). Furthermore, using Red-Al as hydride source again generated the tertiary amine in 20% yield. The use of borane based reducing agents like borane dimethyl sulfide complex led to decomposition (Entry 8). The same is true for the *in situ* preparation of borane[109] and the sodium borohydride supported reduction.[110] Also the use of lithium borohydride as reducing agent provided no product (Entry 10, 11). At that point, also alternative reducing procedures were considered. Unfortunately, Charette's reduction using trifluoromethanesulfonic anhydride and Hantzsch ester was unsuccessful.[111] A different method, which was developed by the Beller group, utilizes zinc acetate in combination with triethoxy silane to reduce amide moieties.[112] However, also this protocol proved to be unsuitable

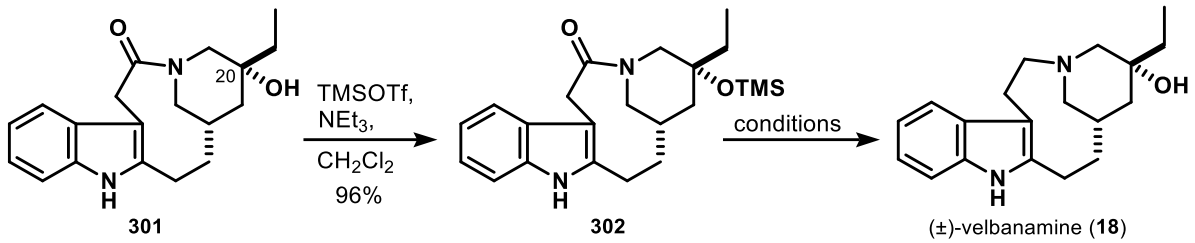
(Entry 12). Furthermore, the use of a stronger Lewis acid did not improved the reaction (Entry 13). A further alternative, which was also invented by the Beller group, based on a rhodium catalyzed reduction with phenyl silane as hydride source.[113] In the first place this experiment was performed at room temperature and resulted in a slow decomposition of the starting material. Surprisingly an elevation of the reaction temperature to 50 °C provides the natural product velbanamine (**18**) in good yields (Entry 15).

Table 17: Reduction conditions to (±)-velbanamine (**18**).

Entry	Reagent	Solvent	Temp.	Results
1	$LiAlH_4$, $AlCl_3$	THF	-20 °C	decomp.
2	$LiAlH_4$, $MgBr_2$•OEt_2	THF	r.t.	10%
3	$LiAlH_4$, LiCl	THF	reflux	30%
4	DIBAL	THF	0 °C	20%
5	Ti(O*i*Pr)$_4$, DIBAL	CH_2Cl_2	50 °C	decomp.
6	Red-Al	THF	r.t.	20%
7	BF_3•OEt_2, $NaBH_4$	THF	r.t.	decomp.
8	BH_3•DMS	THF	reflux	decomp.
9	BH_3•DMS, $NaBH_4$	THF	50 °C	decomp.
10	Tf_2O, H.E.	CH_2Cl_2	r.t.	decomp.
11	Tf_2O, $LiBH_4$	CH_2Cl_2	r.t.	no reaction
12	$Zn(OAc)_2$, $(EtO)_3SiH$	THF	r.t.	no reaction
13	Ti(O*i*Pr)$_4$, $(EtO)_3SiH$	THF	r.t.	no reaction
14	$HRh(CO)(PPh_3)_3$, $PhSiH_3$	THF	r.t.	decomp.
15	$HRh(CO)(PPh_3)_3$, $PhSiH_3$	THF	50 °C	53%

Remarkably the reduction of the C-20 epimer of lactam **301** converted quite easily with lithium aluminum hydride into isovelbanamine (**19**). This experimental outcome led to the conclusion that the stereochemistry of the alcohol has a major steric or electronic effect with respect to the reactivity of the amide moiety. To become a better understanding of this stereochemical relationship further experiments were performed. Therefore, the alcohol was protected with TMSOTf and triethylamine to silyl ether **302** in excellent yields (Scheme 81). With the protected alcohol in hands, several reduction attempts were performed (Table 18). Unfortunately treatment of starting material **302** with lithium aluminum hydride only resulted in degradation products. Treatment of compound **302** with DIBAL resulted in decomposition. Moreover, the use of Charette´s reduction procedure did not provide better results. Only the rhodium catalyzed

reduction afforded the desired product in 25% yield. It is also noteworthy that a careful reaction monitoring revealed a partial cleavage of the TMS ether during the reaction, thus it remains unclear if the protection of tertiary alcohol in **301** is necessary.

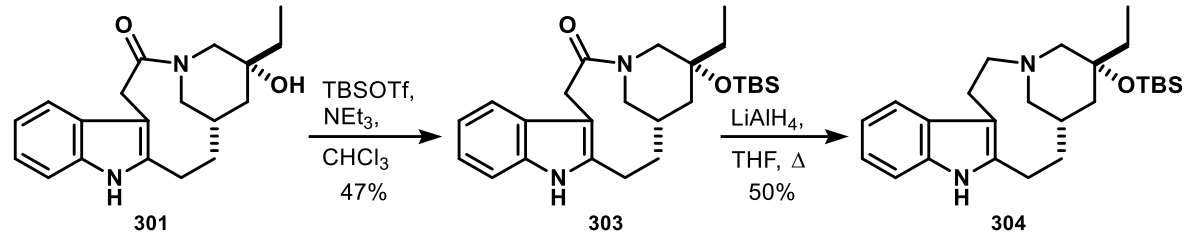


Scheme 81: Alternative reduction attempts form lactam **302** to (±)-velbanamine (**18**).

Table 18: Conditions for the reduction of lactam **302**.

Entry	Reagent	Solvent	Temp.	Results
1	$LiAlH_4$	THF	reflux	decomp.
2	DIBAL	THF	0 °C	decomp.
3	Tf_2O, H.E.	CH_2Cl_2	r.t.	decomp.
4	$HRh(CO)(PPh_3)_3$, $PhSiH_3$	THF	50 °C	25% of (**18**)

Hence, it was decided to install a more stable TBS group. This was accomplished by the use of TBSOTf and triethylamine in refluxing chloroform and provided silyl ether **303** in 47% yield (Scheme 82). A subsequent reduction of the lactam with lithium aluminum hydride in refluxing THF furnished smoothly the tertiary amine **304**.



Scheme 82: Synthesis and reduction of compound **303**.

Noteworthy in this experiment were the required refluxing conditions, which could be explained by an increased steric hindrance due to the TBS ether. Moreover, this behavior additionally revealed the close proximity of the alcohol or the silyl ether derivative to the amide moiety. Worth mentioning is also the higher stability of this intermediate, even under harsher reaction conditions. Furthermore, no other side products were observed by TLC. Based on this experimental outcome, the occurring

decomposition during the reduction of lactam **301** could be explained by an unfavorable electronic effect of the *in situ* generated alkoxide towards the amide functionality (Figure 12). Moreover, a bulky group on the hydroxyl functionality only seem to have an influence on the required reaction temperature.

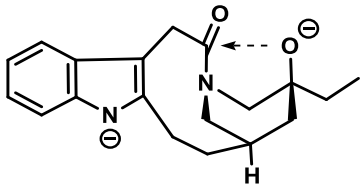
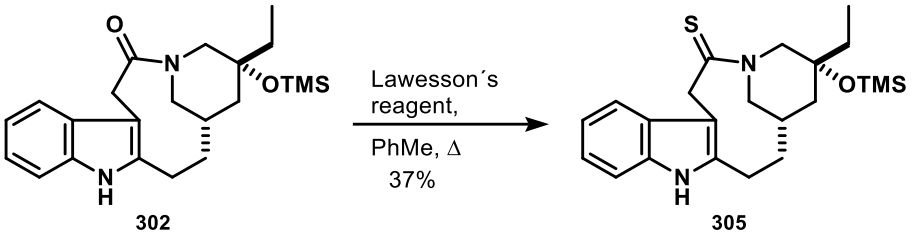


Figure 12: Electronic effect of the alkoxide towards the lactam moiety.

A second approach to solve this problem is based on a nickel-mediated reduction of the thioamide **305**. Unfortunately, conversion of the lactam to the thioamide by the use of Lawesson´s reagent provided only small amounts of the desired product **305** (Scheme 83). Hence, no attempts to reduce the thioamide to the tertiary amine were applied.

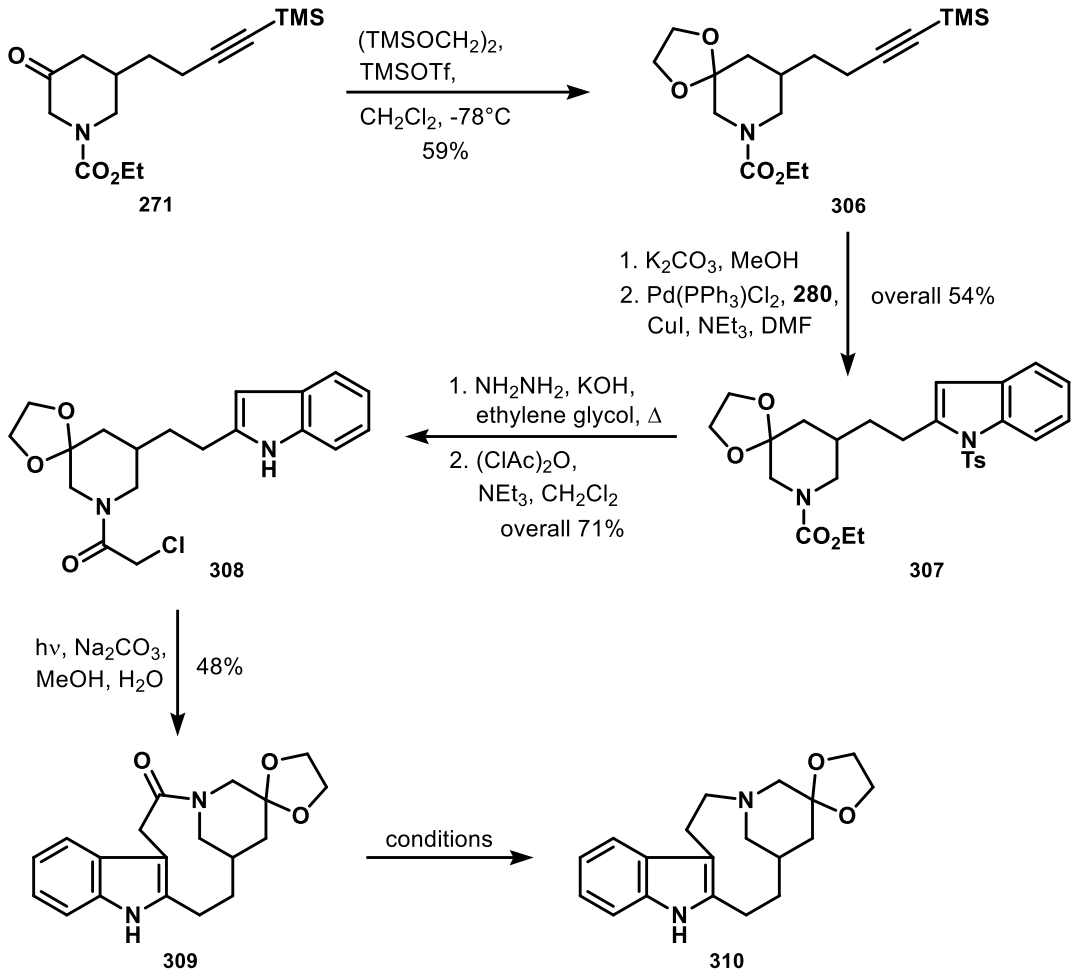


302 305

Scheme 83: Synthesis of thioamide **305** by the use of Lawesson´s reagent.

A last attempt to avoid the reduction of compound **301** dealt with an alternative synthetic strategy. This approach focused on an installation of the ethyl side chain after the reduction of the lactam moiety. However, a replacement of these synthetic steps could be achieved by a protection of the ketone in compound **271**. As depicted in Scheme 84, this key transformation was accomplished in good yields by the use of Noyori´s ketalization protocol.[114] Cleavage of the TMS group at the alkyne with potassium carbonate in methanol and a subsequent Larock indole synthesis provided compound **307**. A detachment of the carbamate and tosyl group under the established conditions followed by an amide formation with chloroacetic anhydride afforded the Witkop precursor **308**. The photocyclization proceeded smoothly in 48% yield by the use of sodium carbonate in a 3:2 mixture of methanol and water. It is also noteworthy

that the entire starting material was consumed and no formation of other side products was observed.



Scheme 84: Synthesis of lactam **309** and reduction attempts to provide amine **310**.

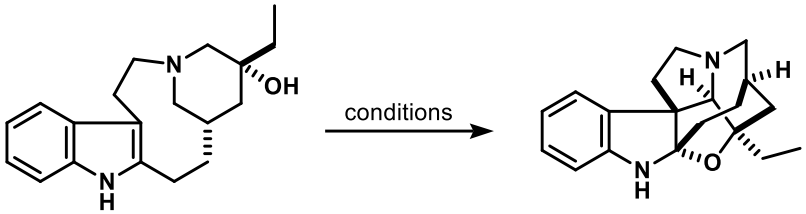
Table 19: Conditions for the lactam reduction to provide amine **310**.

Entry	Reagent	Solvent	Temp.	Results
1	$LiAlH_4$	THF	50 °C	decomp.
2	$Zn(OAc)_2$, $(EtO)_3SiH$	THF	r.t.	no reaction
3	$HRh(CO)(PPh_3)_3$, $PhSiH_3$	THF	50 °C	decomp.
4	Lawesson´s reagent	PhMe	100 °C	30%

With lactam **309** in hands, several reduction attempts were performed (Table 19). In the first place, the starting material was subjected to lithium aluminum hydride, but without any success. Treatment of the amide with zinc acetate and triethoxysilane did not give any response. Even the use of the rhodium catalyzed reduction protocol resulted in decomposition. As an additional experiment, the transformation of the

amide to the corresponding thiolactam was examined. Unfortunately, using Lawesson´s reagent in toluene under reflux provided only poor yields of the desired product (Entry 4).

With this disappointing optimization attempts in mind, it was decided to proceed with the direct reduction of compound **301** to the natural product (±)-velbanamine (**18**) by the use of Beller´s method (Table 17, Entry 15). Therefore, the oxidation of (±)-velbanamine (**18**) remains the last major task en route to the synthesis of dichomine (Scheme 85). As documented in Table 20 several different oxidation attempts towards (±)-dichomine (**1**) were performed.



(±)-velbanamine (**18**) (±)-dichomine (**1**)

Scheme 85: Oxidation attempts of (±)-velbanamine (**18**) to (±)-dichomine (**1**).

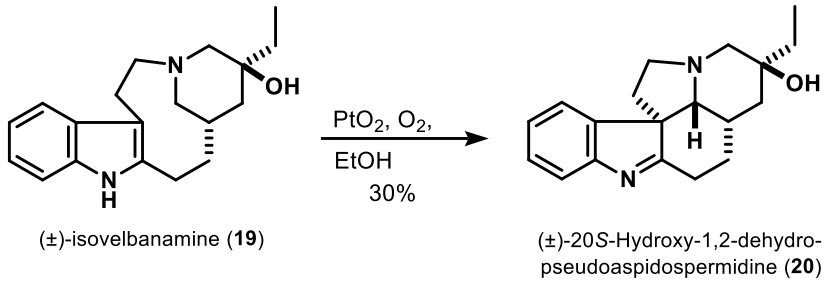
Table 20: Conditions for the oxidation of (±)-velbanamine (**18**).

Entry	Reagent	Solvent	Temp.	Yield
1	Silver(II) picolinate	H_2O/TFA	0 °C	decomp.
2	*m*CPBA, TFAA	CH_2Cl_2	0 °C	decomp.
3	PIDA, MS 4Å	DME	r.t.	no reaction
3	PIDA, MS 4Å	CH_3CN	50 °C	decomp.
4	DDQ	MeOH	r.t.	decomp.
5	$K_3[Fe(CN)_6]$	MeOH/H_2O	r.t.	decomp.
6	$Co(acac)_2$, O_2	CH_3CN	50 °C	decomp.
7	$RuCl_3$, O_2	MeOH	reflux	no reaction

In the first attempt silver picolinate was used in a mixture of water and trifluoroacetic acid.[115] Unfortunately, this oxidation reagent proved to be too reactive. The performance of a Polonovsky oxidation by the use of *m*CPBA in combination with trifluoroacetic anhydride was also unsuccessful.[116] Thereby, it is noteworthy that the starting material decomposed during the oxidation step. Treatment of the starting material with PIDA under ambient temperature gave no response, whereas an increase of the reaction temperature resulted in decomposition (Entry 3, 4).[117] The use of DDQ lead to almost spontaneous decomposition of the amine.[118] Furthermore, also

an oxidation with potassium hexacyanoferrate(III) resulted in decomposition, albeit at a much slower rate.[119] An attempted cobalt catalyzed oxidation of the amine in acetonitrile under room temperature provided no conversion of the starting material. On the other hand, an elevation of the reaction temperature resulted in decomposition (Entry 6).[120] Moreover, a ruthenium catalyzed oxidation of the natural product provided, even under reflux, no conversion of the starting material.[121] Based on these disappointing results, the envisioned oxidation at the C-21 position of velbanamine (**18**) appeared to be unfeasible.

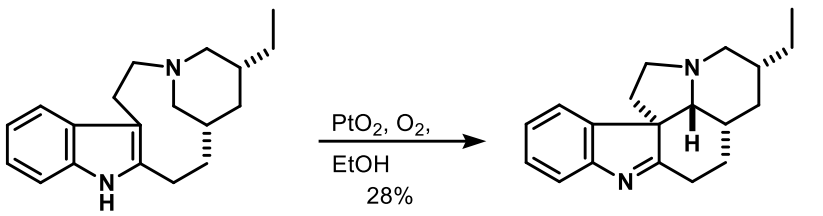
However, parallel to the oxidation attempts of velbanamine (**18**), also a retro-biomimetic oxidation at the C-3 position of (±)-isovelbanamine (**19**), which should generate (±)-20*S*-hydroxy-1,2-dehydro-pseudoaspidospermidine (**20**) was envisioned (Scheme 86). Fortunately, this transformation could be achieved under oxygen atmosphere and the use of Adam´s catalyst in ethanol. [122]



(±)-isovelbanamine (**19**) — (±)-20*S*-Hydroxy-1,2-dehydro-pseudoaspidospermidine (**20**)

Scheme 86: Retro-biomimetic oxidation of (±)-isovelbanamine (**19**).

Furthermore, the application of the same reaction conditions by the oxidation of (±)-20*R*-dihydro-cleavamine (**17**) provided quite smoothly the desired natural product (±)-20*R*-1,2-dehydro-pseudoaspidospermidine (**21**) (Scheme 87).



(±)-20*R*-dihydrocleavamine (**17**) — (±)-20*R*-1,2-Dehydro-pseudoaspidospermidine (**21**)

Scheme 87: Retro-biomimetic oxidation of (±)-20*R*-dihydro-cleavamine (**17**).

4.5.1. Conclusions of the fourth synthetic approach

The initial approach to synthesize the Witkop precursor is based on a copper mediated Michael addition between indole **248** and dihydropyridone **62** followed by an *in situ* trapping of the resulting enolate with a triflation reagent to obtain the enol triflate. A subsequent Negishi coupling reaction with diethylzinc should establish the desired substitution pattern at the tetrahydropyridine ring. Unfortunately, after several attempts the indole **248** proved to be an unsuitable nucleophile for this reaction. At that time, carefully literature research identified alkyne **270** as a potential nucleophile and a feasible surrogate for an indole moiety. After extensive experimental work, it was possible to perform a 1,4-addition with this building block and dihydropyridone **62**. (Scheme 63). However, a subsequent trapping of the resulted enolate with several triflation reagents was not possible. Hence, it was determined to achieve a S_N2' displacement at allylic compound **273** to install the remaining side chain and the required C-15, C-20 double bond in a single step (Scheme 65). But even after several attempts it was not possible to realize that reaction. Due to these experimental results it was decided to establish a synthetic route to provide the first Witkop precursor **285** from the Michael addition product **271**. After succeeding in the synthesis of this compound, first photocyclization experiments commencing in the preparation of macrolactams **296a** and **296b** (Scheme 69). With the synthetic route in hands, it was possible to generate the ethylene analogs **290** and **291**. Moreover, these compounds provided the access to the *iboga* alkaloids (±)-cleavamine (**49**) and (±)-dihydrocleavamine (**17**). However, the attempted double bond isomerization of compound **292** to prepare enamine **165** could not be achieved. Based on this fact, a retro-biomimetic oxidation approach starting from the natural product velbanamine (**18**) was envisioned (Scheme 76). With that in mind, it was necessary to introduce a tertiary alcohol at the C-20 position instead of the double bond. This was accomplished in the first place *via* a Corey Chaykovsky epoxidation at ketone **271** followed by subsequent opening of the epoxide with methylmagnesium bromide (Scheme 77). Due to the unfavorable diastereomeric ratio of this epoxidation reaction, only the related alkaloid (±)-isovelbanamine (**19**) could be synthesized in acceptable yields. After further investigations, a simple epoxidation of intermediate **279** with *m*CPBA afforded the best diastereomeric ratio in a 1:1 mixture. Furthermore, the unexpected difficulties in the reduction of lactam **301** to the desired natural product (±)-velbanamine (**18**), require

additional experimental investigations. However, derivatization of the tertiary alcohol to a silyl ether or even the establishment of a ketal protection group instead of the alcohol moiety did not provide better yields in the reduction reaction. Nevertheless, these examinations could enlighten the potential electronic effect of the alcohol with respect to the amide functionality. Unfortunately, the envisioned retro-biomimetic oxidation at the C-21 positon of velbanamine (**18**) to dichomine (**1**) could not be realized. On the other hand, during these oxidation attempts it was possible to perform a C-3 oxidation of (±)-isovelbanamine (**19**) to the natural product (±)-20*S*-hydroxy-1,2-dehydro-pseudoaspidospermidine (**20**). Moreover, this conditions could also be used to synthesize the related alkaloid (±)-20*R*-1,2-dehydro-pseudoaspidospermidine (**21**) from (±)-20*R*-dihydro-cleavamine (**17**).

5. Summary and Conclusions

In this work, four different approaches to synthesize dichomine (**1**) were investigated. In general, key steps in these attempts were the Witkop photocyclization to generate the 9-membered lactam and an oxidative biomimetic ring-closing reaction to synthesize the unique bicyclo[5.3.2]dodecane system (Scheme 34). Therefore, the synthesis of Witkop precursor **166** was the first goal.

In the first attempt this should be accomplished by a condensation reaction between tetrahydropyridine **167** and aromatic compound **168**. Furthermore, the building block **167** should be generated by a hydride reduction from the pyridinium salt of intermediate **169**. Unfortunately, the condensation reaction to generate the indole as well as the reduction of the pyridinium salt proved to be unsuitable. To overcome these problems, an alternative C-C bond formation *via* an alkylation reaction between the indole **180** and the piperidone **181** was envisioned (Scheme 39). But even after extensive experimental research it was not possible to provide a reasonable amount of the desired alkylated product.

Hence, a different retrosynthetic strategy based on a [2,3]-Wittig-Still rearrangement of aziridine **209** was developed (Scheme 49). This intermediate should be generated *via* a Wittig olefination from aziridine **211** and indole **210**. However, several attempts were performed to synthesize a feasible aziridine precursor for the Wittig olefination, but unfortunately none of them was successful.

The third approach focused on the synthesis of compound **245** (Scheme 56). The required piperidone key structural motif should be synthesized *via* a lactamization reaction between the *in situ* generated amine from the primary azide and the adjacent γ-lactone in intermediate **246**. However, the desired lactone **246** could be obtained in 6 steps starting from indole **248** (Scheme 57). Unfortunately, several attempts to perform the lactamization reaction were fruitless. Furthermore, also the reductive amination of lactol **253** could not be accomplished.

In the last approach, a 1,4-addition between the already synthesized primary iodide **248** and dihydropyridone **62** (Scheme 60) was envisioned. After several attempts, the indole **248** proved to be an unsuitable nucleophile and was replaced by the alkyne **280**. Further experimental investigations succeeded in the synthesis of the Witkop precursor **285** and the first photocyclization products **296a** and **296b**. With the synthetic route in hands, it was possible to prepare the ethylene analogs **290** and **291** commencing in the total synthesis of (±)-cleavamine (**49**) and (±)-dihydrocleavamine (**17**). Unfortunately, the attempted double bond isomerization of compound **292** to prepare the biomimetic precursor **165** was unsuccessful. Based on this fact, a retro-biomimetic oxidation approach starting from the natural product velbanamine (**18**) was envisioned (Scheme 76). With that in mind, it was necessary to introduce a tertiary alcohol at the C-20 position. This was accomplished in the first place *via* a Corey Chaykovsky epoxidation at ketone **271**. Due to the preferred generation of the (20*S*)-diastereomer, only the related alkaloid (±)-isovelbanamine (**19**) could be synthesized in acceptable yields (Scheme 78). However, further experimental investigations provided a better diastereomeric ratio of the tertiary alcohol and therefore a promising approach to (±)-velbanamine (**18**). Unfortunately, the envisioned retro-biomimetic oxidation of (±)-velbanamine (**18**) to (±)-dichomine (**1**) could not be realized under various conditions. On the other hand, it was possible to oxidize (±)-isovelbanamine (**19**) to the natural product (±)-20*S*-hydroxy-1,2-dehydro-pseudoaspidospermidine (**20**) and (±)-20*R*-dihydro-cleavamine (**17**) to the related alkaloid (±)-20*R*-1,2-dehydro-pseudoaspidospermidine (**21**).

6. Experimentals

6.1. General information

All moisture and oxygen sensitive reactions were performed in flame-dried glassware under a slight argon overpressure. All reactions were stirred magnetically. Sensitive solutions, solvents or reagents were transferred *via* cannula or syringe. Reactions were monitored by thin-layer chromatography (TLC) or NMR of the crude mixture. Evaporations were conducted under reduced pressure at temperatures less than 40°C, unless otherwise noted. Further dryings of the residues were accomplished using a high vacuum pump.

All solvents were purchased as the highest available grade from Sigma-Aldrich, Acros-Organics or Fisher-Chemicals. Solvents for Pd-catalyzed coupling reactions were used after sparging the solvent with nitrogen for 30 min under ultrasonification. Ethyl acetate, hexane and dichloromethane for column chromatography were distilled and used without further purification. All other reagents were used as received from Sigma-Aldrich, Acros-Organics, TCI or Fisher-Chemicals unless otherwise noted.

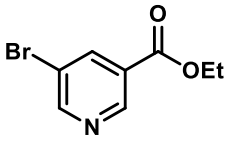
Thin-layer chromatographies (TLC) were carried out on pre-coated Merk silica gel 60 F254 to monitor all reactions. The detection was first performed using UV (254 nm) as a visualizing agent followed by immersion in an aqueous solution of phosphomolybdic acid (20 g), ceric(IV)sulfate (2 g) and 22 mL of sulfuric acid. Treatment with a heat-gun eventually revealed the state of the reaction. Preparative column chromatography was performed with silica gel 60 from Merk (0.040-0.063 µm, 240-400 mesh). The columns were packed with a suspension of gel in hexane and eluted with an appropriate solvent combination using a hand-pump overpressure.

All NMR spectra were measured on a Bruker DPX 200, AV400 or DRX600. Chemical shifts are given in ppm and referenced to the solvent residual peaks ($CDCl_3$ ^1H, δ= 7.26 ppm, ^{13}C, δ= 77.00 ppm; methanol-d_4 ^1H, δ= 3.31 ppm, ^{13}C, δ= 49.00 ppm; DMSO-d_6 ^1H, δ= 2.50 ppm, ^{13}C, δ= 39.52 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant *J*, integration. Infrared spectra were recorded as thin films of pure products on an ATR-unit on a Bruker Vector 22 or Shimadzu IRAffinity 1S. High-resolution mass spectra were measured on Waters QTOF-Premier (Waters Aquity Ultra Performance, electron spray ionization)

6.2. Experimental procedures

6.2.1. Experimentals of the first approach

Ethyl 5-bromonicotinate **203**

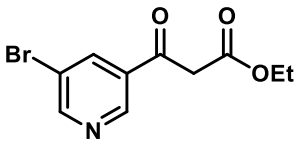


203

Thionyl chlorid (80 mL) was added to 5-bromonicotinic acid **170** (10 g, 49.5 mmol) at r.t. and the resulting mixture was heated to reflux for 3 h. The remaining thionyl chlorid was evaporated under reduced pressure and the resulting precipitate was dissolved at 0°C in EtOH (150 mL). After stirring at r.t. for 15 h most of the EtOH was evaporated under reduced pressure, the concentrated solution was quenched with sat. $NaHCO_3$, the aqueous layer was extracted with CH_2Cl_2 (3x), the organic layer was washed with brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation to the crude product **203** (11.4 g, 99%) as white solid, which was used in the next step without further purification. The analytical data matches the data in literature.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.13 (d, *J* = 1.8 Hz, 1H), 8.83 (d, *J* = 2.3 Hz, 1H), 8.43 (dd, *J* = 2.3, 1.8 Hz, 1H), 4.42 (q, *J* = 7.1 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 3H); ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.0, 154.4, 148.8, 139.6, 127.8, 120.6, 62.0, 14.2; ppm.
IR: 2984, 1725, 1581, 1269, 1170, 1103, 1022, 902, 763, 738 cm^{-1}
HRMS: m/z calculated for $C_8H_8O_2N_1Br_1H^+$: 229.9817; found: 229.9817;

Ethyl 3-(5-bromopyridin-3-yl)-3-oxopropanoate **174**



174

To a mixture of NHMDS (8.7 mL, 2 eq., 2 M in THF, 17.4 mmol) in THF (60 mL) was added ethyl acetate (0.94 mL, 1.1 eq., 9.6 mmol) at -78 °C. After stirring for 30 min at the same temperature, a solution of **203** (2 g, 8.7 mmol) in THF (20 mL) was added dropwise. The mixture was stirred for 1.5 h at -78 °C and afterwards warmed to r.t. over a period of 3 h. After further stirring for 1.5 h at r.t., the reaction was treated with 1 M HCl, the aqueous layer was extracted with diethyl ether (3x), the combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation to the crude product **174** (2.19 g, 93%) as slightly yellow liquid, which was used in the next step without further purification.

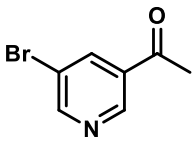
^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.5 (s, 1H), 8.89 (d, *J* = 1.9 Hz, 1H), 8.74 (d, *J* = 2.1 Hz, 1H), 8.20 (t, *J* = 2.1 Hz, 1H), 5.70 (s, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H); ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.2, 172.5, 166.9, 166.4, 155.0, 152.4, 147.8, 145.1, 138.3, 136.3, 132.6, 131.1, 121.4, 120.9, 89.8, 61.9, 60.9, 46.0, 14.2, 14.0; ppm.

IR: 2982, 1741, 1696, 1627, 1422, 1311, 1261, 1207, 1018, 805 cm^{-1}

HRMS: m/z calculated for $C_{10}H_{10}O_3N_1Br_1H^+$: 270.9922; found: 270.9922;

1-(5-Bromopyridin-3-yl) ethan-1-one **175**

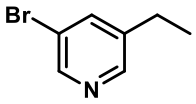


175

To a mixture of **174** (2.19 g 8.1 mmol) in water (40 mL) was added conc. HCl (4 mL). After stirring for 5 h under reflux, the solution was cooled to room temperature, and treated with NaOH. The basic mixture was extracted with ethyl acetate (3x), the organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to the crude product **175** (1.49 g, 92%) as colorless clear oil, which was used in the next step without further purification. The analytical data matches the data in literature.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.06 (d, *J* = 1.8 Hz, 1H), 8.85 (d, *J* = 2.3 Hz, 1H), 8.36 (dd, *J* = 2.3, 1.8 Hz, 1H), 2.64 (s, 3H); ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.2, 154.5, 147.7, 138.1, 133.5, 121.3, 26.8; ppm.
IR: 3034, 1677, 1572, 1421, 1356, 1275, 1172, 1011, 897, 799 cm^{-1}

3-Bromo-5-ethylpyridine **176**

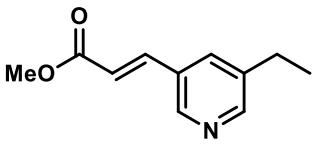


176

To a mixture of **175** (1.49 g, 7.44 mmol) in diethylene glycol (14 mL) was added KOH (3.9 g, 10 eq., 74 mmol) and hydrazine (2.2 mL, 10 eq., 74 mmol). The resulting mixture was stirred for 5 h at 140 °C and then cooled to room temperature. The solution was treated with water, the aqueous phase was extracted with diethyl ether (3x), the combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation. The residue was purified by column chromatography (hexane/EtOAc, 5:1) to give **176** (1.07 g, 77%) as clear liquid. The analytical data matches the data in literature.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.50 (d, *J* = 2.2 Hz, 1H), 8.38 (d, *J* = 2.0 Hz, 1H), 7.66 (m, 1H), 2.65 (q, *J* = 7.5 Hz, 2H) 1.26 (t, *J* = 7.5 Hz, 3H); ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.2, 147.6, 141.1, 138.0, 120.6, 25.7, 15.0; ppm.
IR: 2975, 1554, 1420, 1251, 1097, 1021, 877, 832, 702, 663 cm^{-1}
HRMS: m/z calculated for $C_7H_8N_1Br_1H^+$: 185.9918; found: 185.9917;

Methyl (*E*)-3-(5-ethylpyridin-3-yl) acrylate **204**

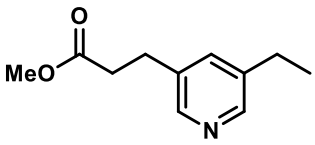


204

To a solution of **176** (1.07 g, 5.73 mmol) in DMF (25 mL) was added methyl acrylate (2.6 mL, 5 eq., 28.7 mmol) and NEt_3 (1.6 mL, 2 eq., 11.5 mmol). The mixture was degassed followed by addition of $Pd(dppf)Cl_2$ (465 mg, 0.1 eq., 0.57 mmol). After stirring for 48 h at 105 °C, the resulting solution was poured into sat. NH_4Cl, the aqueous layer was extracted with diethyl ether (3x), the combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc, 2:1) to afford **204** (942 mg, 86%) as slightly brown oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.56 (d, *J* = 1.9 Hz, 1H), 8.46 (d, *J* = 1.8 Hz, 1H), 7.67 (d, *J* = 16.0 Hz, 1H), 7.65 (m, 1H), 6.51 (d, *J* = 16.0 Hz, 1H), 3.82 (s, 3H), 2.69 (q, *J* = 7.6 Hz, 1H), 1.28 (t, *J* = 7.6 Hz, 1H); ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.9, 151.1, 147.3, 141.5, 139.4, 133.4, 129.8, 119.65, 51.9, 25.9, 15.2; ppm.
HRMS: m/z calculated for $C_{11}H_{13}O_2N_1H^+$: 192.1025; found: 192.1024;

Methyl 3-(5-ethylpyridin-3-yl) propanoate **169**

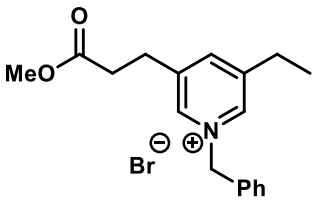


169

A mixture of **204** (942 mg, 4.93 mmol), EtOH (20 mL) and Pd/C (10 wt%, 76 mg) was stirred for 7 h at r.t. under hydrogen atmosphere (1 atm). The resulting suspension was diluted with diethyl ether and filtered through a pad of celite. The solvent was removed by rotary evaporation. The remaining crude product was purified by column chromatography (hexane/EtOAc, 1:1) to yield **169** (895 mg, 94%) as clear liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.31 (bs, 1H), 8.29 (bs, 1H), 7.35 (m, 1H), 3.67 (s, 3H), 2.93 (t, *J* = 7.6 Hz, 2H), 2.64 (m, 4H), 1.24 (t, *J* = 7.5 Hz, 3H); ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.8, 147.5, 147.1, 139.0, 135.4, 135.4, 51.7, 35.3, 28.0, 25.9, 15.3; ppm.
HRMS: m/z calculated for $C_{11}H_{15}O_2N_1H^+$: 194.1181; found: 194.1177;

1-Benzyl-3-ethyl-5-(3-methoxy-3-oxopropyl) pyridin-1-ium bromide **177**

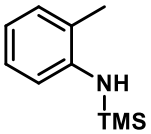


177

To a solution of **169** (500 mg, 2.59 mmol) in acetone (2.6 mL) was added benzyl bromide (0.31 mL, 1 eq., 2.59 mmol). After stirring for 24 h at r.t., the solvent was removed by rotary evaporation to the crude product **177** (932 mg, 99%) as clear low viscous oil.

^{1}H NMR (400 MHz, CD_3OD): δ = 8.87 (m, 1H), 8.85 (m, 1H), 8.41 (m, 1H), 7.48 (m, 5H), 5.77 (s, 2H), 3.60 (s, 3H), 3.13 (t, *J* = 7.1 Hz, 2H), 2.88 (q, *J* = 7.6 Hz, 2H), 2.81 (t, *J* = 7.1 Hz, 2H), 1.33 (t, *J* = 7.6 Hz, 3H); ppm.
^{13}C NMR (100 MHz, CD_3OD): δ = 173.9, 146.9, 146.8, 143.8, 143.3, 142.8, 134.9, 130.9, 130.7, 129.8, 65.6, 52.3, 34.5, 28.5, 26.8, 14.7; ppm.
HRMS: m/z calculated for $C_{18}H_{22}O_2N_1^+$: 284.1646; found: 284.1640;

1,1,1-Trimethyl-*N*-(*o*-tolyl) silanamine **168**

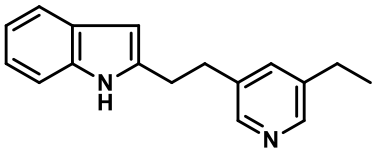


168

To a solution of *o*-toluidine (7 g, 65 mmol) in HMDS (42 mL, 3.1 eq., 203 mmol) was added TMSCl (0.5 mL, 0.06 eq., 3.92 mmol) and lithium iodid (175 mg, 0.02 eq., 1.31 mmol). After stirring for 20 h under reflux, cyclohexene oxide (1.3 mL, 0.2 eq., 13 mmol) was added. The mixture was stirred for further 15 min under reflux before further cyclohexene oxide (1.3 mL) was added. Afterwards the mixture was cooled to r.t. and HMDS was removed by vacuum distillation (100 mbar, 60 °C). A subsequent vacuum distillation (15 mbar, 98-100 °C) of the residue afforded product **168** (22.4 g, 86%) as clear colorless liquid. The analytical data matches the data in literature.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.06 (m, 2H), 6.75 (d, *J* = 8.5 Hz, 1H), 6.67 (dd, *J* = 7.5, 1.3 Hz, 1H) 3.27 (bs, 1H), 2.15 (s, 3H), 0.30 (s, 9H); ppm.

2-(2-(5-Ethylpyridin-3-yl)ethyl)-1H-indole **179**

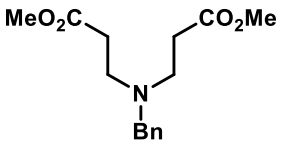


179

To a solution of **168** (120 mg, 1.3 eq., 0.67 mmol) in hexane (5 mL) was added *n*BuLi (0.6 mL, 2.85 eq., 2.5 M in hexane, 1.48 mmol) dropwise at 0 °C. After stirring for 6.5 h under reflux, the mixture was cooled to -78 °C and a precooled solution (-78 °C) of **169** (100 mg, 0.52 mmol) in THF (2.5 mL) was added *via* cannula. The stirring mixture was allowed to warm up to r.t. and was then treated with sat. NH_4Cl. The aqueous layer was extracted with diethyl ether (3x), the combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation and the residue was purified by column chromatography (hexane/EtOAc, 1:1) to give **179** (24 mg, 18%) as clear colorless liquid.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.50 (bs, 1H), 8.33 (d, *J* = 1.8 Hz, 1H), 8.30 (d, *J* = 1.8 Hz, 1H), 7.54 (m, 1H), 7.29 (m, 2H), 7.10 (m, 2H), 6.27 (m, 1H), 3.03 (m, 4H), 2.60 (q, *J* = 7.6 Hz, 2H), 1.20 (t, *J* = 7.6 Hz, 3H); ppm.
HRMS: m/z calculated for $C_{17}H_{18}N_2H^+$: 251.1548; found: 251.1548;

Dimethyl 3,3'-(benzylazanediyl) dipropionate **205**



205

To a solution of methyl acrylate (37 mL, 1.85 eq., 404 mmol) in MeOH (190 mL) was added a solution of benzyl amine (20 mL, 183 mmol) in MeOH (90 mL) dropwise whereupon the reaction temperature was kept under 50 °C. The mixture was stirred for 30 min at r.t. and for further 8 h under reflux. The reaction was cooled to r.t. and most of the MeOH was distilled off. The concentrated solution was treated with sat. NH_4Cl, the aqueous layer was extracted with diethyl ether (3x), the combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc, 4:1) to yield **205** (47.7 g, 93%) as clear liquid. The analytical data matches the data in literature.

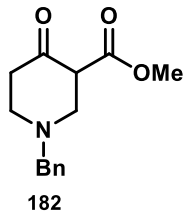
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28 (m, 5H), 3.65 (s, 6H), 3.59 (s, 2H), 2.80 (t, *J* = 7.1 Hz, 2H), 2.47 (t, *J* = 7.1 Hz, 2H); ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.9, 139.0, 128.7, 128.2, 127.0, 58.3, 51.5, 49.2, 32.6; ppm.

IR: 2952, 2833, 1734, 1436, 1250, 1194, 1173, 1042, 738, 699 cm^{-1}

HRMS: m/z calculated for $C_{15}H_{21}O_4N_1H^+$: 280.1549; found: 280.1548;

Methyl 1-benzyl-4-oxopiperidine-3-carboxylate **182**

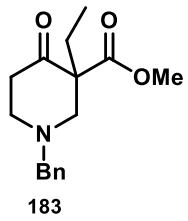


182

To a mixture of NaH (10.9 g, 1.6 eq., 60% in mineral oil, 273 mmol) in toluene (750 mL) was added a solution of **205** (47.7 g, 171 mmol) in toluene (100 mL) and MeOH (0.7 mL). After stirring for 2 h at 93 °C, the mixture was cooled to r.t. and quenched with 1 M HCl. The aqueous solution was treated with sat. $NaHCO_3$ until pH = 8-9. The mixture was extracted with ethyl acetate (3x), the combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation and the residue was purified by column chromatography (hexane/EtOAc, 3:1) to give **182** (35.1 g, 83%) as clear colorless liquid. The analytical data matches the data in literature.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.94 (s, 1H), 7.31 (m, 5H), 3.72 (s, 2H), 3.63 (s, 3H), 3.18 (t, *J* = 1.7 Hz, 2H), 2.61 (m, 2H), 2.40 (m, 2H); ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.0, 171.35, 170.4, 169.3, 129.0, 128.8, 128.4, 128.4, 127.5, 127.3, 96.6, 62.1, 61.6, 56.5, 55.0, 53.1, 52.2, 51.4, 49.9, 48.7, 40.8, 29.3; ppm.
IR: 2953, 2811, 1746, 1720, 1664, 1623, 1443, 1305, 1235, 1126 cm^{-1}
HRMS: m/z calculated for $C_{14}H_{17}O_3N_1H^+$: 248.1287; found: 248.1295;

Methyl 1-benzyl-3-ethyl-4-oxopiperidine-3-carboxylate **183**

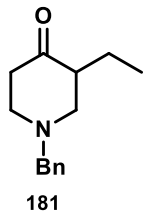


183

A mixture of **182** (35.1 g, 142 mmol) and K_2CO_3 (39 g, 2 eq., 284 mmol) in acetone (280 mL) was placed in an ultrasonic bath for 30 min. Afterwards, ethyl iodide (34.4 mL, 3 eq., 426 mmol) was added and the mixture was stirred for 18 h at 65 °C. The reaction was quenched with water, the aqueous layer was extracted with diethyl ether (3x), the combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc, 4:1) to yield **183** (32 g, 82%) as clear oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 (m, 5H), 3.74 (s, 3H), 3.59 (s, 2H), 3.37 (dd, *J* = 11.6, 2.6 Hz, 1H), 3.00 (m, 1H), 2.86 (m, 1H), 2.42 (m, 2H), 2.22 (d, *J* = 11.6 Hz, 1H), 1.86 (m, 1H), 1.56 (m, 1H), 0.84 (t, *J* = 7.5 Hz, 3H); ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.4, 172.2, 137.9, 128.8, 128.2, 127.3, 68.8, 61.6, 60.8, 53.6, 52.1, 40.6, 25.2, 9.2; ppm.
IR: 2952, 2809, 1718, 1454, 1349, 1230, 1140, 1027, 744, 699 cm^{-1}
HRMS: m/z calculated for $C_{16}H_{21}O_3N_1H^+$: 276.1600; found: 276.1600;

1-Benzyl-3-ethylpiperidin-4-one **181**

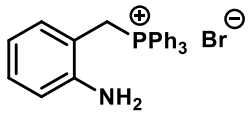


181

To a mixture of **183** (32 g, 116 mmol) in water (260 mL) was added conc. HCl (130 mL). After stirring for 12 h under reflux, the solution was cooled to r.t. and treated with 2 M NaOH until pH > 8. The aqueous phase was extracted with diethyl ether (3x), the combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation to the crude product **181** (24.2 g, 96%) as clear slightly yellow oil, which was used in the next step without further purification. The analytical data matches the data in literature.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (m, 4H), 7.28 (m, 1H), 3.66 (d, *J* = 13.3 Hz, 1H), 3.56 (d, *J* = 13.3 Hz, 1H), 3.02 (ddd, *J* = 11.0, 5.5, 2.1 Hz, 1H), 2.95 (ddd, *J* = 9.9, 5.5, 2.4 Hz, 1H), 2.51 (m, 2H), 2.40 (m, 2H), 2.25 (dd, *J* = 11.0, 9.8 Hz, 1H), 1.82 (m, 1H), 1.30 (m, 1H), 0.87 (t, *J* = 7.5 Hz, 3H); ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 211.1, 138.3, 128.8, 128.4, 127.3, 62.0, 58.5, 53.6, 51.4, 40.9, 20.7, 11.7; ppm.
IR: 2961, 2081, 1715, 1455, 1356, 1193, 1137, 739, 867, 699 cm^{-1}
HRMS: m/z calculated for $C_{14}H_{19}O_1N_1H^+$: 218.1545; found: 218.1547;

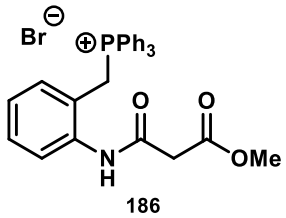
(2-Aminobenzyl) triphenylphosphonium bromide **185**



185

To a solution of 2-Aminobenzyl alcohol (13.5 g 109 mmol) in MeCN (750 mL) was added triphenylphosphonium bromide (37.5 g, 1 eq., 109 mmol). After stirring for 8 h under reflux, the mixture was cooled to r.t. and the resulting precipitate was filtered off. The filtrate was concentrated to approx. 100 mL and the occurring precipitate was filtered off. The combined salts were dried under reduced pressure to the crude product **185** (43.1 g, 88%).

(2-(3-Methoxy-3-oxopropanamido) benzyl) triphenylphosphonium bromide **186**

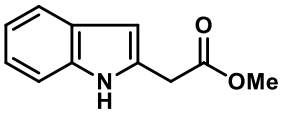


186

To a mixture of **185** (43.1 g, 96 mmol) in CH_2Cl_2 (200 mL) was added methyl malonyl chloride (10.3 mL, 1 eq., 96 mmol) dropwise. The solution was stirred for 3.5 h at r.t.. The solvent was evaporated under reduced pressure and the precipitate was recrystallized in MeOH to product **186** (42.3 g, 80%). The analytical data matches the data in literature.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 10.43 (s, 1H), 7.68 (m, 15H), 7.23 (m, 2H), 6.80 (m, 2H), 5.54 (d, *J* = 14.5 Hz, 2H) 3.65 (s, 3H), 3.52 (s, 2H); ppm.
HRMS: m/z calculated for $C_{29}H_{27}O_3N_1P_1^+$: 468.1723; found: 468.1727;

Methyl 2-(1*H*-indol-2-yl) acetate **187**

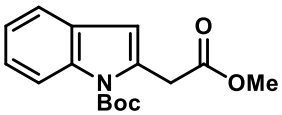


187

To a mixture of **186** (30 g, 54.7 mmol) in toluene (270 mL) was added *t*BuOK (55 mL, 1 eq., 1 M in *t*BuOH, 54.7 mmol) dropwise at 90 °C. After stirring for 1 h at the same temperature the resulting mixture was cooled to r.t. and quenched with water. The aqueous phase was extracted with diethyl ether (3x), the combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation and the residue was purified by column chromatography (hexane/EtOAc, 3:1) to give **187** (7.66 g, 74%) as slightly yellow clear oil. The analytical data matches the data in literature.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.65 (bs, 1H), 7.56 (m, 1H), 7.35 (m, 1H), 7.13 (m, 2H), 6.36 (m, 1H) 3.85 (s, 2H), 3.76 (s, 3H); ppm.

tert-Butyl 2-(2-methoxy-2-oxoethyl)-1*H*-indole-1-carboxylate **206**

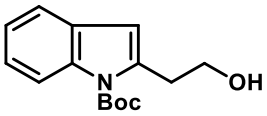


206

To a solution of **187** (7.66 g, 40.5 mmol) in CH_2Cl_2 (90 mL) was added Boc_2O (11.5 g, 1.3 eq., 52.6 mmol) and DMAP (500 mg, 0.1 eq., 4.1 mmol) at r.t.. The mixture was stirred for 18 h at the same temperature and then quenched with water. The aqueous layer was extracted with diethyl ether (3x), the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc, 6:1) to yield **206** (11.4 g, 97%) as clear colorless oil. The analytical data matches the data in literature.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.09 (m, 1H), 7.49 (m, 1H), 7.23 (m, 2H), 6.47 (m, 1H), 4.04 (s, 2H) 3.71 (s, 3H), 1.65 (s, 9H); ppm.

tert-Butyl 2-(2-hydroxyethyl)-1*H*-indole-1-carboxylate **188**

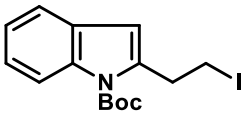


188

To a stirred solution of **206** (2.5 g, 8.6 mmol) in THF (40 mL) was added DIBAL (26 mL, 3 eq., 1 M in hexane, 25.9 mmol) dropwise at -78 °C. After stirring at the same temperature for 1 h the mixture was quenched with MeOH. Afterwards, the solution was poured into an aqueous solution of Na/K tartrate. The aqueous phase was extracted with diethyl ether (3x), the combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation and the residue was purified by column chromatography (hexane/EtOAc, 3:1) to give **188** (1.71 g, 76%) as clear colorless oil. The analytical data matches the data in literature.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.07 (m, 1H), 7.48 (m, 1H), 7.22 (m, 2H), 6.46 (s, 1H) 3.95 (t, *J* = 6.2 Hz, 2H), 3.32 (t, *J* = 6.2 Hz, 2H), 1.89 (bs, 1H), 1.69 (s, 9H); ppm.

tert-Butyl 2-(2-iodoethyl)-1*H*-indole-1-carboxylate **180**

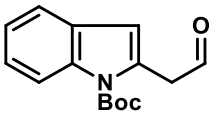


180

To a solution of **188** (700 mg, 2.68 mmol) in CH_2Cl_2 (13 mL) were added imidazole (382 mg, 2.1 eq., 5.63 mmol) and PPh_3 (1.41 g, 2 eq., 5.36 mmol) at r.t.. The solution was cooled to 0 °C and iodine (1.36 g, 2 eq., 5.36 mmol) was added in small portions. The mixture was stirred for 2 h at the same temperature and afterwards quenched with an aqueous $Na_2S_2O_3$ solution. The aqueous layer was extracted with diethyl ether (3x), the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc, 10:1) to afford **180** (856 mg, 86%) as orange oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (d, *J* = 8.2 Hz, 1H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.27 (m, 1H), 7.21 (dt, *J* = 7.6, 1.4 Hz, 1H), 6.45 (s, 1H), 3.65 (t, *J* = 7.5 Hz, 2H), 3.44 (t, *J* = 7.5 Hz, 2H), 1.70 (s, 9H); ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.3, 139.7, 136.6, 128.9, 123,9, 122.9, 120.2, 115.8, 109.0, 84.3, 34.8, 28.3, 3.6; ppm.
IR: 2977, 1731, 1454, 1370, 1327, 1213, 1157, 1119, 1083, 748 cm^{-1}
HRMS: m/z calculated for $C_{15}H_{18}O_2N_1I_1Na^+$: 394.0280; found: 394.0276;

tert-Butyl 2-(2-oxoethyl)-1*H*-indole-1-carboxylate **191**

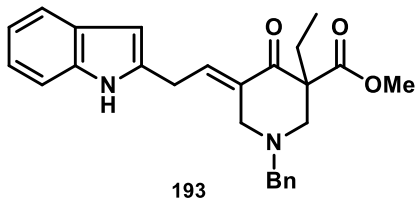


191

To a stirred solution of **206** (4.5 g, 15.6 mmol) in CH_2Cl_2 (80 mL) was added DIBAL (18.7 mL, 1.2 eq., 1 M in hexane, 18.7 mmol) dropwise at -78 °C. After stirring for 1 h at the same temperature the mixture was quenched with MeOH. Afterwards, the solution was poured into an aqueous solution of Na/K tartrate. The aqueous phase was extracted with diethyl ether (3x), the combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation and the residue was purified by column chromatography (hexane/EtOAc, 3:1) to give **191** (3.5 g, 87%) as slightly yellow oil. The analytical data matches the data in literature.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.80 (t, *J* = 1.2 Hz, 1H), 8.07 (m, 1H), 7.50 (m, 1H), 7.25 (m, 2H), 6.51 (s, 1H) 4.07 (s, 2H), 1.67 (s, 9H); ppm.

Methyl (*E*)-5-(2-(1*H*-indol-2-yl) ethylidene)-1-benzyl-3-ethyl-4-oxopiperidine-3-carboxylate **193**

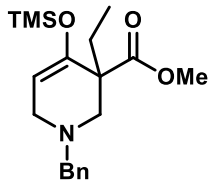


193

To a mixture of NHMDS (65 μL, 1.2 eq., 2 M in THF, 0.13 mmol) in THF (1 mL) was added **183** (30 mg, 0.11 mmol) at -78 °C. After stirring for 1 h at the same temperature, a solution of **191** (28 mg, 1 eq., 0.11 mmol) in THF (0.5 mL) was added dropwise. The mixture was stirred for 1.5 h at -78 °C and afterwards quenched with MeOH. The reaction was warmed to r.t. and sat. NH_4Cl was added. The aqueous layer was extracted with diethyl ether (3x), the combined etheral phases were washed with brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation and the residue was purified by column chromatography (hexane/EtOAc, 6:1) to give **193** (18 mg, 39%) as clear colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.27 (s, 1H), 7.54 (d, *J* = 7.9 Hz, 1H), 7.34 (m, 6H), 7.16 (m, 1H), 7.06 (m, 1H), 6.42 (s, 1H), 6.21 (dd, *J* = 16.3, 7.5 Hz, 1H), 3.85 (m, 1H), 3.79 (s, 3H), 3.68 (d, *J* = 13.5 Hz, 1H), 3.60 (d, *J* = 13.5 Hz, 1H), 3.53 (dd, *J* = 11.6, 2.8 Hz, 1H), 3.21 (m, 1H), 2.34 (t, *J* = 11.3 Hz, 1H), 2.18 (d, *J* = 11.6 Hz, 1H), 1.90 (m, 1H), 1.52 (m, 1H), 0.87 (t, *J* = 7.6 Hz, 3H); ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.8, 172.3, 128.8, 128.7, 128.3, 127.5, 123.6, 122.8, 122.6, 120.6, 119.9, 110.6, 103.0, 61.7, 61.6, 61.5, 60.0, 52.2, 51.9, 25.2, 9.3; ppm.
HRMS: m/z calculated for $C_{26}H_{28}O_3N_2H^+$: 417.2178; found: 417.2175;

Methyl 1-benzyl-3-ethyl-4-((trimethylsilyl) oxy)-1,2,3,6-tetrahydropyridine-3-carboxylate **195**

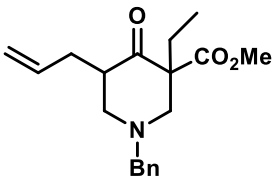


195

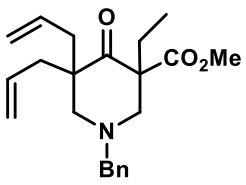
To a stirred mixture of NHMDS (1 mL, 1.1 eq., 2 M in THF, 2 mmol) in THF (8 mL) was added a solution of **183** (500 mg, 1.82 mmol) in THF (1 mL) at -78 °C. After stirring for 1 h at the same temperature, TMSCl (0.3 mL, 1.3 eq., 2.37 mmol) was added dropwise. After further stirring for 1 h at -78 °C, the reaction was treated with sat. $NaHCO_3$, the aqueous layer was extracted with diethyl ether (3x), the combined etheral phases were washed with brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation to the crude product **195** (626 mg, 99%) as clear colorless liquid, which was used in the next step without further purification.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.28 (m, 5H), 4.80 (dd, *J* = 4.1 2.9 Hz, 1H), 3.64 (s, 3H), 3.61 (d, *J* = 13.2 Hz, 1H), 3.46 (d, *J* = 13.2 Hz, 1H), 3.14 (ddd, *J* = 14.9, 4.0, 1.0 Hz, 1H), 2.91 (m, 2H), 2.33 (d, *J* = 11.2 Hz, 1H), 1.73 (q, *J* = 7.5 Hz, 2H), 0.85 (t, *J* = 7.5 Hz, 3H) 0.21 (s, 9H); ppm.

Methyl 5-allyl-1-benzyl-3-ethyl-4-oxopiperidine-3-carboxylate **197**



197



198

To a solution of **183** (50 mg, 0.18 mmol) in THF (1 mL) was added KO*t*Bu (0.27 mL, 1.5 eq., 1 M in *t*BuOH, 0.27 mmol) at r.t.. After stirring for 15 min at the same temperature, allyl bromide (23 μL, 1.5 eq., 0.27 mmol) was added. The resulting mixture was stirred for 1 h at r.t. and afterwards quenched with sat. NH_4Cl. The aqueous layer was extracted with diethyl ether (3x), the combined etheral phases were washed with brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation and the residue was purified by column chromatography (hexane/EtOAc, 10:1) to provide the double allylated product **198** (24 mg, 38%) and the desired product **197** (35 mg, 62%) as clear liquids.

Fr. 1: (**198**)

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.33 (m, 5H), 5.56 (m, 2H), 4.98 (m, 4H), 3.69 (d, *J* = 13.2 Hz, 1H), 3.67 (s, 3H), 3.53 (dd, *J* = 11.6, 2.7 Hz, 1H), 3.49 (d, *J* = 13.2 Hz, 1H), 2.66 (dd, *J* = 11.6, 2.7 Hz, 1H), 2.40 (m, 2H), 2.28 (m, 2H), 2.13 (m, 2H), 1.97 (m, 1H), 1.67 (m, 1H), 0.78 (t, *J* = 7.5 Hz, 3H); ppm.

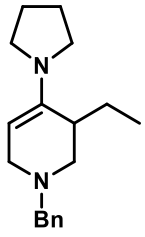
Fr. 2: (**197**)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 (m, 5H), 5.75 (m, 1H), 5.00 (m, 2H), 3.73 (s, 3H), 3.69 (d, *J* = 14.4 Hz, 1H), 3.67 (d, *J* = 13.6 Hz, 1H), 3.50 (d, *J* = 13.6 Hz, 1H), 3.46 (m, 1H), 3.14 (m, 1H), 3.02 (m, 1H), 2.58 (m, 1H), 2.05 (dd, *J* = 11.4, 3.1 Hz, 1H), 1.95 (m, 1H), 1.84 (m, 1H), 1.46 (m, 1H), 0.83 (t, *J* = 7.5 Hz, 3H); ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.7, 172.4, 137.7, 135.8, 128.8, 128.2, 127.3, 116.4, 61.7, 61.2, 59.7, 52.0, 47.9, 31.1, 25.2, 9.2; ppm.

HRMS: m/z calculated for $C_{19}H_{25}O_3N_1Na^+$: 338.1732; found: 338.1729;

1-Benzyl-3-ethyl-4-(pyrrolidin-1-yl)-1,2,3,6-tetrahydropyridine **199**

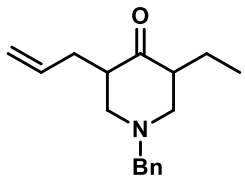


199

A solution of **181** (5 g, 23 mmol) and pyrrolidine (2.8 mL, 1.5 eq., 34.5 mmol) in benzene (23 mL) was placed in a dean stark apparatus. The mixture was heated for 36 h under reflux. Evaporation of the solvent and the excess of pyrrolidine under reduced pressure afforded the rather unstable crude product **199** (6.1 g, 98%) as orange oil, which was used immediately in the next step without further purification.

^{1}H NMR (400 MHz, C_6D_6): δ = 7.37 (d, *J* = 7.4 Hz, 2H), 7.16 (m, 2H), 7.08 (m, 1H), 4.20 (dd, *J* = 4.4, 2.3 Hz, 1H), 3.57 (d, *J* = 13.2 Hz, 1H), 3.38 (dd, *J* = 14.3, 4.5 Hz, 1H), 3.33 (d, *J* = 13.2 Hz, 1H), 2.84 (m, 3H), 2.71 (m, 3H), 2.26 (dd, *J* = 11.2, 3.3 Hz, 1H), 1.97 (m, 2H), 1.69 (m, 1H), 1.47 (m, 4H), 0.80 (t, *J* = 7.5 Hz, 3H); ppm.
^{13}C NMR (100 MHz, C_6D_6): δ = 146.0, 140.5, 129.6, 128.8, 127.5, 92.8, 63.5, 54.4, 53.2, 47.8, 40.8, 26.2, 25.1, 12.9; ppm.

3-Allyl-1-benzyl-5-ethylpiperidin-4-one **200**

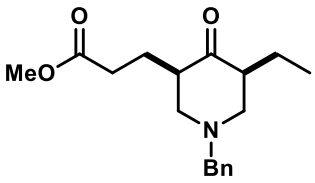


200

To a solution of freshly prepared **199** (100 mg, 0.37 mmol) in acetonitrile (1 mL) was added allyl bromide (38 μL, 1.2 eq., 0.44 mmol) at r.t.. After stirring under reflux for 3 h the reaction was treated with sat. NH_4Cl. The aqueous phase was extracted with diethyl ether (3x), the combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation and the residue was purified by column chromatography (hexane/EtOAc, 5:1) to afford **200** (37 mg, 39%) as colorless clear oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (m, 5H), 5.75 (m, 1H), 4.98 (m, 2H), 3.64 (d, *J* = 13.1 Hz, 1H), 3.59 (d, *J* = 13.1 Hz, 1H), 3.19 (m, 2H), 2.67 (m, 1H), 2.52 (m, 2H), 2.07 (d, *J* = 11.1 Hz, 1H), 2.02 (d, *J* = 11.1 Hz, 1H), 1.90 (m, 1H), 1.78 (m, 1H), 1.14 (m, 1H), 0.87 (t, *J* = 7.5 Hz, 3H); ppm.
HRMS: m/z calculated for $C_{17}H_{23}O_1N_1H^+$: 258.1858; found: 258.1861;

Methyl 3-(1-benzyl-5-ethyl-4-oxopiperidin-3-yl) propanoate **202**



202

To a solution of **199** (1 g, 3.7 mmol) in MeCN (4 mL) was added methyl acrylate (0.5 mL, 1.5 eq., 5.6 mmol). After stirring for 24 h under reflux, the reaction was quenched with sat. NH_4Cl, the mixture was extracted with diethyl ether (3x), the combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography (hexane/EtOAc, 10:1) to give side product **181** (402 mg, 50%) and the desired product **202** (303 mg, 27%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (m, 4H), 7.27 (m, 1H), 3.65 (s, 3H), 3.65 (d, *J* = 13.2 Hz, 1H), 3.46 (d, *J* = 13.2 Hz, 1H), 2.82 (ddd, *J* = 11.2, 5.4, 1.7 Hz, 1H), 2.66 (dd, *J* = 11.4, 4.7 Hz, 1H), 2.56 (m, 2H), 2.37 (m, 2H), 2.30 (m, 2H), 2.12 (m, 1H), 1.85 (m, 1H), 1.68 (m, 1H), 1.51 (m, 1H), 0.84 (t, *J* = 7.5 Hz, 3H); ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 213.2, 173.6, 138.5, 128.6, 128.3, 127.2, 61.9, 58.8, 58.0, 51.6, 51.0, 47.6, 31.7, 24.0, 22.6, 11.7; ppm.
IR: 2959, 2801, 1736, 1708, 1453, 1253, 1196, 1162, 737, 669 cm^{-1}
HRMS: m/z calculated for $C_{18}H_{25}O_3N_1H^+$: 304.1913; found: 304.1916;

6.2.2. Experimental procedures of the second approach

tert-Butyl hydroxycarbamate **234**

BocHN—OH
234

A mixture of hydroxylammonium chloride (2 g, 28.8 mmol) in Et_2O (8 mL) was sonificated for 20 min. Then water (0.4 mL) and Na_2CO_3 (2 g, 0.66 eq., 19 mmol) was added and the resulting mixture was stirred vigorously for 1 h at r.t.. After cooling to 0 °C solved Boc_2O (4.15 g, 0.66 eq., 19 mmol) in Et_2O (5 mL) was added over 30 min. The mixture was stirred additionally for 12 h at r.t.. Afterwards, the precipitate was filtered and washed with Et_2O. The solvent was removed by rotary evaporation and the remaining crude product **234** (2.26 g, 89%) was used in the next step without further purification. The analytical data matches the data in literature.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.00 (s, 1H), 6.55 (bs, 1H), 1.47 (s, 9H); ppm.

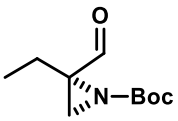
tert-Butyl (tosyloxy) carbamate **213**

BocHN—OTs
213

To a solution of **234** (1.2 g, 9 mmol) and TsCl (1.72 g, 1 eq., 9 mmol) in Et_2O (30 mL) was added a solution of NEt_3 (1.25 mL, 1 eq., 9 mmol) in Et_2O (5 mL) at 0 °C. After stirring at the same temperature for 1.5 h the precipitate was filtered and washed with Et_2O. The solvent was removed under reduced pressure and the residue was purified by column chromatography (hexane/EtOAc, 5:1) to give **213** (1.86 g, 72%) as white solid. The analytical data matches the data in literature.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (d, J = 8.4 Hz, 2H), 7.60 (s, 1H), 7.36 (d, J = 8.4 Hz, 2H), 2.46 (s, 3H), 1.30 (s, 9H); ppm.
HRMS: m/z calculated for $C_{12}H_{17}O_5N_1S_1Na^+$: 310.0725; found: 310.0727;

tert-Butyl (*S*)-2-ethyl-2-formylaziridine-1-carboxylate **211**

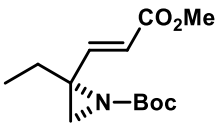


211

To a solution of the Hayashi-Jorgensen catalyst (190 mg, 0.2 eq., 0.58 mmol) in toluene (6 mL), were added α-ethylacrolein (0.3 mL, 2.9 mmol), **213** (1 g, 1.2 eq., 3.48 mmol) and NaOAc (357 mg, 1.5 eq., 4.35 mmol) at 0 °C. The mixture was stirred vigorously for 16 h at 4 °C and then quenched with brine. The mixture was extracted with diethyl ether (3x), the combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography (hexane/EtOAc, 10:1) to provide **211** (466 mg, 81%) as clear colorless liquid.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.81 (s, 1H), 2.65 (s, 1H), 2.41 (s, 1H), 1.83 (m, 2H), 1.45 (s, 9H), 1.03 (t, *J* = 7.4 Hz, 3H); ppm.

tert-Butyl (*R*,*E*)-2-ethyl-2-(3-methoxy-3-oxoprop-1-en-1-yl) aziridine-1-carboxylate **215**

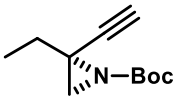


215

To a solution of the Wittig reagent (320 mg, 2.5 eq., 0.95 mmol) in CH_2Cl_2 (2 mL) was added **211** (76 mg, 0.38 mmol) at r.t.. After stirring for 4 h at r.t. the reaction was treated with water. The aqueous phase was extracted with CH_2Cl_2 (3x), the combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography (hexane/EtOAc, 10:1) to afford **215** (77 mg, 79%) as clear colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.57 (d, *J* = 15.7 Hz, 1H), 6.07 (d, *J* = 15.7 Hz, 1H), 3.74 (s, 3H), 2.34 (s, 1H), 2.32 (s, 1H), 1.78 (m, 1H), 1.68 (m, 1H), 1.43 (s, 9H), 1.03 (t, *J* = 7.4 Hz, 3H); ppm.

tert-Butyl (*R*)-2-ethyl-2-ethynylaziridine-1-carboxylate **216**

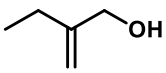


216

A mixture of powdered K_2CO_3 (694 mg, 4. eq., 5.0 mmol) in MeOH (10 mL) was sonificated for 30 min. Then a solution of **211** (250 mg, 1.25 mmol) in MeOH (2.5 mL) and the Bestmann-Ohira reagent (482 mg, 2 eq., 2.51 mmol) were added. The mixture was stirred for 1 h at r.t. and then treated with water. The mixture was extracted with diethyl ether (3x), the combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the remaining crude product was purified by column chromatography (pentane/Et_2O, 10:1) to yield **216** (210 mg, 86%) as volatile colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.54 (s, 1H), 2.23 (s, 1H), 2.15 (s, 1H), 1.63 (q, *J* = 7.5 Hz, 2H), 1.47 (s, 9H), 1.12 (t, *J* = 7.5 Hz, 3H); ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.1, 81.5, 81.1, 71.1, 38.0, 29.9, 28.9, 28.0, 10.1; ppm.

2-Methylenebutan-1-ol **224**

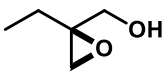


224

To a mixture of propargylic alcohol (7 mL, 121 mmol) and CuI (2.31 g, 0.1 eq., 12.1 mmol) in THF (400 mL) was added dropwise EtMgBr (93 mL, 2.3 eq., 3 M in Et_2O, 278 mmol) at -78 °C. The reaction was allowed to warm to r.t. and was stirred overnight. Afterwards, the solution was cooled to -78 °C and quenched with water and 1 M HCl. The aqueous layer was extracted with diethyl ether (3x), the combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Vacuum distillation (50 mbar, 60-70 °C) of the residue afforded product **224** (6.65 g, 64%) as clear colorless liquid. The analytical data matches the data in literature.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.00 (m, 1H), 4.87 (m, 1H), 4.08 (s, 2H), 2.08 (q, *J* = 7.5 Hz, 2H), 1.44 (bs, 1H), 1.07 (t, *J* = 7.5 Hz, 3H); ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.7, 108.1, 66.0, 25.7, 12.2; ppm.

(*S*)-(2-Ethyloxiran-2-yl) methanol **225**

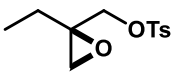


225

To a mixture of activated powdered molecular sieves (4Å, 1.2 g) and L-(+)-Diethyl tartrate (0.48 mL, 0.07 eq., 2.8 mmol) in CH_2Cl_2 (65 mL) was added $Ti(OiPr)_4$ (0.59 mL, 0.05 eq., 2.0 mmol) at 0 °C. After stirring for 1 h at the same temperature the reaction was cooled to –20 °C and TBHP (21.8 mL, 3 eq., 5.5 M in decane, 120 mmol) was added. The resulting mixture was stirred vigorously for 30 min and then **xx** (3.45 g, 40 mmol) was added dropwise over a period of 30 min. The reaction was stirred for 4 h at the same temperature and subsequently stored at -15 °C for 12 h. Afterwards, the mixture was quenched with water, warmed to r.t. and stirred with 2 M NaOH for 2 h. The resulting mixture was filtered through a pad of Celite, the aqueous phase was extracted with CH_2Cl_2 (3x), the combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation and the residue was purified by column chromatography (hexane/EtOAc, 10:1) to obtain **225** (2.9 g, 71%) as clear colorless oil. The analytical data matches the data in literature.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.78 (dd, *J* = 12.2, 4.4 Hz, 1H), 3.65 (dd, *J* = 12.2, 8.5 Hz, 1H), 2.88 (d, *J* = 4.7 Hz, 1H), 2.68 (d, *J* = 4.7 Hz, 1H), 1.80 (m, 1H), 1.68 (m, 1H), 1.59 (m, 1H), 0.95 (t, *J* = 7.5 Hz, 3H); ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 62.7, 60.4, 49.4, 24.7, 8.6; ppm.

(*R*)-(2-Ethyloxiran-2-yl) methyl 4-methylbenzenesulfonate **226**

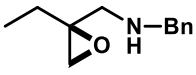


226

To a solution of **225** (200 mg, 2 mmol) in CH_2Cl_2 (4 mL) were added NEt_3 (0.97 mL, 3.5 eq., 7 mmol), DMAP (24 mg, 0.1 eq., 0.2 mmol) and TsCl (953 mg, 2.5 eq., 5 mmol) at 0 °C. The mixture was stirred for 3 h at the same temperature and afterwards treated with sat. $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2 (3x), the combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation and the residue was purified by column chromatography (hexane/EtOAc, 3:1) to provide **226** (510 mg, 99%) as colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (m, 2H), 7.35 (m, 2H), 4.06 (d, *J* = 10.9 Hz, 1H), 3.99 (d, *J* = 10.9 Hz, 1H), 2.67 (d, *J* = 4.5 Hz, 1H), 2.65 (d, *J* = 4.5 Hz, 1H), 2.45 (s, 3H), 1.76 (m, 1H), 1.63 (m, 1H), 0.88 (t, *J* = 7.5 Hz, 3H); ppm.

(*S*)-*N*-Benzyl-1-(2-ethyloxiran-2-yl) methanamine **227**

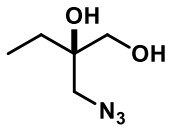


227

To a mixture of **226** (25 mg, 0.1 mmol) and pyridine (16 μL, 2 eq., 0.2 mmol) in DMF (1 mL) was added benzyl amine (13 μL, 0.12 mmol). The solution was stirred for 6 h at 65 °C and then quenched with sat. NH_4Cl. The mixture was extracted with Et_2O (3x), the combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation and the residue was purified by column chromatography (hexane/EtOAc, 1:1) to give **227** (7 mg, 36%) as clear oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 (m, 4H), 7.25 (m, 1H), 3.82 (d, *J* = 13.4 Hz, 1H), 3.78 (d, *J* = 13.4 Hz, 1H), 2.87 (d, *J* = 12.7 Hz, 1H), 2.80 (d, *J* = 5.0 Hz, 1H), 2.75 (d, *J* = 12.7 Hz, 1H), 2.62 (d, *J* = 5.0 Hz, 1H), 1.83 (m, 1H), 1.59 (m, 1H), 1.49 (bs, 1H), 0.93 (t, *J* = 7.5 Hz, 3H); ppm.

(*R*)-2-(Azidomethyl) butane-1,2-diol **235**



235

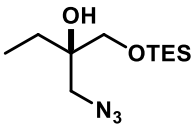
To a solution of **225** (300 mg, 2.94 mmol) in DME/H_2O (8:1, 15 mL) were added NaN_3 (0.96 g, 5 eq., 14.7 mmol) and NH_4Cl (0.47 g, 3 eq., 8.82 mmol) at r.t.. After stirring for 16 h at 55 °C the mixture was quenched with brine and extracted with EtOAc (3x). The combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography (hexane/EtOAc, 1:1) to give **235** (352 mg, 82%) as slightly yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.52 (m, 2H), 3.37 (m, 2H), 2.63 (bs, 1H), 2.53 (bs, 1H), 1.55 (m, 2H), 0.90 (t, *J* = 7.6 Hz, 3H); ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 74.4, 65.8, 55.8, 27.7, 7.4; ppm.

IR: 3387, 2972, 2938, 2097, 2884, 1461, 1281, 1143, 1058, 931 cm^{-1}

(*R*)-1-Azido-2-(((triethylsilyl) oxy) methyl) butan-2-ol **228**



228

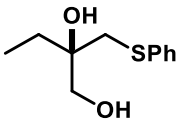
To a solution of **235** (100 mg, 0.69 mmol) in CH_2Cl_2 (3.5 mL) were added NEt_3 (0.26 mL, 2.7 eq., 1.86 mmol) and TESCl (0.15 mL, 1.3 eq., 0.9 mmol) at 0 °C. The reaction was stirred for 2 h at the same temperature and then quenched with sat. NH_4Cl. The aqueous phase was extracted with CH_2Cl_2 (3x), the combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation and the residue was purified by column chromatography (hexane/EtOAc, 10:1) to afford **228** (177 mg, 99%) as clear colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.54 (d, *J* = 9.8 Hz, 1H), 3.42 (d, *J* = 9.8 Hz, 1H), 3.30 (m, 2H), 2.47 (s, 1H), 1.53 (q, *J* = 7.5 Hz, 2H), 0.97 (t, *J* = 8.0 Hz, 9H), 0.92 (t, *J* = 7.5 Hz, 3H), 0.63 (q, *J* = 8.0 Hz, 6H); ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 74.3, 65.4, 55.1, 27.1, 7.2, 6.7, 4.3; ppm.

IR: 3465, 2956, 2878, 2102, 1460, 1279, 1240, 1094, 1007, 820 cm^{-1}

(*R*)-2-((Phenylthio) methyl) butane-1,2-diol **230**



230

To a solution of **225** (200 mg, 2 mmol) and thiophenol (2.6 ml, 1.3 eq., 1 M in Et_2O, 2.6 mmol) in DMF (4 mL) was added NaH (170 mg, 2.1 eq., 60% in mineral oil, 4.2 mmol) at r.t.. After stirring for 1.5 h, the suspension was quenched with water. The aqueous layer was extracted with Et_2O (3x), the combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc, 1:1) to afford **230** (358 mg, 85%) as clear colorless oil.

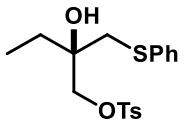
^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.41 (m, 2H), 7.25 (m, 3H), 3.55 (m, 2H), 3.23 (d, *J* = 13.4 Hz, 1H), 3.14 (d, *J* = 13.4 Hz, 1H), 2.47 (s, 1H), 1.85 (t, *J* = 6.1 Hz, 1H), 1.63 (m, 2H), 0.90 (t, *J* = 7.5 Hz, 3H); ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.6, 129.7, 129.1, 126.5, 74.7, 66.8, 41.2, 29.0, 7.7; ppm.

IR: 3368, 2967, 2936, 1584, 1481, 1438, 1055, 911, 737, 690 cm^{-1}

HRMS: m/z calculated for $C_{11}H_{16}O_2S_1Na^+$: 235.0769; found: 235.0769;

(*R*)-2-Hydroxy-2-((phenylthio) methyl) butyl 4-methylbenzenesulfonate **231**

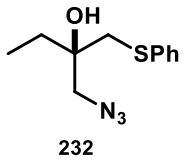


231

To a stirred solution of **230** (360 mg, 1.69 mmol), NEt_3 (0.7 mL, 3 eq., 5.06 mmol) and DMAP (21 mg, 0.1 eq., 0.17 mmol) in CH_2Cl_2 (3.5 mL) was added TsCl (611 mg, 1.9 eq., 3.2 mmol) at 0 °C. After stirring for 30 min at the same temperature the mixture was allowed to warm to room temperature. The reaction was stirred for further 4 h and afterwards treated with sat. NH_4Cl. The aqueous layer was extracted with diethyl ether (3x), the combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc, 3:1) to give **231** (545 mg, 88%) as clear colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (m, 2H), 7.28 (m, 7H), 3.95 (d, *J* = 9.8 Hz, 1H), 3.88 (d, *J* = 9.8 Hz, 1H), 3.17 (d, *J* = 13.6 Hz, 1H), 3.04 (d, *J* = 13.6 Hz, 1H), 2.44 (s, 3H), 2.32 (s, 1H), 1.61 (q, *J* = 7.5 Hz, 2H), 0.84 (t, *J* = 7.5 Hz, 3H); ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.0, 135.9, 132.4, 129.9, 129.8, 129.1, 128.0, 126.6, 73.2, 72.3, 41.3, 28.8, 21.6, 7.1; ppm.
IR: 3520, 2970, 1598, 1356, 1173, 1096, 977, 833, 739, 666 cm^{-1}
HRMS: m/z calculated for $C_{18}H_{22}O_4S_2Na^+$: 389.0857; found: 389.0859;

(*R*)-1-Azido-2-((phenylthio) methyl) butan-2-ol **232**



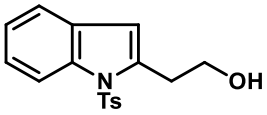
232

To a mixture of **231** (490 mg, 1.34 mmol) and Na_2CO_3 (285 mg, 2 eq., 2.68 mmol) in MeOH (6.7 mL) was added NaN_3 (432 mg, 5 eq., 6.65 mmol) in one protion. The mixture was stirred for 18 h at 60 °C and afterwards poured into water. The mixture was extracted with Et_2O (3x), the combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation and the remaining crude product **232** (254 mg, 80%), which was used in the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43 (m, 2H), 7.30 (m, 2H), 7.22 (1H), 3.39 (d, *J* = 12.3 Hz, 1H), 3.32 (d, *J* = 7.5 Hz, 1H), 3.18 (d, *J* = 13.4 Hz, 1H), 3.09 (d, *J* = 13.4 Hz, 1H), 2.32 (s, 1H), 1.64 (m, 2H), 0.91 (t, *J* = 7.5 Hz, 3H); ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.1, 130.0, 129.2, 126.7, 74.7, 57.1, 42.0, 29.7, 7.6; ppm.
IR: 3451, 2969, 2928, 2102, 1584, 1481, 1439, 1292, 740, 691 cm^{-1}

6.2.3. Experimental procedures of the third approach

2-(1-Tosyl-1*H*-indol-2-yl) ethan-1-ol **249**

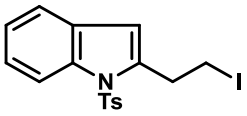


249

To a solution of **280** (500 mg, 1.34 mmol) in DMF (10 mL) were added 3-butyn-1-ol (0.15 mL, 1.5 eq., 2.01 mmol), NEt_3 (1.1 mL, 6 eq., 8.0 mmol) and CuI (25 mg, 0.1 eq., 0.13 mmol). The mixture was degassed and $PdCl_2(PPh_3)_2$ (47 mg, 0.05 eq., 0.07 mmol) was added. After stirring for 3 h at 70 °C, the resulting solution was poured into water. The aqueous layer was extracted with diethyl ether (3x), the combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc, 1:1) to afford **249** (405 mg, 96%) as clear colorless oil. The analytical data matches the data in literature.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.17 (m, 1H), 7.62 (m, 2H), 7.43 (m, 1H), 7.27 (m, 2H), 7.18 (m, 2H), 6.51 (s, 1H), 4.02 (dd, *J* = 12.2, 6.2 Hz, 2H), 3.29 (dt, *J* = 6.2, 0.8 Hz, 2H), 2.33 (s, 3H), 1.60 (m, 1H); ppm.

2-(2-Iodoethyl)-1-tosyl-1*H*-indole **248**

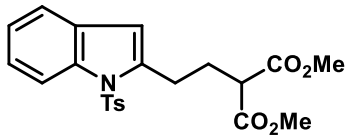


248

To a solution of **249** (800 mg, 2.54 mmol) in CH_2Cl_2 (25 mL) were added imidazole (190 mg, 1.1 eq., 2.79 mmol) and PPh_3 (699 mg, 1.05 eq., 2.66 mmol) at r.t.. The solution was cooled to 0 °C and iodine (708 mg, 1.1 eq., 2.79 mmol) was added in small portions. The mixture was stirred for 2 h at the same temperature and afterwards quenched with an aqueous $Na_2S_2O_3$ solution. The aqueous layer was extracted with diethyl ether (3x), the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc, 10:1) to afford **248** (856 mg, 91%) as orange oil. The analytical data matches the data in literature.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.17 (m, 1H), 7.61 (m, 2H), 7.46 (m, 1H), 7.28 (m, 2H), 7.19 (m, 2H), 6.51 (s, 1H), 3.54 (m, 4H), 2.33 (s, 3H); ppm.

Dimethyl 2-(2-(1-tosyl-1*H*-indol-2-yl) ethyl) malonate **250**



250

A mixture of dimethyl malonate (0.77 mL, 1.1 eq., 6.7 mmol) and K_2CO_3 (926 mg, 1.1 eq., 6.7 mmol) in DMF (12 mL) was placed in an ultrasonic bath for 15 min. Afterwards, **248** (2.6 g 6.1 mmol) was added and the mixture was stirred for 24 h at 40 °C. The reaction was quenched with water, the aqueous layer was extracted with diethyl ether (3x), the combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated by rotary evaporation. The residue was purified by column chromatography (hexane/EtOAc, 1:1) to yield **250** (2.65 g, 92%) as clear liquid.

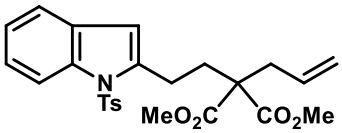
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 8.2 Hz, 1H), 7.59 (m, 2H), 7.41 (d, *J* = 7.6 Hz, 1H), 7.26 (m, 1H), 7.22 (m, 1H), 7.17 (m, 2H), 6.42 (s, 1H), 3.75 (s, 6H), 3.49 (t, *J* = 7.3 Hz, 1H), 3.07 (t, *J* = 7.5 Hz, 2H), 2.38 (q, *J* = 7.5 Hz, 2H), 2.32 (s, 3H); ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.5, 144.8, 140.1, 137.2, 135.9, 129.8, 129.6, 126.3, 124.2, 123.6, 120.3, 114.9, 109.8, 52.6, 50.9, 28.1, 26.7, 21.5; ppm.

IR: 1732, 1452, 1368, 1175, 1090, 1045, 750, 667, 590, 542 cm^{-1}

HRMS: m/z calculated for $C_{22}H_{23}O_6N_1S_1H^+$: 430.1324; found: 430.1317;

Dimethyl 2-allyl-2-(2-(1-tosyl-1*H*-indol-2-yl) ethyl) malonate **247**

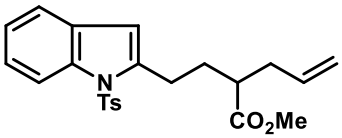


247

To a solution of **250** (2.65 g, 6.16 mmol) in THF (30 mL) was added NaH (370 mg, 1.5 eq., 60% in mineral oil, 9.2 mmol) at r.t.. After stirring for 15 min, allyl bromide (1.6 mL, 3 eq., 18.5 mmol) was added and the mixture was stirred for further 1.5 h at the same temperature. The reaction was quenched with sat. NH_4Cl, the aqueous layer was extracted with diethyl ether (3x), the combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc, 3:1) to afford **247** (2.8 g, 97%) as clear colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16 (d, *J* = 8.2 Hz, 1H), 7.58 (m, 2H), 7.40 (m, 1H), 7.23 (m, 2H), 7.17 (m, 2H), 6.42 (s, 1H), 5.69 (m, 1H), 5.11 (m, 2H), 3.75 (s, 6H), 2.94 (m, 2H), 2.77 (d, *J* = 7.4 Hz, 2H), 2.33 (m, 2H), 2.32 (s, 3H); ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.4, 144.7, 140.8, 137.2, 136.0, 132.2, 129.8, 129.7, 126.3, 124.1, 123.6, 120.2, 119.2, 114.8, 109.3, 57.4, 52.5, 37.3, 32.1, 23.9, 21.5; ppm.
IR: 1728, 1450, 1368, 1173, 1090, 812, 748, 667, 581, 542 cm^{-1}
HRMS: m/z calculated for $C_{25}H_{27}O_6N_1S_1H^+$: 470.1637; found: 470.1620;

Methyl 2-(2-(1-tosyl-1*H*-indol-2-yl) ethyl) pent-4-enoate **251**

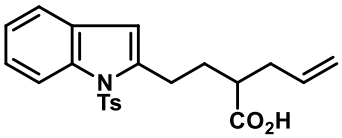


251

To a solution of **247** (2.8 g, 5.96 mmol) in DMSO (38 mL) were added water (0.27 mL) and LiCl (1 g, 4 eq., 23.9 mmol). The mixture was heated to 150 °C and stirred for 3 h. Afterwards, water was added and the aqueous phase was extracted with diethyl ether (3x). The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography (hexane/EtOAc, 1:1) to give **251** (1.72 g, 70%) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16 (d, *J* = 8.2 Hz, 1H), 7.60 (m, 2H), 7.41 (m, 1H), 7.23 (m, 2H), 7.17 (m, 2H), 6.39 (s, 1H), 5.75 (m, 1H), 5.06 (m, 2H), 3.69 (s, 3H), 3.00 (m, 2H), 2.59 (m, 1H), 2.42 (m, 1H), 2.32 (s, 3H), 2.29 (m, 1H), 2.03 (m, 2H); ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.6, 144.7, 141.1, 137.2, 136.0, 135.1, 129.8, 129.7, 126.2, 124.0, 123.5, 120.2, 117.1, 114.8, 109.3, 51.6, 44.7, 36.4, 31.0, 26.8, 21.5; ppm.
IR: 1730, 1450, 1366, 1173, 1090, 812, 748, 667, 585, 542 cm^{-1}
HRMS: m/z calculated for $C_{23}H_{25}O_4N_1S_1H^+$: 412.1583; found: 412.1580;

2-(2-(1-Tosyl-1*H*-indol-2-yl) ethyl) pent-4-enoic acid **254**



254

To a mixture of **251** (1.72 g, 4.17 mmol) in EtOH (8 mL) was added LiOH (21 mL, 10 eq., 2 M in water, 41.7 mmol). After stirring for 20 h at r.t., the mixture was quenched with aqueous 1 M HCl until the solution was acidic (pH= 0). The mixture was extracted with EtOAc (3x), the combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure to the crude product **254** (1.63 g, 98%) as clear colorless liquid, which was used in the next step without further purification.

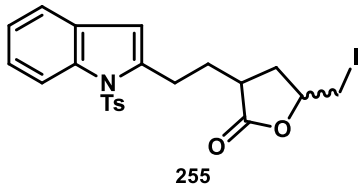
^{1}H NMR (400 MHz, CD_3OD): δ = 8.11 (d, *J* = 8.3 Hz, 1H), 7.60 (m, 2H), 7.41 (d, *J* = 7.6 Hz, 1H), 7.25 (m, 2H), 7.20 (m, 2H), 6.47 (s, 1H), 5.80 (m, 1H), 5.03 (d, *J* = 10.3 Hz, 1H), 3.05 (m, 2H), 2.51 (m, 1H), 2.41 (m, 1H), 2.30 (m, 1H), 1.99 (m, 2H); ppm.

^{13}C NMR (100 MHz, CD_3OD): δ = 178.9, 146.5, 142.6, 138.7, 137.2, 136.7, 131.4, 130.9, 127.3, 125.0, 124.8, 121.4, 117.3, 115.8, 110.6, 46.1, 37.5, 32.2, 27.9, 21.4; ppm.

IR: 3068, 2940, 1703, 1452, 1368, 1175, 1090, 579, 524 cm^{-1}

HRMS: m/z calculated for $C_{22}H_{22}O_4N_1S_1^-$: 396.1270; found: 396.1270;

5-(Iodomethyl)-3-(2-(1-tosyl-1*H*-indol-2-yl) ethyl) dihydrofuran-2(3*H*)-one **255**



255

To a mixture of **254** (1.63 g, 4.09 mmol) in MeCN (40 mL) and sat. $NaHCO_3$ (4.9 mL) was added iodine (3.74 g, 3.6 eq., 14.7 mmol) in small portions at 0 °C. The solution was stirred for 3 h at the same temperature and then quenched with aq. $Na_2S_2O_3$. The aqueous phase was extracted with diethyl ether (3x), the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc, 3:1) to yield **255** (2.1 g, 98%) as colorless oil in a 3:1 mixture of diastereomers.

Fr. 1 (minor):

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (d, *J* = 8.3 Hz, 1H), 7.60 (d, *J* = 8.1 Hz, 2H), 7.41 (m, 1H), 7.25 (m, 2H), 7.18 (d, *J* = 8.1 Hz, 2H), 6.46 (s, 1H), 4.62 (m, 1H), 3.38 (dd, d, *J* = 10.4, 4.5 Hz, 1H), 3.28 (dd, d, *J* = 10.4, 7.4 Hz, 1H), 3.17 (m, 2H), 2.82 (m, 1H), 2.33 (s, 3H), 2.26 (m, 3H), 2.04 (m, 1H); ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.0, 144.9, 140.2, 137.3, 135.8, 129.9, 129.6, 126.2, 124.2, 123.7, 120.3, 114.9, 110.0, 76.8, 38.8, 33.7, 31.0, 26.9, 21.6, 7.4; ppm.

HRMS: m/z calculated for $C_{22}H_{22}O_4N_1S_1I_1Na^+$: 546.0212; found: 546.0211;

Fr. 2 (major):

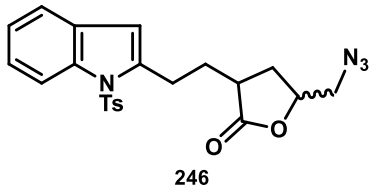
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 8.2 Hz, 1H), 7.60 (d, *J* = 8.2 Hz, 2H), 7.41 (d, *J* = 7.6 Hz, 1H), 7.24 (m, 2H), 7.19 (d, *J* = 8.1 Hz, 2H), 6.45 (s, 1H), 4.39 (m, 1H), 3.44 (dd, *J* = 10.5, 4.6 Hz, 1H), 3.29 (dd, d, *J* = 10.5, 7.4 Hz, 1H), 3.18 (m, 2H), 2.77 (m, 1H), 2.68 (ddd, *J* = 12.3, 8.9, 5.6 Hz, 1H), 2.34 (m, 1H), 2.33 (s, 3H), 2.01 (m, 1H), 1.68 (dt, *J* = 11.9, 10.0 Hz, 1H); ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.5, 144.9, 140.3, 137.3, 135.8, 129.9, 129.6, 126.2, 124.2, 123.7, 120.3, 114.9, 109.8, 76.7, 40.5, 35.6, 29.9, 26.7, 21.6, 6.8; ppm.

IR: 1771, 1452, 1366, 1173, 1090, 1005, 748, 669, 583, 544 cm^{-1}

HRMS: m/z calculated for $C_{22}H_{22}O_4N_1S_1I_1Na^+$: 546.0212; found: 546.0211;

5-(Azidomethyl)-3-(2-(1-tosyl-1*H*-indol-2-yl) ethyl) dihydrofuran-2(3*H*)-one **246**



246

To a solution of **255** (major, Fr. 2) (200 mg, 0.38 mmol) in DMSO (4 mL) was added NaN_3 (124 mg, 5 eq., 1.91 mmol) in one portion. After stirring for 1.5 h at 50 °C, the solution was treated with sat. $NaHCO_3$, the aqueous layer was extracted with diethyl ether (3x), the combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation and the residue was purified by column chromatography (hexane/EtOAc, 1:1) to afford **246** (156 mg, 94%) as slightly yellow clear liquid.

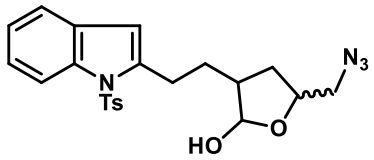
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 8.2 Hz, 1H), 7.60 (d, *J* = 8.2 Hz, 2H), 7.42 (d, *J* = 7.5 Hz, 1H), 7.24 (m, 2H), 7.18 (d, *J* = 8.2 Hz, 2H), 6.46 (s, 1H), 4.52 (m, 1H), 3.61 (dd, d, *J* = 13.3, 3.6 Hz, 1H), 3.45 (dd, d, *J* = 13.3, 5.2 Hz, 1H), 3.19 (m, 2H), 2.74 (m, 1H), 2.45 (ddd, *J* = 12.7, 9.0, 6.3 Hz, 1H), 2.35 (m, 1H), 2.33 (s, 3H), 2.01 (m, 1H), 1.83 (dt, *J* = 12.0, 1.8 Hz, 1H); ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.4, 144.9, 140.4, 137.3, 135.8, 129.9, 129.6, 126.2, 124.2, 123.7, 120.3, 114.9, 109.8, 76.3, 53.6, 39.7, 31.4, 30.0, 26.6, 21.5; ppm.

IR: 2104, 1771, 1452, 1366, 1173, 1119, 706, 669, 573, 544 cm^{-1}

HRMS: m/z calculated for $C_{22}H_{22}O_4N_4S_1H^+$: 439.1440; found: 439.1436;

5-(Azidomethyl)-3-(2-(1-tosyl-1*H*-indol-2-yl) ethyl) tetrahydrofuran-2-ol **253**



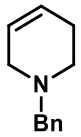
253

To a stirred solution of **246** (23 mg, 0.05 mmol) in CH_2Cl_2 (0.5 mL) was added DIBAL (0.16 mL, 3 eq., 1 M in hexane, 0.16 mmol) dropwise at -78 °C. After stirring for 1 h at the same temperature the mixture was poured into an aqueous solution of Na/K tartrate. The aqueous phase was extracted with CH_2Cl_2 (3x), the combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation to the crude product **253** in a 1:1 mixture of diastereoisomers (23 mg, 98%) as clear colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 8.4 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 7.9 Hz, 1H), 7.24 (m, 2H), 7.17 (d, *J* = 8.4 Hz, 2H), 6.41 (m, 1H), 5.32 (m, 1H), 4.50-4.19 (m, 1H), 3.44 (m, 1H), 3.28 (m, 1H), 3.06 (m, 2H), 2.32 (s, 3H), 2.27 (m, 2H), 2.09 (m, 1H), 1.99 (m, 1H), 1.85 (m, 1H), 1.70-1.41 (m, 1H); ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.8, 144.7, 141.7, 141.6, 137.3, 137.2, 136.1, 136.0, 129.8, 129.8, 129.7, 129.7, 126.2, 126.1, 124.1, 124.0, 123.7, 123.6, 120.2, 120.2, 114.9, 114.9, 109.5, 109.4, 98.9, 98.6, 78.3, 78.0, 56.1, 56.0, 46.5, 46.1, 32.0, 31.9, 29.7, 29.7, 27.7, 27.7, 21.5; ppm.

6.2.4. Experimental procedures of the fourth approach

1-Benzyl-1,2,3,6-tetrahydropyridine **265**

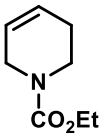


265

Benzyl chloride (36 mL, 1.03 eq., 320 mmol) was added to pyridine (25 mL, 310 mmol) and was crystallized for two days at r.t.. The resulting solid was heated to 140 °C for 1 h to complete the salt formation. Afterwards, the mixture was cooled to r.t. and solved in a 1:1 mixture of EtOH/H_2O (150 mL). The resulting solution was added dropwise to a stirred mixture of NaOH (25 g, 2.02 eq., 625 mmol) and $NaBH_4$ (14 g, 1.2 eq., 370 mmol) in EtOH/H_2O (1:1) (150 mL) at r.t.. After stirring for 12 h, the mixture was treated with water. The aqueous layer was extracted with diethyl ether (3x), the combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Vacuum distillation (0.2 mbar, 68-74 °C) of the residue afforded product **265** (39 g, 73%) as clear colorless oil. The analytical data matches the data in literature.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 (m, 4H), 7.29 (m, 1H), 5.79 (m, 1H), 5.69 (m, 1H), 3.62 (s, 2H), 3.01 (m, 2H), 2.59 (m, 1H), 2.55 (d, *J* = 5.6 Hz, 1H), 2.20 (m, 2H); ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.4, 129.2, 128.2, 127.0, 125.5, 125.2, 63.0, 52.8, 49.7, 26.2; ppm.
IR: 3030, 2911, 2798, 2750, 1659, 1492, 1454, 1361, 1133, 1036 cm^{-1}
HRMS: m/z calculated for $C_{12}H_{15}N_1H^+$: 174.1283; found: 174.1283;

Ethyl 3,6-dihydropyridine-1(2*H*)-carboxylate **256**

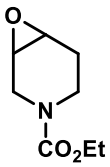


256

To a solution of **265** (39 g, 226 mmol) in toluene (110 mL) was added ethyl chloroformate (23.7 mL, 1.1 eq., 249 mmol) at r.t.. After stirring for 2.5 h under reflux, the resulting solution was cooled to r.t. and treated with a sat. $NaHCO_3$. The mixture was extracted with ethyl acetate (3x), the organic layer was washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography (hexane/EtOAc, 10:1) to give **256** (33 g, 95%) as clear colorless liquid. The analytical data matches the data in literature.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.82 (m, 1H), 5.64 (m, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.92 (qi, *J* = 2.8 Hz, 2H), 3.53 (t, *J* = 5.7 Hz, 2H), 2.13 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 3H); ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.8, 125.3, 124.3, 61.2, 43.4, 40.3, 25.0, 14.7; ppm.
IR: 2931, 2842, 1697, 1429, 1281, 1237, 1109, 1038, 769, 656 cm^{-1}
HRMS: m/z calculated for $C_8H_{13}O_2N_1H^+$: 156.1025; found: 156.1024;

Ethyl 7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate **266**

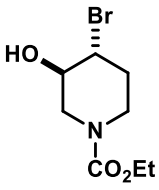


266

To a solution of **256** (33 g, 215 mmol) in $CHCl_3$ (540 mL) was added *m*CPBA (56 g, 1.5 eq., 323 mmol) in small portions. The reaction mixture was stirred for 18 h at r.t.. The suspension was neutralized with sat. $NaHCO_3$ and quenched with aq. $Na_2S_2O_3$, the aqueous layer was extracted with CH_2Cl_2 (3x), the combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation and the residue was purified by vacuum distillation (0.2 mbar, 95-100 °C) to yield **266** (32.7 g, 89%) as clear colorless oil. The analytical data matches the data in literature.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.12 (q, *J* = 7.1 Hz, 2H), 3.90 (m, 1H), 3.73 (m, 1H), 3.48 (m, 1H), 3.30 (m, 1H), 3.17 (m, 2H), 2.07 (m, 1H), 1.90 (m, 1H), 1.25 (t, *J* = 7.1 Hz, 3H); ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.7, 61.4, 50.6, 50.2, 42.3, 37.2, 24.3, 14.6; ppm.
IR: 3524, 2984, 1692, 1429, 1243, 1216, 1106, 1038, 798, 768 cm^{-1}
HRMS: m/z calculated for $C_8H_{13}O_3N_1Na^+$: 194.0793; found: 194.0788;

Ethyl 4-bromo-3-hydroxypiperidine-1-carboxylate **257**

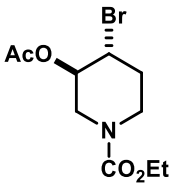


257

To a solution of **266** (32.7 g, 191 mmol) in $CHCl_3$ (320 mL) was added conc. HBr (48 wt%, 166 mL) at -50 °C over a period of 30 min. The resulting mixture was stirred vigorously for 3 h at the same temperature. Then water was added, the organic layer was extracted with CH_2Cl_2 (3x), neutralized with sat. $NaHCO_3$, washed with brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation to yield the crude product **257** (48 g, quant.) as clear slightly red liquid, which was used in the next step without further purification. The analytical data matches the data in literature.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.25 (ddd, *J* = 13.5, 4.4, 1.8 Hz, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.98 (ddd, *J* = 10.2, 8.2, 4.4 Hz, 1H), 3.94 (m, 1H), 3.72 (m, 1H), 3.01 (m, 1H), 2.94 (dd, *J* = 13.1, 8.5 Hz, 1H), 2.49 (bs, 1H), 2.32 (dq, *J* = 13.7, 3.2 Hz, 1H), 1.97 (m, 1H), 1.26 (t, *J* = 7.1 Hz, 3H); ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.6, 71.3, 61.8, 55.6, 48.2, 43.1, 33.6, 14.6; ppm.
IR: 3416, 2932, 1671, 1436, 1470, 1240, 1189, 968, 910, 767 cm^{-1}
HRMS: m/z calculated for $C_8H_{14}O_3N_1Br_1Na^+$: 274.0055; found: 274.0053;

Ethyl 3-acetoxy-4-bromopiperidine-1-carboxylate **267**



267

To a solution of **257** (48 g, 191 mmol) in pyridine (95 mL) was added acetic anhydride (52.4 mL, 2.9 eq., 554 mmol). After stirring for 18 h at r.t., the resulting solution was cooled to 0 °C and neutralized with 1 M $NaHSO_4$. The aqueous layer was extracted with diethyl ether (3x), the etheral phase was washed with $NaHCO_3$ and brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation to provide the crude product **267** (52 g, 93%) as clear brownish oil, which was used in the next step without further purification. The analytical data matches the data in literature.

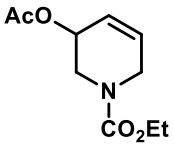
^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.91 (m, 1H), 4.15 (m, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.90 (dd, *J* = 14.1, 3.3 Hz, 1H), 3.55 (ddd, *J* = 13.6, 8.0, 3.6 Hz, 1H), 3.53 (dd, *J* = 14.0, 6.0 Hz, 1H), 3.50 (m, 1H), 2.31 (m, 1H), 2.08 (s, 3H), 1.94 (m, 1H), 1.25 (t, *J* = 7.1 Hz, 3H); ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.6, 155.6, 70.7, 61.7, 48.2, 44.3, 41.0, 31.6, 20.8, 14.6; ppm.

IR: 2983, 1743, 1698, 1471, 1429, 1219, 1193, 1046, 1026, 768 cm^{-1}

HRMS: m/z calculated for $C_{10}H_{16}O_4N_1Br_1H^+$: 294.0341; found: 294.0338;

Ethyl 3-acetoxy-3,6-dihydropyridine-1(2*H*)-carboxylate **258**



258

DBU (50 mL, 1.9 eq., 337 mmol) was added to compound **267** (52 g, 177 mmol) and stirred for 2 h at 90 °C. The resulting mixture was cooled to r.t., diluted with toluene and filtered to separate the precipitate. The solution was treated with sat. NH_4Cl, the aqueous phase was extracted with diethyl ether (3x), the combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation. The residue was purified by column chromatography (hexane/EtOAc, 3:1) to give **258** (29.8 g, 79%) as clear slightly yellow liquid. The analytical data matches the data in literature.

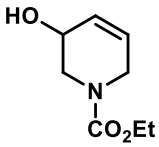
^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.92 (m, 1H), 5.87 (m, 1H), 5.20 (m, 1H), 4.16 (m, 3H), 3.82 (m, 2H), 3.53 (dd, *J* = 13.9, 3.9 Hz, 1H), 2.05 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H); ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5, 155.7, 130.1, 123.8, 65.5, 61.6, 44.5, 43.1, 21.1, 14.7; ppm.

IR: 2983, 1733, 1699, 1430, 1372, 1228, 1125, 1040, 1016, 769 cm^{-1}

HRMS: m/z calculated for $C_{10}H_{15}O_4N_1Na^+$: 236.0899; found: 236.0897;

Ethyl 3-hydroxy-3,6-dihydropyridine-1(2*H*)-carboxylate **268**

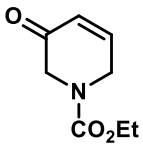


268

To a solution of **258** (29.8 g, 140 mmol) in EtOH (90 mL) was added a solution of NaOH in EtOH (0.2 M, 120 mL) over a period of 30 min at 0 °C. After stirring for 1 h at the same temperature, the resulting solution was quenched with sat. NH_4Cl, the mixture was extracted with diethyl ether (3x), the combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure to give the crude product **268** (24.5 g, 98%) as colorless liquid, which was used in the next step without further purification. The analytical data matches the data in literature.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.91 (m, 1H), 5.82 (m, 1H), 4.21 (m, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 4.01 (m, 1H), 3.84 (dq, *J* = 18.6, 2.2 Hz, 1H), 3.62 (m, 1H), 3.56 (m, 1H), 2.14 (bs, 1H), 1.26 (t, *J* = 7.1 Hz, 3H); ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.1, 128.3, 127.5, 126.7, 63.5, 61.6, 47.7, 43.2, 14.6; ppm.
IR: 3415, 2981, 2878, 1676, 1428, 1230, 1113, 1060, 1001, 769 cm^{-1}
HRMS: m/z calculated for $C_8H_{13}O_3N_1Na^+$: 194.0793; found: 194.0795;

Ethyl 3-oxo-3,6-dihydropyridine-1(2*H*)-carboxylate **62**

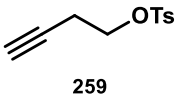


62

Jones reagent (6.4 mL, 1 eq., 19.3 mmol) was added to a mixture of **268** (3 g, 19.3 mmol) in aceton (95 mL) at 0 °C over a period of 30 min. The resulting mixture was quenched with MeOH and diluted with water. The aqueous phase was extracted with CH_2Cl_2 (3x), the combined organic phases were neutralized with sat. $NaHCO_3$, washed with water, brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation at **room temperature** to obtain the rather unstable crude product **62** (2.48 g, 84%) as clear colorless liquid, which was used immediately in the next step without further purification. The analytical data matches the data in literature.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.03 (m, 1H), 6.17 (dt, *J* = 10.2, 2.1 Hz, 1H), 4,27 (m, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 4.15 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H); ppm.

But-3-yn-1-yl 4-methylbenzenesulfonate **259**

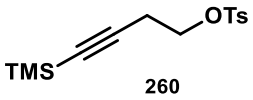


259

To a solution of but-3-yn-1-ol (10 g, 143 mmol) in CH_2Cl_2 (240 mL) were added NEt_3 (40 mL, 2 eq., 285 mmol) and TsCl (27.5 g, 1.01 eq., 144 mmol) at 0 °C. The solution was stirred for 18 h at r.t. and then quenched with sat. NH_4Cl. The mixture was extracted with CH_2Cl_2 (3x), the combined organic layers were neutralized with sat. $NaHCO_3$, washed with brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation to afford the crude product **259** (30 g, 94%) as clear colorless oil, which was used in the next step without further purification. The analytical data matches the data in literature.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (m, 2H), 7.35 (m, 2H), 4.10 (t, *J* = 7.0 Hz, 2H), 2.55 (dt, *J* = 7.0, 2.6 Hz, 2H), 2.44 (s, 3H), 1.97 (t, *J* = 2.6 Hz, 1H); ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.0, 132.8, 129.9, 128.0, 78.4, 70.7, 67.4, 21.6, 19.4; ppm.
IR: 3290, 1598, 1356, 1173, 1096, 976, 902, 814, 764, 661 cm^{-1}
HRMS: m/z calculated for $C_{11}H_{12}O_3S_1Na^+$: 247.0405; found: 247.0400;

4-(Trimethylsilyl) but-3-yn-1-yl 4-methylbenzenesulfonate **260**

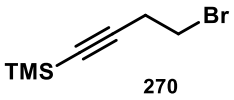


260

To a solution of **259** (30 g, 134 mmol) in THF (80 mL) was added *n*BuLi (59 mL, 1.1 eq., 2.5 M in hexane, 147 mmol) dropwise at -78 °C. The resulting dark brown solution was stirred for 1 h at -78 °C and TMSCl (22 mL, 1.3 eq., 174 mmol) was added. The solution was allowed to warm up to r.t. overnight and was then treated with sat. NH_4Cl. The aqueous layer was extracted with diethyl ether (3x), the combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure to afford the crude product **260** (37.7 g, 95%) as brown oil, which was used in the next step without further purification. The analytical data matches the data in literature.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (m, 2H), 7.34 (m, 2H), 4.07 (t, *J* = 7.3 Hz, 2H), 2.58 (t, *J* = 7.3 Hz, 2H), 2.44 (s, 3H), 0.11 (s, 9H); ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.9, 132.9, 129.9, 127.9, 100.3, 87.4, 67.5, 21.6, 20.7, -0.2; ppm.
IR: 2960, 2181, 1599, 1362, 1250, 1175, 978, 905, 840, 760 cm^{-1}
HRMS: m/z calculated for $C_{14}H_{20}O_3Si_1S_1Na^+$: 319.0800; found: 319.0798;

(4-Bromobut-1-yn-1-yl) trimethylsilane **270**

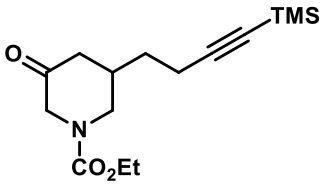


270

To a solution of **260** (37.7 g, 127 mmol) in acetone (160 mL) were added LiBr (23.2 g, 2.1 eq., 267 mmol) in small portions and TBAI (938 mg, 0.02 eq., 2.54 mmol). After stirring for 36 h at r.t., the resulting mixture was treated with sat. $NaHCO_3$. The mixture was extracted with diethyl ether (3x), the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Vacuum distillation (10 mbar, 62-64 °C) of the residue afforded product **270** (22.4 g, 86%) as clear colorless liquid. The analytical data matches the data in literature.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.43 (t, *J* = 7.5 Hz, 2H), 2.77 (t, *J* = 7.5 Hz, 2H), 0.16 (s, 9H); ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 103.2, 87.0, 29.2, 24.3, -0.1; ppm.
IR: 2960, 2179, 1250, 1212, 1055, 998, 837, 759, 699, 679 cm^{-1}

Ethyl 3-oxo-5-(4-(trimethylsilyl) but-3-yn-1-yl) piperidine-1-carboxylate **271**



271

To a stirred mixture of Mg turnings (856 mg, 2.4 eq., 35.2 mmol) in THF (20 mL) was added dropwise a solution of **270** (7.25 g, 2.4 eq., 35.2 mmol) in THF (60 mL) at r.t.. The resulting Grignard reagent was stirred for 1 h at 40 °C. Afterwards, the suspension was cooled to r.t. and LiCl (1.24 g, 2 eq., 29.4 mmol) was added. After stirring for 30 min at r.t., the resulting mixture was cooled to -48 °C and CuCN (1.58 g, 1.2 eq., 17.6 mmol) was added. The reaction was stirred for 1 h at the same temperature and then cooled to -70 °C. Thereafter, a solution of **62** (2.48 g, 14.7 mmol) in THF (10 mL) was added dropwise *via* syringe. After stirring at -70 °C for 1 h, the mixture was quenched with an aq. solution of NH_4Cl/NH_3 (8:1). The aqueous phase was extracted with diethyl ether (3x), the combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation. The residue was purified by column chromatography (hexane/EtOAc, 5:1) to give **271** (3.79 g, 87%) as clear slightly yellow liquid.

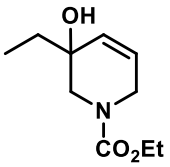
^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.15 (q, *J* = 7.0 Hz, 2H), 4.07 (d, *J* = 18.0 Hz, 1H), 3.97 (bm, 1H), 3.87 (bm, 1H), 3.21 (dd, *J* = 12.3, 8.8 Hz, 1H), 2.63 (dd, *J* = 14.7, 3.0 Hz, 1H), 2.30 (t, *J* = 7.2 Hz, 2H), 2.20 (m, 2H), 1.63 (m, 1H), 1.51 (m, 1H), 1.26 (t, *J* = 7.0 Hz, 3H), 0.13 (s, 9H); ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.8, 155.3, 105.6, 85.7, 61.9, 54.0, 46.9, 44.5, 33.3, 31.9, 17.2, 14.6, 0.1; ppm.

IR: 2959, 2176, 1697, 1431, 1248, 1225, 1209, 1120, 841, 760 cm^{-1}

HRMS: m/z calculated for $C_{15}H_{25}O_3N_1Si_1H^+$: 296.1687; found: 296.1682;

Ethyl 3-ethyl-3-hydroxy-3,6-dihydropyridine-1(2*H*)-carboxylate **273**

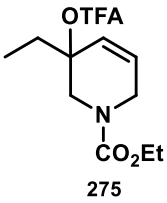


273

To a solution of **62** (1.71 g, 10.1 mmol) in Et_2O (51 mL) was added dropwise EtMgBr (8.1 mL, 2.4 eq., 3 M in Et_2O, 24.2 mmol) at -20 °C. The suspension was stirred for 40 min at the same temperature and then quenched with sat. NH_4Cl. The mixture was extracted with diethyl ether (3x), the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc, 3:1) to yield **273** (1.08 g, 54%) as clear colorless oil. The analytical data matches the data in literature.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.78 (m, 2H), 4.17 (m, 2H), 4.08 (d, *J* = 18.5 Hz, 1H) 3.78 (d, *J* = 18.5 Hz, 1H), 3.62 (m, 1H), 3.36 (d, *J* = 13.2 Hz, 1H), 1.77 (bs, 1H), 1.59 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H) 0.97 (t, *J* = 7.5 Hz, 3H); ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.1, 131.6, 125.7, 69.4, 61.6, 51.0, 43.4, 31.5, 14.7, 7.5; ppm.
IR: 3426, 2979, 2932, 2881, 1681, 1435, 1239, 1132, 1026, 768 cm^{-1}
HRMS: m/z calculated for $C_{10}H_{17}O_3N_1Na^+$: 222.1106; found: 222.1105;

Ethyl 3-ethyl-3-(2,2,2-trifluoroacetoxy)-3,6-dihydropyridine-1(2*H*)-carboxylate **275**

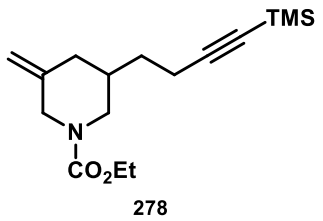


275

To a solution of **273** (85 mg, 0.43 mmol) in CH_2Cl_2 (2.2 mL) was added TFAA (0.12 mL, 2 eq., 0.85 mmol) at 0 °C. The solution was warmed to room temperature and stirred for 3 h. The reaction was quenched with sat. $NaHCO_3$, the mixture was extracted with CH_2Cl_2 (3x), the combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation to provide the crude product **275** (102 mg, 80%) as clear yellow oil, which was used in the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.64 (bs, 1H), 5.36 (bm, 1H), 4.31 (m, 1H), 4.16 (m, 3H), 3.65 (m, 1H), 3.38 (m, 1H), 2.10 (m, 2H), 1.09 (t, *J* = 7.5 Hz, 3H); ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.1, 155.4, 115.9, 114.1, 113.0, 70.6, 61.8, 45.8, 44.1, 27.2, 14.5, 11.6; ppm.
IR: 2975, 1779, 1702, 1430, 1380, 1235, 1149, 1101, 886, 769 cm^{-1}
HRMS: m/z calculated for $C_{12}H_{16}O_4N_1F_3Na^+$: 318.0929; found: 318.0929;

Ethyl 3-methylene-5-(4-(trimethylsilyl) but-3-yn-1-yl) piperidine-1-carboxylate **278**



278

A mixture of $MePPh_3Br$ (3.6 g, 3 eq., 10.1 mmol) in THF (34 mL) was placed in an ultrasonic bath for 10 min. Afterwards, KO*t*Bu (1.24 g, 3 eq., 10.1 mmol) was added in one portion and the mixture was stirred for 30 min at r.t.. Then a solution of **271** (1 g, 3.38 mmol) in THF was added and the resulting mixture was stirred for 1 h at the same temperature. The reaction was quenched with sat. NH_4Cl, the aqueous layer was extracted with diethyl ether (3x), the combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc, 10:1) to yield **278** (720 mg, 73%) as clear slightly yellow oil.

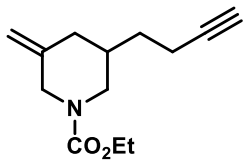
^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.87 (s, 1H), 4.78 (s, 1H), 4.13 (m, 3H), 3.74 (m, 2H), 2.98 (bs, 1H), 2.44 (dd, *J* = 13.4, 4.2 Hz, 1H), 2.27 (t, *J* = 7.4 Hz, 2H), 1.92 (dd, *J* = 12.5, 8.9 Hz, 1H), 1.77 (m, 1H), 1.53 (m, 1H), 1.43 (m, 1H), 1.25 (t, *J* = 7.1 Hz, 3H), 0.14 (s, 9H); ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.5, 141.2, 110.9, 106.7, 84.9, 61.3, 50.2, 48.3, 38.4, 35.7, 31.3, 17.4, 14.7, 0.1; ppm.

IR: 2960, 2174, 1679, 1428, 1248, 1221, 1119, 842, 761 640 cm^{-1}

HRMS: m/z calculated for $C_{16}H_{27}O_2N_1Si_1Na^+$: 316.1709; found: 316.1710;

Ethyl 3-(but-3-yn-1-yl)-5-methylenepiperidine-1-carboxylate **279**



279

To a solution of **278** (720 mg, 2.45 mmol) in MeOH (25 mL) was added K_2CO_3 (677 mg, 2 eq., 4.9 mmol). After stirring for 6 h at r.t., the mixture was treated with water, the aqueous layer was extracted with diethyl ether (3x), the combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation. The residue was purified by column chromatography (hexane/EtOAc, 10:1) to give **279** (483 mg, 89%) as clear colorless liquid.

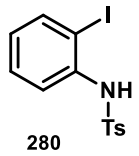
^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.87 (s, 1H), 4.77 (s, 1H), 4.12 (m, 3H), 3.77 (bm, 2H), 2.98 (bs, 1H), 2.43 (dd, *J* = 13.4, 4.0 Hz, 1H), 2.25 (dt, *J* = 7.3, 2.6 Hz, 2H), 1.95 (t, *J* = 2.5 Hz, 1H), 1.91 (m, 1H), 1.81 (m, 1H), 1.53 (m, 1H), 1.43 (m, 1H), 1.25 (t, *J* = 7.2 Hz, 3H); ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.5, 141.1, 111.0, 83.8, 68.7, 61.3, 50.2, 48.2, 38.4, 35.4, 31.1, 15.8, 14.7; ppm.

IR: 3300, 2984, 2933, 1694, 1429, 1221, 1120, 901, 767, 638 cm^{-1}

HRMS: m/z calculated for $C_{13}H_{19}O_2N_1Na^+$: 244.1313; found: 244.1318;

N-(2-Iodophenyl)-4-methylbenzenesulfonamide **280**

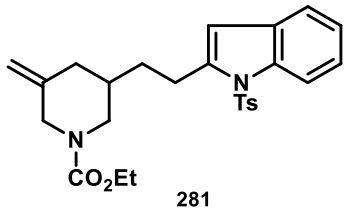


280

To a solution of *o*-iodoaniline (15 g, 68.5 mmol) in CH_2Cl_2 (140 mL) were added pyridine (16.6 mL, 3 eq., 205 mmol) and TsCl (13.3 g, 1.02 eq., 69.8 mmol) at r.t.. After stirring for 18 h at the same temperature, the resulting mixture was quenched with water, the aqueous layer was extracted with CH_2Cl_2 (3x), the combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation and the residue was purified by column chromatography (hexane/EtOAc, 5:1) to give **280** (22.5 g, 87%) as white solid. The analytical data matches the data in literature.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (m, 4H), 7.30 (m, 1H), 7.21 (m, 2H), 6.82 (ddd, *J* = 15.4, 7.4, 1.6 Hz, 1H), 6.80 (bs, 1H), 2.38 (s, 3H); ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.2, 139.1, 137.5, 135.9, 129.6, 129.5, 127.4, 126.8, 122.4, 92.3, 21.6; ppm.
IR: 3301, 1473, 1395, 1336, 1162, 1091, 1015, 911, 813, 753 cm^{-1}
HRMS: m/z calculated for $C_{13}H_{12}O_2N_1S_1I_1Na^+$: 395.9531; found: 395.9537;

Ethyl 3-methylene-5-(2-(1-tosyl-1*H*-indol-2-yl) ethyl) piperidine-1-carboxylate **281**

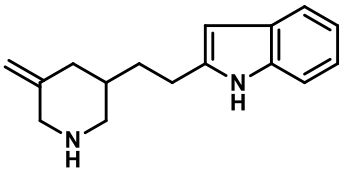


281

To a solution of **279** (500 mg, 2.26 mmol) in DMF (8 mL) were added **280** (886 mg, 1.1 eq., 2.37 mmol) and NEt_3 (0.94 mL, 3 eq., 6.8 mmol). The mixture was degassed followed by addition of CuI (43 mg, 0.1 eq., 0.23 mmol) and $PdCl_2(PPh_3)_2$ (79 mg, 0.05 eq., 0.11 mmol). After stirring for 3 h at 70 °C, the resulting solution was poured into sat. NH_4Cl, the aqueous layer was extracted with diethyl ether (3x), the combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc, 3:1) to afford **281** (939 mg, 89%) as brown oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 8.4 Hz, 1H), 7.60 (d, *J* = 8.2 Hz, 2H), 7.40 (d, *J* = 7.5 Hz, 1H), 7.22 (m, 2H), 7.18 (d, *J* = 8.2 Hz, 2H), 6.39 (s, 1H), 4.87 (s, 1H), 4.78 (s, 1H), 4.18 (d, *J* = 14.2 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.90 (bm, 1H), 3.66 (d, *J* = 13.3 Hz, 1H), 3.04 (t, *J* = 7.4 Hz, 2H), 2.98 (bm, 1H), 2.46 (d, *J* = 13.3 Hz, 1H), 2.33 (s, 3H), 1.97 (dd, *J* = 13.3, 8.3 Hz, 1H), 1.72 (m, 3H), 1.26 (t, *J* = 7.1 Hz, 3H); ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.5, 144.7, 141.7, 141.4, 137.2, 136.0, 129.8, 129.7, 126.2, 124.0, 123.6, 120.1, 114.9, 110.9, 109.1, 61.3, 50.3, 48.6, 38.9, 36.3, 32.3, 26.5, 21.6, 14.7; ppm.
IR: 2934, 1695, 1452, 1369, 1222, 1175, 1119, 1092, 749, 667 cm^{-1}
HRMS: m/z calculated for $C_{26}H_{30}O_4N_2S_1Na^+$: 489.1824; found: 489.1820;

2-(2-(5-methylenepiperidin-3-yl) ethyl)-1*H*-indole **282**

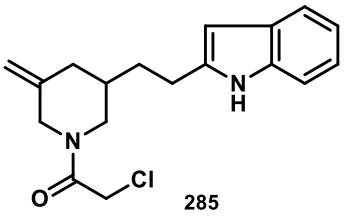


282

To a mixture of **281** (500 mg, 1.07 mmol) in ethylene glycol (11 mL) were added KOH (1.2 g, 20 eq., 21.5 mmol) and hydrazine (0.34 mL, 10 eq., 10.7 mmol). The mixture was stirred for 4 h at 140 °C, cooled to r.t. and treated with water. The mixture was extracted with CH_2Cl_2 (3x), the combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation to the crude product **282** (245 mg, 95%) as chewy oil, which was used in the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (bs, 1H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.30 (d, *J* = 7.9 Hz, 1H), 7.09 (m, 2H), 6.24 (s, 1H), 4.72 (s, 1H), 4.68 (s, 1H), 3.67 (d, *J* = 13.4 Hz, 1H), 3.18 (d, *J* = 13.4 Hz, 1H), 3.11 (d, *J* = 12.8 Hz, 1H), 2.79 (t, *J* = 7.4 Hz, 2H), 2.48 (m, 2H), 1.95 (m, 2H), 1.66 (m, 3H); ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.5, 139.4, 135.9, 128.8, 121.0, 119.8, 119.7, 110.3, 108.5, 99.6; 53.1, 51.8, 39.6, 39.2, 33.1, 25.5; ppm.
IR: 3402, 3142, 3071, 2916, 1456, 1288, 1097, 902, 782, 748 cm^{-1}
HRMS: m/z calculated for $C_{16}H_{20}N_2H^+$: 241.1705; found: 241.1705;

1-(3-(2-(1*H*-indol-2-yl) ethyl)-5-methylenepiperidin-1-yl)-2-chloroethan-1-one **285**

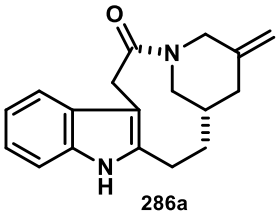


285

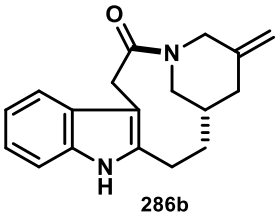
To a solution of **282** (245 mg, 1.02 mmol) in CH_2Cl_2 (3.5 mL) were added at 0 °C NEt_3 (0.14 mL, 1 eq., 1.02 mmol) and $(ClAc)_2O$ (261 mg, 1.5 eq., 1.53 mmol). The solution was stirred for 30 min at the same temperature and quenched with water. The aqueous phase was extracted with CH_2Cl_2 (3x), the combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation. The residue was purified by column chromatography (hexane/EtOAc, 1:1) to give **285** (254 mg, 79%) as chewy yellow oil.

^{1}H NMR (400 MHz, T = 370 K, DMSO-d^6): δ = 10.58 (s, 1H), 7.39 (d, *J* = 7.7 Hz, 1H), 7.28 (d, *J* = 7.9 Hz, 1H), 6.98 (dt, *J* = 7.9, 1.2 Hz, 1H), 6.91 (dt, *J* = 7.7, 1.2 Hz, 1H), 6.15 (s, 1H), 4.91 (s, 1H), 4.81 (s, 1H), 4.30 (d, *J* = 12.9 Hz, 1H), 4.24 (d, *J* = 12.9 Hz, 1H), 3.79 (bm, 2H), 3.56 (bs, 1H), 3.07 (dd, *J* = 13.2, 8.2 Hz, 1H), 2.80 (t, *J* = 7.4 Hz, 2H), 2.48 (m, 1H), 2.05 (m, 1H), 1.68 (m, 3H); ppm.
^{13}C NMR (100 MHz, T = 298 K, $CDCl_3$, two rotamers): δ = 165.5, 164.8, 140.2, 140.0, 139.2, 136.0, 136.0, 128.6, 121.2, 120.9, 119.8, 119.7, 119.6, 119.4, 112.1, 112.1, 110.6, 110.5, 99.6, 99.3, 53.2, 51.2, 48.7, 46.7, 46.0, 41.2, 41.0, 39.0, 38.7, 36.9, 35.7, 32.1, 25.5, 25.4; ppm.
IR: 3397, 3302, 2928, 1638, 1457, 1287, 1234, 905, 784, 750 cm^{-1}
HRMS: m/z calculated for $C_{18}H_{21}O_1N_2Cl_1Na^+$: 339.1240; found: 339.1233;

5-Methylene-1,4,5,6,7,8,9,10-octahydro-2*H*-3,7-methano[1]azacycloundecino[5,4-b] indol-2-one **286a** and **286b**



286a



286b

A mixture of **285** (120 mg, 0.38 mmol) and Na_2CO_3 (120 mg, 3 eq., 1.14 mmol) in MeOH (42 mL) and water (21 mL) was placed in a quarz vessel. The vessel was sonificated under a nitrogen atmosphere for 30 min and then irradiated (λ=254 nm) for 1 h at r.t.. Afterwards, the methanol was evaporated under reduced pressure and the residue was diluted with $NaHCO_3$. The aqueous layer was extracted with diethyl ether (3x), the combined organic phases were washed with brine, dried over $MgSO_4$ and the solvent was removed by rotary evaporation. The residue was purified by column chromatography (hexane/EtOAc, 1:1) to afford starting material **285** (24 mg, 20%), and the two separable amide rotamers **286** Fr.1 (18 mg, 17%) and Fr. 2 (23 mg, 22%).

Fr. 1:

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.94 (bs, 1H), 7.87 (m, 1H), 7.25 (m, 1H), 7.13 (m, 2H), 4.83 (dd, *J* = 14.8, 1.5 Hz, 1H), 4.72 (m, 1H), 4.59 (m, 1H), 4.58 (s, 1H), 4.09 (d, *J* = 13.9 Hz, 1H), 3.80 (d, *J* = 13.9 Hz, 1H), 3.48 (d, *J* = 14.8 Hz, 1H), 3.24 (m, 1H), 2.90 (m, 1H), 2.68 (dd, *J* = 14.3, 9.1 Hz, 1H), 2.18 (m, 2H), 1.46 (m, 3H); ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.3, 142.0, 134.7, 132.7, 129.9, 121.9, 120.2, 119.7, 112.6, 110.1, 107.3, 51.0, 50.8, 41.1, 40.5, 32.6, 28.3, 25.6; ppm.

IR: 3275, 2930, 1628, 1459, 1418, 1338, 1236, 1101, 905, 732 cm^{-1}

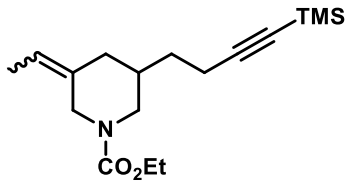
HRMS: m/z calculated for $C_{18}H_{20}O_1N_2Na^+$: 303.1473; found: 303.1474;

Fr. 2:

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.80 (bs, 1H), 7.66 (m, 1H), 7.22 (m, 1H), 7.10 (m, 2H), 5.08 (d, *J* = 14.0 Hz, 1H), 4.85 (s, 1H), 4.72 (s, 1H), 4.69 (m, 1H), 4.02 (d, *J* = 14.3 Hz, 1H), 3.66 (d, *J* = 14.3 Hz, 1H), 3.35 (dd, *J* = 14.2, 2.3 Hz, 1H), 3.20 (d, *J* = 13.7 Hz, 1H), 2.79 (m, 2H), 2.50 (m, 1H), 2.09 (m, 2H), 1.89 (m, 1H), 1.54 (m, 1H); ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.1, 138.8, 137.3, 134.4, 129.6, 121.5, 119.9, 118.2, 113.3, 110.1, 105.1, 48.9, 47.7, 39.3, 35.8, 30.9, 29.3, 23.1; ppm.
IR: 3249, 2933, 1611, 1466, 1345, 1266, 1230, 1093, 898, 736 cm^{-1}
HRMS: m/z calculated for $C_{18}H_{20}O_1N_2H^+$: 281.1654; found: 281.1654;

Ethyl 3-ethylidene-5-(4-(trimethylsilyl) but-3-yn-1-yl) piperidine-1-carboxylate **261**

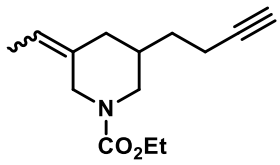


261

A mixture of $EtPPh_3Br$ (4.2 g, 3 eq., 10.1 mmol) in THF (34 mL) was placed in an ultrasonic bath for 10 min. Afterwards, KO*t*Bu (1.24 g, 3 eq., 10.1 mmol) was added in one portion and the mixture was stirred for 30 min at r.t.. Then, a solution of **271** (1 g, 3.38 mmol) in THF was added and the resulting mixture was stirred for 1 h at r.t.. The reaction was quenched with sat. NH_4Cl, the aqueous layer was extracted with diethyl ether (3x), the combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc, 10:1) to yield **261** (777 mg, 75%) as clear colorless oil in a 2:1 mixture of (*Z*/*E*) double bond isomers.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.43 (m, 1H (mi)), 5.26 (q, *J* = 6.8 Hz, 2H (ma)), 4.31 (bm, 2H (ma)), 4.12 (m, 6H (ma,mi)), 4.01 (d, *J* = 13.8 Hz, 1H (mi)), 3.71 (bm, 6H (ma,mi)), 2.99 (bm, 3H (ma,mi)), 2.53 (m, 1H (mi)), 2.36 (dd, *J* = 13.4, 4.1 Hz, 2H (ma)), 2.26 (m, 6H (ma,mi)), 1.86 (m, 3H (ma,mi)), 1.71 (m, 3H (ma,mi)), 1.66 (d, *J* = 6.8 Hz, 6H (ma)), 1.59 (d, *J* = 6.8 Hz, 3H (mi)), 1.50 (m, 3H (ma,mi)), 1.41 (m, 3H (ma,mi)), 1.25 (m, 9H (ma,mi)), 0.14 (s, 27H (ma,mi)); ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.6, 155.5, 132.1, 119.8, 106.9, 106.7, 84.9, 84.8, 61.2, 61.1, 51.8, 48.9, 48.8, 39.9, 36.0, 31.4, 17.5, 17.4, 14.7, 12.8, 12.6, 0.1; ppm.
IR: 2960, 2174, 1697, 1428, 1248, 1204, 1123, 839, 759, 697 cm^{-1}
HRMS: m/z calculated for $C_{17}H_{29}O_2N_1Si_1Na^+$: 330.1865; found: 330.1863;

Ethyl 3-(but-3-yn-1-yl)-5-ethylidenepiperidine-1-carboxylate **287**



287

To a solution of **261** (777 mg, 2.53 mmol) in MeOH (25 mL) was added K_2CO_3 (691 mg, 2 eq., 5 mmol). After stirring for 5 h at r.t., the mixture was treated with water, the aqueous layer was extracted with diethyl ether (3x), the combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation. The residue was purified by column chromatography (hexane/EtOAc, 10:1) to give **287** (570 mg, 96%) as clear colorless liquid.

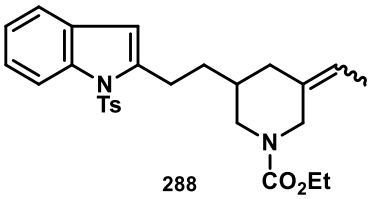
^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.43 (m, 1H (mi)), 5.26 (q, *J* = 6.8 Hz, 2H (ma)), 4.30 (bm, 2H (ma)), 4.12 (m, 6H (ma,mi)), 3.99 (d, *J* = 13.8 Hz, 1H (mi)), 3.71 (bm, 6H (ma,mi)), 2.99 (bm, 3H (ma,mi)), 2.51 (m, 1H (mi)), 2.35 (dd, *J* = 13.2, 4.0 Hz, 2H (ma)), 2.23 (m, 6H (ma,mi)), 1.94 (m, 3h (ma,mi)), 1.86 (m, 3H (ma,mi)), 1.76 (m, 3H (ma,mi)), 1.65 (d, *J* = 6.7 Hz, 6H (ma)), 1.59 (d, *J* = 6.8 Hz, 3H (mi)), 1.50 (m, 3H (ma,mi)), 1.42 (m, 3H (ma,mi)), 1.24 (m, 9H (ma,mi)); ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.6, 155.5, 132.1, 120.0, 84.0, 83.9, 68.7, 68.6, 61.3, 61.2, 51.8, 48.9, 48.8, 44.3, 39.9, 35.7, 35.0, 31.8, 31.2, 16.0, 15.9, 14.7, 12.8, 12.6; ppm.

IR: 3302, 2929, 1692, 1428, 1247, 1229, 1204, 1124, 766, 632 cm^{-1}

HRMS: m/z calculated for $C_{14}H_{21}O_2N_1H^+$: 236.1651; found: 236.1651;

Ethyl 3-ethylidene-5-(2-(1-tosyl-1*H*-indol-2-yl) ethyl) piperidine-1-carboxylate **288**



288

To a solution of **287** (570 mg, 2.42 mmol) in DMF (10 mL) were added **280** (948 mg, 1.05 eq., 2.54 mmol) and NEt_3 (1.34 mL, 4 eq., 9.7 mmol). The mixture was degassed followed by addition of CuI (46 mg, 0.1 eq., 0.24 mmol) and $PdCl_2(PPh_3)_2$ (85 mg, 0.05 eq., 0.12 mmol). After stirring for 3 h at 70 °C, the resulting solution was poured into sat. NH_4Cl, the aqueous layer was extracted with diethyl ether (3x), the combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc, 3:1) to yield **288** (1.03 g, 83%) as brown oil.

Spectroscopic data of the major (*Z*)-DB isomer:

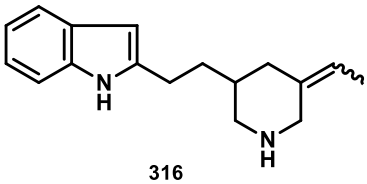
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16 (d, *J* = 8.3 Hz, 1H), 7.60 (d, *J* = 8.2 Hz, 2H), 7.40 (m, 1H), 7.23 (m, 2H), 7.18 (d, *J* = 8.2 Hz, 2H), 6.38 (s, 1H), 5.26 (q, *J* = 6.9 Hz, 1H), 4.42 (d, *J* = 14.1 Hz, 1H), 4.13 (m, 2H), 3.91 (bm, 1H), 3.58 (bm, 1H), 3.02 (t, *J* = 7.3 Hz, 2H), 2.98 (bm, 1H), 2.38 (d, *J* = 13.7 Hz, 1H), 2.32 (s, 3H), 1.92 (m, 1H), 1.67 (m, 6H), 1.27 (m, 3H); ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.6, 144.7, 141.9, 137.3, 136.1, 129.8, 129.8, 126.2, 123.9, 123.5, 120.1, 114.9, 109.1, 61.3, 49.3, 44.3, 40.3, 36.5, 32.3, 26.4, 21.5, 14.7, 12.8; ppm.

IR: 2930, 1694, 1452, 1368, 1246, 1175, 1121, 1092, 579, 544 cm^{-1}

HRMS: m/z calculated for $C_{27}H_{32}O_4N_2S_1H^+$: 481.2161; found: 481.2162;

2-(2-(5-Ethylidenepiperidin-3-yl) ethyl)-1*H*-indole **316**



316

To a mixture of **288** (1 g, 2.08 mmol) in ethylene glycol (10 mL) were added KOH (2.33 g, 20 eq., 41.6 mmol) and hydrazine (0.66 mL, 10 eq., 20.8 mmol). The mixture was stirred for 4 h at 140 °C, cooled to r.t. and treated with water. The mixture was extracted with CH_2Cl_2 (3x), the combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation to obtain the crude product **316** (518 mg, 98%) as chewy oil, which was used in the next step without further purification.

Spectroscopic data of the major (*Z*)-DB isomer:

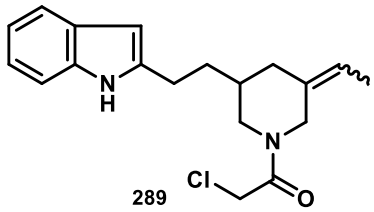
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.24 (s, 1H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.30 (d, *J* = 7.8 Hz, 1H), 7.08 (m, 2H), 6.22 (s, 1H), 5.22 (q, *J* = 6.7 Hz, 1H), 3.68 (m, 1H), 3.15 (d, *J* = 12.0 Hz, 1H), 3.09 (d, *J* = 13.5 Hz, 1H), 2.92 (m, 1H), 2.75 (t, *J* = 7.5 Hz, 2H), 2.52 (m, 1H), 2.35 (m, 1H), 1.87 (m, 1H), 1.66 (m, 3H), 1.59 (d, *J* = 6.7 Hz, 3H); ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.4, 135.9, 128.8, 121.0 (2x), 119.7, 119.6, 118.9, 110.4, 99.4, 51.5, 45.8, 40.9, 38.2, 29.7, 12.7; ppm.

IR: 3404, 3149, 3054, 2915, 1550, 1456, 1287, 1098, 781, 748 cm^{-1}

HRMS: m/z calculated for $C_{17}H_{22}N_2H^+$: 255.1861; found: 255.1859;

1-(3-(2-(1*H*-Indol-2-yl) ethyl)-5-ethylidenepiperidin-1-yl)-2-chloroethan-1-one **289**

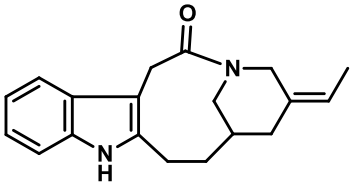


289

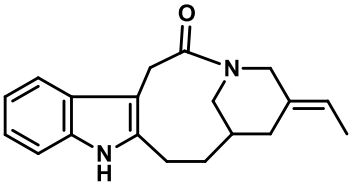
To a solution of **316** (1 g, 3.93 mmol) in CH_2Cl_2 (3.5 mL) were added NEt_3 (0.54 mL, 1 eq., 3.93 mmol) and $(ClAc)_2O$ (2.02 g, 3 eq., 11.8 mmol) at 0 °C. The solution was stirred for 30 min at the same temperature and quenched with water. The aqueous phase was extracted with CH_2Cl_2 (3x), the combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation. The residue was purified by column chromatography (hexane/EtOAc, 1:1) to give **289** (1.18 g, 89%) as chewy yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$, two rotamers): δ = 8.46 (s, 2H (ma)), 8.11 (s, 1H (mi)), 7.52 (m, 3H (ma,mi)), 7.31 (m, 3H (ma,mi)), 7.08 (m, 6H (ma,mi)), 6.26 (s, 1H (mi)), 6.22 (s, 2H (ma)), 5.44 (q, *J* = 6.7 Hz, 1H (mi)), 5.30 (q, *J* = 6.7 Hz, 2H (ma)), 4.14 (m, 6H (ma,mi)), 3.93 (m, 7H (ma,mi)), 3.73 (m, 1H (mi)), 3.44 (d, *J* = 14.3 Hz, 1H (mi)); 3.32 (m, 2H (ma)), 2.99 (dd, *J* = 13.2, 8.9 Hz, 1H (mi)), 2.81 (m, 6H (ma,mi)), 2.41 (m, 2H (mi)), 1.99 (m, 3H (ma,mi)), 1.66 (m, 19H (ma,mi)); ppm.
^{13}C NMR (100 MHz, $CDCl_3$, two rotamers): δ = 168.9, 165.6, 165.5, 164.9, 164.7, 139.3, 138.7, 136.1, 136.0, 131.5, 130.9, 128.7, 121.5, 121.3, 121.1, 120.9, 120.7, 119.8, 119.7, 119.5, 110.6, 110.5, 99.8, 99.4, 54.9, 51.8, 50.3, 47.4, 47.0, 43.0, 41.3, 41.1, 40.5, 40.2, 37.1, 36.5, 35.8, 35.4, 32.4, 32.4, 32.3, 25.6, 25.5, 13.1, 12.7; ppm.
IR: 3300, 2919, 1742, 1637, 1457, 1287, 1242, 1144, 784, 749 cm^{-1}
HRMS: m/z calculated for $C_{19}H_{23}O_1N_2Cl_1H^+$: 353.1397; found: 353.1395;

(*Z*)-5-Ethylidene-1,4,5,6,7,8,9,10-octahydro-2*H*-3,7-methano[1]azacycloundecino[5,4-b]indol-2-one **290** and (*E*)-5-Ethylidene-1,4,5,6,7,8,9,10-octahydro-2*H*-3,7-methano[1]azacycloundecino[5,4-b]indol-2-one **291**



290



291

A mixture of **289** (250 mg, 0.76 mmol) and Na_2CO_3 (240 mg, 3 eq., 2.27 mmol) in MeOH (84 mL) and water (42 mL) was placed in a quarz vessel. The vessel was sonificated under a nitrogen atmosphere for 30 min and then irradiated (λ=254 nm) at r.t. for 1 h. Afterwards, the methanol was evaporated under reduced pressure and the residue was diluted with $NaHCO_3$. The aqueous layer was extracted with diethyl ether (3x), the combined organic phases were washed with brine, dried over $MgSO_4$ and the solvent was removed by rotary evaporation. The residue was purified by column chromatography (hexane/EtOAc, 1:1) to afford starting material **289** (72 mg, 29%) and the desired products **290** (50 mg, 22%) and **291** (20 mg, 9%).

Fr. 1 (major **290** (*Z*)-DB):

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (bs, 1H), 7.67 (m, 1H), 7.26 (m, 1H), 7.13 (m, 2H), 5.49 (bd, *J* = 14.1 Hz, 1H), 5.23 (bq, *J* = 6.8 Hz, 1H), 4.67 (bd, *J* = 14.1 Hz, 1H), 4.04 (d, *J* = 14.3 Hz, 1H), 3.71 (d, *J* = 14.3 Hz, 1H), 3.39 (dd, *J* = 14.1, 2.8 Hz, 1H), 3.01 (d, *J* = 14.1 Hz, 1H), 2.81 (m, 2H), 2.52 (m, 1H), 2.05 (m, 1H), 2.03 (m, 1H), 1.89 (m, 1H), 1.61 (d, *J* = 1.3 Hz, 3H), 1.55 (m, 1H); ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.0, 137.2, 134.2, 129.7 (2x), 121.8, 121.4, 119.8, 118.2, 110.1, 105.2, 48.2, 43.2, 40.7, 35.8, 31.0, 29.6, 23.2, 13.1; ppm.

IR: 3285, 2922, 2855, 1632, 1458, 1240, 1018, 908, 735, 669 cm^{-1}

HRMS: m/z calculated for $C_{19}H_{22}O_1N_2H^+$: 295.1810; found: 295.1815;

Fr. 2 (minor **291** (*E*)-DB):

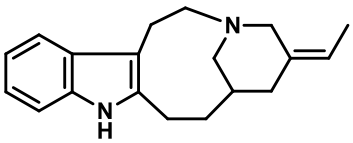
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (bs, 1H), 7.67 (m, 1H), 7.21 (m, 1H), 7.10 (m, 2H), 5.43 (m, 1H), 4.95 (m, 1H), 4.69 (m, 1H), 4.01 (d, *J* = 14.3 Hz, 1H), 3.64 (d, *J* = 14.3 Hz, 1H), 3.39 (dd, *J* = 14.1, 2.6 Hz, 1H), 3.17 (d, *J* = 13.5 Hz, 1H), 2.79 (m, 2H), 2.44 (m, 1H), 2.19 (m, 1H), 2.10 (m, 1H), 1.87 (m, 1H), 1.54 (m, 1H), 1.50 (dt, *J* = 6.8, 1.5 Hz, 3H); ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9, 137.3, 134.2, 129.8, 129.7, 122.7, 121.4, 119.8, 118.3, 110.1, 105.3, 50.7, 48.4, 36.1, 32.6, 30.9, 29.3, 23.1, 12.5; ppm.

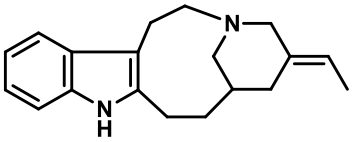
IR: 3261, 2927, 1613, 1465, 1329, 1232, 1164, 1101, 1011, 739 cm^{-1}

HRMS: m/z calculated for $C_{19}H_{22}O_1N_2H^+$: 295.1810; found: 295.1817;

(*Z*)-5-Ethylidene-1,4,5,6,7,8,9,10-octahydro-2*H*-3,7-methano[1]azacycloundecino[5,4-b]indole **292a** and (*E*)-5-Ethylidene-1,4,5,6,7,8,9,10-octahydro-2*H*-3,7-methano[1]azacycloundecino[5,4-b]indole **292b**



(*Z*)-**292a**



(*E*)-**292b**

To a mixture of **290** and **291** (36 mg, 0.12 mmol) in THF (4 mL) was added LAH (0.24 mL, 2 eq., 1 M in THF, 0.24 mmol) at 0 °C. After stirring for 1 h at 50 °C, the solution was cooled to 0 °C and poured into an aqueous solution of Na/K tartrate. The aqueous phase was extracted with CH_2Cl_2 (3x), the combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation to obtain the rather unstable crude products **292a** and **292b** (30 mg, 89%) as clear colorless oils, which was used in the next step without further purification.

(*Z*)-DB **292a**:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (bs, 1H), 7.48 (m, 1H), 7.27 (m, 1H), 7.08 (m, 2H), 5.13 (q, *J* = 6.7 Hz, 1H), 3.40 (d, *J* = 12.9 Hz, 1H), 3.30 (dd, *J* = 14.0, 11.2 Hz, 1H), 2.93 (m, 4H), 2.68 (dd, *J* = 14.7, 7.5 Hz, 1H), 2.46 (m, 2H), 2.16 (m, 2H), 2.02 (m, 1H), 1.90 (m, 1H), 1.82 (m, 1H), 1.74 (m, 1H), 1.48 (d, *J* = 6.7 Hz, 3H); ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.3, 135.6, 135.1, 128.8, 120.5, 118.7, 117.6, 117.5, 110.5, 109.3, 56.1, 52.7, 52.4, 38.5, 33.7, 32.4, 24.6, 22.5, 12.7; ppm.

IR: 3360, 2922, 2856, 2782, 1631, 1463, 1437, 1335, 908, 739 cm^{-1}

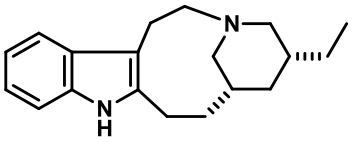
HRMS: m/z calculated for $C_{19}H_{24}N_2H^+$: 281.2018; found: 281.2020;

(*E*)-DB **292b**:

Due to the instability of the product it was not possible to obtain defined analytical data.

HRMS: m/z calculated for $C_{19}H_{24}N_2H^+$: 281.2018; found: 281.2022;

(20*R*)-15,20-Dihydro-cleavamine (**17**)

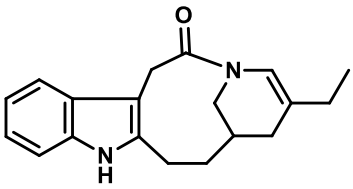


17

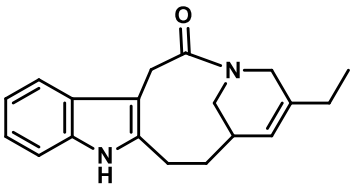
A mixture of **292** (30 mg, 0.11 mmol), EtOAc (4 mL) and Pd/C (10 wt%, 10 mg) was stirred for 20 h at r.t. under hydrogen atmosphere (1 atm). The resulting suspension was diluted with EtOAc and filtered through a pad of celite. The solvent was removed by rotary evaporation and the remaining crude product was purified by column chromatography (hexane/EtOAc, 1:1) to yield **17** (18 mg, 58%) as clear colorless liquid. The analytical data matches the data in literature.[25,123]

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.79 (bs, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.28 (m, 1H), 7.09 (m, 2H), 3.70 (dd, *J* = 13.0, 13.0 Hz, 1H), 2.86 (m, 2H), 2.64 (m, 2H), 2.48 (m, 2H), 2.34 (m, 1H), 2.26 (d, *J* = 12.1 Hz, 1H), 2.17 (m, 1H), 1.91 (m, 1H), 1.75 (m, 2H), 1.50 (m, 1H), 1.45 (m, 1H), 1.29 (m, 3H), 0.88 (t, *J* = 7.4 Hz, 3H); ppm.
^{13}C NMR (150 MHz, $CDCl_3$): δ = 138.9, 135.6, 128.7, 120.8, 118.9, 117.9, 110.2, 110.1, 59.1, 52.4, 51.8, 35.3, 33.9, 32.9, 31.3, 28.9, 26.4, 21.3, 11.9; ppm.
IR: 3400, 2914, 2784, 1635, 1463, 1440, 1336, 1136, 909, 739 cm^{-1}
HRMS: m/z calculated for $C_{19}H_{26}N_2H^+$: 283.2174; found: 283.2169;

5-Ethyl-1,6,7,8,9,10-hexahydro-2*H*-3,7-methano[1]azacycloundecino[5,4-b]indol-2-one **293** and 5-Ethyl-1,4,7,8,9,10-hexahydro-2*H*-3,7-methano[1]azacycloundecino [5,4-b]indol-2-one **294**



293



294

To a solution of **290** and **291** (17 mg, 58 μmol) in EtOAc (3 mL) was added Pd/C (10 wt%, 10 mg). The mixture was stirred for 6.5 h at r.t. under hydrogen atmosphere (1 atm). The resulting suspension was diluted with Et_2O and filtered through a pad of Celite. The solvent was removed by rotary evaporation and the remaining crude product was purified by column chromatography (hexane/EtOAc, 2:1) to yield **293** (3 mg, 18%) and **294** (6 mg, 35%) in a 1:2 mixture.

Fr. 1 (minor **293**):

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.86 (m, 1H), 7.82 (bs, 1H), 7.25 (m, 1H), 7.14 (m, 2H), 6.59 (s, 1H), 4.64 (d, *J* = 13.3 Hz, 1H), 4.21 (d, *J* = 13.8 Hz, 1H), 3.79 (*J* = 13.8 Hz, 1H), 3.35 (m, 1H), 2.93 (ddd, *J* = 15.1, 6.0, 0.9 Hz, 1H), 2.69 (dd, *J* = 13.3, 9.2 Hz, 1H), 2.03 (m, 1H), 1.92 (m, 2H), 1.74 (m, 1H), 1.68 (m, 1H), 1.55 (m, 1H), 1.49 (m, 1H), 0.94 (t, *J* = 7.5 Hz, 3H); ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.9, 134.6, 132.9, 130.5, 129.6, 123.8, 121.9, 120.1, 119.7, 109.9, 106.2, 49.1, 36.5, 35.1, 33.2, 27.9, 27.8, 25.7, 12.6; ppm.

IR: 3273, 2927, 1634, 1460, 1402, 1337, 1227, 1023, 911, 734 cm^{-1}

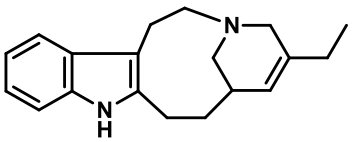
HRMS: m/z calculated for $C_{19}H_{22}O_1N_2Na^+$: 317.1630; found: 317.1630;

Fr. 2 (major **294**):

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.70 (bs, 1H), 7.47 (d, *J* = 7.7 Hz, 1H), 7.26 (m, 1H), 7.15 (m, 1H), 7.10 (m, 1H), 5.39 (d, *J* = 4.7 Hz, 1H) 4.95 (d, *J* = 17.7 Hz, 1H), 4.14 (d, *J* = 13.6 Hz, 1H), 3.96 (d, *J* = 15.4 Hz, 1H), 3.92 (d, *J* = 15.4 Hz, 1H), 3.40 (dd, *J* = 13.6, 4.9 Hz, 1H), 3.35 (d, *J* = 17.7 Hz, 1H), 2.90 (m, 1H), 2.49 (dd, *J* = 15.8, 9.7 Hz, 1H), 2.39 (m, 1H), 2.09 (q, *J* = 7.5 Hz, 2H), 1.92 (m, 1H), 1.82 (m, 1H), 1.09 (t, *J* = 7.5 Hz, 3H); ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.1, 138.2, 136.9, 134.5, 129.3, 121.8, 121.3, 119.5, 117.9, 110.1, 103.9, 46.1, 43.5, 33.6, 33.1, 32.4, 27.5, 20.7, 12.2; ppm.
IR: 3273, 2928, 2356, 1619, 1463, 1330, 1232, 1170, 917, 740 cm^{-1}
HRMS: m/z calculated for $C_{19}H_{22}O_1N_2H^+$: 295.1810; found: 295.1806;

Cleavamine (**49**)

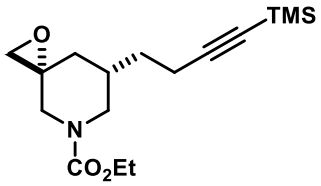


49

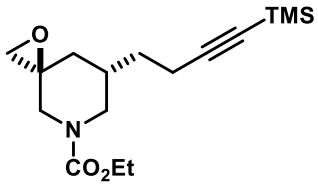
To a solution of **294** (10 mg, 34 μmol) in THF (1 mL) was added LAH (70 μL, 2 eq., 1 M in THF, 70 μmol). After stirring for 2 h at r.t. the solution was cooled to 0 °C and poured into an aqueous solution of Na/K tartrate. The aqueous phase was extracted with Et_2O (3x), the combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation. The residue was purified by column chromatography (hexane/EtOAc, 3:1) to give **49** (6 mg, 50%) as clear colorless oil. The analytical data matches the data in literature. [25,124]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (bs, 1H), 7.,48 (m, 1H), 7.28 (m, 1H), 7.08 (m, 2H), 5.30 (m, 1H), 3.71 (m, 1H), 3.16 (d, *J* = 15.3 Hz, 1H), 3.07 (m, 1H), 2.78 (m, 3H), 2.61 (m, 1H), 2.43 (m, 3H), 2.13 (m, 1H), 2.05 (q, *J* = 7.5 Hz, 2H), 1.96 (m, 2H), 1.07 (t, *J* = 7.5 Hz, 3H); ppm.
^{13}C NMR (150 MHz, $CDCl_3$): δ = 140.8, 139.5, 135.3, 128.7, 122.4, 120.6, 118.7, 117.8, 109.9, 55.1, 54.0, 53.5, 35.3, 34.1, 27.7, 26.1, 22.5, 12.6; ppm.
IR: 3401, 2917, 2853, 2785, 2736, 1717, 1463, 1336, 1165, 740 cm^{-1}
HRMS: m/z calculated for $C_{19}H_{24}N_2H^+$: 281.2012; found: 281.1999;

Ethyl (3*R*,7*S*)-7-(4-(trimethylsilyl)but-3-yn-1-yl)-1-oxa-5-azaspiro[2.5]octane-5-carboxylate **317** and Ethyl (3*S*,7*S*)-7-(4-(trimethylsilyl)but-3-yn-1-yl)-1-oxa-5-azaspiro[2.5]octane-5-carboxylate **295**



317



295

Trimethylsulfoxonium iodide (560 mg, 1.5 eq., 2.54 mg) was dissolved in a solution of THF/DMSO (1:1) (17 mL). The solution was cooled to 0 °C and NaH (102 mg, 1.5 eq., 60% in mineral oil, 2.54 mmol) was added. After stirring for 30 min, **271** (500 mg, 1.69 mmol) was added and the resulting solution was stirred for 2 h at the same temperature. The reaction was treated with sat. NH_4Cl, the mixture was extracted with diethyl ether (3x), the combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc, 3:1) to give **317** and **295** (327 mg, 77%) as clear colorless oils in a 1:5 mixture of stereoisomers.

Fr. 1 (minor (3*R*,7*S*) **317**):

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.13 (q, *J* = 7.1 Hz, 2H), 3.89 (bs, 1H), 3.60 (bs, 1H), 3.24 (d, *J* = 13.2 Hz, 1H), 2.84 (dd, *J* = 13.2, 9.8 Hz, 1H), 2.75 (bs, 1H), 2.61 (dd, *J* = 4.7, 1.3 Hz, 1H), 2.29 (m, 2H), 1.92 (bs, 1H), 1.70 (dd, *J* = 13.2, 4.2 Hz, 1H), 1.64 (m, 1H), 1.56 (m, 1H), 1.50 (m, 1H), 1.25 (t, *J* = 7.1 Hz, 3H), 0.14 (s, 9H); ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.5, 106.3, 85.3, 61.5, 55.5, 53.4, 50.0, 48.2, 37.2, 34.7, 31.3, 17.4, 14.7, 0.1; ppm.

IR: 2957, 2174, 1699, 1429, 1248, 1213, 1115, 841, 760, 417 cm^{-1}

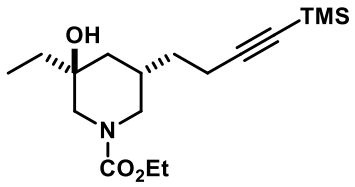
HRMS: m/z calculated for $C_{16}H_{27}O_3N_1Si_1H^+$: 310.1838; found: 310.1843;

Fr. 2 (major (3*S*,7*S*) **295**):

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.13 (q, *J* = 7.0 Hz, 2H), 4.03 (bm, 1H), 3.55 (m, 1H), 3.33 (d, *J* = 13.7 Hz, 1H), 2.67 (m, 1H), 2.71 (bm, 1H), 2.68 (d, *J* = 4.7 Hz, 1H), 2.26 (t, *J* = 7.5 Hz, 2H), 2.01 (m, 1H), 1.59 (m, 3H), 1.45 (m, 1H), 1.24 (t, *J* = 7.0 Hz, 3H), 0.13 (s, 9H); ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.7, 106.4, 85.1, 61.5, 55.4, 52.3, 49,9, 47.9, 37.1, 33.6, 32.1, 17.4, 14.6, 0.0; ppm.
IR: 2959, 2174, 1699, 1429, 1248, 1209, 1121, 843, 762, 403 cm^{-1}
HRMS: m/z calculated for $C_{16}H_{27}O_3N_1Si_1H^+$: 310.1838; found: 310.1843;

Ethyl (3*S*,5*S*)-3-ethyl-3-hydroxy-5-(4-(trimethylsilyl) but-3-yn-1-yl) piperidine-1-carboxylate **318**

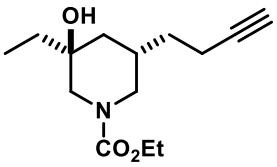


318

To a solution of **295** (270 mg, 0.87 mmol) in THF (4.5 mL) was added CuI (17 mg, 0.1 eq., 0.09 mmol). The mixture was cooled to -40 °C and MeMgBr (0.38 mL, 1.3 eq., 3 M in Et_2O, 1.13 mmol) was added. After stirring for 30 min at the same temperature, the reaction was quenched with sat. NH_4Cl, the aqueous phase was extracted with diethyl ether (3x), the combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc, 3:1) to afford **318** (256 mg, 90%) as clear colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.18 (bs, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.98 (bs, 1H), 2.60 (d, *J* = 2.6 Hz, 1H), 2.26 (m, 3H), 1.93 (m, 1H), 1.82 (m, 1H), 1.74 (bs, 1H), 1.48 (m, 3H), 1.40 (m, 1H), 1.25 (t, *J* = 7.1 Hz, 3H), 0.98 (m, 1H), 0.95 (t, *J* = 7.5 Hz, 3H), 0.13 (s, 9H); ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.6, 106.8, 84.8, 70.1, 61.5, 53.3, 49.4, 41.1, 33.2, 32.7, 31.2, 17.3, 14.6, 7.1, 0.1; ppm.
IR: 3428, 2960, 2927, 2172, 1682, 1436, 1249, 1016, 843, 761 cm^{-1}
HRMS: m/z calculated for $C_{17}H_{31}O_3N_1Si_1H^+$: 326.2151; found: 326.2153;

Ethyl (3*S*,5*S*)-5-(but-3-yn-1-yl)-3-ethyl-3-hydroxypiperidine-1-carboxylate **296**

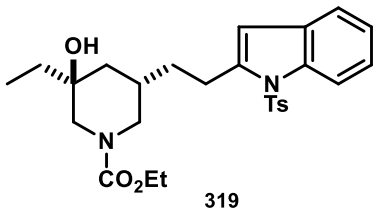


296

To a solution of **318** (770 mg, 2.37 mmol) in MeOH (24 mL) was added K_2CO_3 (817 mg, 2.5 eq., 5.91 mmol). The mixture was stirred for 7 h at r.t. and then treated with water. The aqueous layer was extracted with diethyl ether (3x), the combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation to obtain the crude product **296** (510 mg, 85%) as clear colorless liquid, which was used in the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.22 (bs, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.99 (bs, 1H), 2.61 (d, *J* = 13.6 Hz, 1H), 2.24 (m, 3H), 1.99 (m, 1H), 1.95 (t, *J* = 2.5 Hz, 1H), 1.82 (m, 1H), 1.71 (m, 1H), 1.49 (q, *J* = 7.5 Hz, 2H), 1.41 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 3H), 0.98 (d, *J* = 12.8 Hz, 1H), 0.96 (t, *J* = 7.5 Hz, 3H); ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.2, 83.8, 70.2, 68.7, 61.5, 53.4, 49.3, 41.0, 33.1, 32.5, 30.8, 15.8, 14.7, 7.1; ppm.
IR: 3422, 3300, 2976, 2925, 1679, 1432, 1266, 1162, 1101, 1012 cm^{-1}
HRMS: calculated for $C_{14}H_{23}O_3N_1Na^+$: 276.1576; found: 276.1577;

Ethyl (3*S*,5*S*)-3-ethyl-3-hydroxy-5-(2-(1-tosyl-1*H*-indol-2-yl) ethyl) piperidine-1-carboxylate **319**

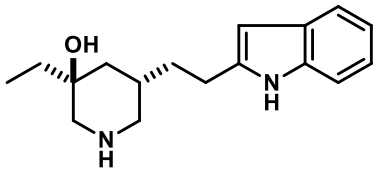


319

To a solution of **296** (510 mg, 2.01 mmol) in DMF (7 mL) were added **280** (825 mg, 1.1 eq., 2.21 mmol) and NEt_3 (0.84 mL, 3 eq., 6.03 mmol). The mixture was degassed followed by addition of CuI (38 mg, 0.1 eq., 0.20 mmol) and $PdCl_2(PPh_3)_2$ (70 mg, 0.05 eq., 0.1 mmol). After stirring for 3 h at 70 °C, the resulting solution was poured into sat. NH_4Cl, the aqueous layer was extracted with diethyl ether (3x), the combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc, 1:1) to afford **319** (840 mg, 84%) as brown oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 8.2 Hz, 1H), 7.60 (d, *J* = 8.2 Hz, 2H), 7.40 (d, *J* = 7.5 Hz, 1H), 7.23 (m, 2H), 7.18 (d, *J* = 8.2 Hz, 2H), 6.39 (s, 1H), 4.28 (bs, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 4.01 (bs, 1H), 3.02 (m, 2H), 2.62 (d, *J* = 13.8 Hz, 1H), 2.35 (m, 1H), 2.33 (s, 3H), 1,97 (m, 1H), 1.89 (m, 1H), 1.65 (m, 4H), 1.51 (q, *J* = 7.5 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 3H), 0.97 (t, *J* = 7.5 Hz, 3H); ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.6, 144.7, 141.7, 137.3, 136.1, 129.8, 129.7, 126.2, 124.0, 123.6, 120.2, 114.9, 109.2, 70.3, 61.5, 53.5, 49.6, 41.3, 33.5, 33.2, 31.4, 26.4, 21.6, 14.7, 7.1; ppm.
IR: 3422, 2976, 2922, 1682, 1451, 1367, 1248, 1180, 1091, 812 cm^{-1}
HRMS: m/z calculated for $C_{27}H_{34}O_5N_2S_1H^+$: 499.2267; found: 499.2266;

(3*S*,5*S*)-5-(2-(1*H*-indol-2-yl) ethyl)-3-ethylpiperidin-3-ol **320**

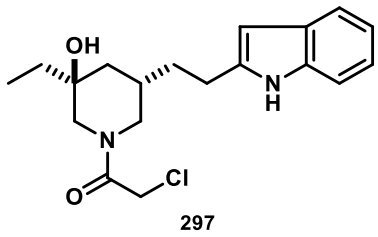


320

To a mixture of **319** (1.42 g, 2.85 mmol) in ethylene glycol (28 mL) were added KOH (3.2 g, 20 eq., 57 mmol) and hydrazine (0.9 mL, 10 eq., 28.5 mmol). The mixture was stirred for 4 h at 140 °C, cooled to r.t. and treated with water. The mixture was extracted with CH_2Cl_2 (3x), the combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation to yield the crude product **320** (690 mg, 89%) as chewy greenish oil, which was used in the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (s, 1H), 7.52 (d, *J* = 7.5 Hz, 1H), 7.31 (d, *J* = 7.3 Hz, 1H), 7.09 (m, 2H), 6.22 (s, 1H), 3.08 (m, 1H), 2.73 (bm, 5H), 2.39 (d, *J* = 11.8 Hz, 1H), 2.12 (t, *J* = 11.3 Hz, 1H), 1.88 (m, 1H), 1.78 (m, 1H), 1.58 (m, 2H), 1.44 (m, 2H), 0.95 (m, 1H), 0.92 (t, *J* = 7.5 Hz, 3H); ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.6, 135.8, 128.8, 121.0, 119.7, 119.6, 110.5, 99.3, 69.3, 55.5, 52.0, 41.7, 33.8, 32.9, 32.1, 25.4, 7.1; ppm.
IR: 3400, 3250, 2920, 1550, 1457, 1286, 967, 887, 782, 732 cm^{-1}
HRMS: m/z calculated for $C_{17}H_{24}O_1N_2H^+$: 273.1967; found: 273.1965;

1-((3*S*,5*S*)-5-(2-(1*H*-indol-2-yl) ethyl)-3-ethyl-3-hydroxypiperidin-1-yl)-2-chloroethan-1-one **297**



297

To a solution of **320** (690 mg, 2.54 mmol) in CH_2Cl_2 (25 mL) were added NEt_3 (0.35 mL, 1 eq., 2.54 mmol) and $(ClAc)_2O$ (650 mg, 1.5 eq., 3.80 mmol) at 0 °C. The solution was stirred for 30 min at the same temperature and quenched with water. The aqueous phase was extracted with CH_2Cl_2 (3x), the combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation. The residue was purified by column chromatography (hexane/EtOAc, 1:1) to give **297** (664 mg, 75%) as slightly yellow oil.

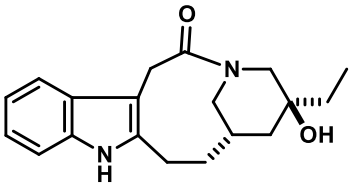
^{1}H NMR (400 MHz, $CDCl_3$, two rotamers): δ = 8.59 (s, 2H (ma)), 8.16 (s, 1H (mi)), 7.51 (m, 3H (ma,mi)), 7.33 (m, 3H (ma,mi)), 7.09 (m, 6H (ma,mi)), 6.26 (s, 1H (mi)), 6.19 (s, 2H (ma)), 4.69 (bd, *J* = 12.8 Hz, 2H (ma)), 4.41 (bd, *J* = 13.7 Hz, 1H (mi)), 4.27 (d, *J* = 12.8 Hz, 2H (ma)), 4.12 (d, *J* = 12.8 Hz, 2H (ma)), 4.02 (d, *J* = 12.6 Hz, 1H (mi)), 3.98 (d, *J* = 12.6 Hz, 1H (mi)), 3.78 (bd, *J* = 13.7 Hz, 1H (mi)), 3.62 (m, 2H (ma)), 2.96 (d, *J* = 13.9 Hz, 2 H (ma)), 2.77 (m, 6H (ma,mi)), 2.62 (m, 1H (mi)), 2.44 (d, *J* = 13.7 Hz, 1H (mi)), 2.12 (m, 6H (ma,mi)), 1.90 (m, 3 H (ma,mi)), 1.76 (m, 4H (ma,mi)), 1.66 (m, 2H (ma,mi)), 1.57 (m, 3H (ma,mi)), 1.51 (m, 5H (ma,mi)), 1.11 (m, 3H (ma,mi)), 0.96 (t, *J* = 7.5 Hz, 9H (ma,mi)); ppm.

^{13}C NMR (100 MHz, $CDCl_3$, two rotamers): δ = 171.2, 167.0, 139.1, 138.8, 136.1, 136.0, 128.7, 128.6, 121.3, 120.9, 119.8, 119.8, 119.7, 119.5, 110.7, 110.4, 99.7, 99.3, 70.8, 70.8, 55.7, 52.1, 51.8, 48.5, 42.1, 41.5, 41.3, 41.1, 33.6, 33.3, 33.2, 33.0, 32.4, 31.0, 25.6, 25.1, 7.1, 7.0; ppm.

IR: 3400, 3310, 2924, 1637, 1458, 1287, 1138, 910, 784, 734 cm^{-1}

HRMS: m/z calculated for $C_{19}H_{25}O_2N_2Cl_1H^+$: 349.1683; found: 349.1679;

(5*S*,7*S*)-5-Ethyl-5-hydroxy-1,4,5,6,7,8,9,10-octahydro-2*H*-3,7-methano[1]azacycloundecino[5,4-b]indol-2-one **321**

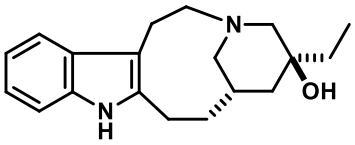


321

A mixture of **297** (250 mg, 0.72 mmol) and Na_2CO_3 (304 mg, 4 eq., 2.87 mmol) in MeOH (72 mL) and water (48 mL) was placed in a quarz vessel. The vessel was sonificated under a nitrogen atmosphere for 30 min and then irradiated (λ=254 nm) at r.t. for 1 h. Afterwards, the methanol was evaporated under reduced pressure and the residue was diluted with $NaHCO_3$. The aqueous layer was extracted with diethyl ether (3x), the combined organic phases were washed with brine, dried over $MgSO_4$ and the solvent was removed by rotary evaporation. The residue was purified by column chromatography (hexane/EtOAc, 1:1) to afford **321** (101 mg, 45%) as white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (m, 1H), 7.81 (bs, 1H), 7.23 (m, 1H), 7.12 (m, 2H), 4.6 (d, *J* = 14.1 Hz, 1H), 4.36 (dt, *J* = 14.1, 1.7 Hz, 1H), 4.12 (d, *J* = 13.7 Hz, 1H) 3.82 (d, *J* = 13.7 Hz, 1H), 3.27 (ddd, *J* = 15.1, 12.0, 6.5 Hz, 1H), 2.91 (ddd, *J* = 15.1, 5.5, 1.2 Hz, 1H), 2.77 (d, *J* = 14.1 Hz, 1H), 2.55 (dd, *J* = 14.1, 10.0 Hz, 1H), 2.13 (m, 1H), 1.51 (m, 2H), 1.44 (m, 2H), 1.35 (m, 3H), 0.84 (t, *J* = 7.5 Hz, 3H); ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.0, 134.5, 132.6, 129.6, 121.7, 120.0, 119.2, 110.1, 107.3, 74.3, 55.2, 51.9, 42.9, 35.2, 34.1, 32.2, 28.0, 25.9, 7.2; ppm.
IR: 3289, 2924, 2855, 1624, 1460, 1241, 1128, 1015, 910, 732 cm^{-1}
HRMS: m/z calculated for $C_{19}H_{24}O_2N_2H^+$: 313.1916; found: 313.1913;

Isovelbanamine (**19**)

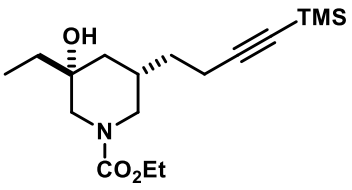


19

To a solution of **321** (100 mg, 0.32 mmol) in THF (12 mL) was added LAH (1.0 mL, 3 eq., 1 M in THF, 1.0 mmol). After stirring for 3 h at 50 °C, the reaction was cooled to r.t. and poured into an aqueous solution of Na/K tartrate. The aqueous phase was extracted with CH_2Cl_2 (3x), the combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation and the residue was purified by column chromatography (CH_2Cl_2/MeOH 20:1) to give **19** (82 mg, 86%) as white solid. The analytical data matches the data in literature.[124,125]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 (s, 1H), 7.45 (m, 1H), 7.28 (m, 1H), 7.09 (m, 2H), 3.50 (dd, *J* = 14.1, 10.6 Hz, 1H), 2.93 (m, 2H), 2.84 (d, *J* = 11.0 Hz, 1H), 2.70 (m, 2H), 2.54 (m, 2H), 2.46 (d, *J* = 11.0 Hz, 1H), 2.35 (m, 1H), 1.94 (m, 2H), 1.79 (m, 1H), 1.62 (dd, *J* = 13.5, 6.7 Hz, 1H), 1.52 (m, 3H), 1.27 (bs, 1H), 0.90 (t, *J* = 7.4 Hz, 3H); ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.0, 135.5, 128.4, 120.9, 119.0, 117.7, 110.1, 109.6, 72.7, 64.5, 52.4, 50.6, 37.4, 35.2, 32.8, 30.7, 24.9, 22.5, 7.5; ppm.
IR: 3402, 3281, 2922, 2854, 1615, 1463, 1337, 1134, 924, 740 cm^{-1}
HRMS: m/z calculated for $C_{19}H_{26}O_1N_2H^+$: 299.2123; found: 299.2122;

Ethyl (3*R*,5*S*)-3-ethyl-3-hydroxy-5-(4-(trimethylsilyl) but-3-yn-1-yl) piperidine-1-carboxylate **322**

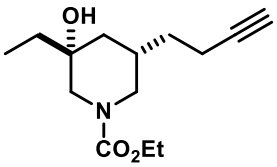


322

To a solution of **317** (180 mg, 0.58 mmol) in THF (6 mL) was added CuI (11 mg, 0.1 eq., 0.06 mmol). The mixture was cooled to -20 °C and MeMgBr (0.29 mL, 1.5 eq., 3 M in Et_2O, 0.87 mmol) was added. After stirring for 1 h at the same temperature, the reaction was quenched with sat. NH_4Cl, the aqueous phase was extracted with diethyl ether (3x), the combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc, 2:1) to afford **322** (156 mg, 83%) as clear colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.13 (m, 3H), 3.93 (d, *J* = 12.9 Hz, 1H), 2.68 (bs, 1H), 2.45 (bm, 1H), 2.28 (t, *J* = 7.2 Hz, 2H), 1.93 (m, 1H), 1.72 (m, 1H), 1.59 (m, 1H), 1.56 (q, *J* = 7.5 Hz, 2H), 1.39 (m, 1H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.10 (m, 1H), 0.94 (t, *J* = 7.5 Hz, 3H), 0.14 (s, 9H); ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.5, 106.4, 85.2, 70.8, 61.4, 53.2, 48.9, 41.9, 32.6, 32.0, 29.3, 17.3, 14.6, 7.0, 0.1; ppm.
IR: 3450, 2933, 2175, 1676, 1436, 1249, 1158, 1044, 842, 761 cm^{-1}
HRMS: m/z calculated for $C_{17}H_{31}O_3N_1Si_1H^+$: 326.2151; found: 326.2153;

Ethyl (3*R*,5*S*)-5-(but-3-yn-1-yl)-3-ethyl-3-hydroxypiperidine-1-carboxylate **323**

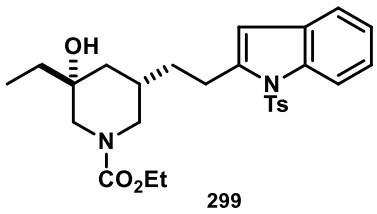


323

To a solution of **322** (150 mg, 0.46 mmol) in MeOH (4.5 mL) was added at r.t. K_2CO_3 (159 mg, 2.5 eq., 1.15 mmol). The mixture was stirred for 7 h at r.t. and then treated with water. The aqueous layer was extracted with diethyl ether (3x), the combined organic phases were washed with brine, dried over $MgSO_4$. The solvent was removed by rotary evaporation to the crude product **323** (103 mg, 92%) as clear colorless liquid, which was used in the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.13 (m, 3H), 3.92 (m, 1H), 2.56 (bm, 2H), 2.24 (dt, *J* = 7.2, 2.6 Hz, 2H), 1.95 (t, *J* = 2.6 Hz, 1H), 1.91 (m, 1H), 1.74 (m, 1H), 1.55 (m, 4H), 1.42 (m, 1H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.12 (m, 1H), 0.93 (t, *J* = 7.5 Hz, 3H); ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.5, 83.6, 70.8, 68.9, 61.4, 53.1, 48.8, 42.5, 41.5, 32.5, 31.9, 15.9, 14.7, 6.9; ppm.
IR: 3425, 3308, 2933, 1673, 1436, 1263, 1158, 980, 891, 768 cm^{-1}
HRMS: m/z calculated for $C_{14}H_{23}O_3N_1H^+$: 254.1756; found: 254.1754;

Ethyl (3*R*,5*S*)-3-ethyl-3-hydroxy-5-(2-(1-tosyl-1*H*-indol-2-yl) ethyl) piperidine-1-carboxylate **299**

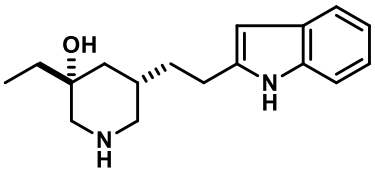


299

To a solution of **323** (110 mg, 0.43 mmol) in DMF (1.5 mL) were added **280** (177 mg, 1.1 eq., 0.47 mmol) and NEt_3 (0.18 mL, 3 eq., 1.29 mmol). The mixture was degassed followed by addition of CuI (8 mg, 0.01 eq., 0.04 mmol) and $PdCl_2(PPh_3)_2$ (15 mg, 0.05 eq., 0.02 mmol). After stirring for 3 h at 70 °C, the resulting solution was poured into sat. NH_4Cl, the aqueous layer was extracted with diethyl ether (3x), the combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc, 1:1) to provide **299** (150 mg, 70%) as yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 8.2 Hz, 1H), 7.59 (d, *J* = 8.3 Hz, 2H), 7.40 (d, *J* = 7.5 Hz, 1H), 7.22 (m, 2H), 7.17 (d, *J* = 8.3 Hz, 2H), 6.38 (s, 1H), 4.14 (m, 3H), 3.98 (d, *J* = 13.0 Hz, 1H), 3.02 (m, 2H), 2.68 (m, 1H), 2.51 (bm, 1H), 2.33 (s, 3H), 1.95 (d, *J* = 12.8 Hz, 1H), 1.68 (m, 3H), 1.54 (m, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.22 (m, 1H), 0.93 (t, *J* = 7.5 Hz, 3H); ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.5, 144.7, 141.6, 137.3, 136.1, 129.8, 129.7, 126.2, 124.0, 123.6, 120.1, 114.9, 109.2, 70.8, 61.4, 52.9, 49.0, 43.3, 33.5, 33.3, 28.9, 26.5, 21.6, 14.7, 7.0; ppm.
IR: 3412, 2928, 1674, 1451, 1367, 1262, 1173, 1091, 911, 732 cm^{-1}
HRMS: m/z calculated for $C_{27}H_{34}O_5N_2S_1H^+$: 499.2267; found: 499.2265;

(3*R*,5*S*)-5-(2-(1*H*-indol-2-yl) ethyl)-3-ethylpiperidin-3-ol **324**

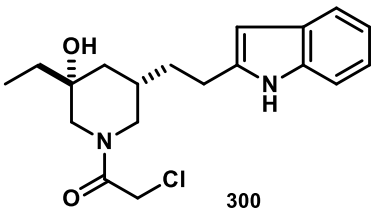


324

To a mixture of **299** (832 mg, 1.67 mmol) in ethylene glycol (17 mL) were added KOH (1.87 g, 20 eq., 33.4 mmol) and hydrazine (0.53 mL, 10 eq., 16.7 mmol). The mixture was stirred for 5 h at 140 °C, cooled to r.t. and treated with water. The mixture was extracted with CH_2Cl_2 (3x), the combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation to the crude product **324** (454 mg, 99%) as clear colorless oil, which was used in the next step without further purification.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.39 (d, *J* = 7.7 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 1H), 6.99 (m, 1H), 6.92 (m, 1H), 6.13 (s, 1H), 2.94 (m, 1H), 2.76 (m, 3H), 2.36 (d, *J* = 12.6 Hz, 1H), 2.11 (dd, *J* = 12.6, 10.7 Hz, 1H), 1.97 (m, 1H), 1.59 (m, 5H), 1.08 (m, 1H), 0.87 (t, *J* = 7.5 Hz, 3H); ppm.
^{13}C NMR (100 MHz, CD_3OD): δ = 140.9, 137.9, 130.2, 121.3, 120.3, 119.8, 111.4, 99.7, 71.0, 56.5, 52.5, 43.1, 35.5, 34.8, 29.7, 26.4, 7.3; ppm.
IR: 3395, 3282, 2927, 1616, 1458, 1287, 974, 909, 783, 733 cm^{-1}
HRMS: m/z calculated for $C_{17}H_{24}O_1N_2H^+$: 273.1967; found: 273.1963;

1-((3*R*,5*S*)-5-(2-(1*H*-indol-2-yl) ethyl)-3-ethyl-3-hydroxypiperidin-1-yl)-2-chloroethan-1-one **300**



300

To a solution of **299** (454 mg, 1.67 mmol) in CH_2Cl_2 (16 mL) were added at 0 °C NEt_3 (0.23 mL, 1 eq., 1.67 mmol) and $(ClAc)_2O$ (428 mg, 1.5 eq., 2.51 mmol). The solution was stirred for 30 min at the same temperature and quenched with water. The aqueous phase was extracted with CH_2Cl_2 (3x), the combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation. The residue was purified by column chromatography (hexane/EtOAc, 1:1) to give **300** (480 mg, 82%) as white foam.

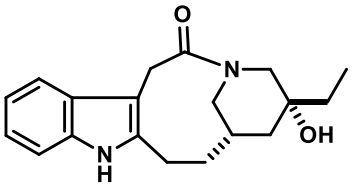
^{1}H NMR (400 MHz, $CDCl_3$, two rotamers): δ = 8.43 (s, 1H), 8.06 (s, 1H), 7.52 (m, 2H), 7.31 (m, 2H), 7.09 (m, 4H), 6.26 (s, 1H), 6.21 (s, 1H), 4.28 (m, 1H), 4.15 (m, 2H), 4.06 (d, *J* = 12.0 Hz, 1H), 3.95 (d, *J* = 12.0 Hz, 1H), 3.93 (m, 1H), 3.70 (m, 1H), 3.40 (d, *J* = 13.5 Hz, 1H), 3.22 (d, *J* = 13.5 Hz, 1H), 3.14 (dd, *J* = 13.1, 7.6 Hz, 1H), 2.81 (m, 5H), 2.64 (d, *J* = 12.8 Hz, 1H), 1.95 (m, 2H), 1.72 (m, 8H), 1.49 (m, 4H), 1.31 (m, 2H), 0.91 (m, 6H); ppm.

^{13}C NMR (100 MHz, $CDCl_3$, two rotamers): δ = 166.3, 165.2, 139.1, 138.6, 136.1, 136.0, 128.7, 121.3, 121.0, 119.9, 119.8, 119.7, 119.5, 110.6, 110.4, 99.8, 99.5, 71.1, 71.0, 56.3, 51.8, 51.5, 46.9, 42.0, 41.3, 41.2, 41.1, 33.9, 33.1, 32.8, 30.8, 29.4, 25.8, 25.7, 7.0, 6.9; ppm.

IR: 3304, 2932, 1638, 1458, 1286, 1122, 978, 910, 786, 735 cm^{-1}

HRMS: m/z calculated for $C_{19}H_{25}O_2N_2Cl_1Na^+$: 371.1502; found: 371.1503;

(5*R*,7*S*)-5-Ethyl-5-hydroxy-1,4,5,6,7,8,9,10-octahydro-2*H*-3,7-methano[1]azacycloundecino[5,4-b]indol-2-one **301**



301

A mixture of **300** (250 mg, 0.72 mmol) and Na_2CO_3 (304 mg, 4 eq., 2.87 mmol) in MeOH (72 mL) and water (48 mL) was placed in a quarz vessel. The vessel was sonificated under a nitrogen atmosphere for 30 min and then irradiated (λ=254 nm) at r.t. for 1 h. Afterwards, the methanol was evaporated under reduced pressure and the residue was diluted with $NaHCO_3$. The aqueous layer was extracted with diethyl ether (3x), the combined organic phases were washed with brine, dried over $MgSO_4$ and the solvent was removed by rotary evaporation. The residue was purified by column chromatography (CH_2Cl_2/MeOH, 25:1) to afford **301** (120 mg, 53%) as white solid.

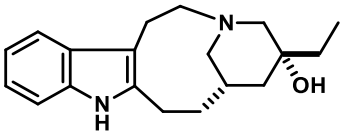
^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.25 (s, 1H), 7.85 (m, 1H), 7.23 (m, 1H), 7.11 (m 2H), 4.48 (m, 1H), 4.37 (m, 1H), 4.07 (d, *J* = 14.0 Hz, 1H), 3.80 (d, *J* = 14.0 Hz, 1H), 3.18 (ddd, *J* = 14.9, 12.1, 6.2 Hz, 1H), 2.94 (ddd, *J* = 14.9, 5.8, 1.0 Hz, 1H), 2.71 (d, *J* = 13.0 Hz, 1H), 2.59 (dd, *J* = 14.0, 9.7 Hz, 1H), 1.90 (bs, 1H), 1.66 (m, 1H), 1.54 (dd, *J* = 12.5, 12.5 Hz, 1H), 1.51 (m, 1H), 1.43 (m, 1H), 1.36 (m, 1H), 1.07 (m, 1H), 0.96 (m, 1H), 0.57 (t, *J* = 7.4 Hz, 3H); ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.5, 134.6, 132.8, 129.3, 121.6, 119.9, 119.3, 110.0, 106.6, 73.1, 54.2, 51.5, 43.7, 36.5, 32.8, 31.2, 28.2, 25.8, 6.9; ppm.

IR: 3289, 2931, 1624, 1459, 1337, 1241, 1124, 945, 907, 726 cm^{-1}

HRMS: m/z calculated for $C_{19}H_{24}O_2N_2H^+$: 313.1916; found: 313.1911;

Velbanamine (**18**)

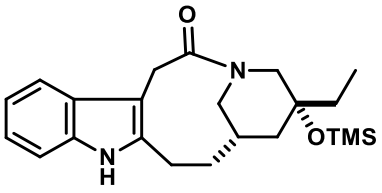


18

To a solution of **301** (70 mg, 0.22 mmol) in THF (5 mL) was added phenylsilane (68 μL, 2.5 eq., 0.55 mmol). The solution was degassed and $HRh(CO)(PPh_3)_3$ (4 mg, 0.05 eq., 0.01 mmol) was added. The solution was stirred for 5 h at 50 °C and afterwards quenched with sat. $NaHCO_3$. The aqueous phase was extracted with Et_2O (3x), the combined organic layers were treated with 1 M HCl (2x). The acidic aqueous phases were treated with $NaHCO_3$ until pH ≥ 9 and then extracted with CH_2Cl_2 (3x), the combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation to product **18** (35 mg, 53%) as clear slightly yellow oil. The analytical data matches the data in literature.[124,126]

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.82 (bs, 1H), 7.45 (m, 1H), 7.22 (m, 1H), 7.06 (m 2H), 3.52 (m, 1H), 3.00 (m, 2H), 2.84 (m, 1H), 2.66 (m, 1H), 2.36 (d, *J* = 11.2 Hz, 1H), 2.29 (m, 2H), 2.24 (m, 1H), 2.18 (m, 1H), 1.98 (m, 1H), 1.94 (m, 1H), 1.57 (m, 1H), 1.37 (dd, *J* = 13.9, 6.0 Hz, 1H), 1.30 (m, 1H), 1.22 (m, 1H), 0.77 (t, *J* = 7.6 Hz, 1H); ppm.
^{13}C NMR (150 MHz, $CDCl_3$): δ = 138.7, 135.3, 128.0, 120.8, 119.0, 117.4, 110.5, 108.6, 71.6, 66.3, 52.5, 51.1, 40.2, 32.6, 31.4, 30.6, 23.3, 23.0, 7.1; ppm.
IR: 3300, 2925, 2800, 1459, 1260, 1040, 915, 800, 736 cm^{-1}
HRMS: m/z calculated for $C_{19}H_{26}O_1N_2Na^+$: 299.2123; found: 299.2122;

(5*R*,7*S*)-5-Ethyl-5-((trimethylsilyl)oxy)-1,4,5,6,7,8,9,10-octahydro-2*H*-3,7-methano[1]azacycloundecino[5,4-b]indol-2-one **302**



302

To a solution of **301** (60 mg, 0.19 mmol) in CH_2Cl_2 (2 mL) were added NEt_3 (47 μL, 1.8 eq., 0.34 mmol) and TMSOTf (62 μL, 1.8 eq., 0.34 mmol) at 0 °C. The reaction was stirred for 30 min at the same temperature and afterwards quenched with water. The aqueous phase was extracted with CH_2Cl_2 (3x), the combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation. The residue was purified by column chromatography (hexane/EtOAc, 3:1) to give **302** (70 mg, 96%) as white foam.

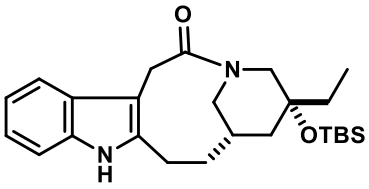
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (m, 1H), 7.81 (bs, 1H), 7.25 (m, 1H), 7.14 (m, 2H), 4.47 (d, *J* = 14.0 Hz, 1H), 4.38 (d, *J* = 13.1 Hz, 1H), 4.07 (d, *J* = 14.0 Hz, 1H), 3.80 (d, *J* = 14.0 Hz, 1H), 3.21 (ddd, *J* = 15.0, 12.1, 6.2 Hz, 1H), 2.91 (dd, *J* = 15.0, 5.5 Hz, 1H), 2.68 (d, *J* = 12.9 Hz, 1H), 2.58 (dd, *J* = 14.0, 9.6 Hz, 1H), 1.62 (m, 2H), 1.51 (dd, *J* = 12.9, 6.2 Hz, 1H), 1.38 (m, 2H), 1.05 (m, 1H), 0.89 (m, 1H), 0.55 (t, *J* = 7.3 Hz, 3H), 0.07 (s, 9H); ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1, 134.5, 132.5, 129.5, 121.8, 120.1, 119.6, 109.8, 107.1, 76.6, 54.4, 51.6, 44.8, 36.6, 32.9, 31.3, 28.4, 25.9, 7.4, 2.6; ppm.

IR: 3252, 2944, 1629, 1460, 1251, 1124, 1063, 879, 839, 743 cm^{-1}

HRMS: m/z calculated for $C_{22}H_{32}O_2N_2Si_1Na^+$: 407.2131; found: 407.2129;

(5*R*,7*S*)-5-((*tert*-Butyldimethylsilyl)oxy)-5-ethyl-1,4,5,6,7,8,9,10-octahydro-2*H*-3,7-methano[1]azacycloundecino[5,4-b]indol-2-one **303**

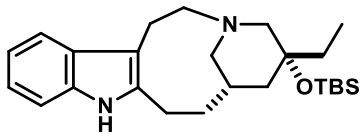


303

To a solution of **301** (40 mg, 0.13 mmol) in $CHCl_3$ (1 mL) were added NEt_3 (90 µL, 5 eq., 0.65 mmol) and TBSOTf (0.12 mL, 4 eq., 0.52 mmol). The reaction was stirred for 2.5 h under reflux and afterwards quenched with water. The aqueous phase was extracted with CH_2Cl_2 (3x), the combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation. The residue was purified by column chromatography (hexane/EtOAc, 3:1) to give **303** (26 mg, 47%) as white foam.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87 (m, 1H), 7.83 (bs, 1H), 7.24 (m, 1H), 7.13 (m, 2H), 4.46 (bd, *J* = 14.1 Hz, 1H), 4.36 (bd, *J* = 13.0 Hz, 1H), 4.07 (d, *J* = 13.9 Hz, 1H), 3.80 (d, *J* = 13.9 Hz, 1H), 3.21 (ddd, *J* = 15.0, 12.0, 6.1 Hz, 1H), 2.91 (ddd, *J* = 15.0, 5.8, 0.8 Hz, 1H), 2.68 (d, *J* = 13.0 Hz, 1H), 2.56 (dd, *J* = 14.1, 9.8 Hz, 1H), 1.66 (m, 1H), 1.58 (m, 1H), 1.51 (m, 1H), 1.42 (m, 1H), 1.34 (m, 1H), 1.05 (m, 1H), 0.90 (m, 1H), 0.82 (s, 9H), 0.54 (t, *J* = 7.3 Hz, 3H), 0.06 (s, 3H), 0.03 (s, 3H); ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1, 134.6, 132.5, 129.5, 121.8, 120.1, 119.6, 109.9, 107.1, 76.2, 54.4, 51.7, 44.6, 36.6, 32.9, 31.7, 28.4, 25.9, 25.8, 18.2, 7.4, -1.8, -2.0; ppm.
IR: 3246, 2929, 2856, 1628, 1461, 1249, 1126, 1067, 835, 742 cm^{-1}
HRMS: m/z calculated for $C_{25}H_{38}O_2N_2Si_1Na^+$: 449.2600; found: 449.2599;

(5*S*,7*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-5-ethyl-1,4,5,6,7,8,9,10-octahydro-2*H*-3,7-methano[1]azacycloundecino[5,4-b]indole **304**

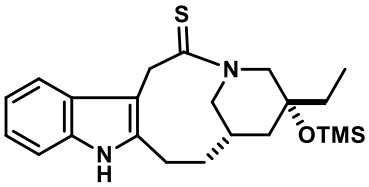


304

To a solution of **303** (13 mg, 30 μmol) in THF (1 mL) was added LAH (76 μL, 2.5 eq., 1 M in THF, 76 μmol). After stirring for 4 h under reflux the reaction was cooled to r.t. and poured into an aqueous solution of Na/K tartrate. The aqueous phase was extracted with CH_2Cl_2 (3x), the combined organic layers were treated with 1 M HCl (2x). The acidic aqueous layers were treated with $NaHCO_3$ until pH ≥ 9 and then extracted with CH_2Cl_2 (3x), the combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation to product **304** (6 mg, 50%) as clear colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (bs, 1H), 7.44 (m, 1H), 7.23 (m, 1H), 7.04, (m, 2H), 3.32 (bm, 1H), 3.14 (bm, 1H), 2.96 (m, 2H), 2.67 (dd, *J* = 14.9, 7.9 Hz, 1H), 2.61 (bd, *J* = 11.9 Hz, 1H), 2.38 (m, 4H), 1.72 (m, 3H), 1.39 (m, 2H), 1.25 (m, 2H), 0.85 (t, *J* = 7.4 Hz, 3H), 0.76 (s, 9H), 0.05 (s, 3H), -0.68 (bs, 3H); ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.3, 135.0, 129.4, 120.4, 118.6, 117.4, 109.9, 108.6, 75.4, 67.6, 52.4, 51.6, 40.1, 35.5, 32.4, 31.5, 32.2, 26.1, 23.5, 18.4, 7.5, -1.9; ppm.
IR: 3402, 3241, 2928, 2856, 2784, 1614, 1463, 1250, 1038, 834 cm^{-1}
HRMS: m/z calculated for $C_{25}H_{40}O_1N_2Si_1H^+$: 413.2988; found: 413.2988;

(5*R*,7*S*)-5-Ethyl-5-((trimethylsilyl)oxy)-1,4,5,6,7,8,9,10-octahydro-2*H*-3,7-methano[1]azacycloundecino[5,4-b]indole-2-thione **305**

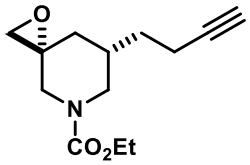


305

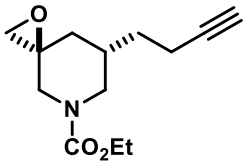
To a solution of **302** (15 mg, 0.04 mmol) in toluene (2 mL) was added Lawesson´s reagent (16 mg, 1 eq., 0.04 mmol) in one portion. The mixture was heated to reflux and stirred for 45 min. The mixture was cooled to r.t. and treated with water. The aqueous layer was extracted with diethyl ether (3x), the combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc, 3:1) to provide **305** (6 mg, 37%) as clear colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22 (m, 1H), 7.77 (bs, 1H), 7.24 (m, 1H), 7.15 (m, 2H), 5.31 (d, *J* = 12.6 Hz, 1H), 4.99 (d, *J* = 13.6 Hz, 1H), 4.66 (d, *J* = 14.9 Hz, 1H), 4.42 (d, *J* = 14.9 Hz, 1H), 3.25 (m, 1H), 3.08 (d, *J* = 12.6 Hz, 1H), 2.91 (m, 1H), 2.77 (dd, *J* = 13.3, 9.4 Hz, 1H), 1.75 (m, 1H), 1.71 (m, 1H), 1.54 (m, 2H), 1.45 (m, 1H), 1.20 (m, 1H), 1.02 (m, 1H), 0.66 (t, *J* = 7.3 Hz, 3H), 0.10 (s, 9H); ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.1, 134.1, 132.0, 129.7, 121.8, 121.2, 120.0, 109.8, 107.5, 78.3, 55.6, 54.6, 45.1, 42.9, 35.8, 31.4, 28.1, 26.2, 8.0, 2.5; ppm.
HRMS: m/z calculated for $C_{22}H_{32}O_1N_2Si_1S_1Na^+$: 423.1902; found: 423.1908;

Ethyl (3*R*,7*S*)-7-(but-3-yn-1-yl)-1-oxa-5-azaspiro[2.5]octane-5-carboxylate **298** and Ethyl (3*S*,7*S*)-7-(but-3-yn-1-yl)-1-oxa-5-azaspiro[2.5]octane-5-carboxylate **324**



298



325

To a solution of **279** (1.7 g, 7.68 mmol) in $CHCl_3$ (75 mL) was added *m*CPBA (2.92 g, 2.2 eq., 16.9 mmol) in small portions. The reaction mixture was stirred for 18 h at r.t.. The suspension was neutralized with sat. $NaHCO_3$ and quenched with aq. $Na_2S_2O_3$, the aqueous layer was extracted with CH_2Cl_2 (3x), the combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation and the residue was purified by column chromatography (hexane/EtOAc, 10:1) to give **298** and **325** (1.62 g, 89%) as clear colorless liquids in a 1:1 mixture of stereoisomers.

Fr. 1 (3*R*, 7*S*) **298**:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.14 (m, 2H), 3.89 (bm, 1H), 3.59 (bm, 1H), 3.25 (d, *J* = 13.4 Hz, 1H), 2.87 (dd, *J* = 13.0, 9.1 Hz, 1H), 2.74 (bm, 1H), 2.62 (m, 1H), 2.27 (m, 2H), 1.97 (bm, 1H), 1.95 (t, *J* = 2.7 Hz, 1H), 1.71 (m, 1H), 1.64 (m, 1H), 1.52 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H); ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.6, 83.5, 69.0, 61.6, 55.5, 53.4, 50.0, 48.0, 37.1, 34.4, 31.1, 15.9, 14.6; ppm.

IR: 3266, 2982, 2930, 2859, 1694, 1429, 1215, 1143, 1117, 768 cm^{-1}

HRMS: calculated for $C_{13}H_{19}O_3N_1Na^+$: 260.1263; found: 260.1260

Fr. 2 (3*S*, 7*S*) **325**:

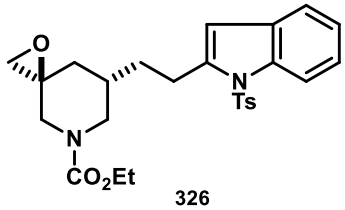
^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.14 (q, *J* = 7.0 Hz, 2H), 4.04 (bm, 1H), 3.56 (m, 1H), 3.34 (d, *J* = 13.6 Hz, 1H), 2.77 (m, 1H), 2.72 (bm, 1H), 2.69 (d, *J* = 4.6 Hz, 1H), 2.24 (m, 2H), 2.07 (m, 1H), 1.96 (t, *J* = 2.7 Hz, 1H), 1.59 (m, 3H), 1.46 (m, 1H), 1.25 (t, *J* = 7.0 Hz, 3H); ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.7, 83.5, 68.9, 61.5, 55.5, 52.3, 49.9, 47.9, 37.1, 33.4, 31.9, 15.9, 14.6; ppm.

IR: 3271, 2920, 2361, 1688, 1427, 1216, 1117, 881, 768, 661 cm^{-1}

HRMS: calculated for $C_{13}H_{19}O_3N_1Na^+$: 260.1263; found: 260.1266

Ethyl (3*S*,7*S*) -7- (2-(1-tosyl-1*H*-indol-2-yl) ethyl) -1-oxa-5-azaspiro [2.5] octane-5-carboxylate **326**



326

To a solution of **325** (1.15 g, 4.85 mmol) in DMF (16 mL) were added **280** (1.99 g, 1.1 eq., 5.33 mmol) and NEt_3 (2 mL, 3 eq., 14.6 mmol). The mixture was degassed followed by addition of CuI (93 mg, 0.1 eq., 0.49 mmol) and $PdCl_2(PPh_3)_2$ (170 mg, 0.05 eq., 0.24 mmol). After stirring for 3 h at 70 °C, the resulting solution was poured into sat. NH_4Cl, the aqueous layer was extracted with diethyl ether (3x), the combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc, 1:1) to afford **326** (2.05 g, 88%) as slightly yellow oil.

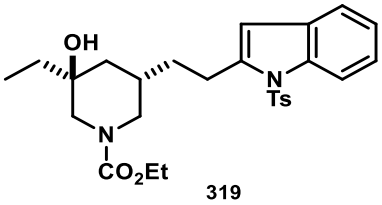
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 8.3 Hz, 1H) 7.59 (m, 2H), 7.40 (d, *J* = 7.6 Hz, 1H), 7.23 (m, 2H), 7.18 (m, 2H), 6.39 (s, 1H), 4.23 (bm, 1H), 4.15 (q, *J* = 7.5 Hz, 2H), 3.60 (bm, 1H), 3.35 (d, *J* = 13.8 Hz, 1H), 3.03 (m, 2H), 2.75 (bm, 2H), 2.72 (d, *J* = 4.4 Hz, 1H), 2.33 (s, 3H), 2.02 (m, 1H), 1.75 (m, 3H), 1.60 (m, 1H), 1.26 (t, *J* = 7.5 Hz, 3H); ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.7, 144.7, 141.5, 137.3, 136.0, 129.8, 129.7, 126.2, 124.0, 123.6, 120.2, 114.9, 109.3, 61.5, 55.7, 52.2, 50.1, 48.3, 37.4, 34.0, 33.2, 26.5, 21.6, 14.7; ppm.

IR: 2923, 1692, 1596, 1451, 1428, 1366, 1218, 1173, 1091, 812 cm^{-1}

HRMS: calculated for $C_{26}H_{30}O_5N_2S_1Na^+$: 505.1773; found: 505.1776

Ethyl (3*S*,5*S*)-3-ethyl-3-hydroxy-5-(2-(1-tosyl-1*H*-indol-2-yl) ethyl) piperidine-1-carboxylate **319**

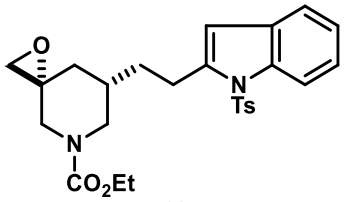


319

To a solution of **326** (1.5 g, 3.11 mmol) in THF (30 mL) was added CuI (59 mg, 0.1 eq., 0.31 mmol). The mixture was cooled to -40 °C and MeMgBr (1.56 mL, 1.5 eq., 3 M in Et_2O, 4.67 mmol) was added. After stirring for 1 h at the same temperature, the reaction was quenched with sat. NH_4Cl, the aqueous phase was extracted with diethyl ether (3x), the combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc, 1:1) to afford **319** (1.42 g, 92%) as clear colorless oil.

The spectroscopic data matched the data reported earlier in this chapter.

Ethyl (3*R*,7*S*) -7- (2-(1-tosyl-1*H*-indol-2-yl) ethyl) -1-oxa-5-azaspiro [2.5] octane-5-carboxylate **327**



327

To a solution of **298** (590 mg, 2.48 mmol) in DMF (8 mL) were added **280** (1.02 g, 1.1 eq., 2.73 mmol) and NEt_3 (1 mL, 3 eq., 7.43 mmol). The mixture was degassed followed by addition of CuI (47 mg, 0.1 eq., 0.25 mmol) and $PdCl_2(PPh_3)_2$ (87 mg, 0.05 eq., 0.12 mmol). After stirring for 3 h at 70 °C, the resulting solution was poured into sat. NH_4Cl, the aqueous layer was extracted with diethyl ether (3x), the combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc, 2:1) to afford **327** (1.13 g, 94%) as yellow oil.

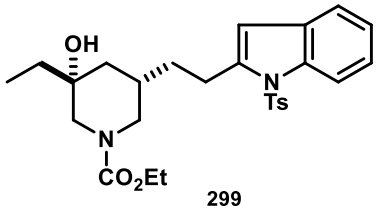
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 8.3 Hz, 1H) 7.59 (m, 2H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.23 (m, 2H), 7.17 (m, 2H), 6.40 (s, 1H), 4.13 (q, *J* = 7.5 Hz, 2H), 4.03 (bm, 1H), 3.62 (bm, 1H), 3.24 (d, *J* = 13.4 Hz, 1H), 3.04 (m, 2H), 2.84 (dd, *J* = 13.3, 9.2 Hz, 1H), 2.74 (m, 1H), 2.60 (d, *J* = 4.8 Hz, 1H), 2.32 (s, 3H), 1.82 (m, 3H), 1.66 (m, 2H), 1.26 (t, *J* = 7.5 Hz, 3H); ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.5, 144.7, 141.4, 137.3, 136.0, 129.8, 129.7, 126.2, 124.0, 123.6, 120.1, 114.9, 109.3, 61.5, 55.6, 53.7, 50.0, 48.4, 37.6, 35.3, 32.4, 26.5, 21.5, 14.6; ppm.

IR: 2956, 1691, 1596, 1451, 1429, 1366, 1215, 1172, 1144, 1091 cm^{-1}

HRMS: calculated for $C_{26}H_{30}O_5N_2S_1H^+$: 483.1954; found: 483.1957

Ethyl (3*R*,5*S*)-3-ethyl-3-hydroxy-5-(2-(1-tosyl-1*H*-indol-2-yl) ethyl) piperidine-1-carboxylate **299**

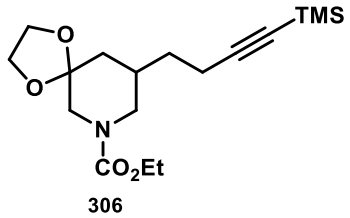


299

To a solution of **327** (830 mg, 1.72 mmol) in THF (17 mL) was added CuI (32 mg, 0.1 eq., 0.17 mmol). The mixture was cooled to -30 °C and MeMgBr (0.86 mL, 1.5 eq., 3 M in Et_2O, 2.58 mmol) was added. After stirring for 45 min at the same temperature, the reaction was quenched with sat. NH_4Cl, the aqueous phase was extracted with diethyl ether (3x), the combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc, 1:1) to afford **299** (780 mg, 91%) as clear colorless oil.

The spectroscopic data matched the data reported earlier in this chapter.

Ethyl 9-(4-(trimethylsilyl) but-3-yn-1-yl)-1,4-dioxa-7-azaspiro[4.5]decane-7-carboxylate **306**



306

To a solution of **271** (1.9 g, 6.43 mmol) and $(TMSOCH_2)_2$ (2.65 g, 2 eq., 12.9 mmol) in CH_2Cl_2 (60 mL) was added TMSOTf (0.93 mL, 0.8 eq. 5.14 mmol) at -78 °C. The reaction was stirred for 1.5 h at the same temperature and quenched afterwards with sat. $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2 (3x), the combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation and the residue was purified by column chromatography (hexane/EtOAc, 3:1) to give **306** (1.29 g, 59%) as clear colorless oil.

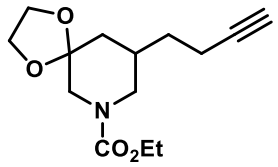
^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.13 (m, 2H), 3.97 (m, 6H), 2.76 (d, *J* = 13.4 Hz, 1H), 2.48 (bm, 1H), 2.26 (m, 2H), 1.91 (m, 2H), 1.55 (m, 1H), 1.45 (m, 1H), 1.36 (m, 1H), 1.25 (t, *J* = 7.1 Hz, 3H), 0.14 (s, 9H); ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.8, 106.7, 105.6, 85.1, 64.8, 64.4, 61.4, 49.4, 48.5, 40.0, 33.7, 32.2, 17.4, 14.7, 0.1; ppm.

IR: 2930, 2174, 1701, 1469, 1428, 1250, 1193, 1094, 842, 761 cm^{-1}

HRMS: m/z calculated for $C_{17}H_{29}O_4N_1Si_1Na^+$: 362.1764; found: 362.1765;

Ethyl 9-(but-3-yn-1-yl)-1,4-dioxa-7-azaspiro[4.5]decane-7-carboxylate **328**

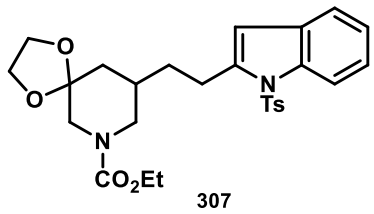


328

To a solution of **306** (1.29 g, 3.79 mmol) in MeOH (35 mL) was added K_2CO_3 (1.31 g, 2.5 eq., 9.5 mmol). After stirring for 5 h at r.t. the mixture was treated with water, the aqueous layer was extracted with diethyl ether (3x), the combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation. The residue was purified by column chromatography (hexane/EtOAc, 2:1) to yield **328** (719 mg, 71%) as clear colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.14 (m, 2H), 3.97 (m, 6H), 2.77 (d, *J* = 13.4 Hz, 1H), 2.48 (bm, 1H), 2.24 (dt, *J* = 7.4, 2.5 Hz, 2H), 1.97 (m, 1H), 1.95 (t, *J* = 2.5 Hz, 1H), 1.90 (m, 1H), 1.55 (m, 1H), 1.45 (m, 1H), 1.38 (m, 1H), 1.25 (t, *J* = 7.1 Hz, 3H); ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.8, 106.7, 83.6, 68.8, 64.8, 64.4, 61.4, 49.4, 48.4, 40.0, 33.3, 31.9, 15.9, 14.7; ppm.
IR: 3284, 2926, 1693, 1429, 1211, 1093, 1065, 1021, 889, 768 cm^{-1}
HRMS: m/z calculated for $C_{14}H_{21}O_4N_1Na^+$: 290.1368; found: 290.1367;

Ethyl 9-(2-(1-tosyl-1H-indol-2-yl) ethyl)-1,4-dioxa-7-azaspiro[4.5]decane-7-carboxylate **307**



307

To a solution of **328** (700 mg, 2.62 mmol) in DMF (9 mL) were added **280** (1.07 g, 1.1 eq., 2.88 mmol) and NEt_3 (1.8 mL, 5 eq., 13.1 mmol). The mixture was degassed followed by addition of CuI (50 mg, 0.1 eq., 0.26 mmol) and $PdCl_2(PPh_3)_2$ (92 mg, 0.05 eq., 0.13 mmol). After stirring for 3 h at 70 °C, the resulting solution was poured into sat. NH_4Cl, the aqueous layer was extracted with diethyl ether (3x), the combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc, 2:1) to afford **307** (1.02 mg, 76%) as brown oil.

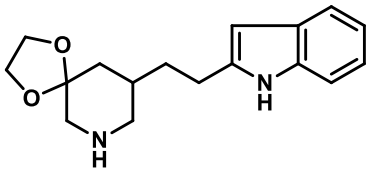
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 8.4 Hz, 1H), 7.60 (m, 2H), 7.40 (m, 2H), 7.22 (m, 2H), 7.17 (m, 2H), 6.39 (s, 1H), 4.14 (m, 4H), 3.99 (m, 4H), 3.03 (m, 2H), 2.75 (bm, 1H), 2.50 (bm, 1H), 2.33 (s, 3H), 1.94 (m, 2H), 1.72 (m, 2H), 1.45 (m, 1H), 1.27 (t, *J* = 7.1 Hz, 3H); ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.8, 144.7, 141.7, 137.3, 136.1, 129.8, 129.8, 126.2, 124.0, 123.5, 120.2, 114.9, 109.2, 105.7, 64.9, 64.5, 61.4, 49.4, 48.7, 40.4, 34.0, 32.9, 26.5, 21.5, 14.7; ppm.

IR: 2923, 1694, 1451, 1367, 1173, 1091, 1022, 911, 731, 667 cm^{-1}

HRMS: m/z calculated for $C_{27}H_{32}O_6N_2S_1Na^+$: 535.1879; found: 535.1880;

9-(2-(1*H*-Indol-2-yl) ethyl)-1,4-dioxa-7-azaspiro[4.5]decane **329**



329

To a mixture of **307** (1.0 g, 1.95 mmol) in ethylene glycol (20 mL) were added KOH (2.2 g, 20 eq., 39 mmol) and hydrazine (0.62 mL, 10 eq., 19.5 mmol). The mixture was stirred for 4 h at 140 °C, cooled to r.t. and treated with water. The mixture was extracted with CH_2Cl_2 (3x), the combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation to the crude product **329** (464 mg, 83%) as chewy oil, which was used in the next step without further purification.

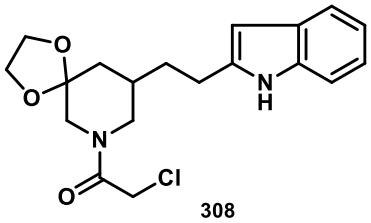
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (bs, 1H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.29 (d, *J* = 7.8 Hz, 1H), 7.09 (m, 2H), 6.23 (s, 1H), 3.94 (m, 4H), 3.07 (m, 1H), 2.85 (dd, *J* = 13.1, 2.4 Hz, 1H), 2.75 (m, 2H), 2.56 (d, *J* = 13.1 Hz, 1H), 2.23 (dd *J* = 12.8, 10.9 Hz, 1H), 1.92 (m, 1H), 1.84 (m, 1H), 1.64 (m, 2H), 1.37 (dd, *J* = 12.3, 12.3 Hz, 1H); ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.3, 135.9, 128.8, 121.0, 119.8, 119.6, 110.4, 106.0, 99.4, 64.7, 64.3, 52.5, 51.1, 40.4, 36.1, 33.4, 25.5; ppm.

IR: 3400, 3170, 2919, 1680, 1457, 1287, 1071, 909, 782, 731 cm^{-1}

HRMS: m/z calculated for $C_{17}H_{22}O_2N_2H^+$: 287.1760; found: 287.1760;

1-(9-(2-(1*H*-Indol-2-yl) ethyl)-1,4-dioxa-7-azaspiro[4.5]decan-7-yl)-2-chloroethan-1-one **308**



308

To a solution of **329** (450 mg, 1.57 mmol) in CH_2Cl_2 (15 mL) were added at 0 °C NEt_3 (0.22 mL, 1.0 eq., 1.57 mmol) and $(ClAc)_2O$ (403 mg, 1.5 eq., 2.36 mmol). The solution was stirred for 30 min at the same temperature and quenched with water. The aqueous phase was extracted with CH_2Cl_2 (3x), the combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation. The residue was purified by column chromatography (hexane/EtOAc, 1:1) to give **308** (416 mg, 73%) as chewy yellow oil.

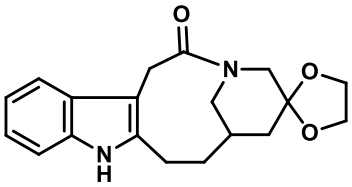
^{1}H NMR (400 MHz, $CDCl_3$, two rotamers): δ = 8.45 (bs, 1H), 8.01 (bs, 1H), 7.53 (m, 1H), 7.51 (m, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.12 (m, 2H), 7.05 (m, 2H), 6.27 (s, 1H), 6.22 (s, 1H), 4.43 (m, 2H), 4.19 (d, *J* = 12.7 Hz, 1H), 4.14 (d, *J* = 7.2 Hz, 1H), 4.11 (d, *J* = 7.2 Hz, 1H), 4.10 (d, *J* = 12.7 Hz, 1H), 3.99 (m, 6H), 3.93 (m, 3H), 3.77 (m, 1H), 3.59 (d, *J* = 14.0 Hz, 1H), 3.22 (d, *J* = 14.0 Hz, 1H), 2.81 (m, 4H), 2.62 (d, *J* = 13.0 Hz, 1H), 2.60 (d, *J* = 13.0 Hz, 1H), 1.98 (m, 1H), 1.89 (m, 2H), 1.74 (m, 2H), 1.66 (m, 3H), 1.50 (m, 2H); ppm.

^{13}C NMR (100 MHz, $CDCl_3$, two rotamers): δ = 166.4, 165.4, 136.2, 136.0, 128.7, 128.6, 121.4, 121.0, 119.9, 119.9, 119.7, 119.5, 110.7, 110.4, 105.7, 105.3, 99.8, 99.6, 65.2, 65.0, 64.8, 64.6, 53.4, 51.2, 47.6, 47.4, 41.2, 41.2, 40.6, 40.5, 34.7, 33.4, 33.0, 32.6, 25.7, 25.4; ppm.

IR: 3292, 2922, 1647, 1458, 1299, 1236, 1151, 1070, 787, 750 cm^{-1}

HRMS: m/z calculated for $C_{19}H_{23}O_3N_2Cl_1Na^+$: 385.1295; found: 385.1297;

1',6',7',8',9',10'-Hexahydro-2'*H*,4'*H*-spiro[[1,3]dioxolane-2,5'-[3,7]methano[1]azacycloundecino[5,4-b]indol]-2'-one **309**

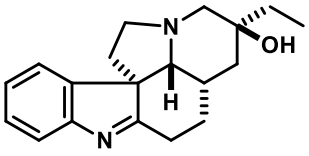


309

A mixture of **308** (60 mg, 0.17 mmol) and Na_2CO_3 (53 mg, 3 eq., 0.5 mmol) in MeOH (18 mL) and water (9 mL) was placed in a quarz vessel. The vessel was sonificated under a nitrogen atmosphere for 30 min and then irradiated (λ=254 nm) for 1 h at r.t.. Afterwards, the methanol was evaporated under reduced pressure and the residue was diluted with $NaHCO_3$. The aqueous layer was extracted with diethyl ether (3x), the combined organic phases were washed with brine, dried over $MgSO_4$ and the solvent was removed by rotary evaporation. The residue was purified by column chromatography (hexane/EtOAc, 1:2) to afford **309** (26 mg, 48%) as white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (bs, 1H), 7.85 (m, 1H), 7.18 (m, 1H), 7.08 (m, 2H), 4.57 (m, 1H), 4.43 (m, 1H), 4.08 (d, *J* = 13.8 Hz, 1H), 3.83 (d, *J* = 13.8 Hz, 1H), 3.78 (m, 1H), 3.69 (m, 2H), 3.56 (1H), 3.19 (m, 1H), 2.92 (m, 1H), 2.77 (d, *J* = 13.5 Hz, 1H), 2.59 (dd, *J* = 14.3, 9.1 Hz, 1H), 1.74 (m, 2H), 1.62 (m, 1H), 1.50 (m, 2H); ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.8, 134.5, 132.3, 129.8, 121.6, 120.0, 119.4, 110.0, 107.1, 106.9, 65.0, 64.0, 51.3, 50.9, 42.9, 37.1, 32.7, 28.1, 25.8; ppm.
IR: 3266, 2922, 1632, 1460, 1339, 1242, 1071, 1021, 908, 733 cm^{-1}

(20*S*)-Hydroxy-1,2-dehydro-pseudoaspidospermidine (**20**)



20

To a solution of **19** (10 mg, 34 μmol) in EtOH (1 mL) was added PtO_2 (4 mg, 0.5 eq., 18 μmol). The mixture was stirred for 15 min under hydrogen atmosphere (1 atm) and then purged with nitrogen. Afterwards, the reaction mixture was stirred under oxygen (1 atm) for 6 h. The resulting mixture was diluted with Et_2O and filtered through a pad of Celite. The solvent was removed under reduced pressure and the residue was purified by column chromatography (CH_2Cl_2 /MeOH 15:1) to give **20** (3 mg, 30%) as yellow oil. The analytical data matches the data in literature.[123]

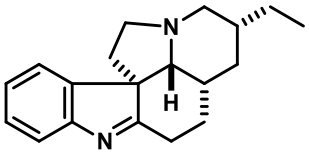
^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.51 (d, *J* = 7.7 Hz, 1H), 7.37 (m, 1H), 7.30 (m, 1H), 7.18 (m, 1H), 3.19 (m, 1H), 3.12 (dd, *J* = 10.7, 1.0 Hz, 1H), 2.98 (ddd, *J* = 15.0, 10.8, 3.6 Hz, 1H), 2.90 (bm, 1H), 2.85 (bm, 1H), 2.80 (m, 1H), 2.50 (m, 1H), 2.40 (m, 1H), 2.31 (m, 1H), 1.94 (m, 1H), 1.83 (m, 3H), 1.76 (m, 2H), 1.55 (bm, 1H), 1.44 (m, 1H), 0.97 (t, *J* = 7.5 Hz, 3H); ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ = 190.0, 154.7, 146.8, 127.9, 125.5, 121.7, 120.0, 74.5, 71.1, 63.0, 61.6, 54.3, 39.4, 35.5, 34.2, 31.7, 25.7, 25.6, 8.1; ppm.

IR: 3297, 2924, 2856, 2788, 1576, 1456, 1260, 1096, 1017, 798 cm^{-1}

HRMS: m/z calculated for $C_{19}H_{24}O_1N_2H^+$: 297.1967; found: 297.1965;

(20*R*)-1,2-Dehydro-pseudoaspidospermidine (**21**)



21

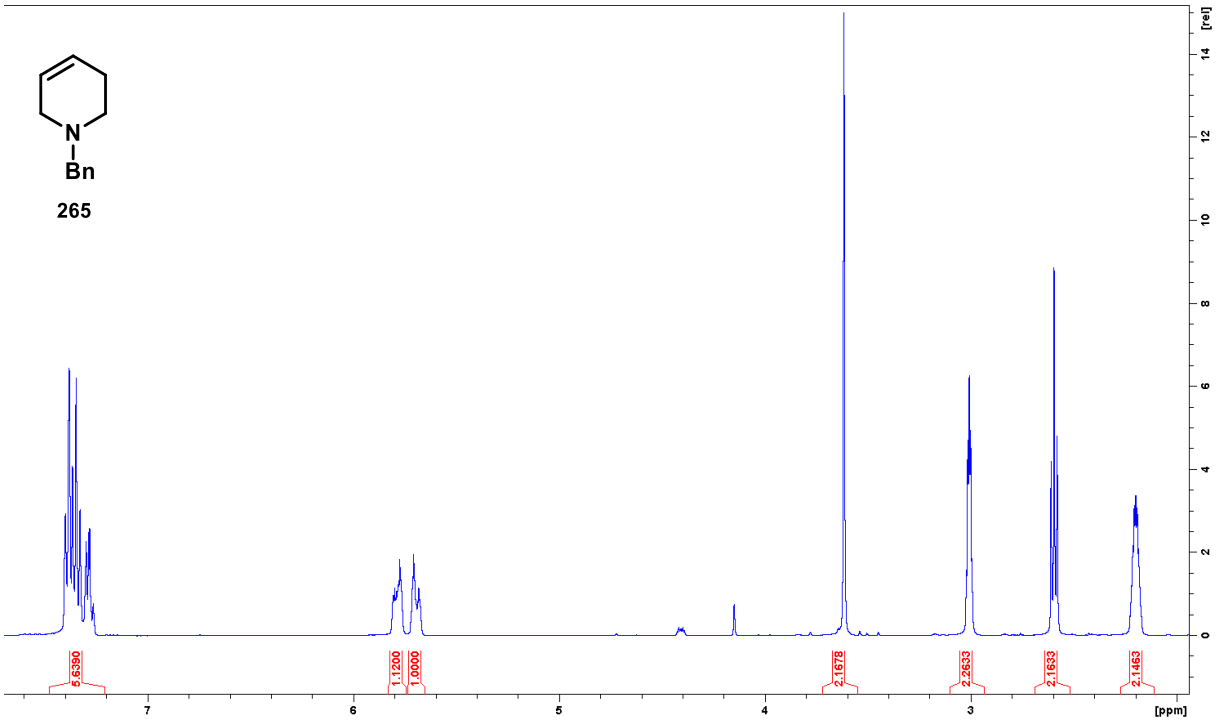
To a solution of **17** (25 mg, 0.09 mmol) in EtOH (2 mL) was added PtO_2 (20 mg, 1 eq., 0.09 mmol). The mixture was stirred for 15 min under hydrogen atmosphere (1 atm) and then purged with nitrogen. Afterwards, the reaction mixture was stirred under oxygen (1 atm) for 7.5 h. The resulting mixture was diluted with CH_2Cl_2 and filtered through a pad of Celite. The solvent was removed under reduced pressure and the residue was purified by column chromatography (CH_2Cl_2 /MeOH 10:1) to give **21** (7 mg, 28%) as brown oil. The analytical data matches the data in literature.[123]

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.50 (d, *J* = 7.8 Hz, 1H), 7.35 (bm, 1H), 7.29 (m, 1H), 7.17 (m, 1H), 3.20 (m, 1H), 3.00 (m, 1H), 2.97 (ddd, *J* = 14.9, 10.9, 3.4 Hz, 1H), 2.77 (m, 2H), 2.71 (m, 1H), 2.55 (m, 2H), 2.29 (m, 1H), 1.79 (m, 2H), 1.70 (m, 1H), 1.58 (m, 1H), 1.50 (m, 2H), 1.48 (m, 1H), 1.43 (m, 1H), 0.92 (t, *J* = 7.3 Hz, 3H); ppm.
^{13}C NMR (150 MHz, $CDCl_3$): δ = 190.9, 154.7, 147.0, 127.6, 125.1, 121.5, 119.8, 74.6, 62.1, 55.5, 54.9, 35.6, 34.9, 32.4, 32.1, 29.1, 27.2, 25.5, 13.2; ppm.
IR: 2958, 2930, 2872, 2784, 1576, 1456, 1336, 1257, 1118, 748 cm^{-1}
HRMS: m/z calculated for $C_{19}H_{24}N_2H^+$: 281.2018; found: 281.2020;

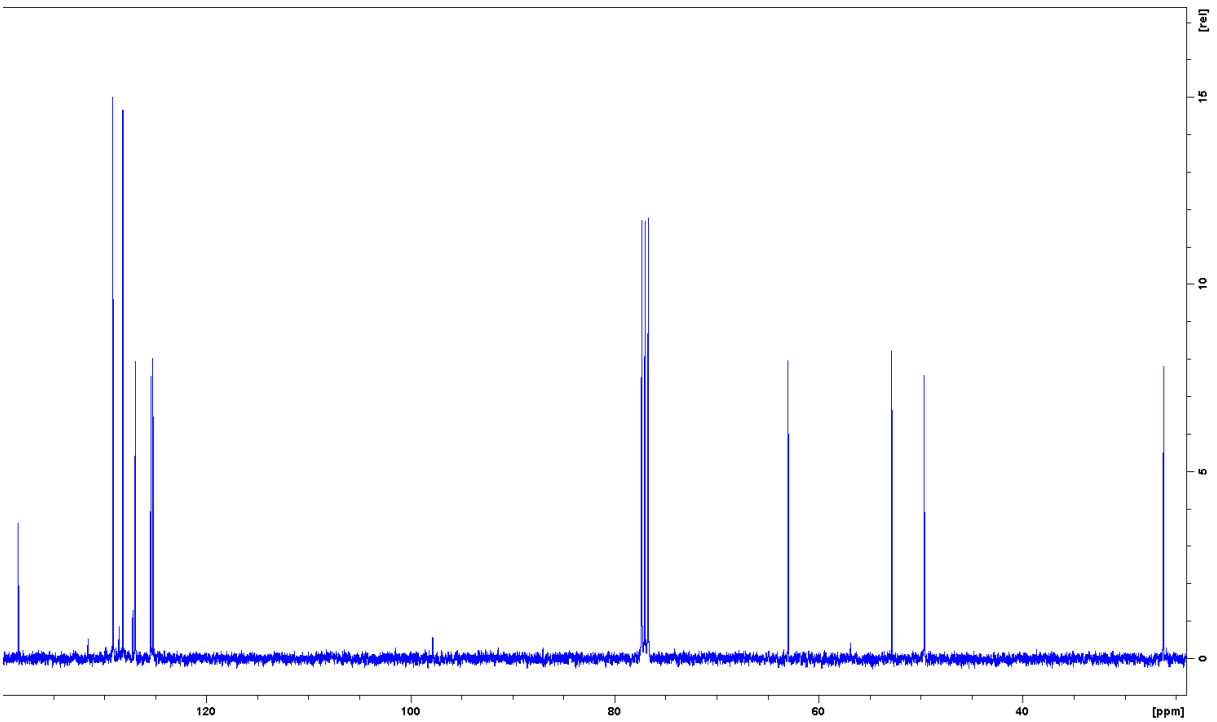
7. Appendix

7.1. Spectra

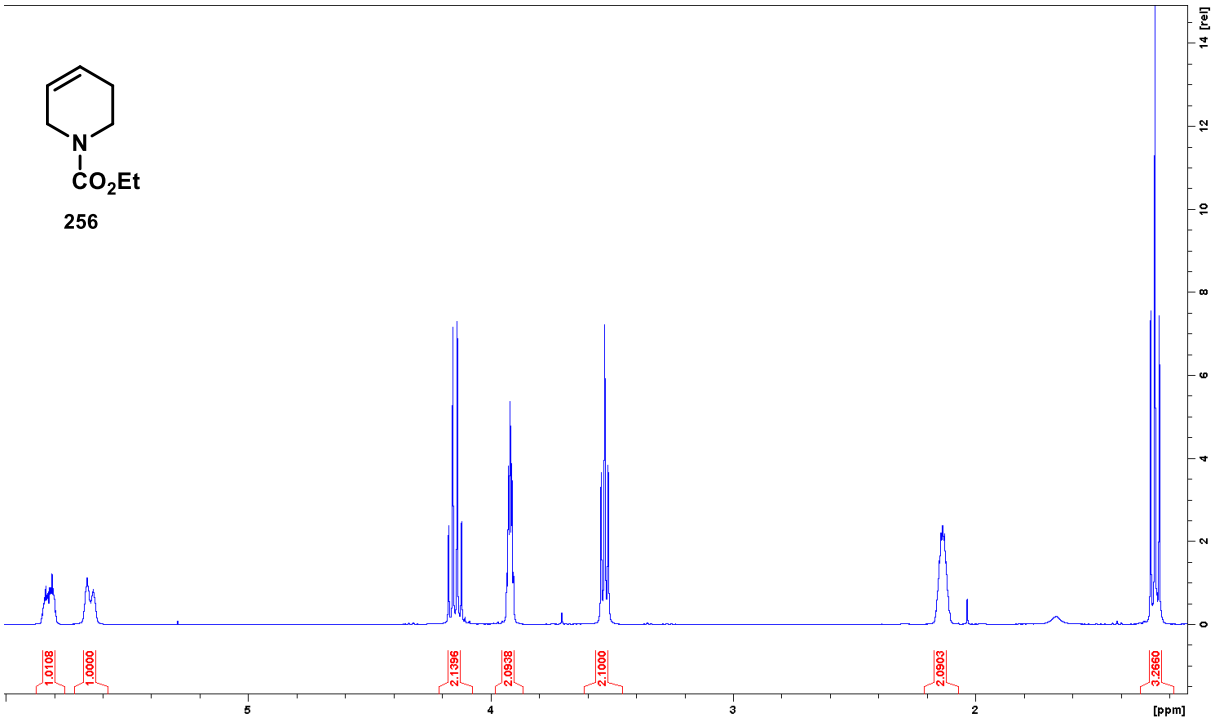
^{1}H NMR (400 MHz, $CDCl_3$)



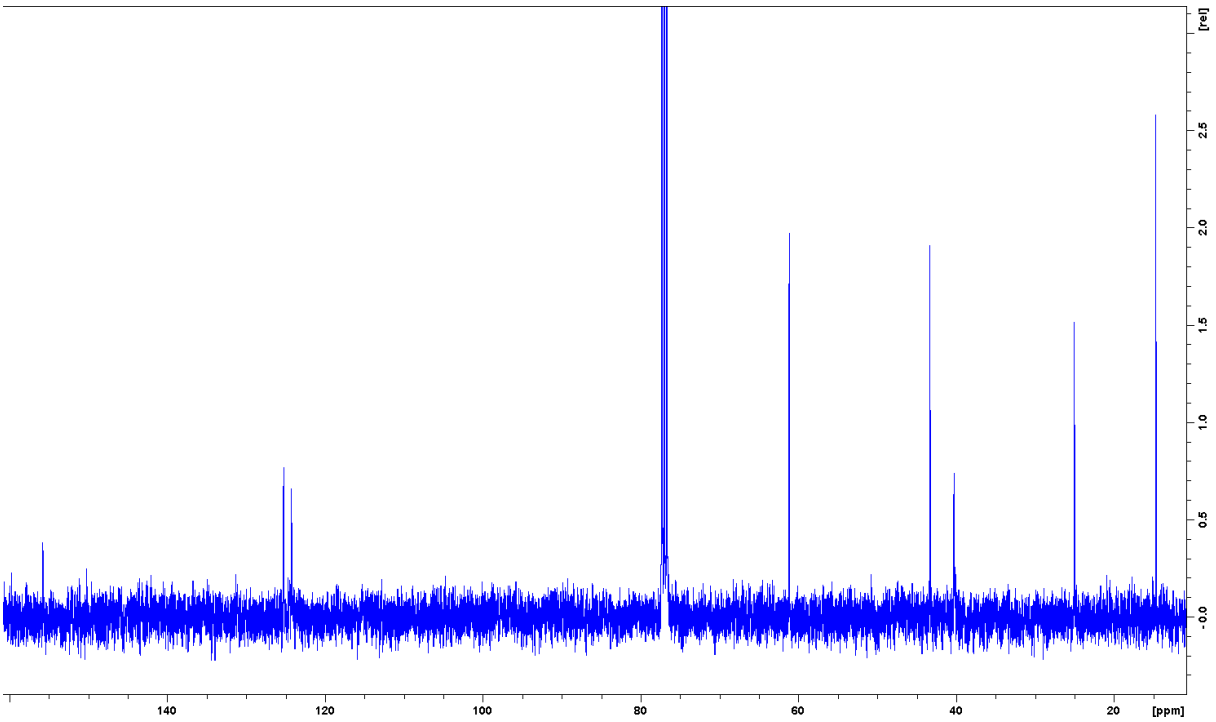
^{13}C NMR (100 MHz, $CDCl_3$)



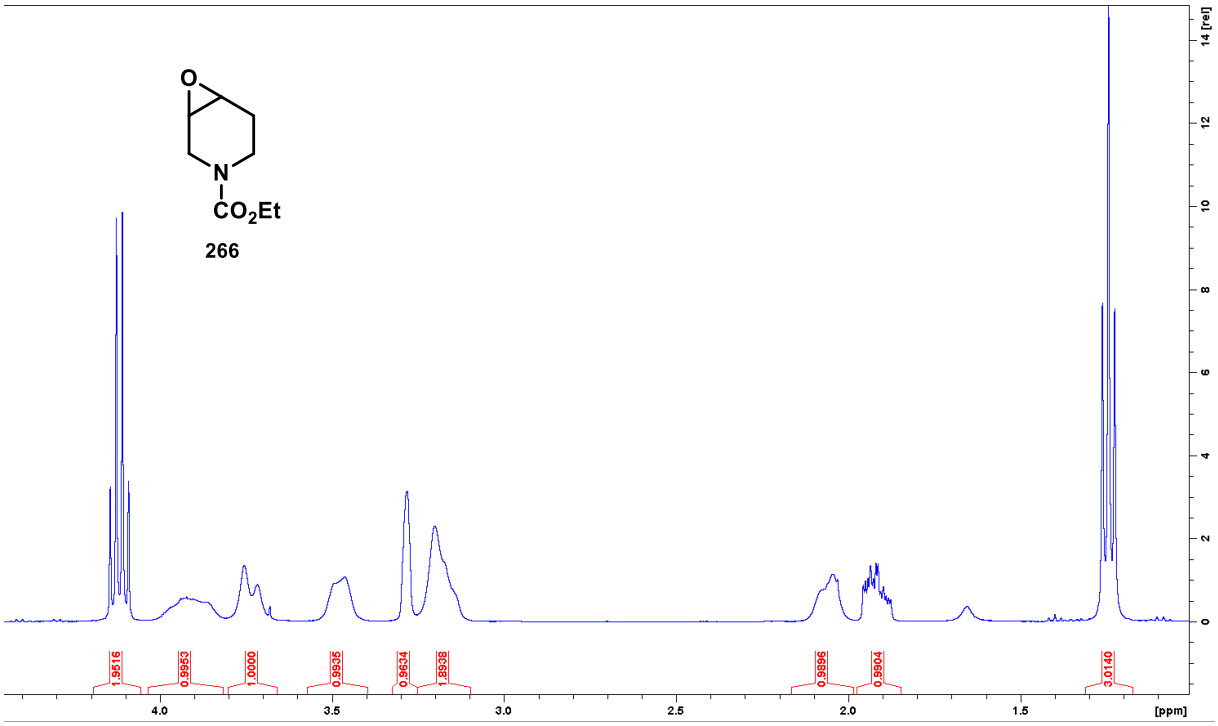
^{1}H NMR (400 MHz, $CDCl_3$)



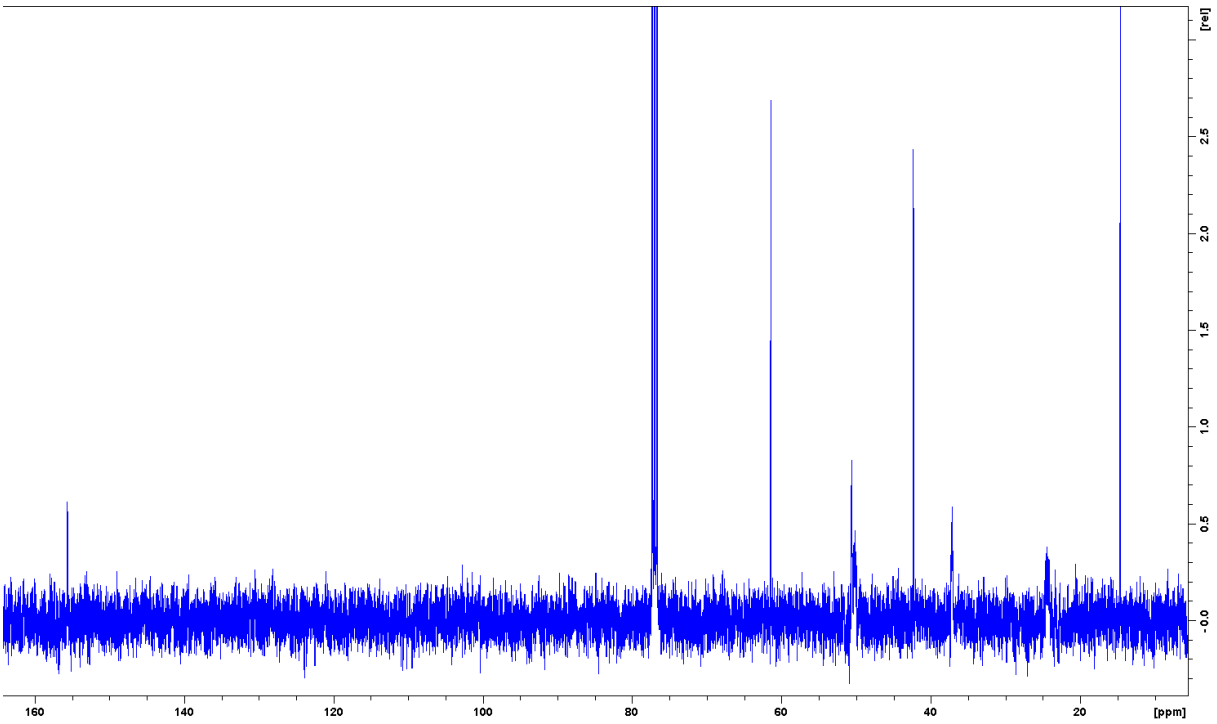
^{13}C NMR (100 MHz, $CDCl_3$)



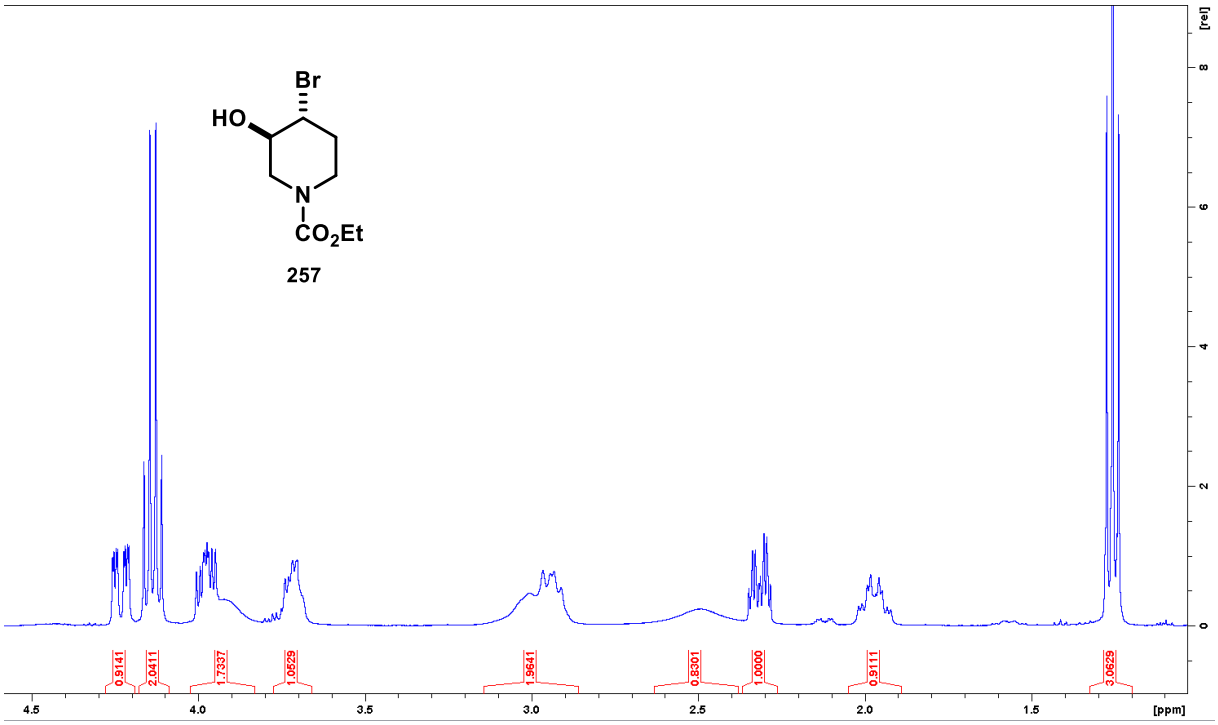
^{1}H NMR (400 MHz, $CDCl_3$)



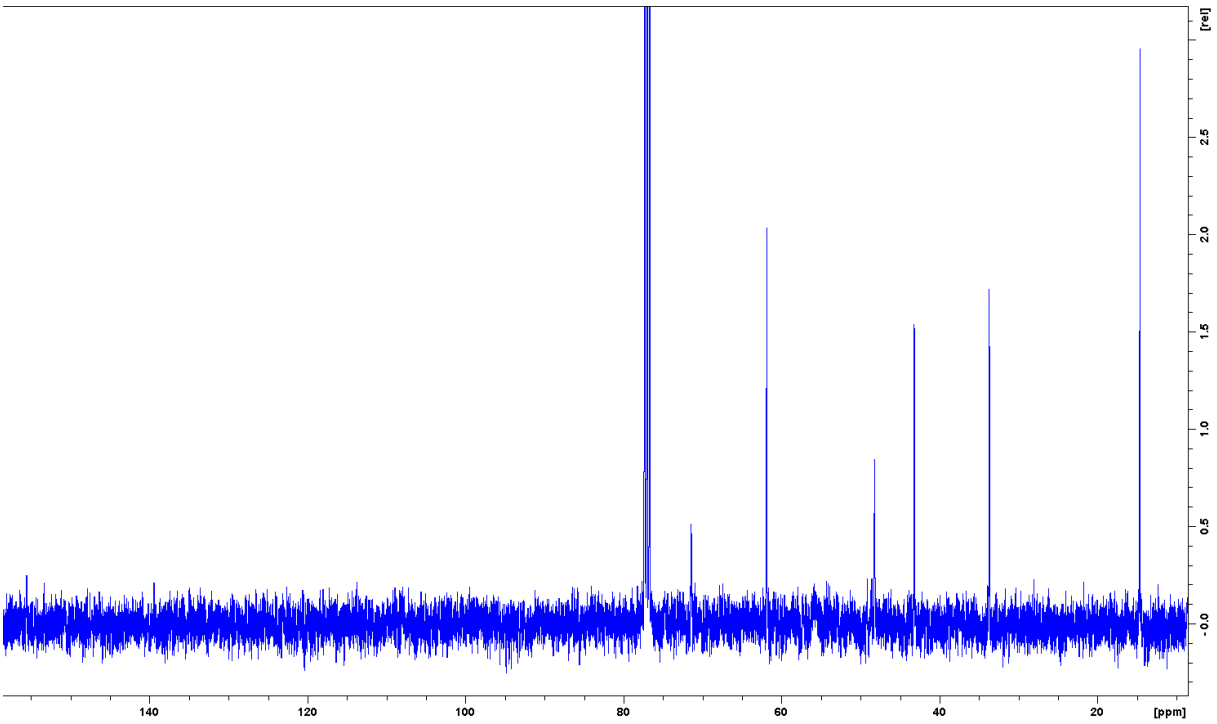
^{13}C NMR (100 MHz, $CDCl_3$)



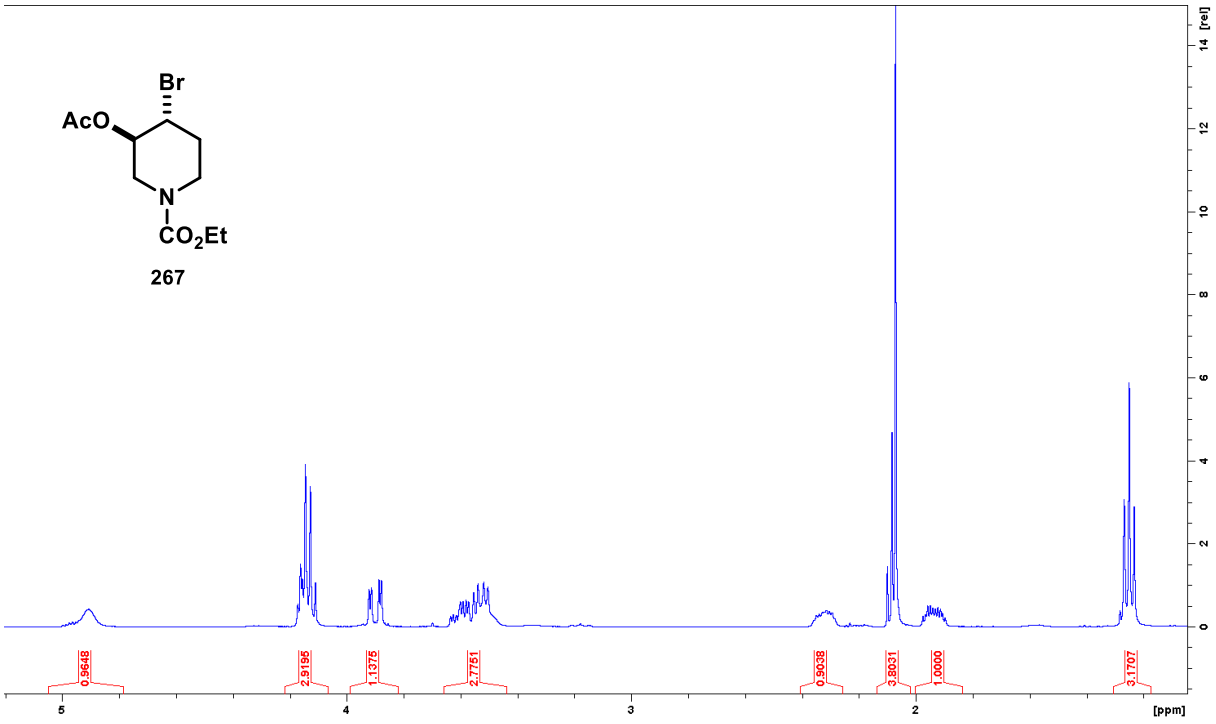
^{1}H NMR (400 MHz, $CDCl_3$)



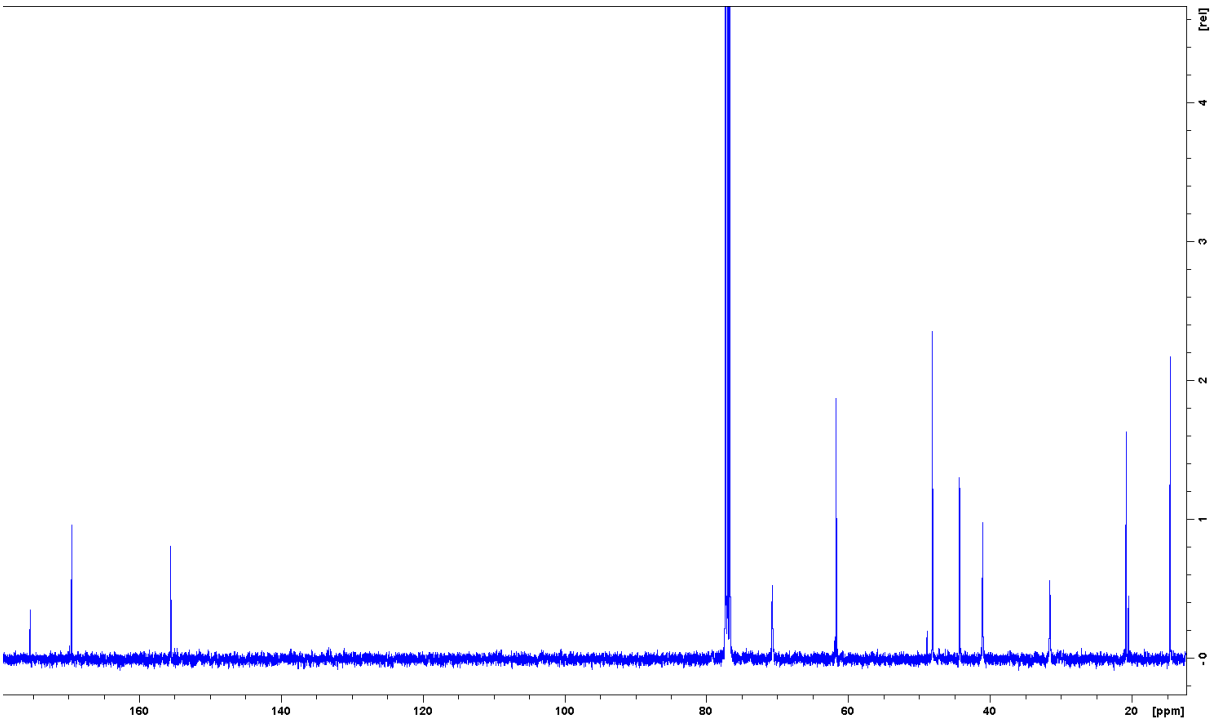
^{13}C NMR (100 MHz, $CDCl_3$)



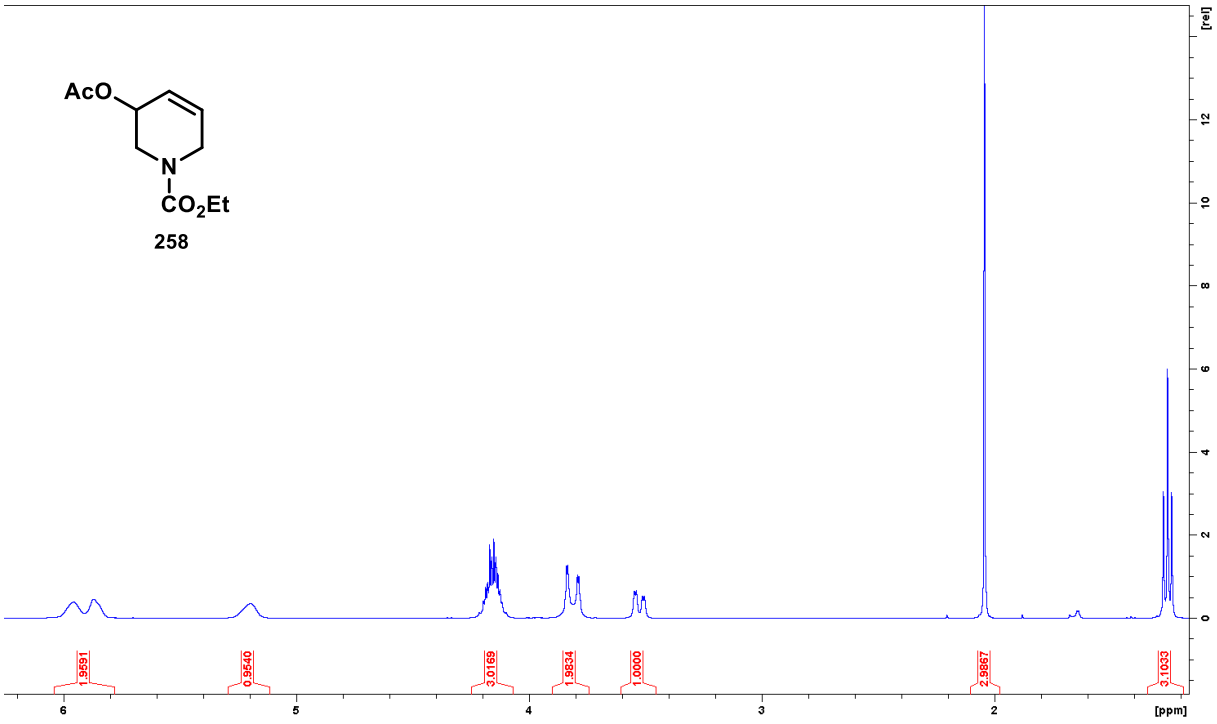
^{1}H NMR (400 MHz, $CDCl_3$)



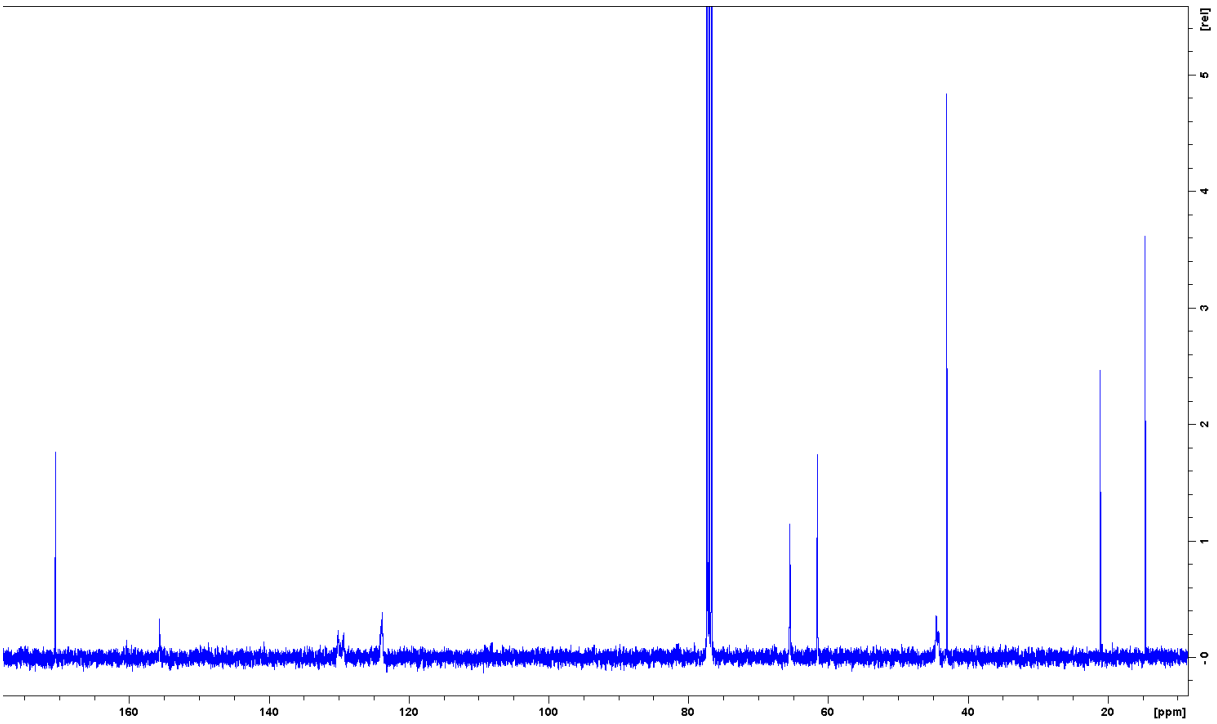
^{13}C NMR (100 MHz, $CDCl_3$)



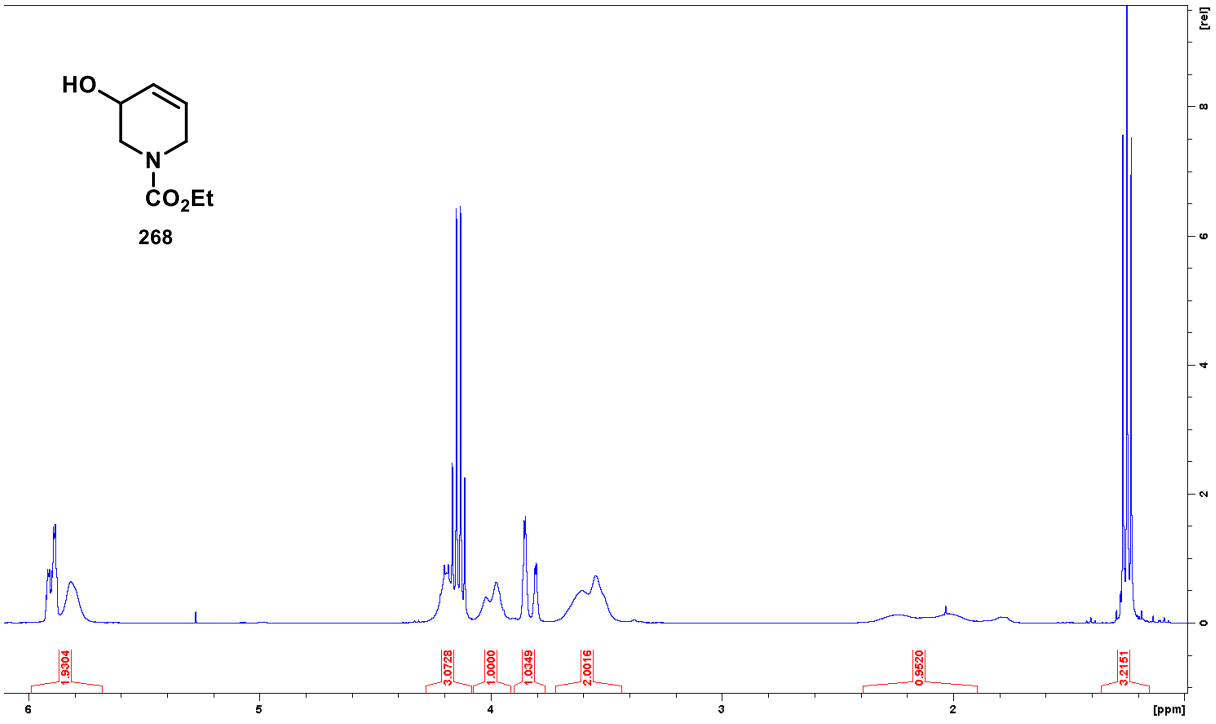
^{1}H NMR (400 MHz, $CDCl_3$)



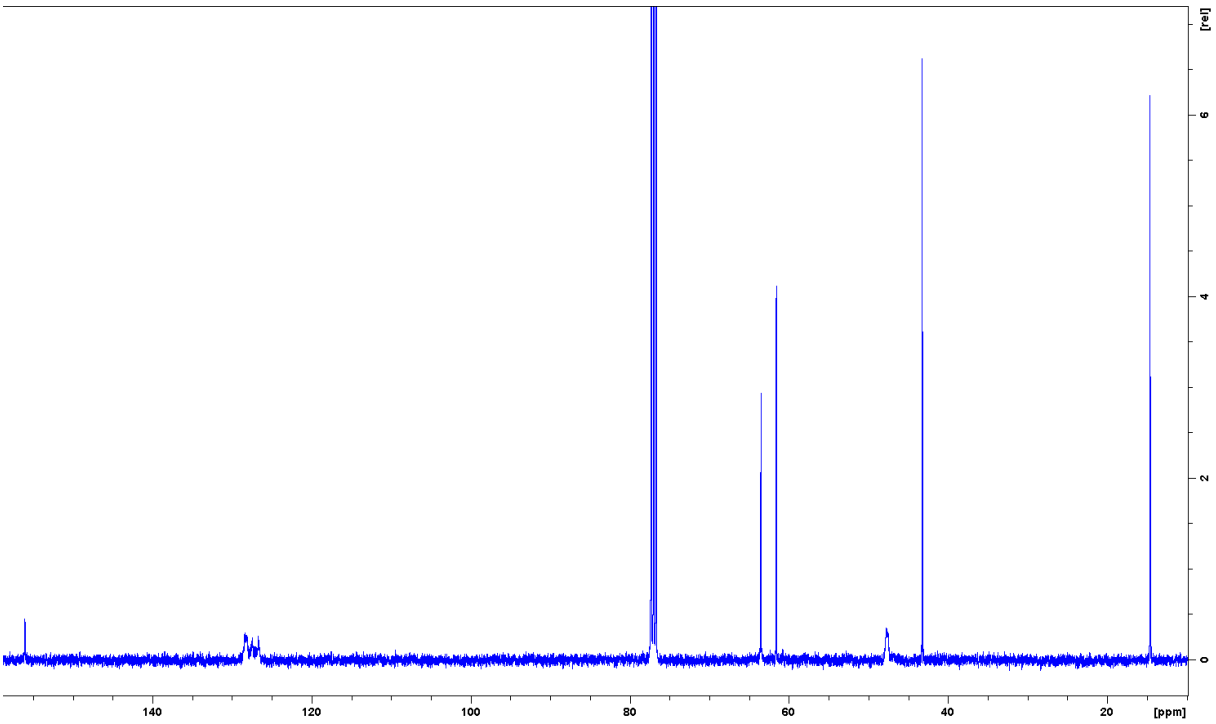
^{13}C NMR (100 MHz, $CDCl_3$)



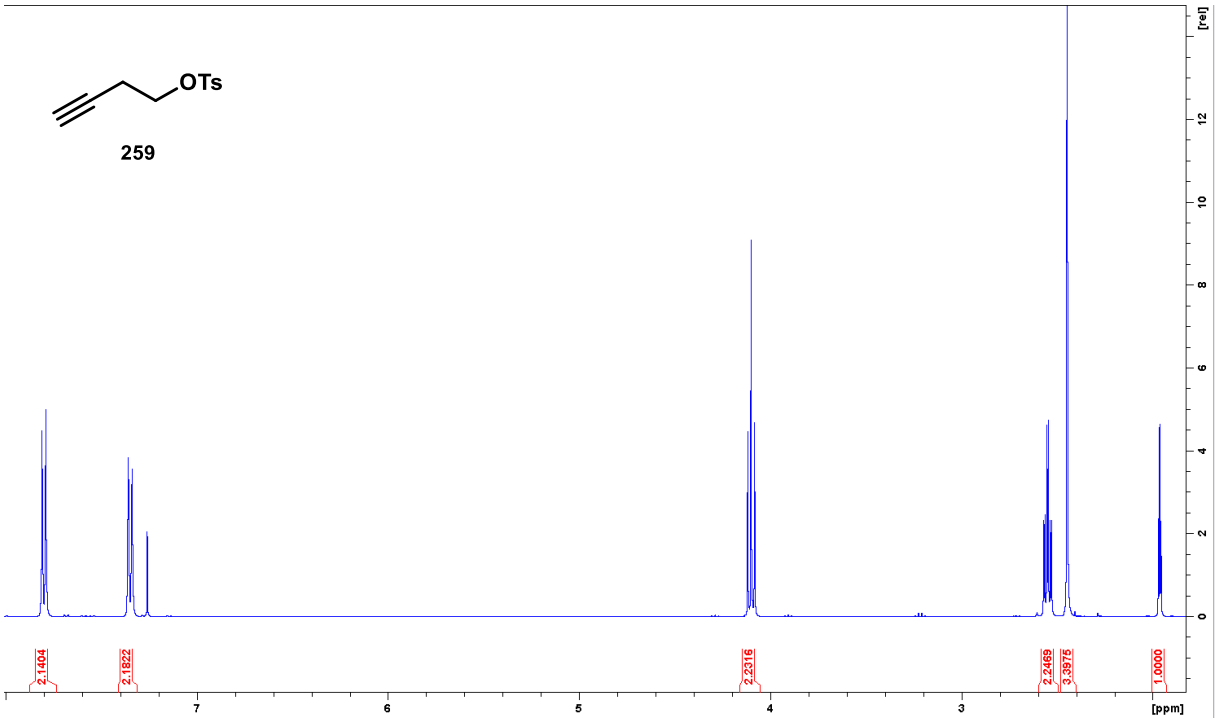
^{1}H NMR (400 MHz, $CDCl_3$)



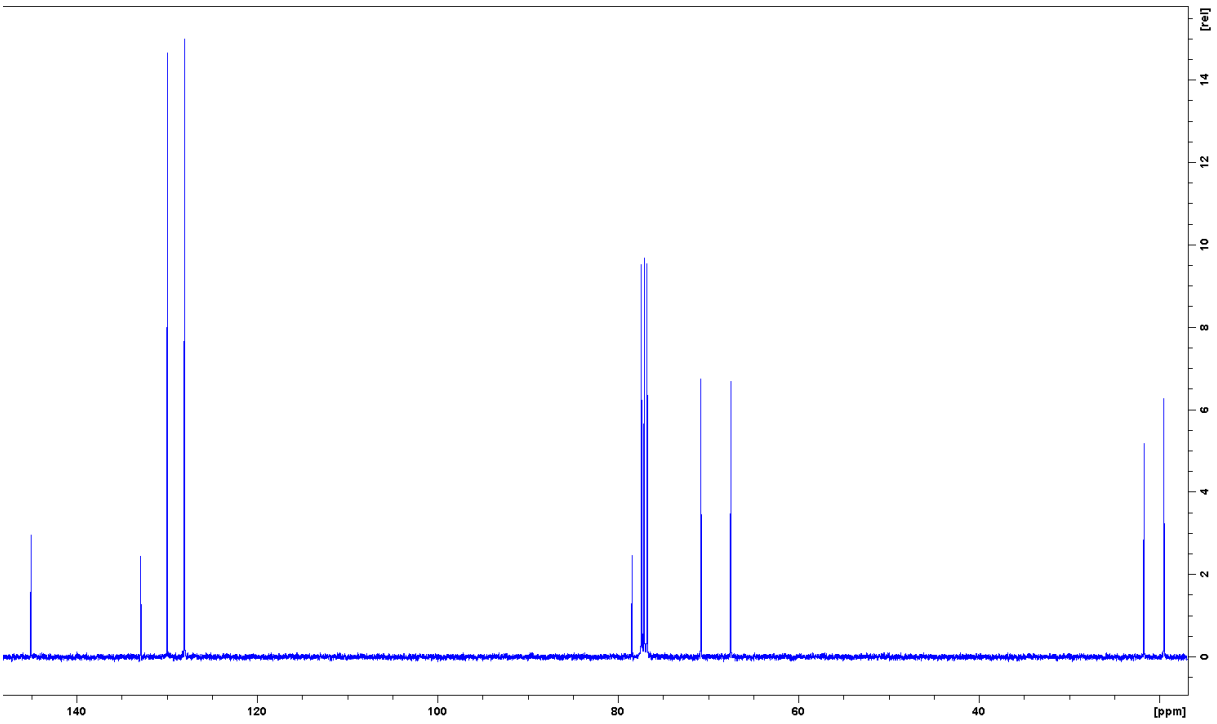
^{13}C NMR (100 MHz, $CDCl_3$)



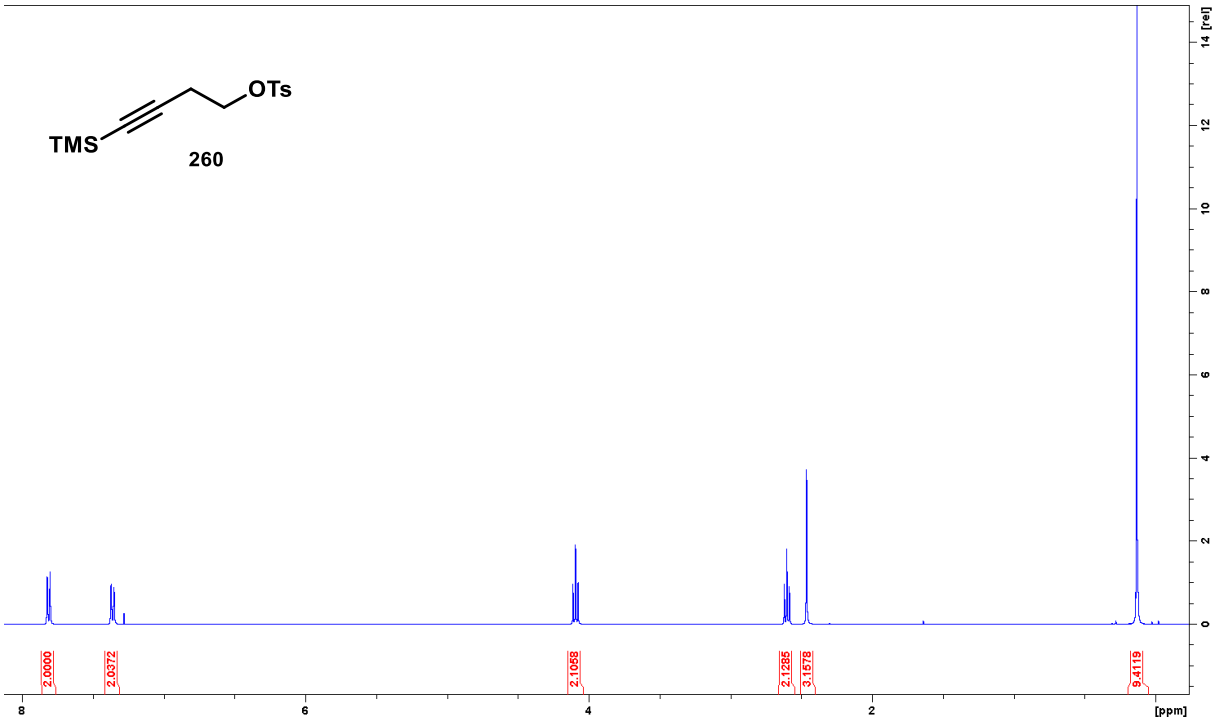
^{1}H NMR (400 MHz, $CDCl_3$)



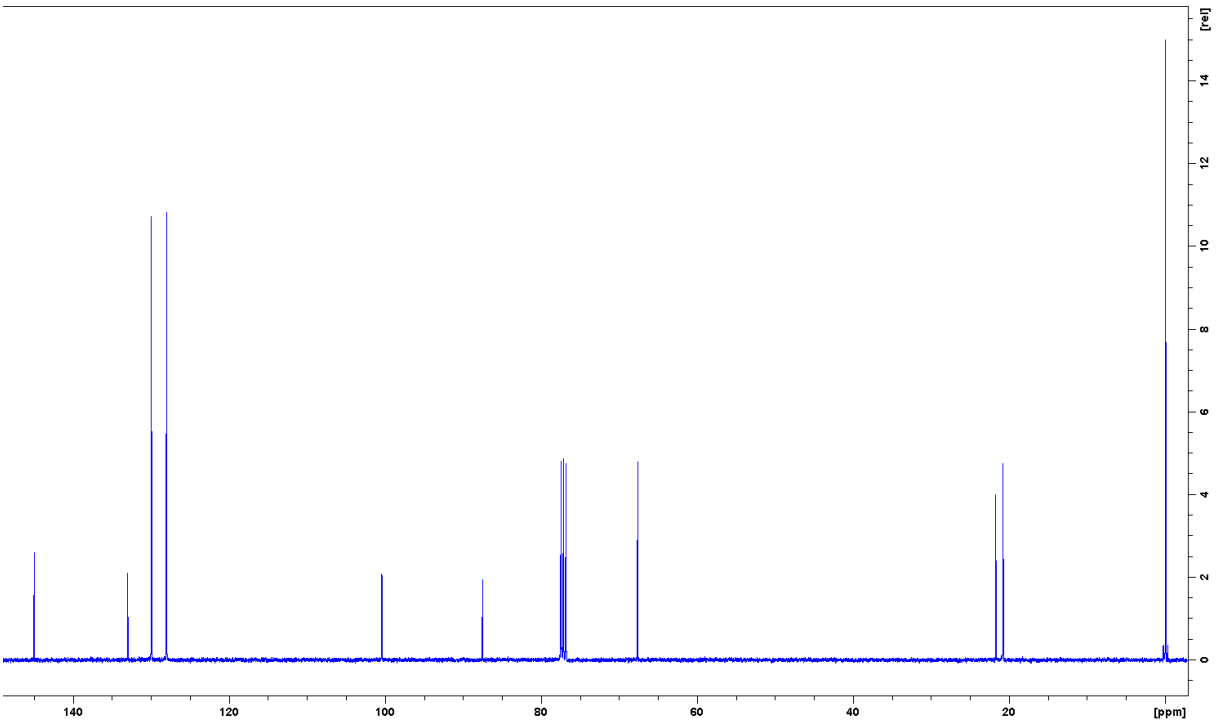
^{13}C NMR (100 MHz, $CDCl_3$)



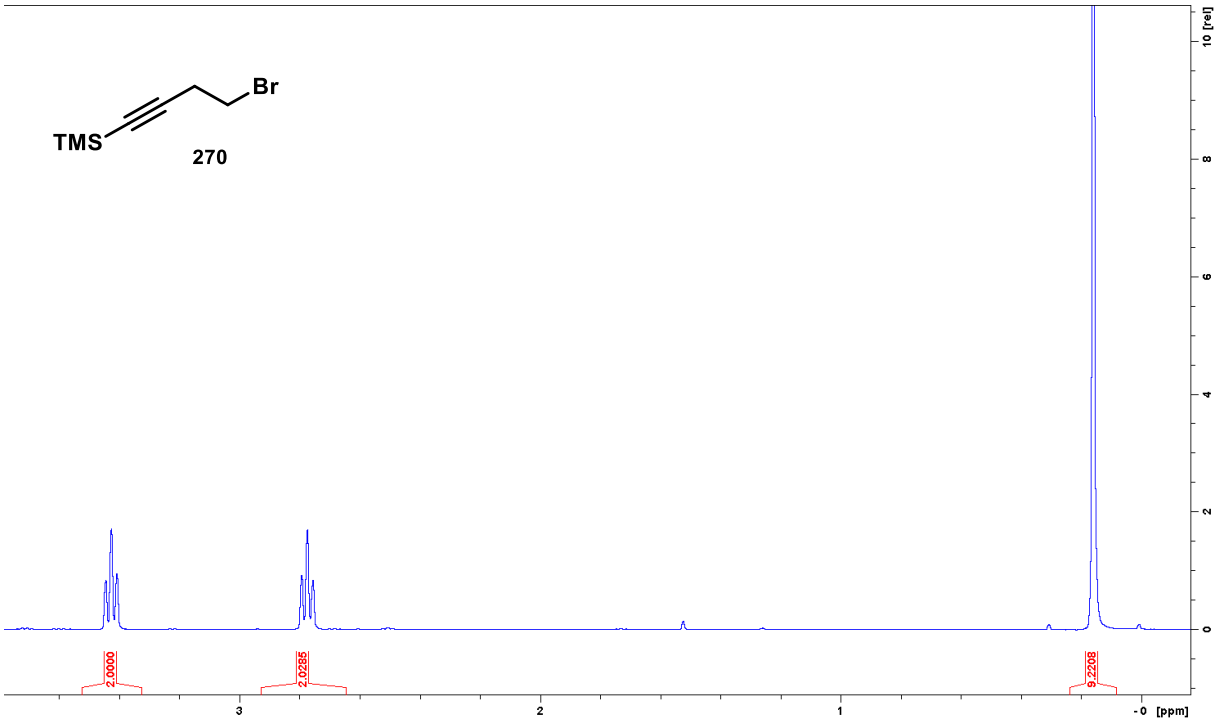
^{1}H NMR (400 MHz, $CDCl_3$)



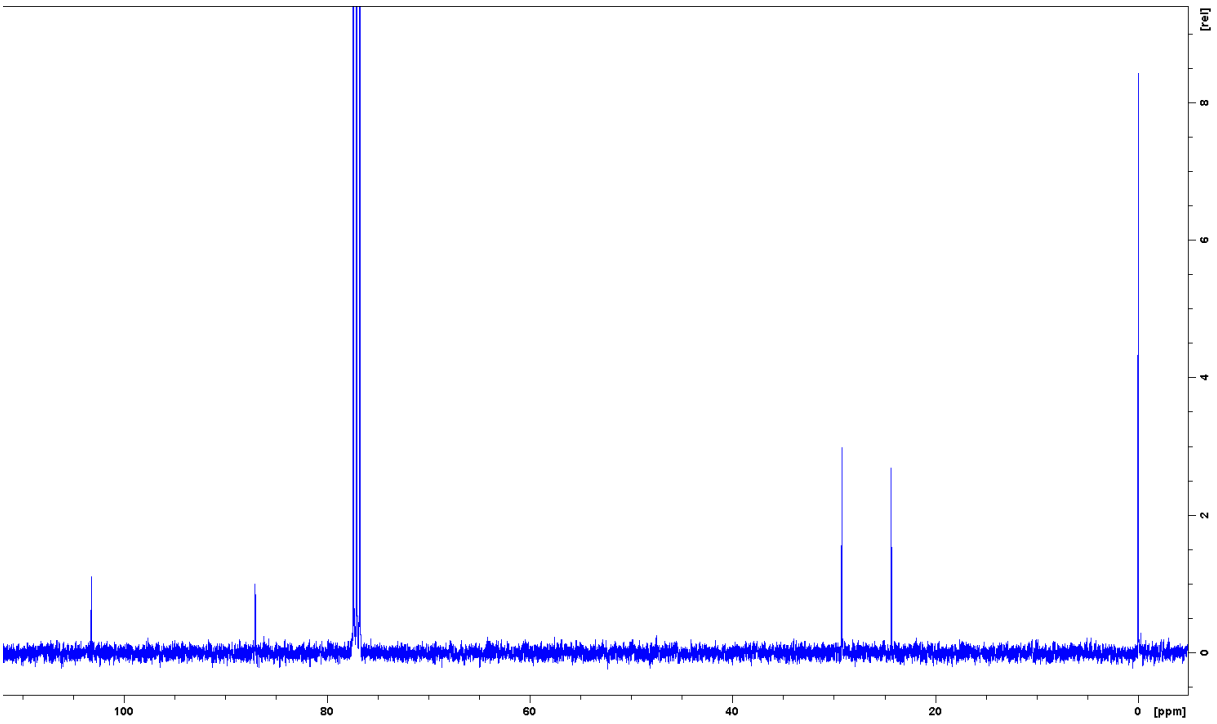
^{13}C NMR (100 MHz, $CDCl_3$)



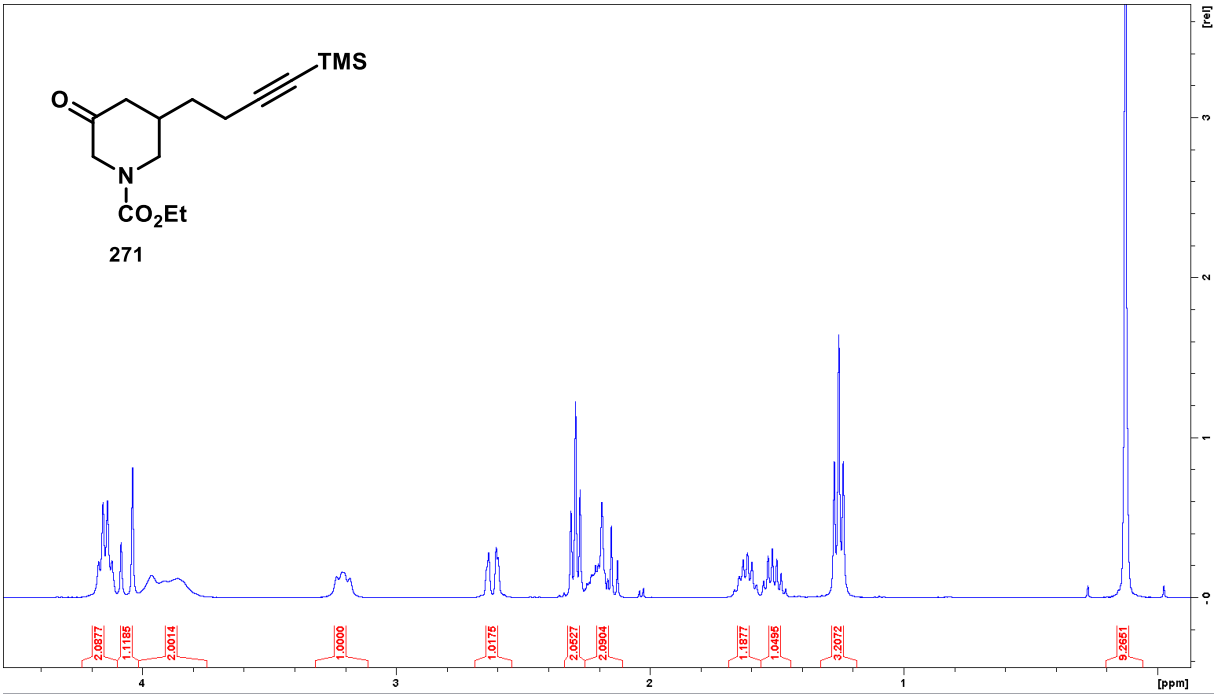
^{1}H NMR (400 MHz, $CDCl_3$)



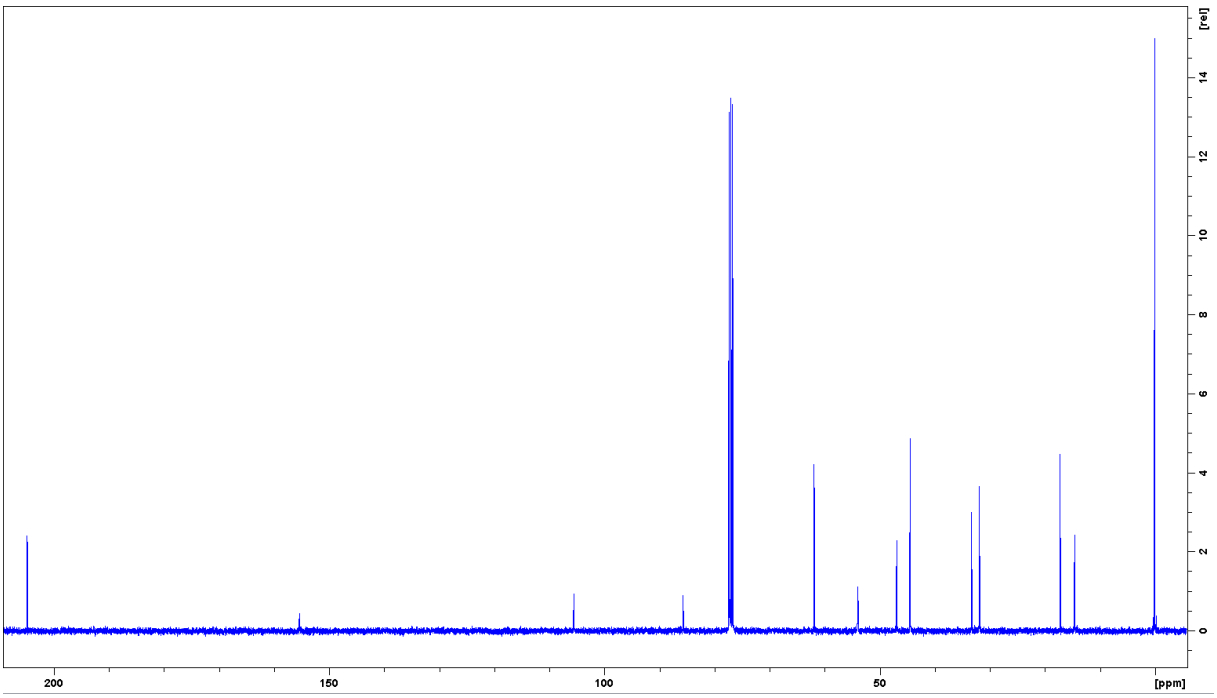
^{13}C NMR (100 MHz, $CDCl_3$)



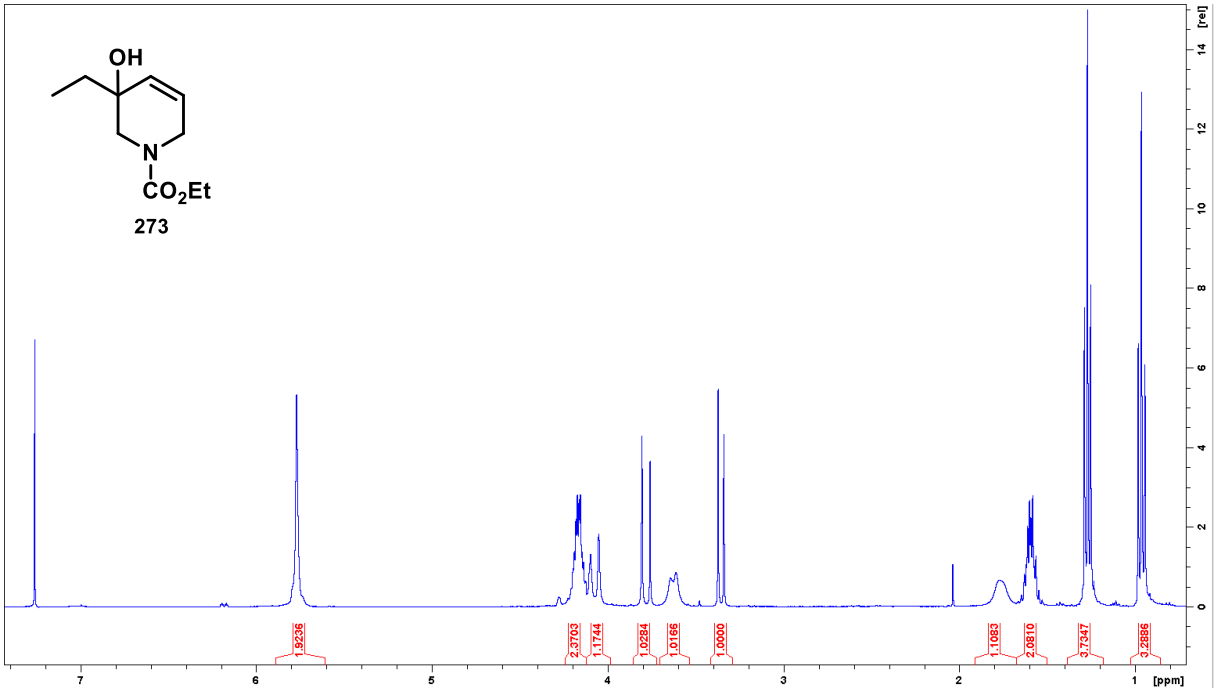
^{1}H NMR (400 MHz, $CDCl_3$)



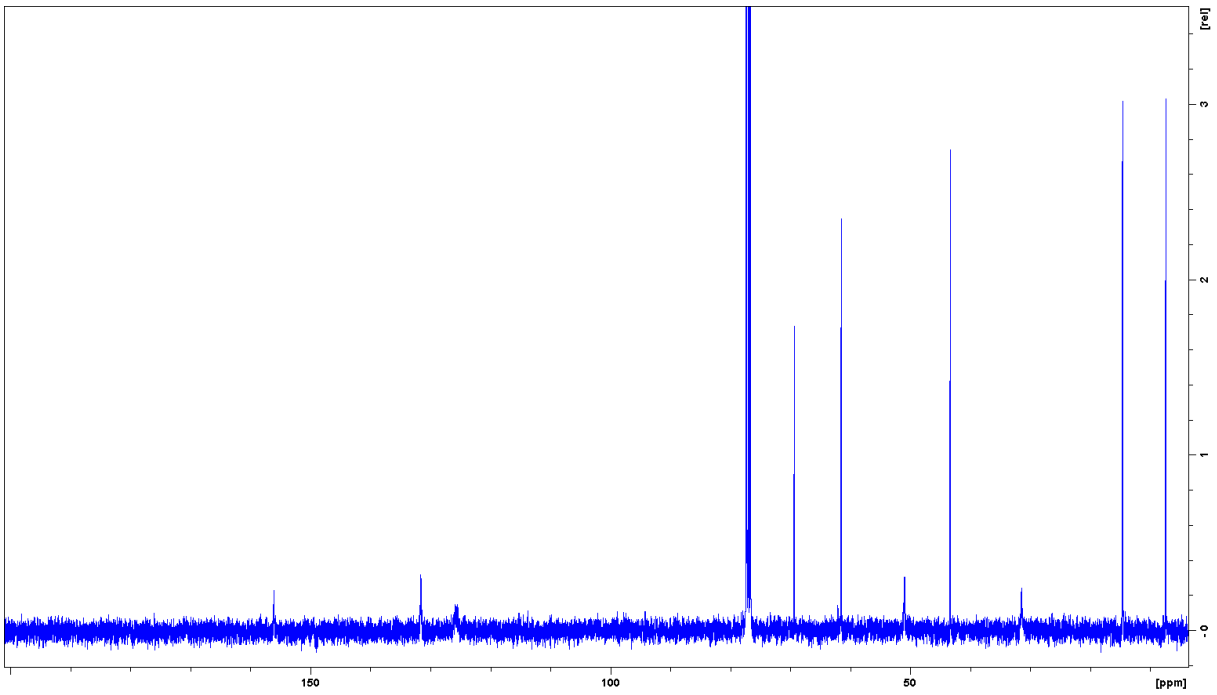
^{13}C NMR (100 MHz, $CDCl_3$)



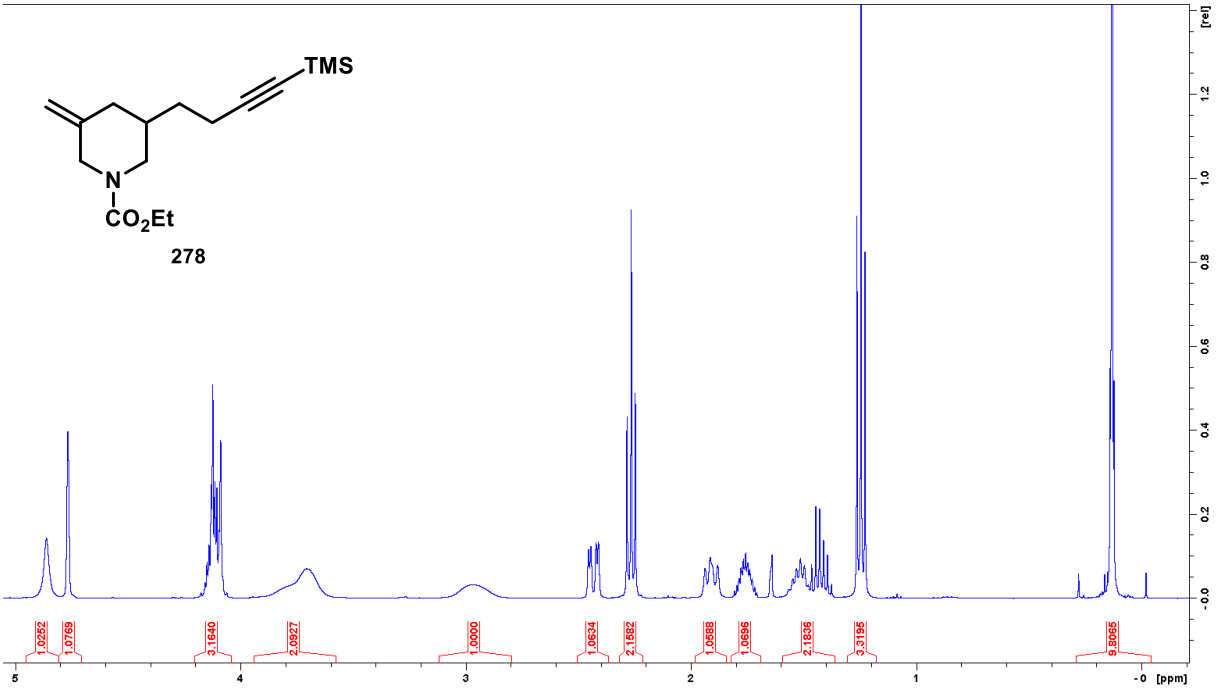
^{1}H NMR (400 MHz, $CDCl_3$)



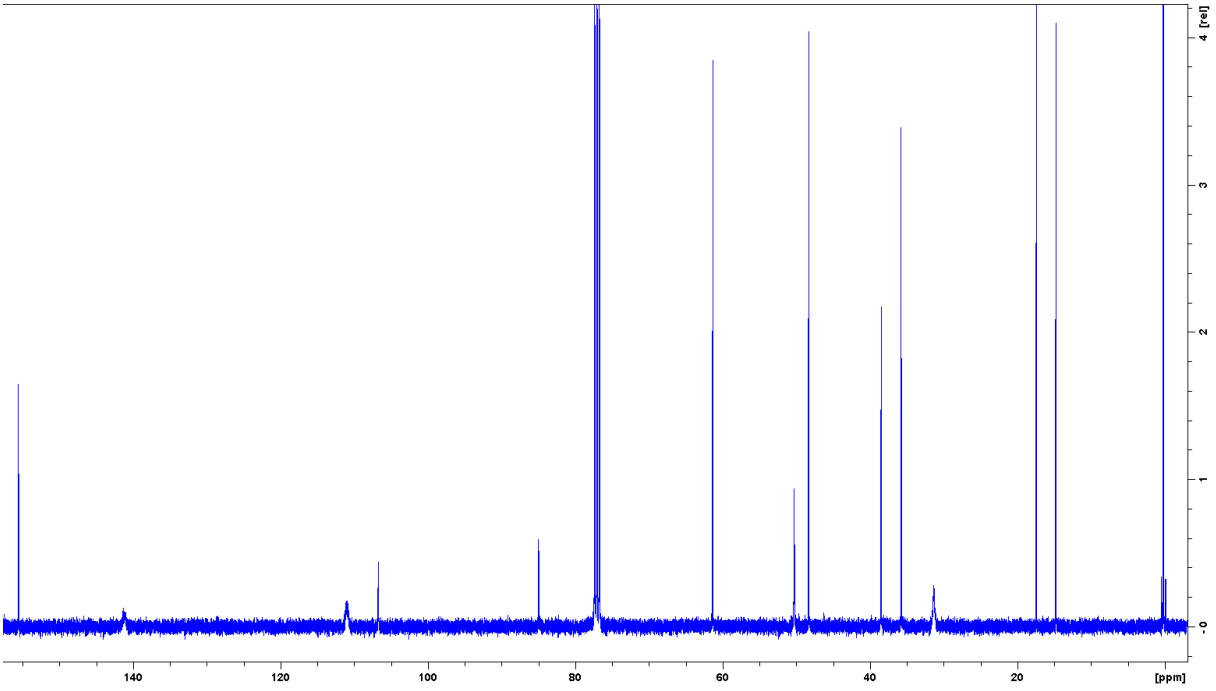
^{13}C NMR (100 MHz, $CDCl_3$)



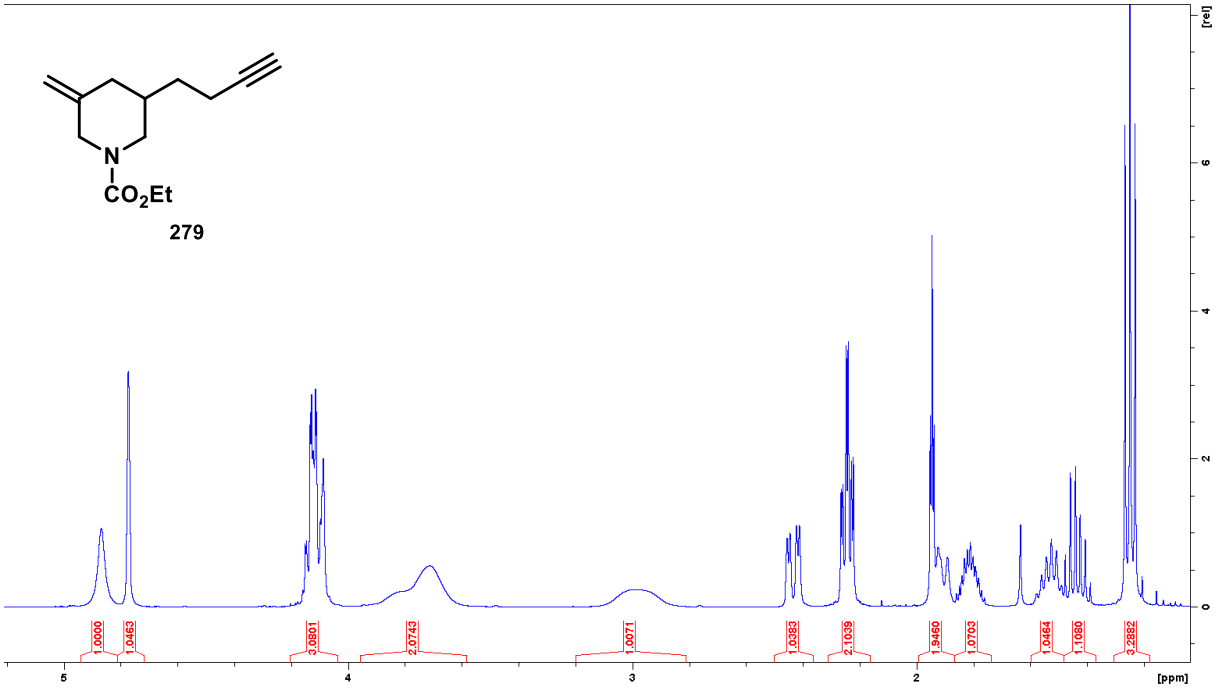
^{1}H NMR (400 MHz, $CDCl_3$)



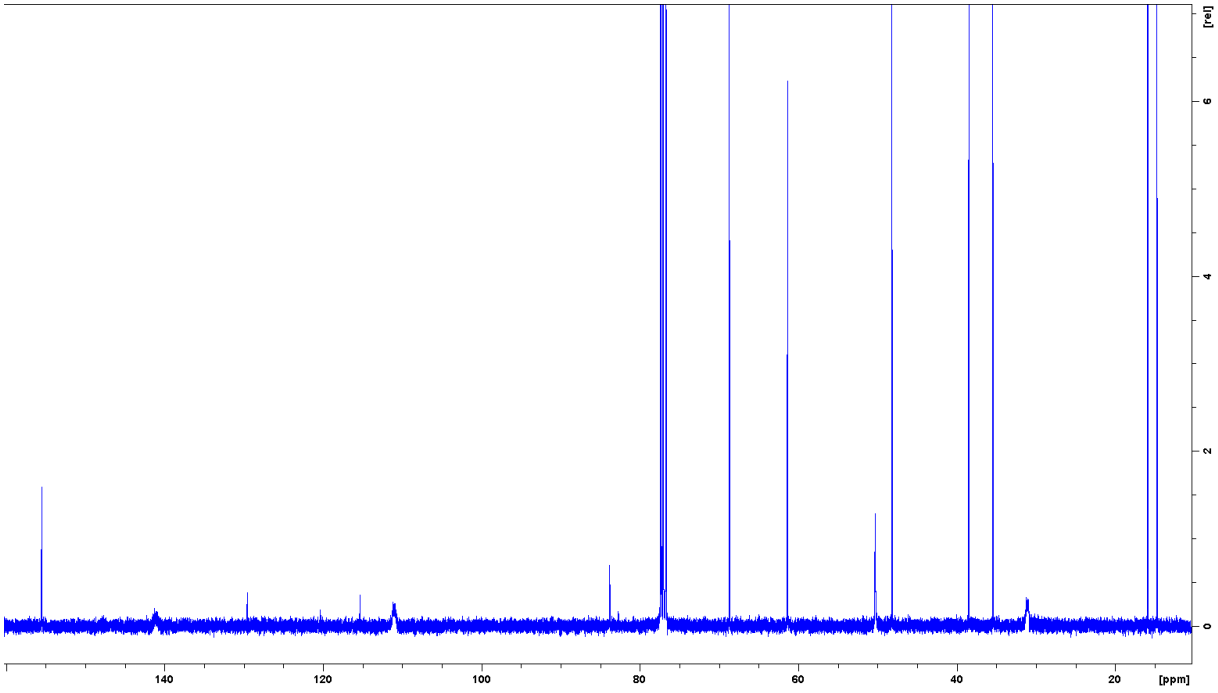
^{13}C NMR (100 MHz, $CDCl_3$)



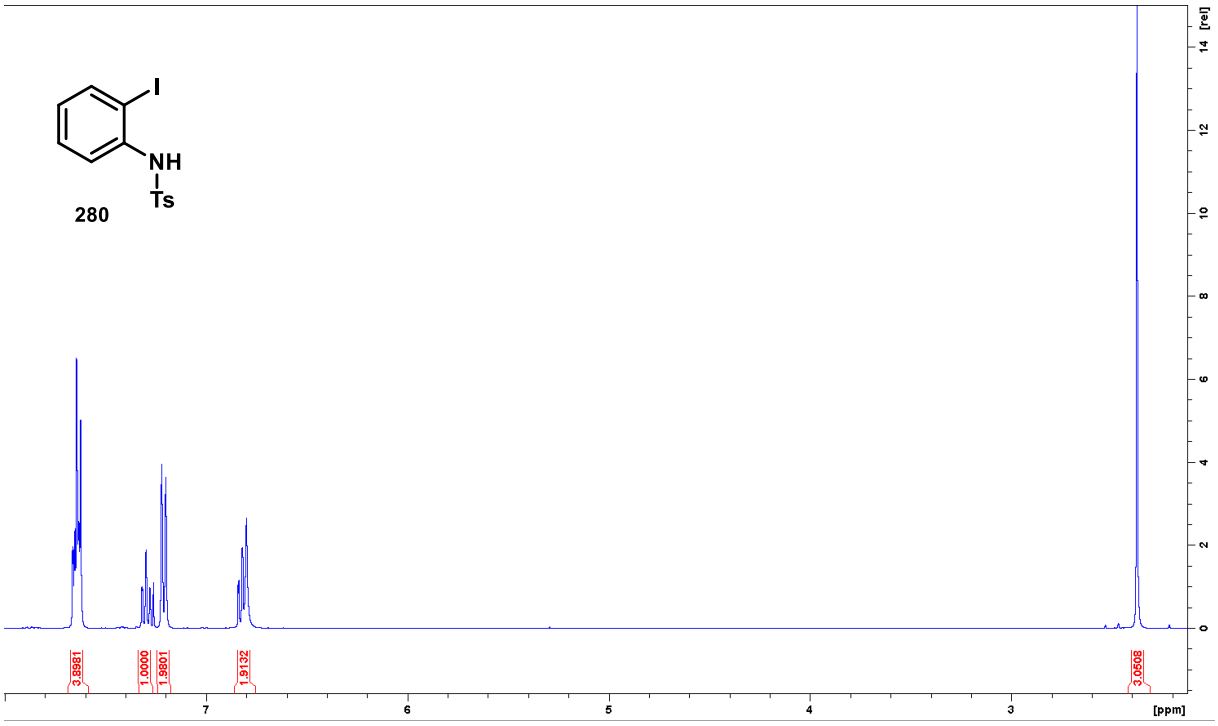
^{1}H NMR (400 MHz, $CDCl_3$)



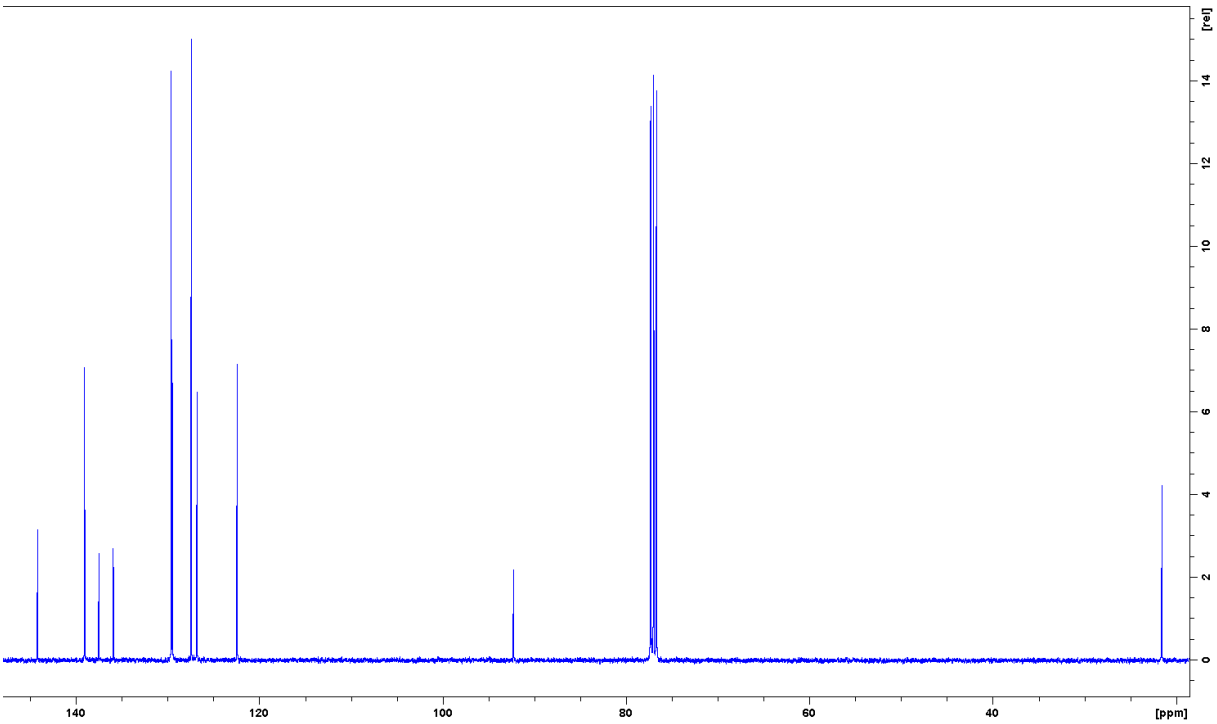
^{13}C NMR (100 MHz, $CDCl_3$)



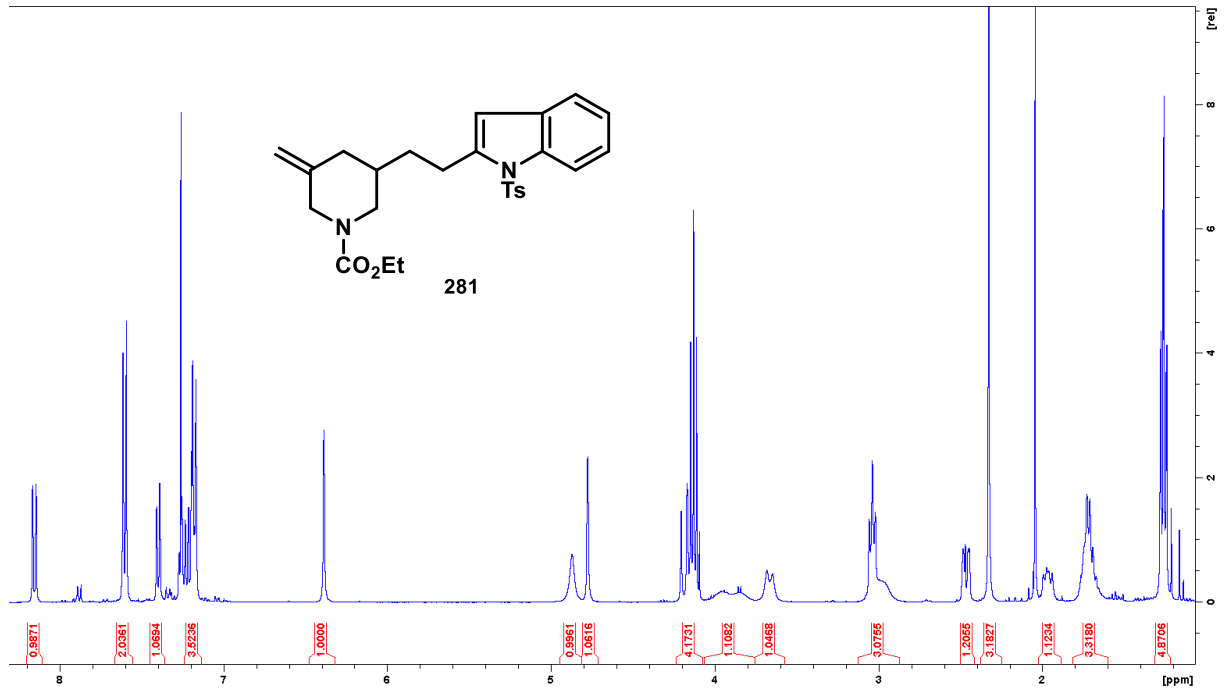
^{1}H NMR (400 MHz, $CDCl_3$)



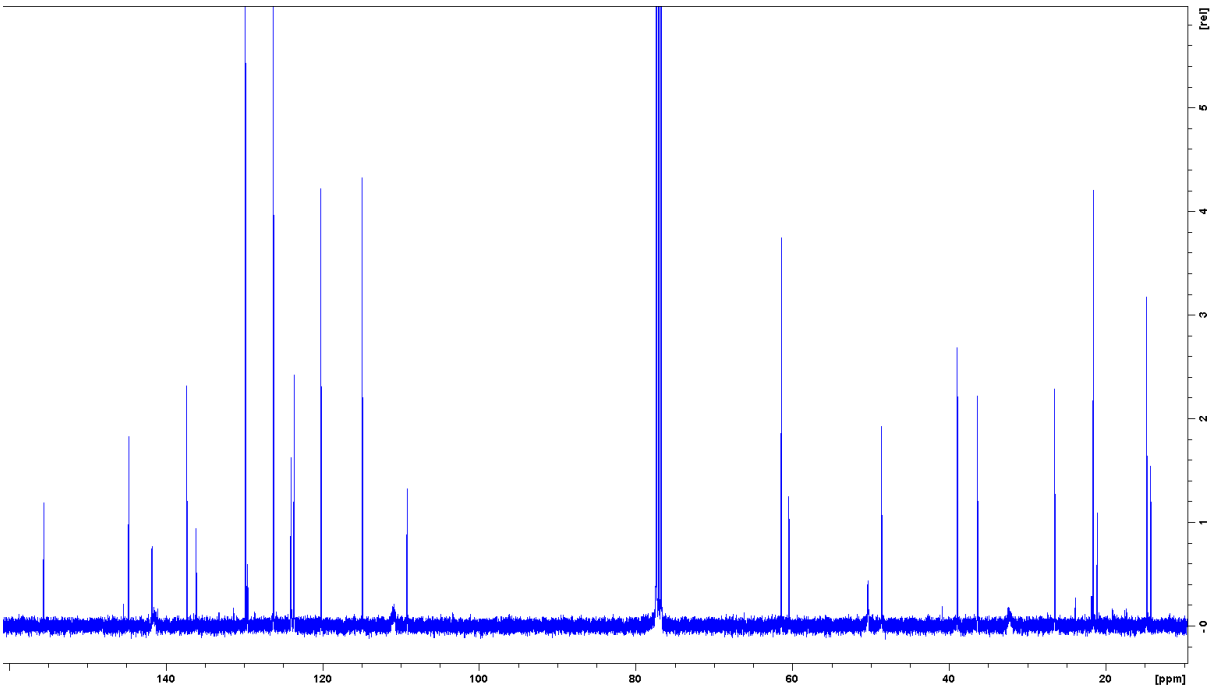
^{13}C NMR (100 MHz, $CDCl_3$)



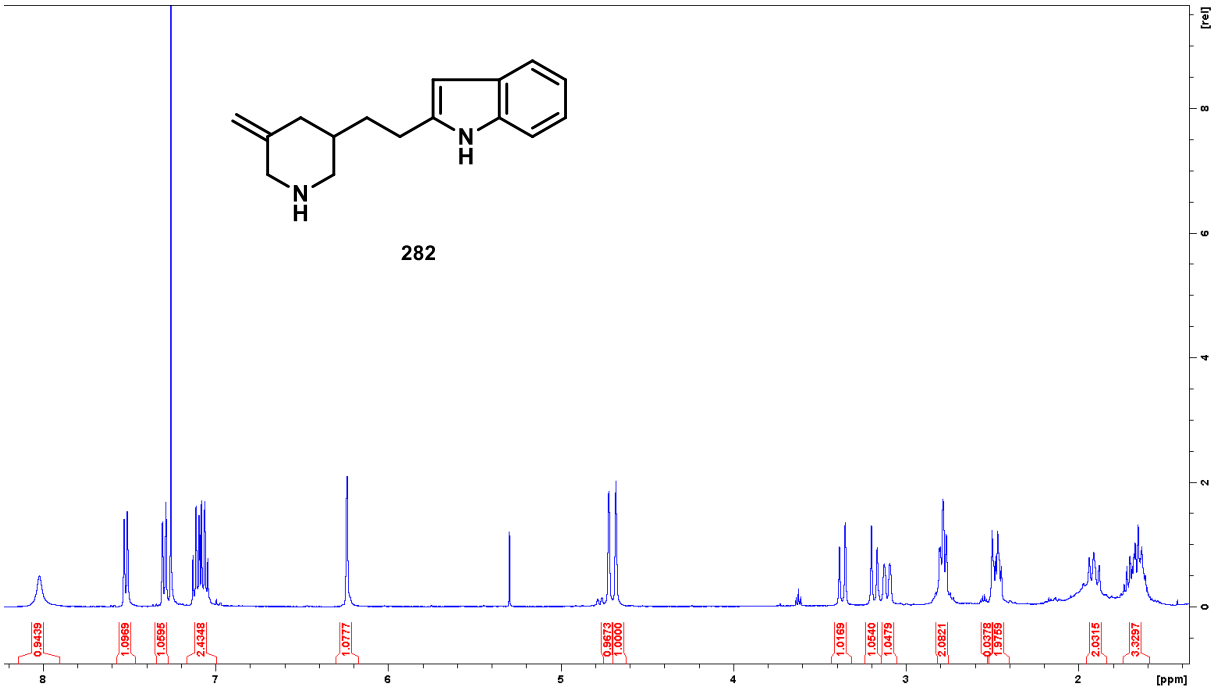
^{1}H NMR (400 MHz, $CDCl_3$)



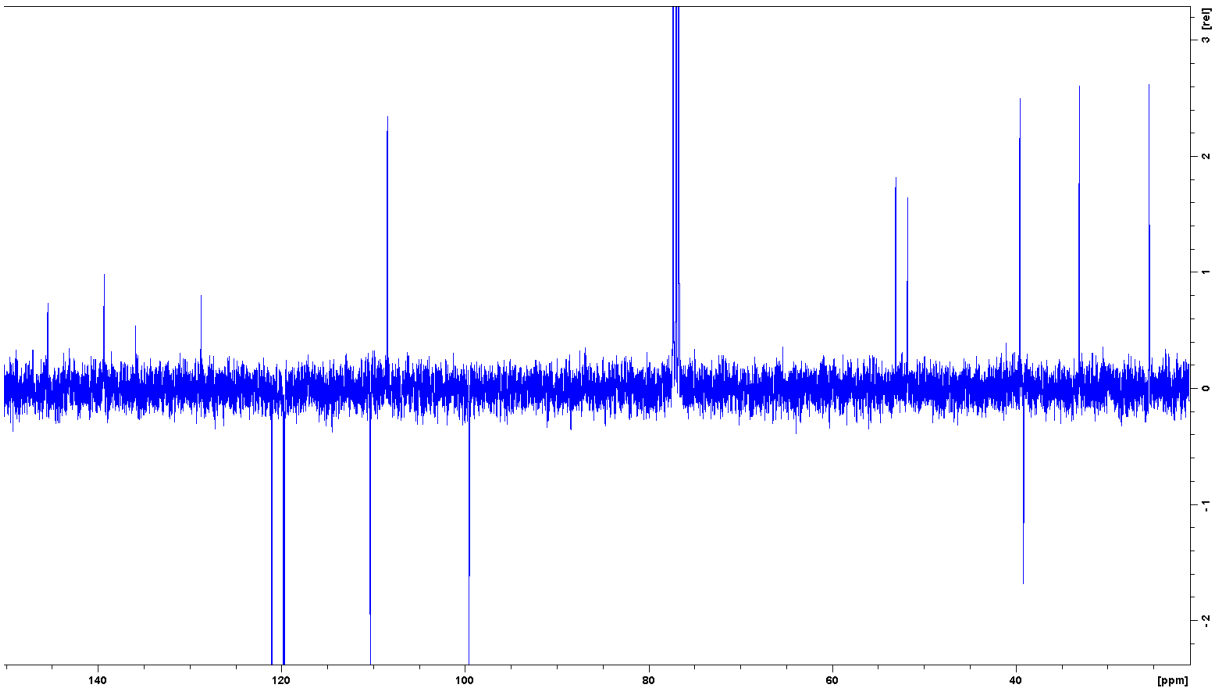
^{13}C NMR (100 MHz, $CDCl_3$)



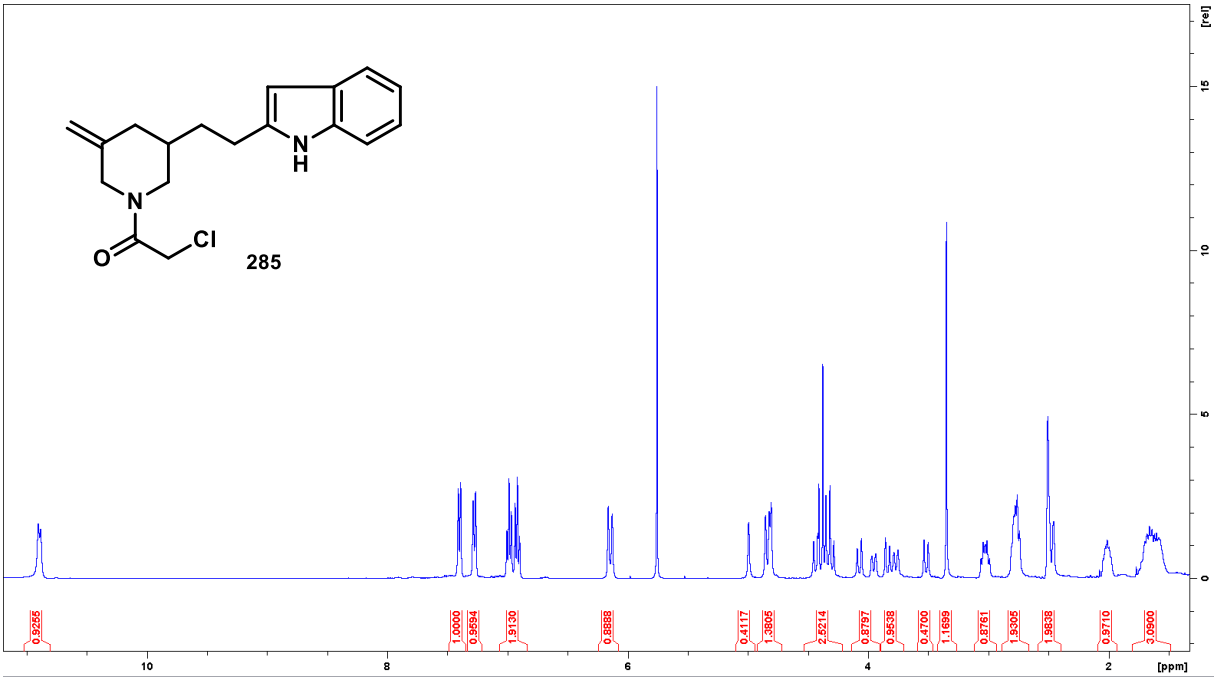
^{1}H NMR (400 MHz, $CDCl_3$)



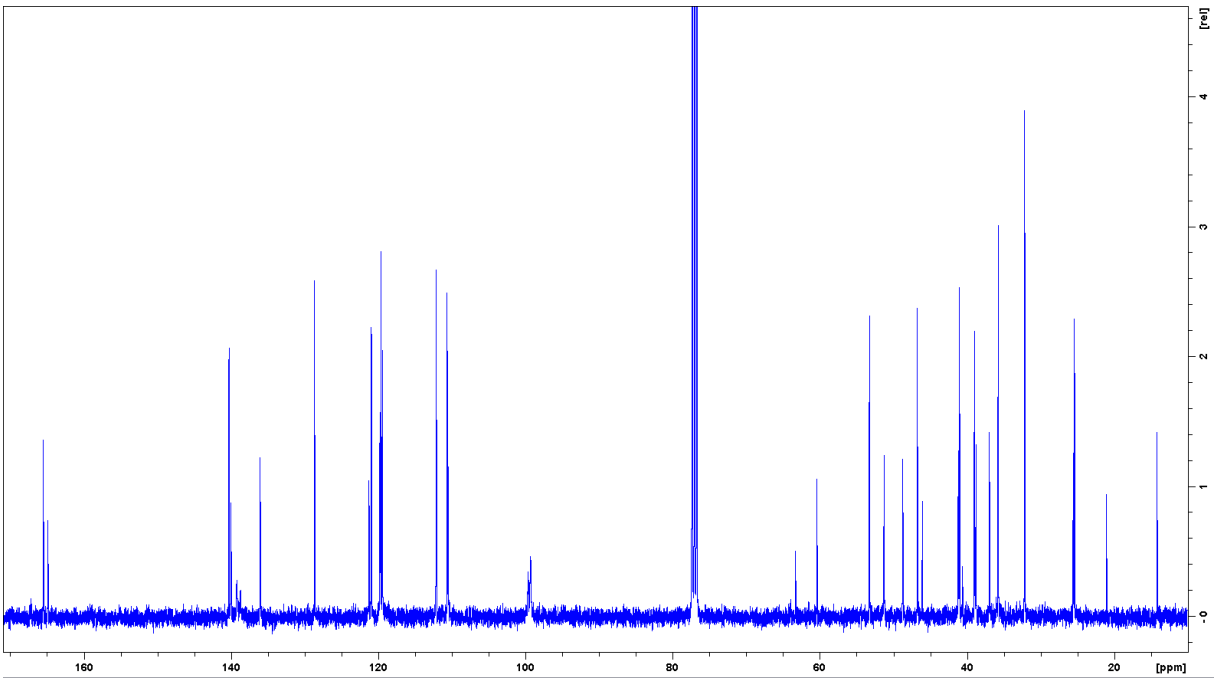
^{13}C NMR (100 MHz, $CDCl_3$)



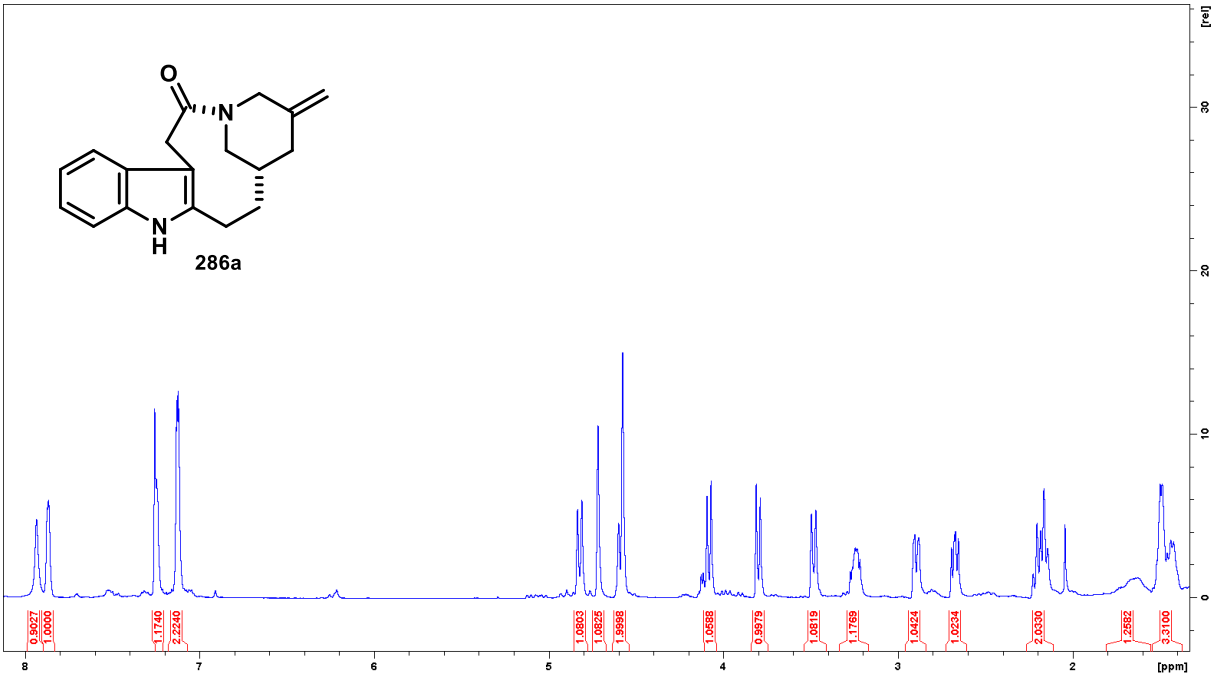
^{1}H NMR (400 MHz, T = 370 K, DMSO-d^{6})



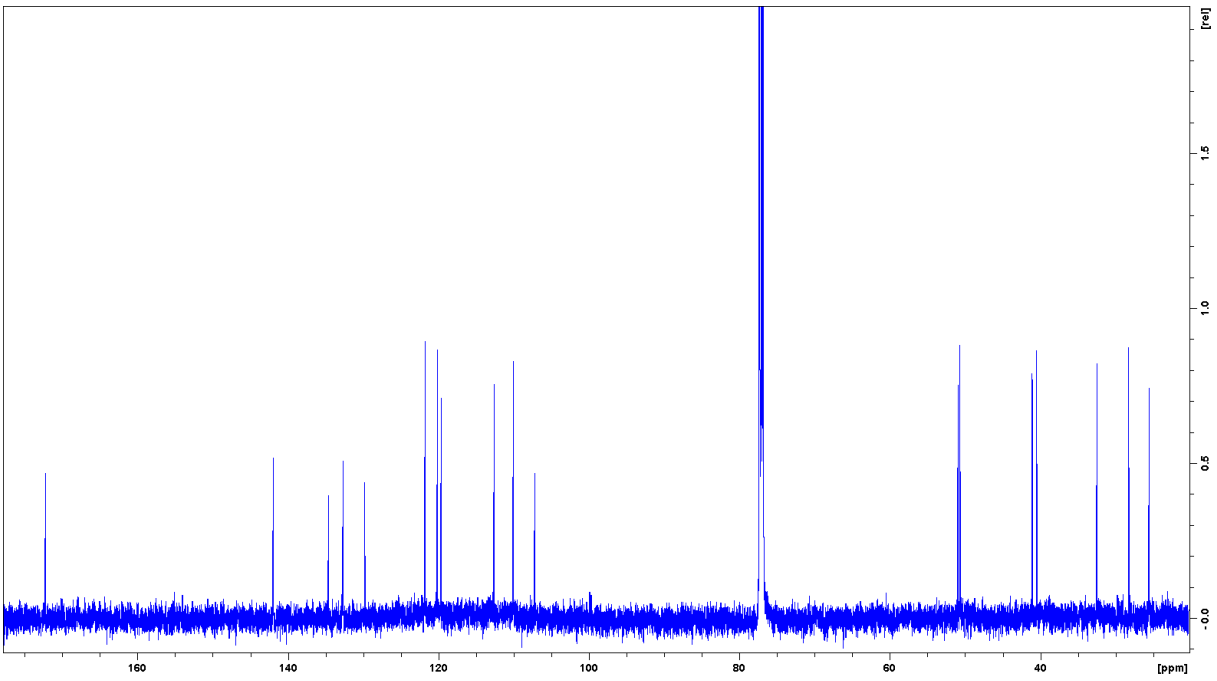
^{13}C NMR (100 MHz, $CDCl_3$)



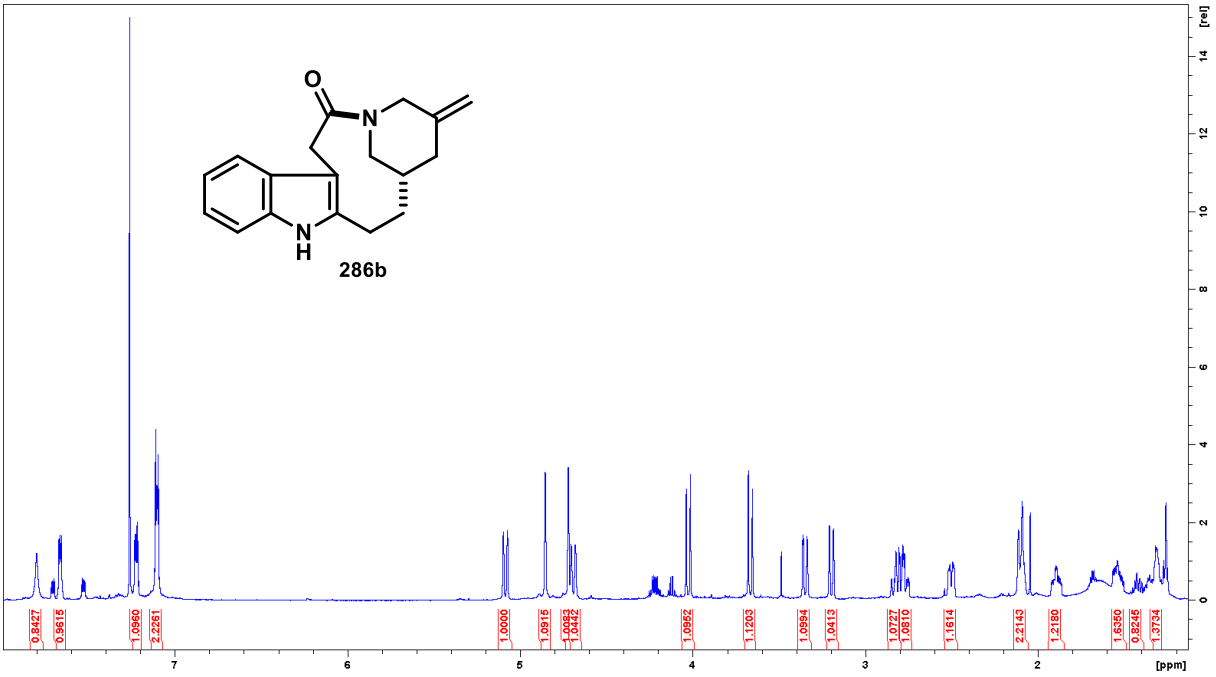
^{1}H NMR (600 MHz, $CDCl_3$)



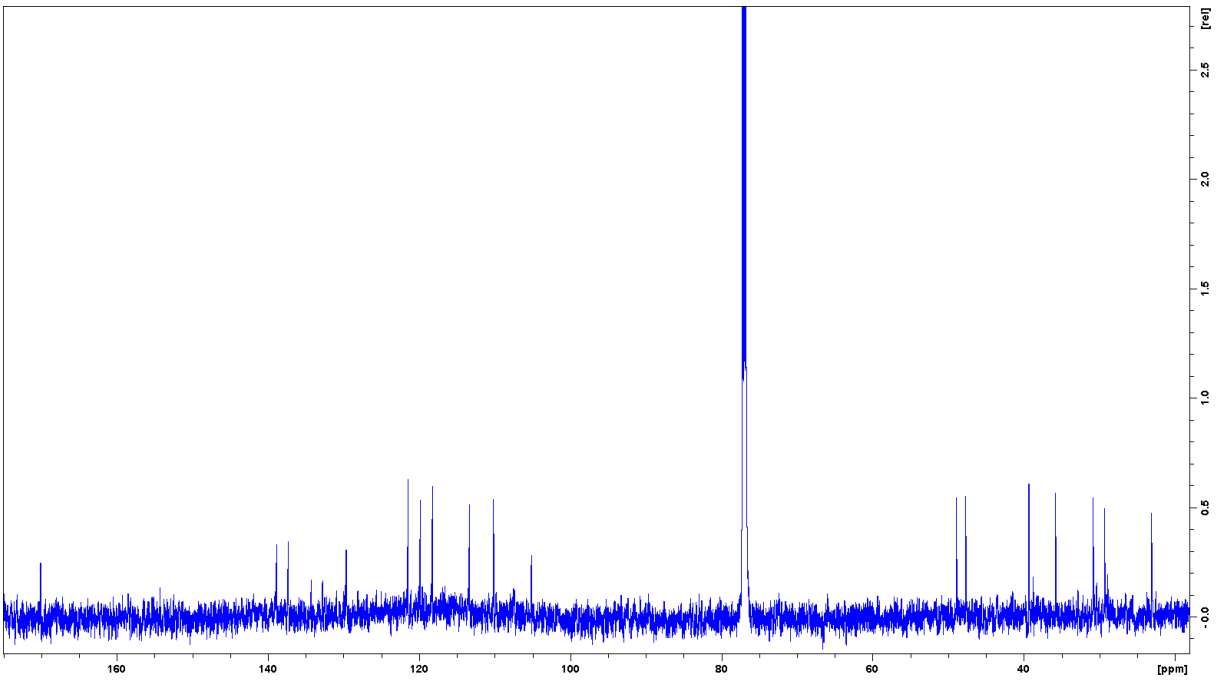
^{13}C NMR (150 MHz, $CDCl_3$)



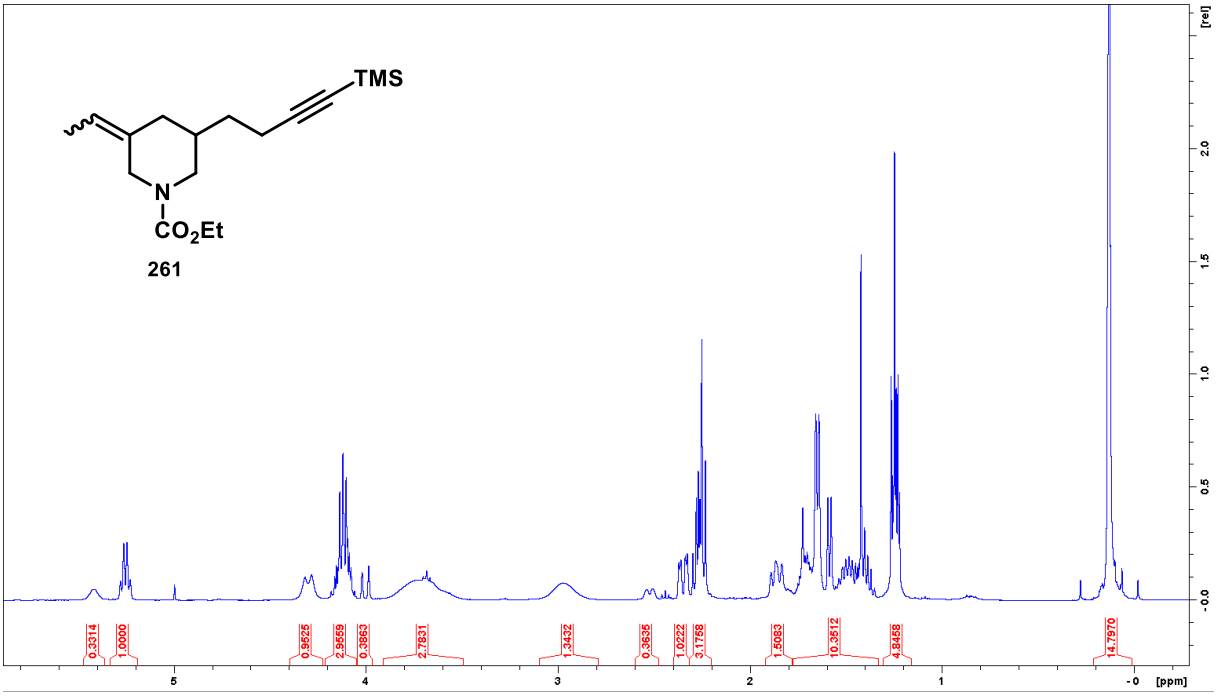
^{1}H NMR (600 MHz, $CDCl_3$)



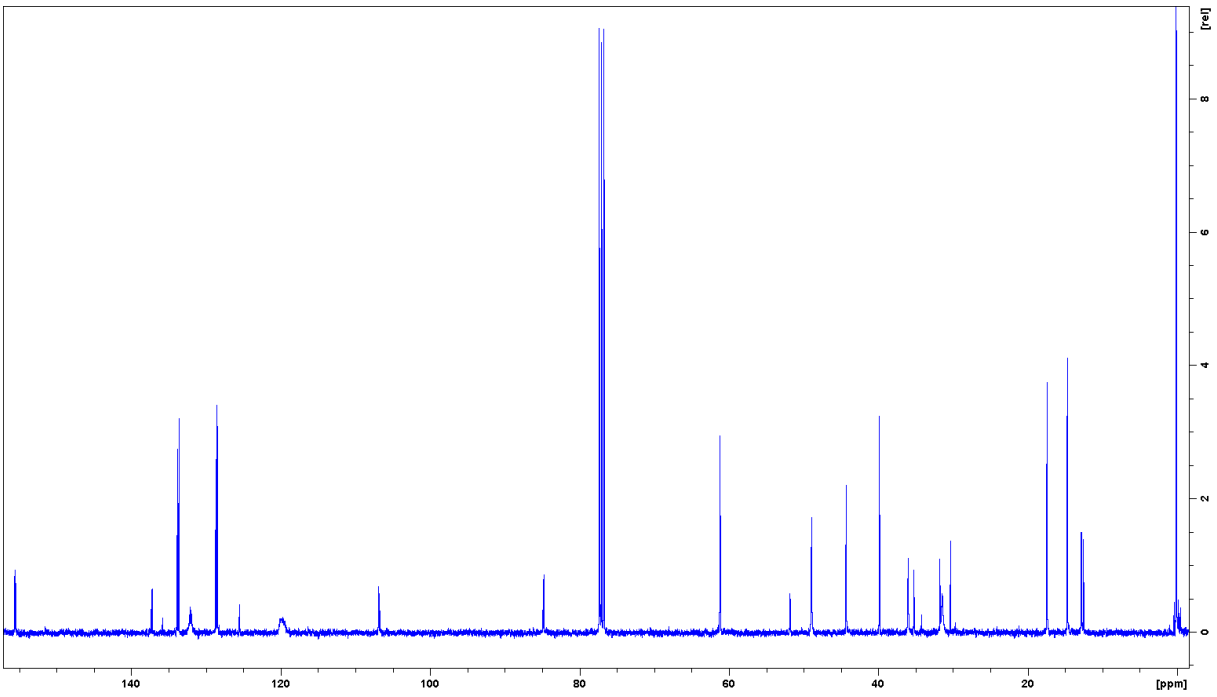
^{13}C NMR (150 MHz, $CDCl_3$)



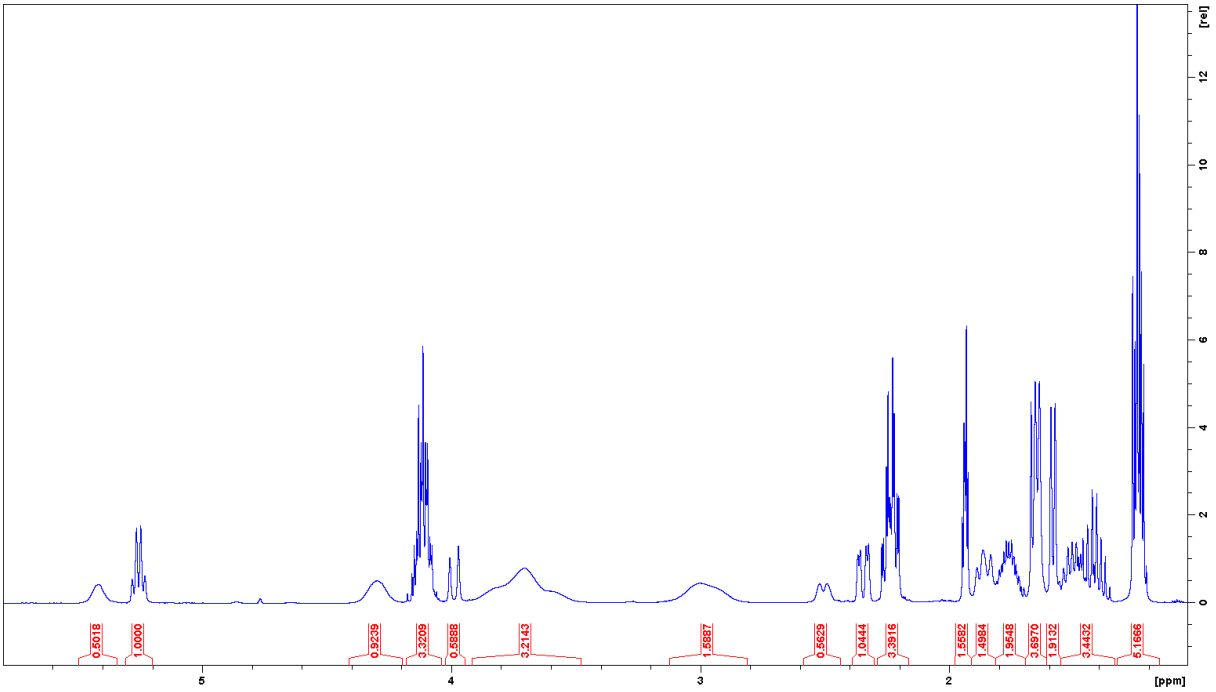
^{1}H NMR (400 MHz, $CDCl_3$)



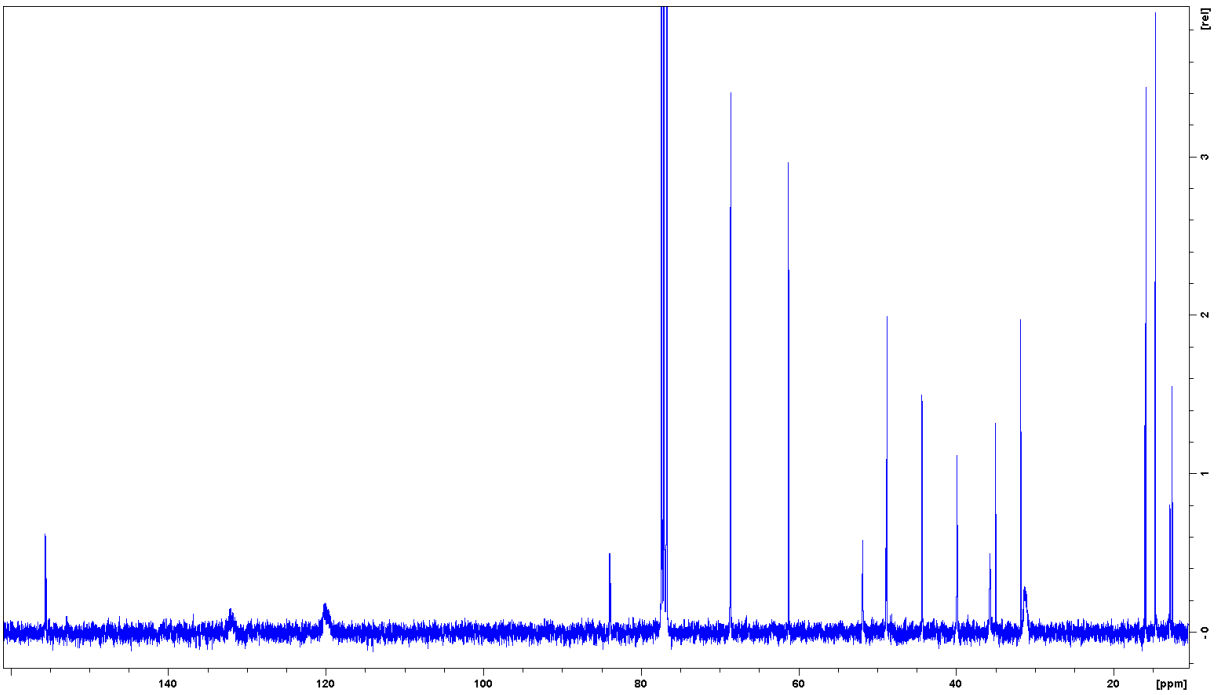
^{13}C NMR (100 MHz, $CDCl_3$)



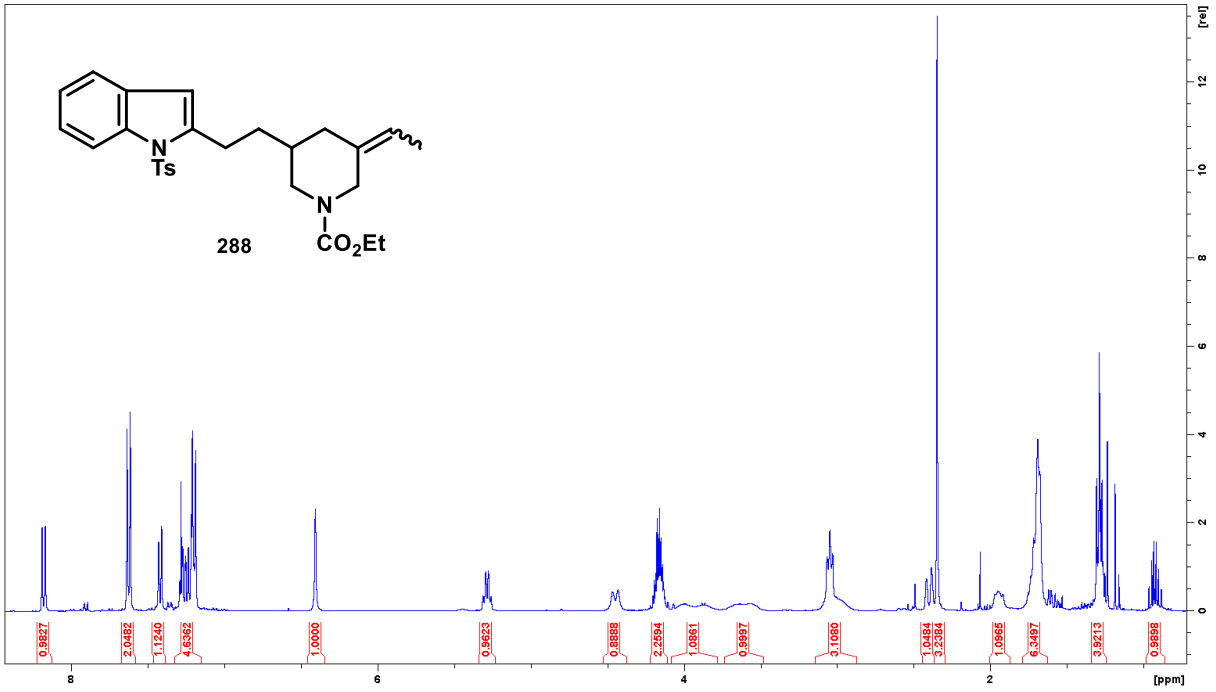
^{1}H NMR (400 MHz, $CDCl_3$)



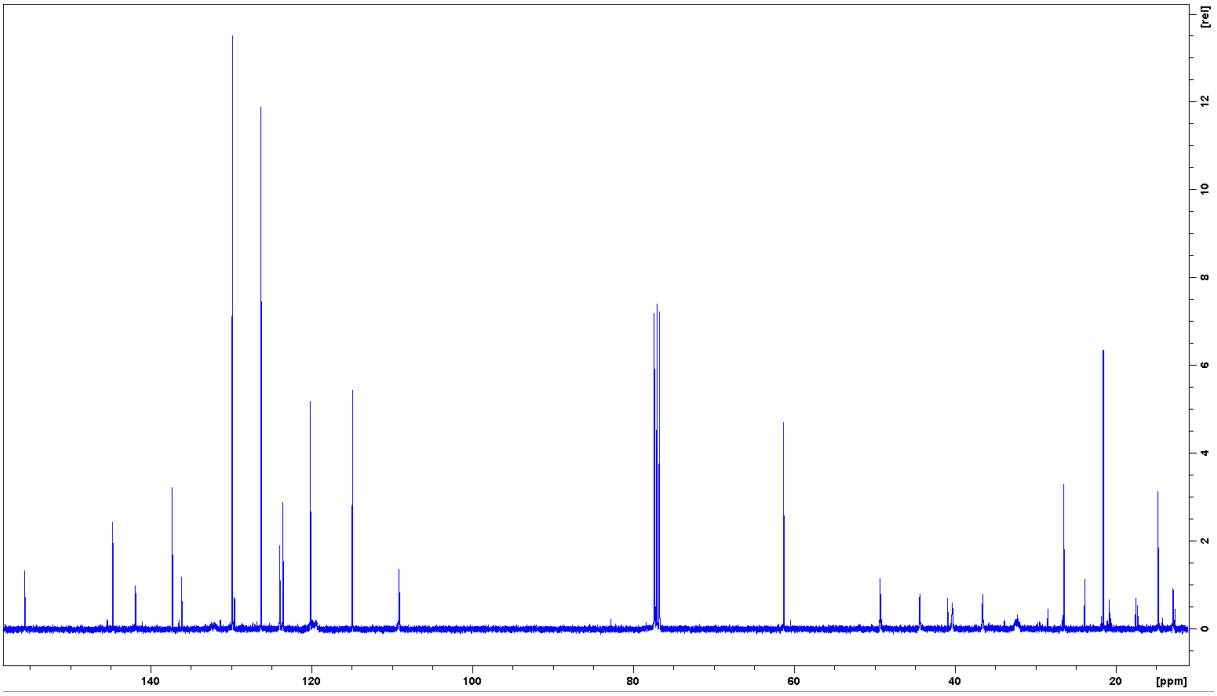
^{13}C NMR (100 MHz, $CDCl_3$)



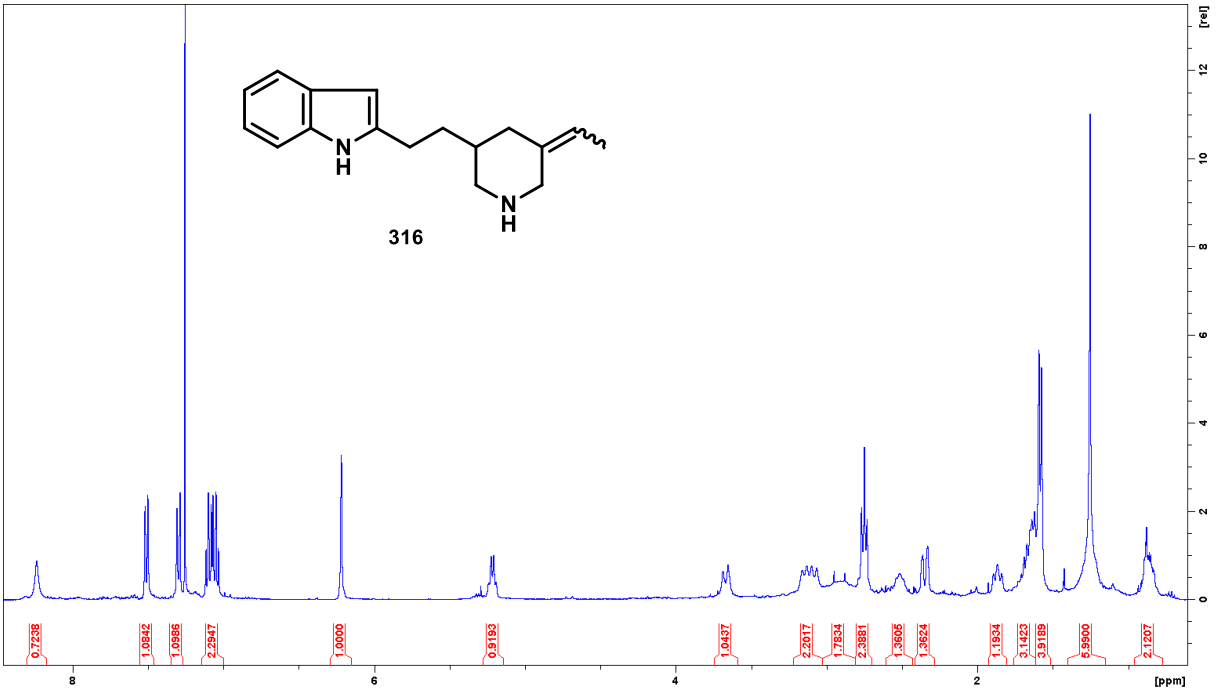
^{1}H NMR (400 MHz, $CDCl_3$); spectroscopic data of the major (*Z*)-DB isomer



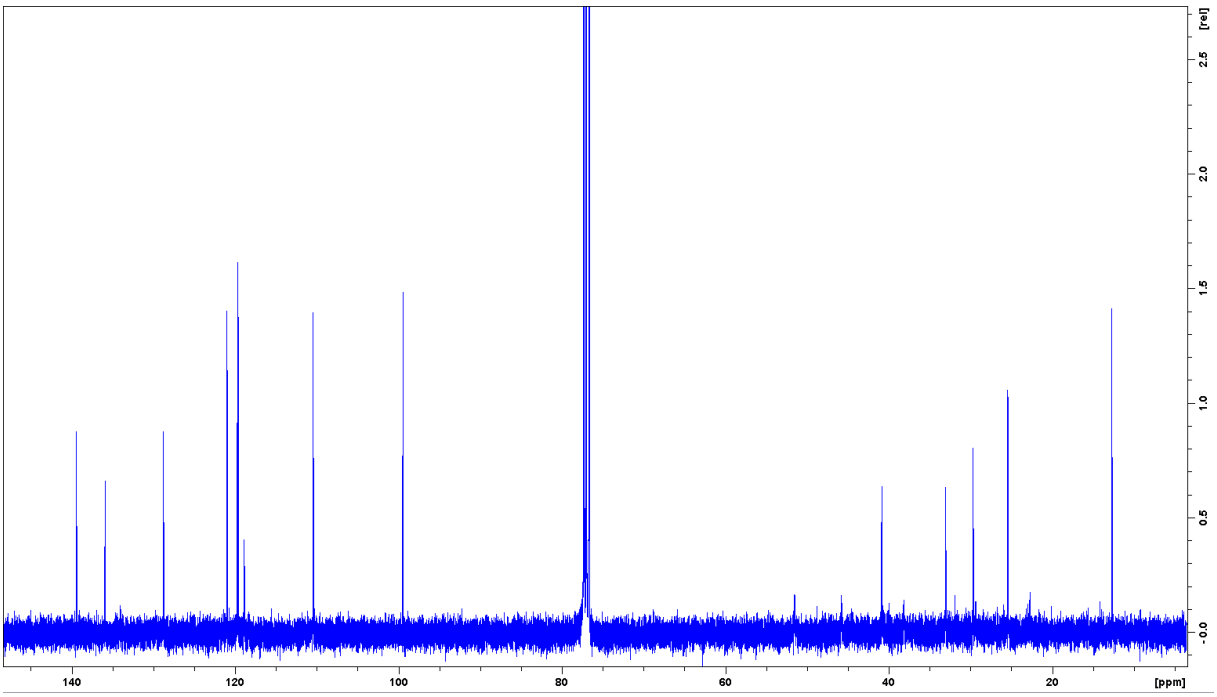
^{13}C NMR (100 MHz, $CDCl_3$); spectroscopic data of the major (*Z*)-DB isomer



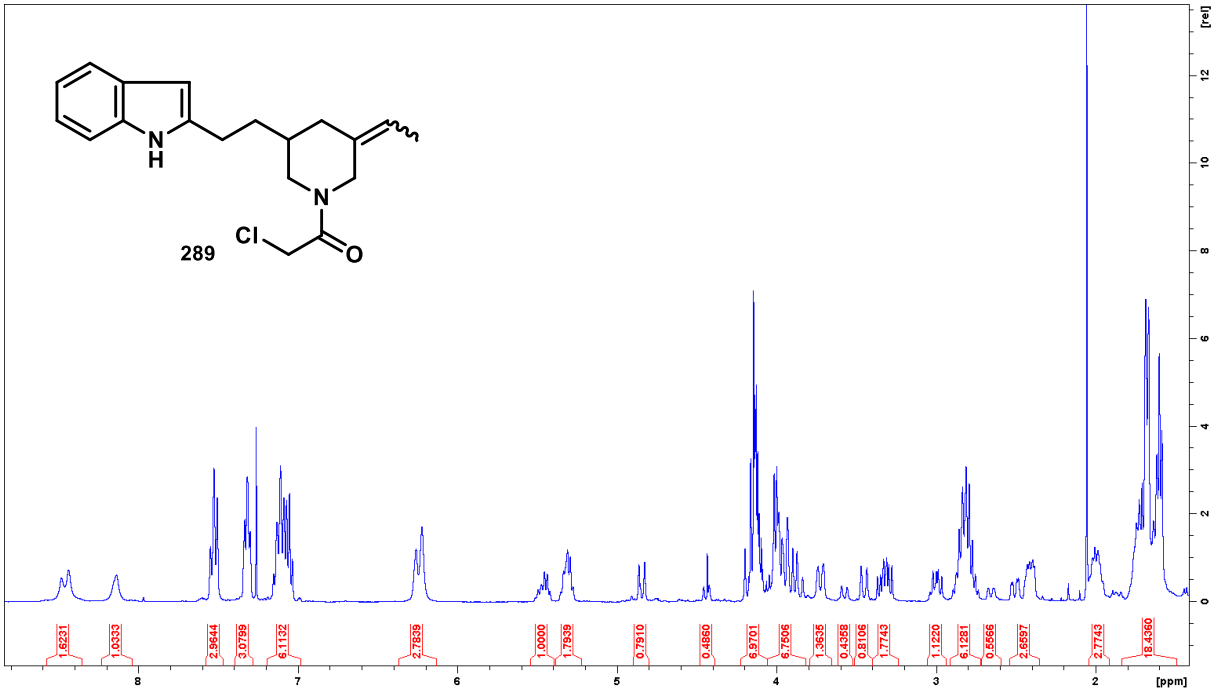
^{1}H NMR (400 MHz, $CDCl_3$); spectroscopic data of the major (*Z*)-DB isomer



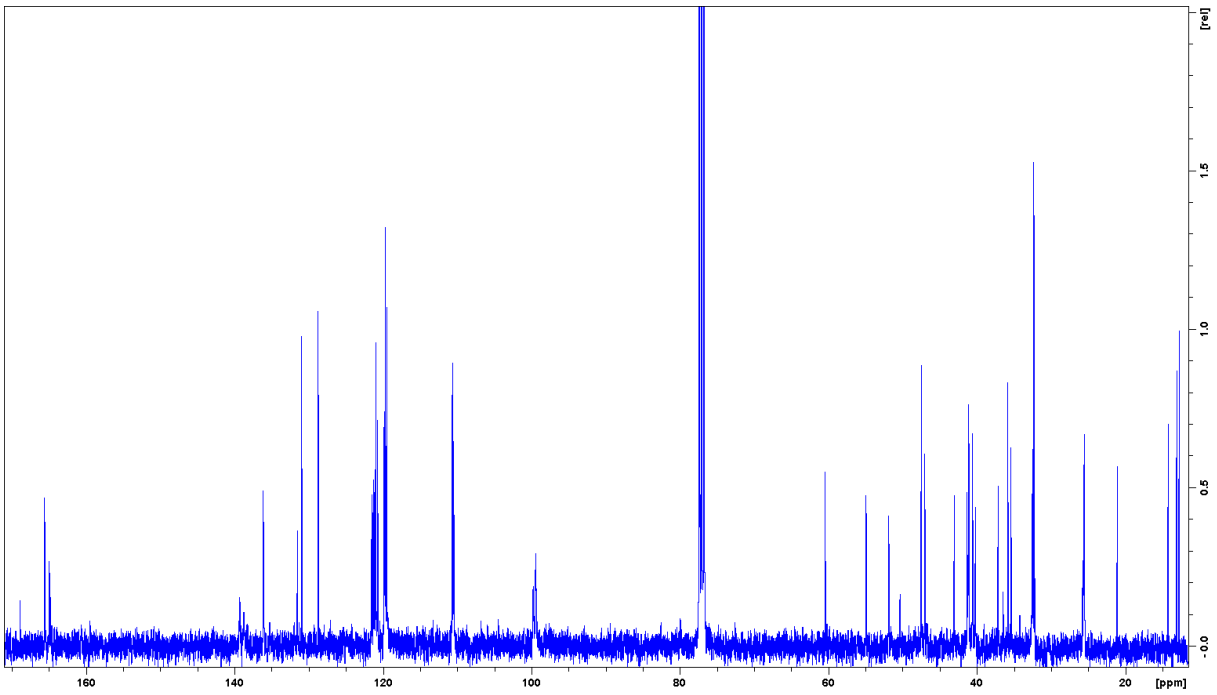
^{13}C NMR (100 MHz, $CDCl_3$); spectroscopic data of the major (*Z*)-DB isomer



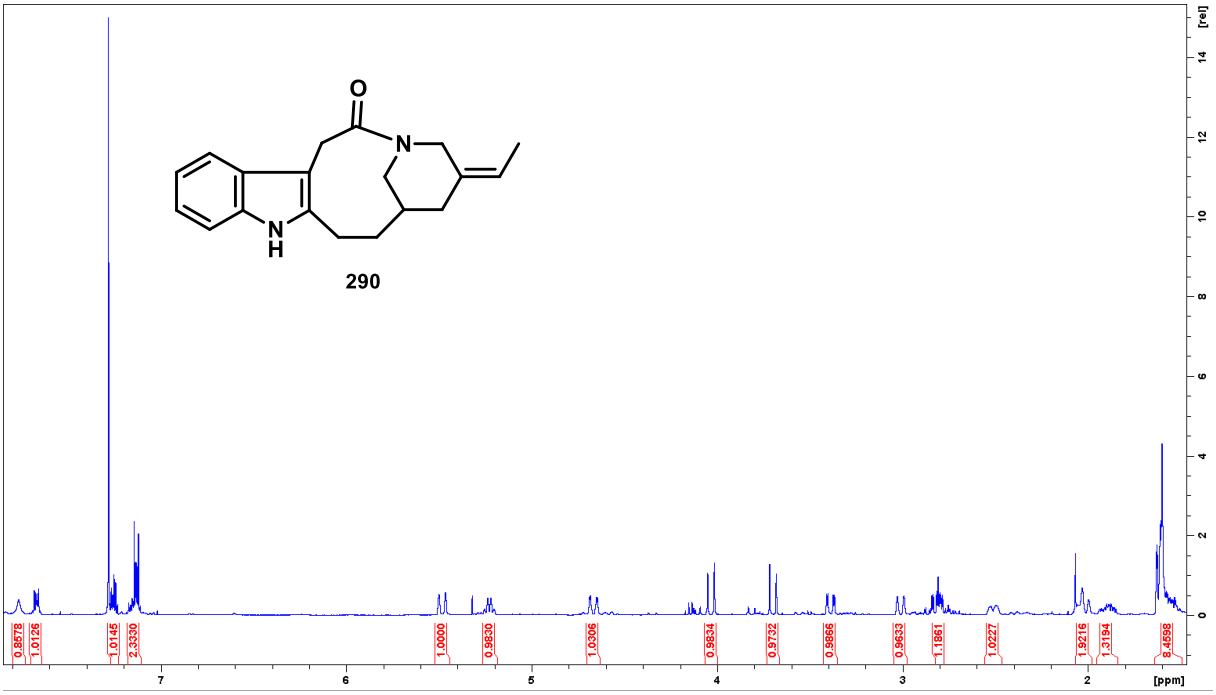
^{1}H NMR (400 MHz, $CDCl_3$, two rotamers)



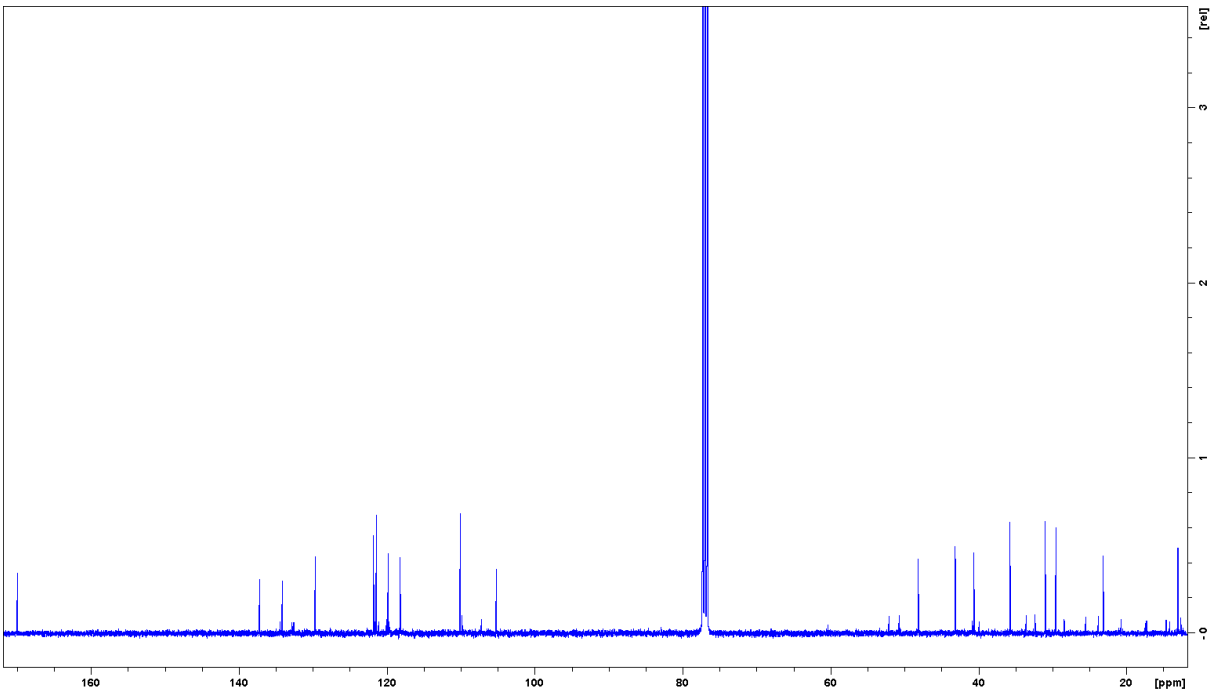
^{13}C NMR (100 MHz, $CDCl_3$, two rotamers)



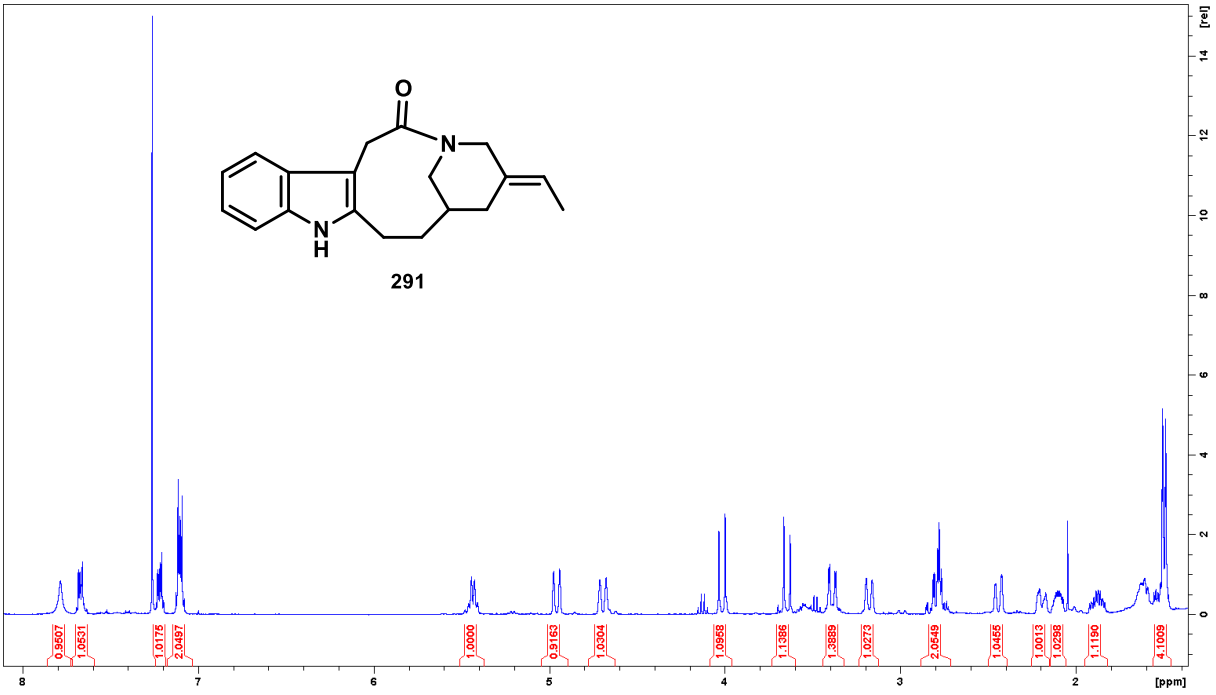
^{1}H NMR (400 MHz, $CDCl_3$)



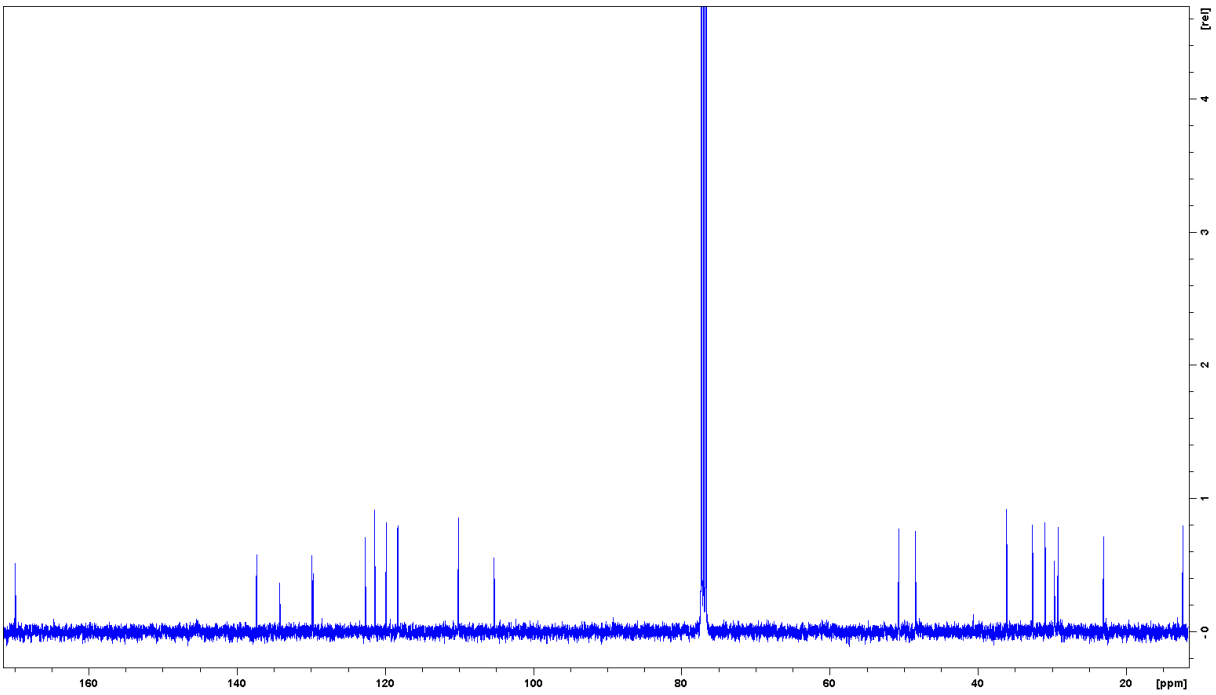
^{13}C NMR (100 MHz, $CDCl_3$)



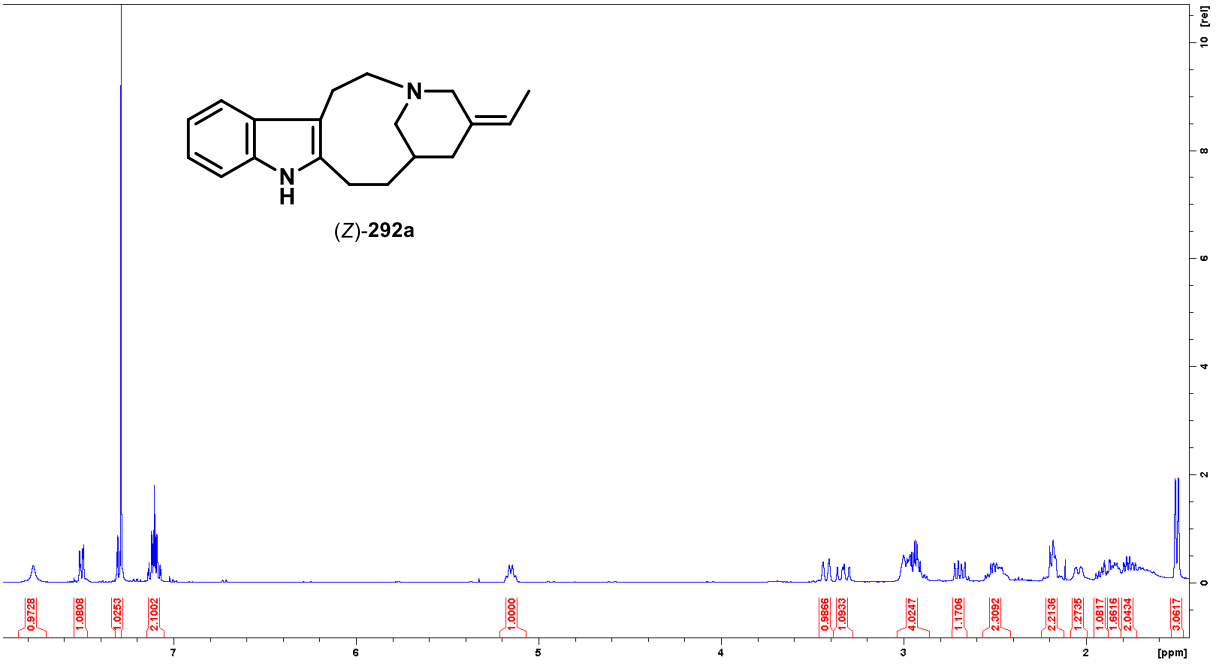
^{1}H NMR (400 MHz, $CDCl_3$)



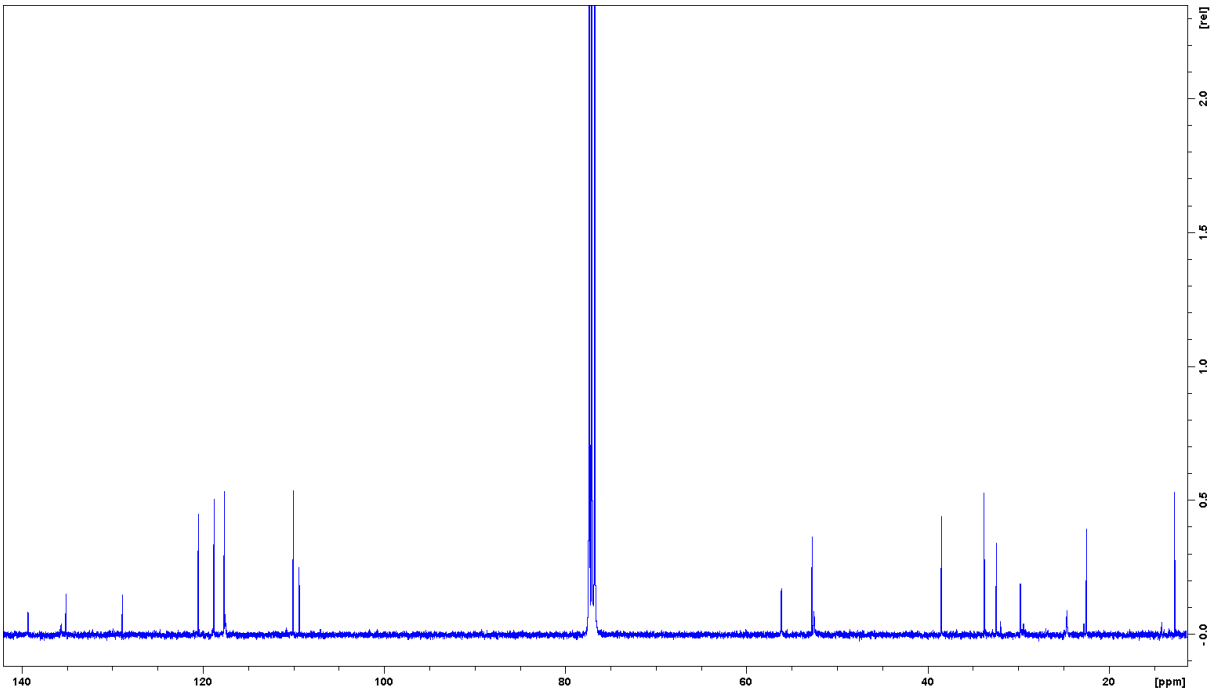
^{13}C NMR (100 MHz, $CDCl_3$)



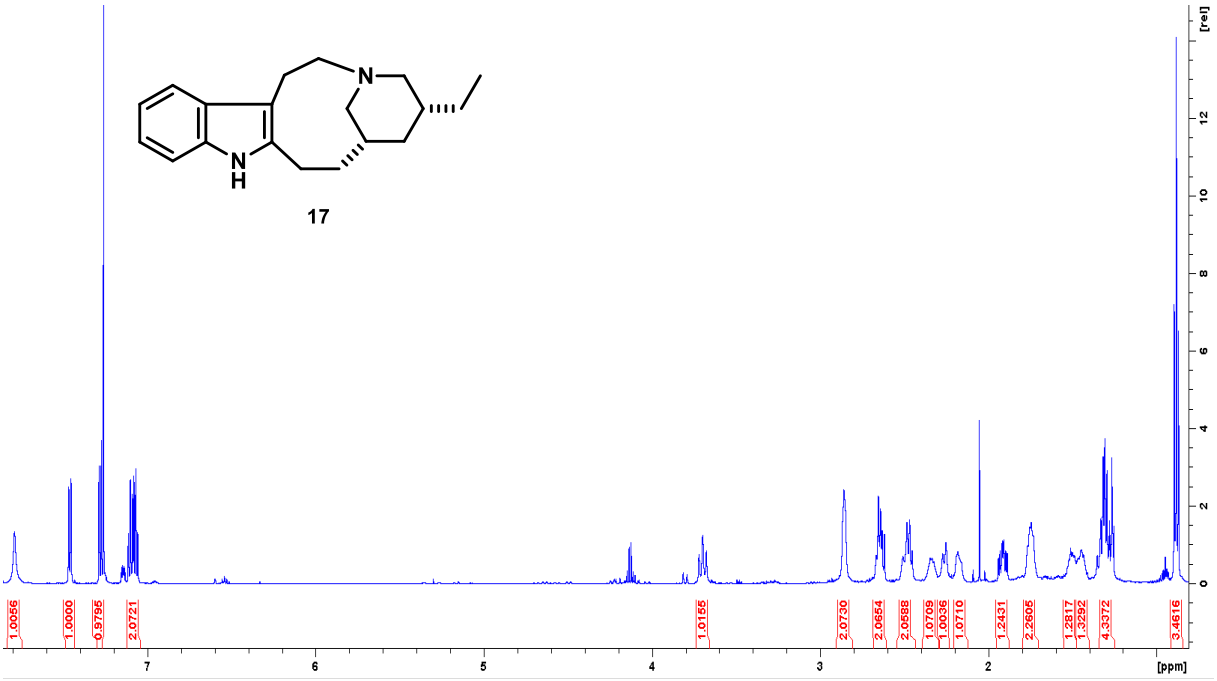
^{1}H NMR (400 MHz, $CDCl_3$)



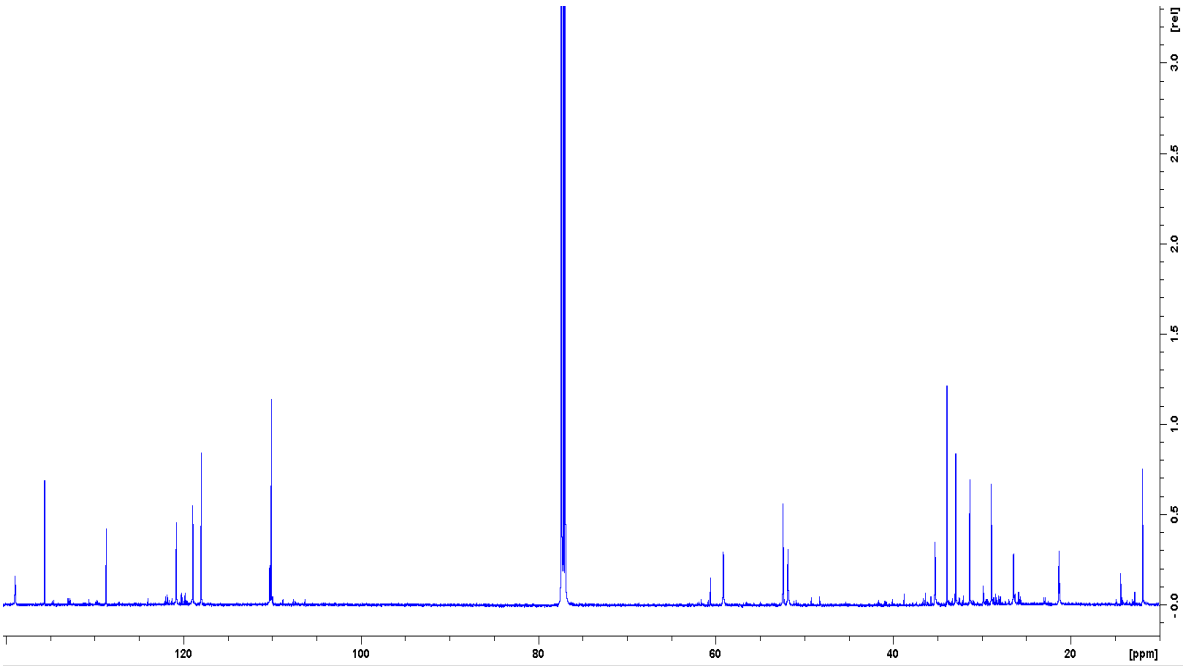
^{13}C NMR (100 MHz, $CDCl_3$)



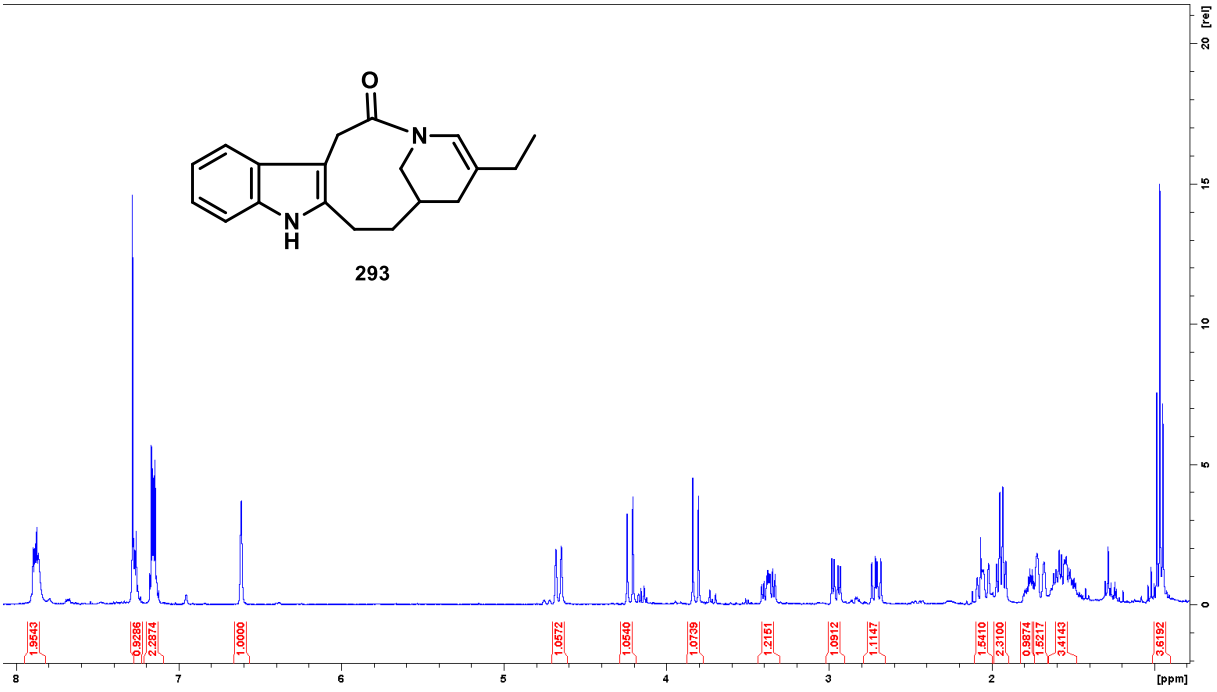
^{1}H NMR (600 MHz, $CDCl_3$)



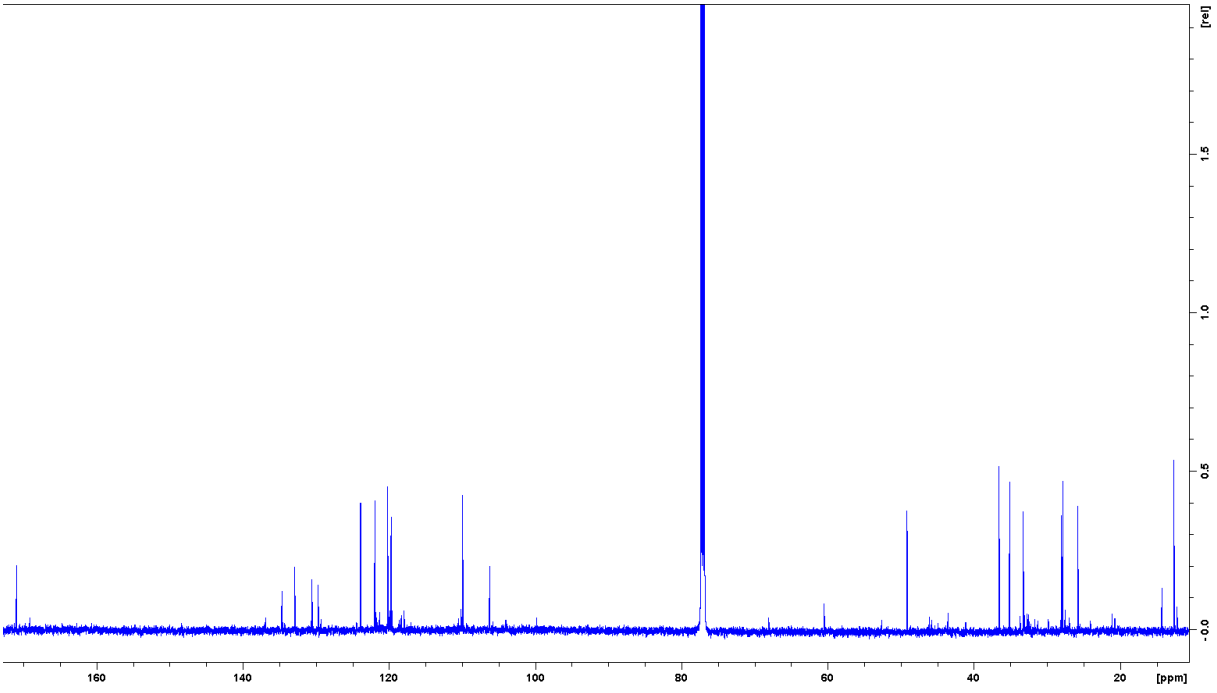
^{13}C NMR (150 MHz, $CDCl_3$)



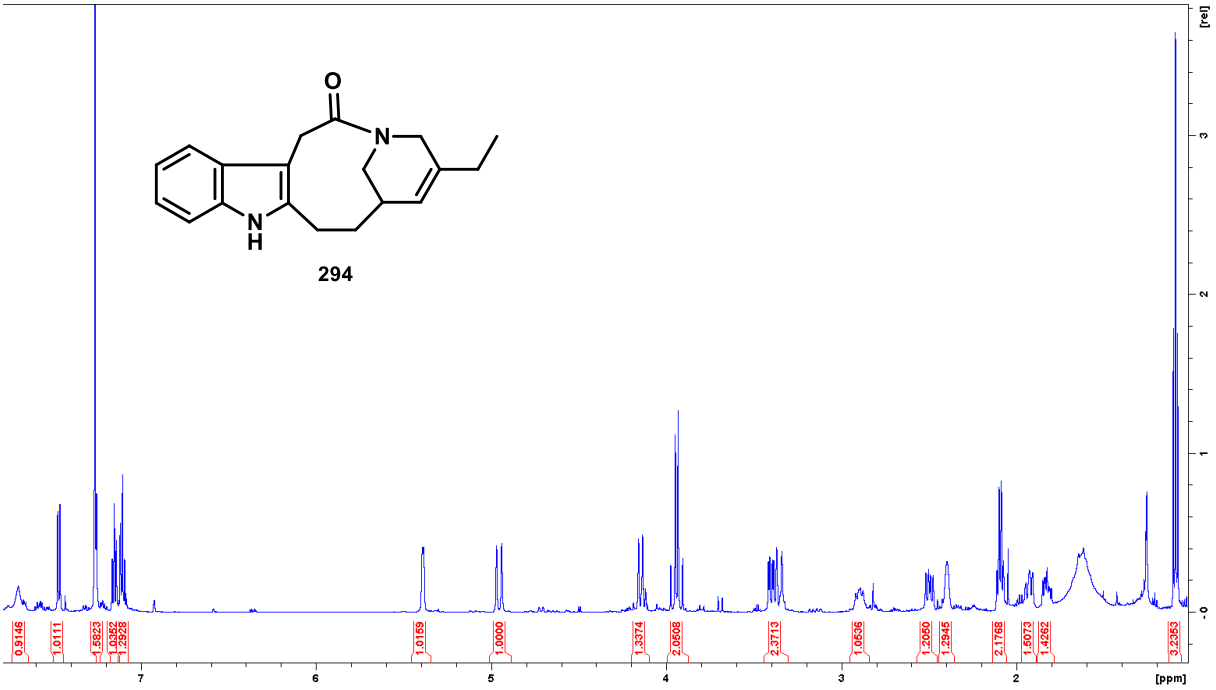
^{1}H NMR (600 MHz, $CDCl_3$)



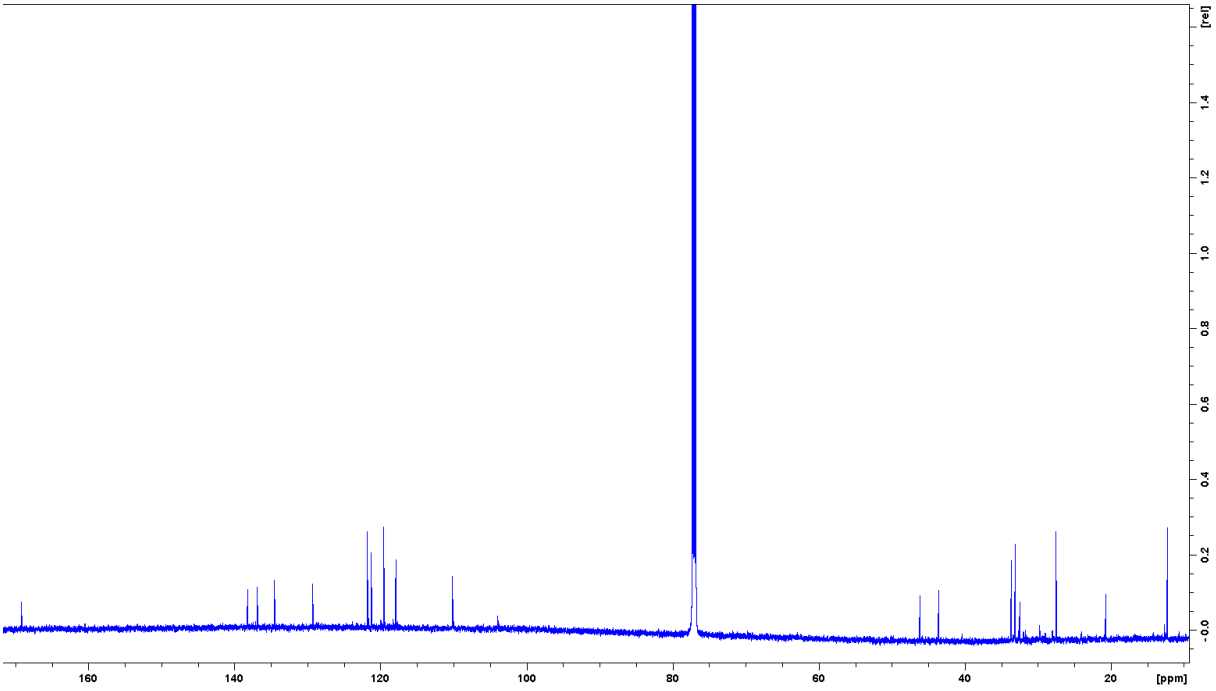
^{13}C NMR (150 MHz, $CDCl_3$)



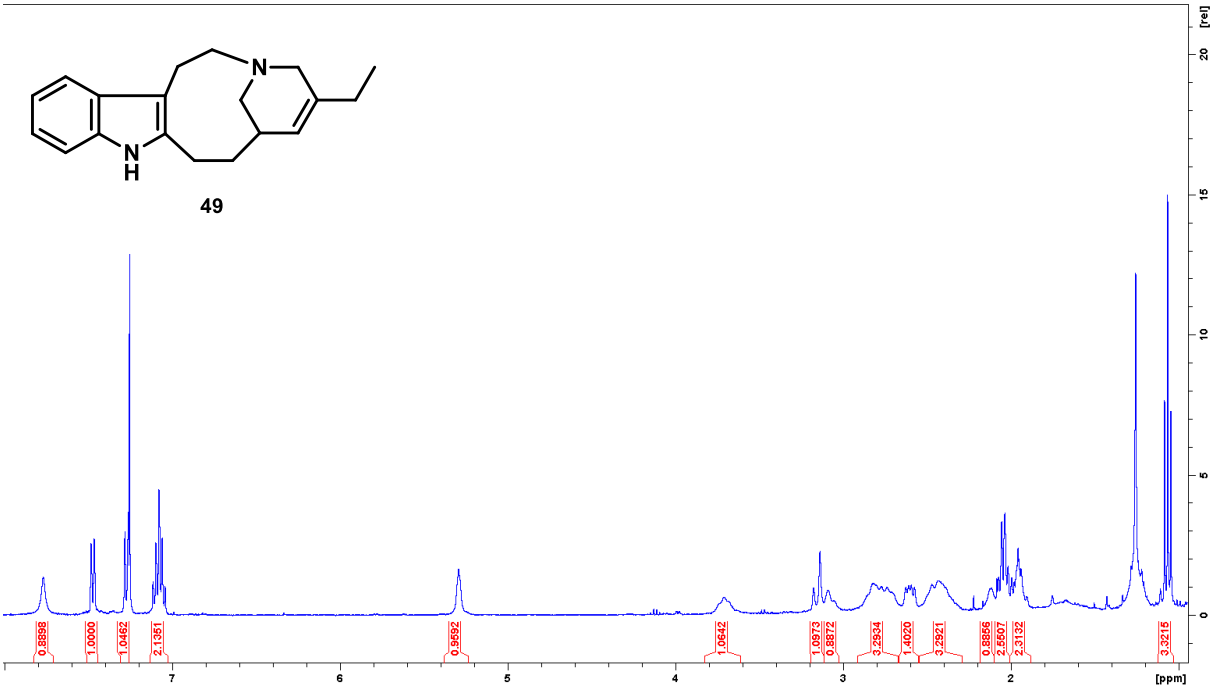
^{1}H NMR (600 MHz, $CDCl_3$)



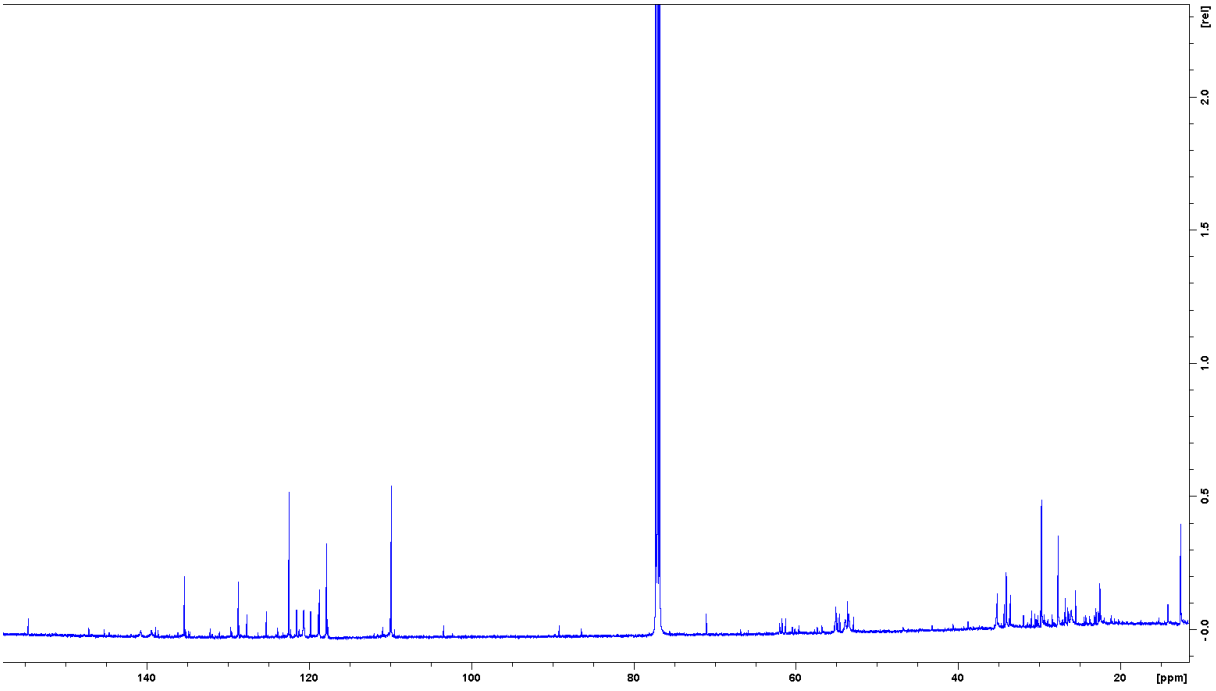
^{13}C NMR (150 MHz, $CDCl_3$)



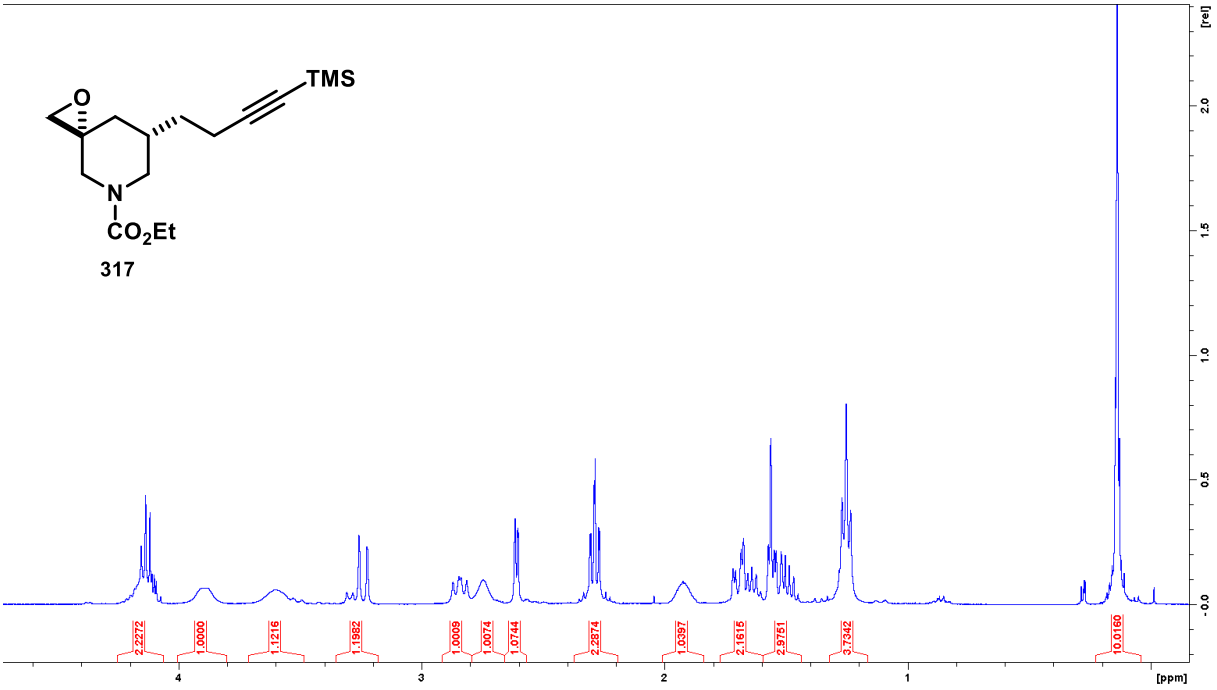
^{1}H NMR (400 MHz, $CDCl_3$)



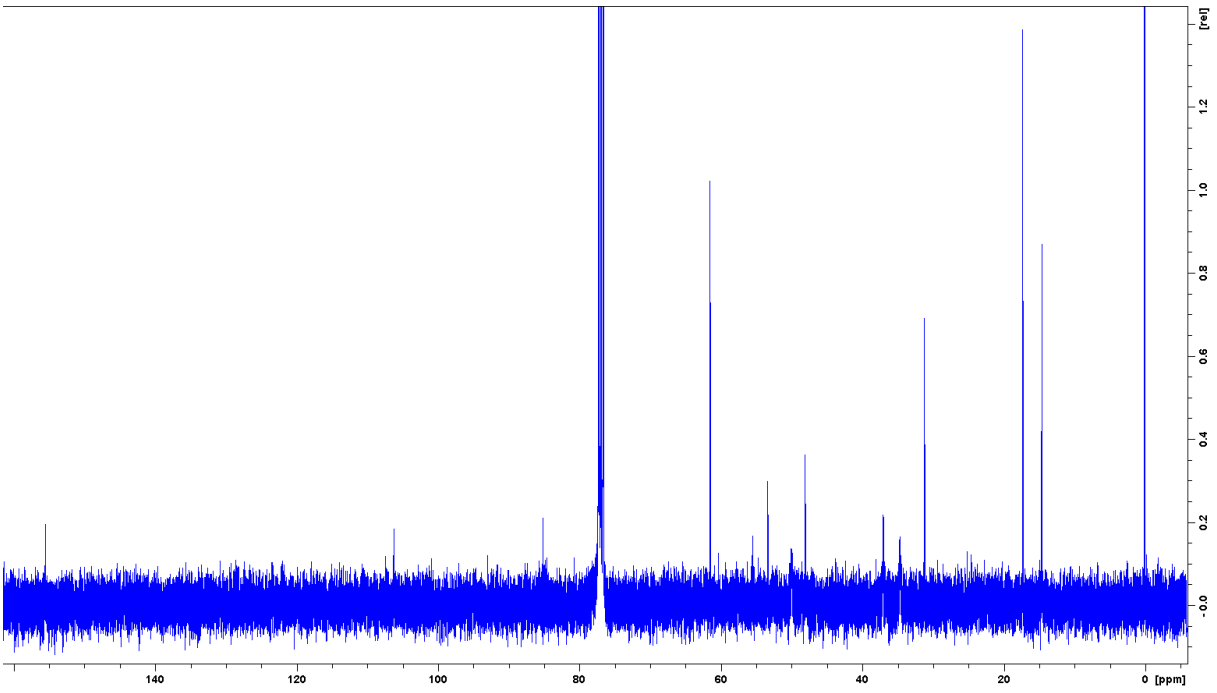
^{13}C NMR (150 MHz, $CDCl_3$)



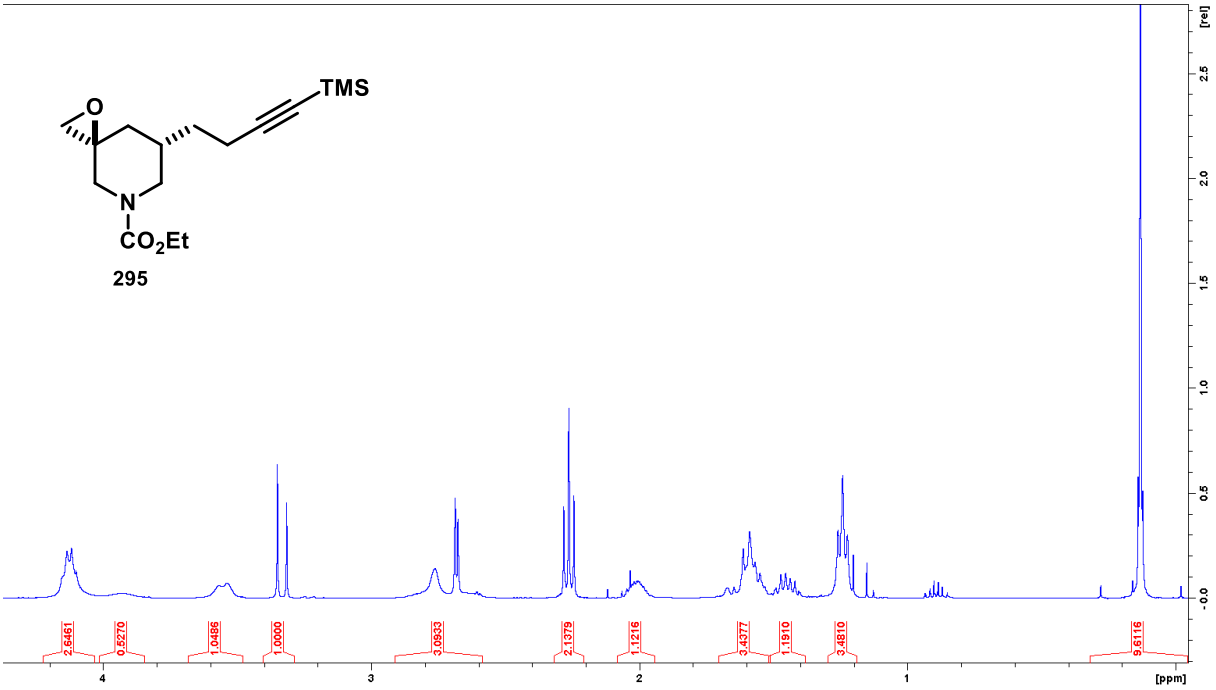
^{1}H NMR (400 MHz, $CDCl_3$)



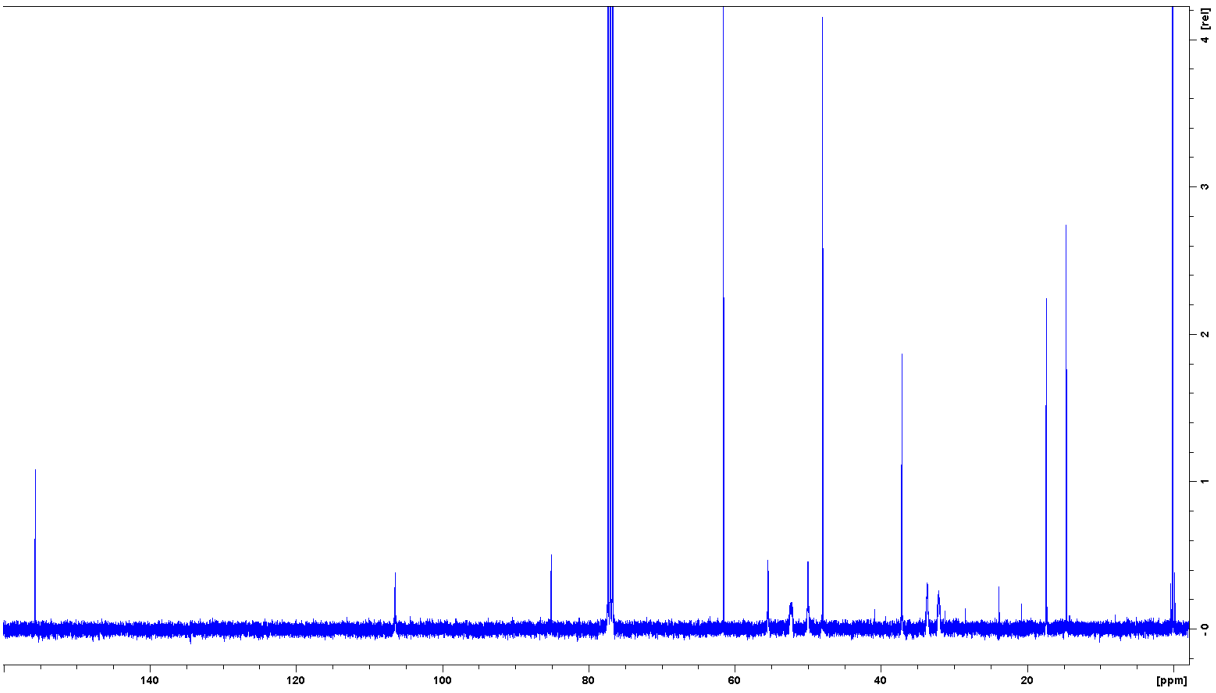
^{13}C NMR (100 MHz, $CDCl_3$)



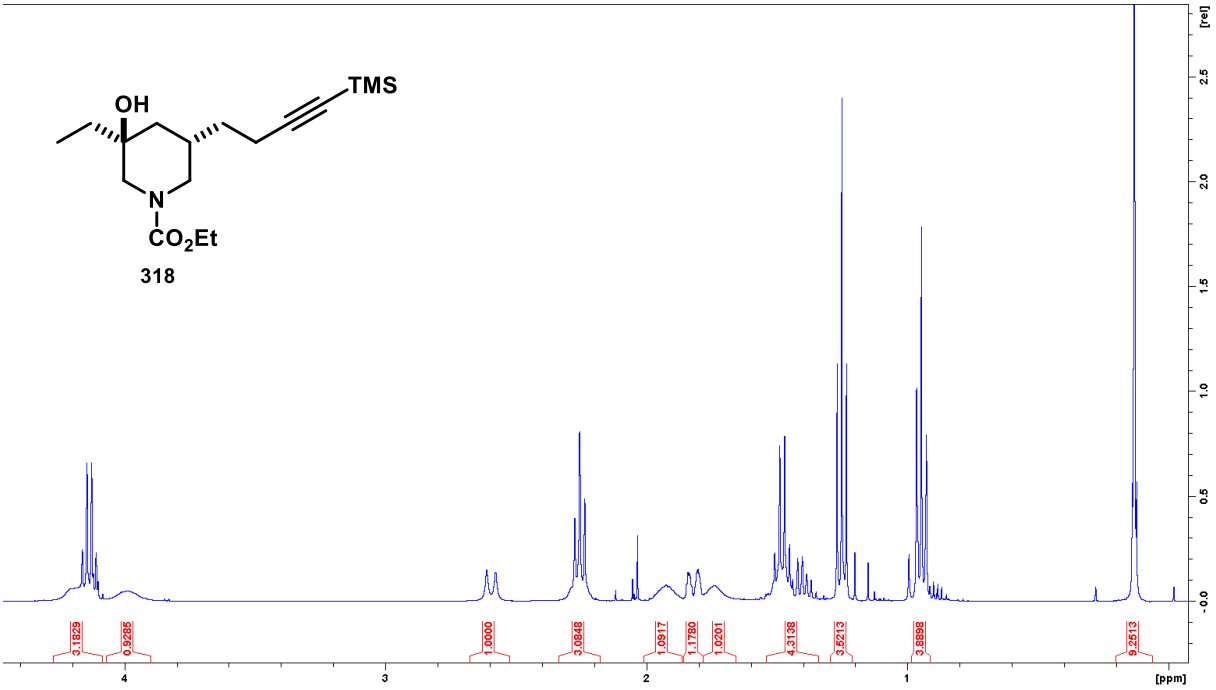
^{1}H NMR (400 MHz, $CDCl_3$)



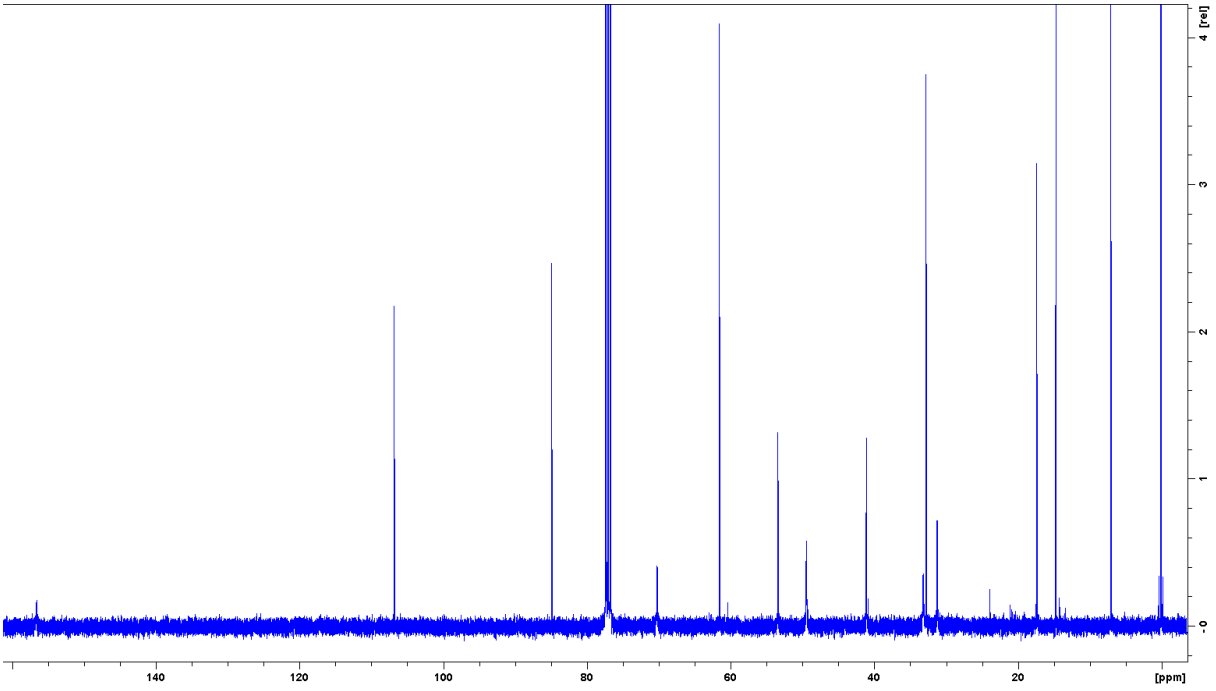
^{13}C NMR (100 MHz, $CDCl_3$)



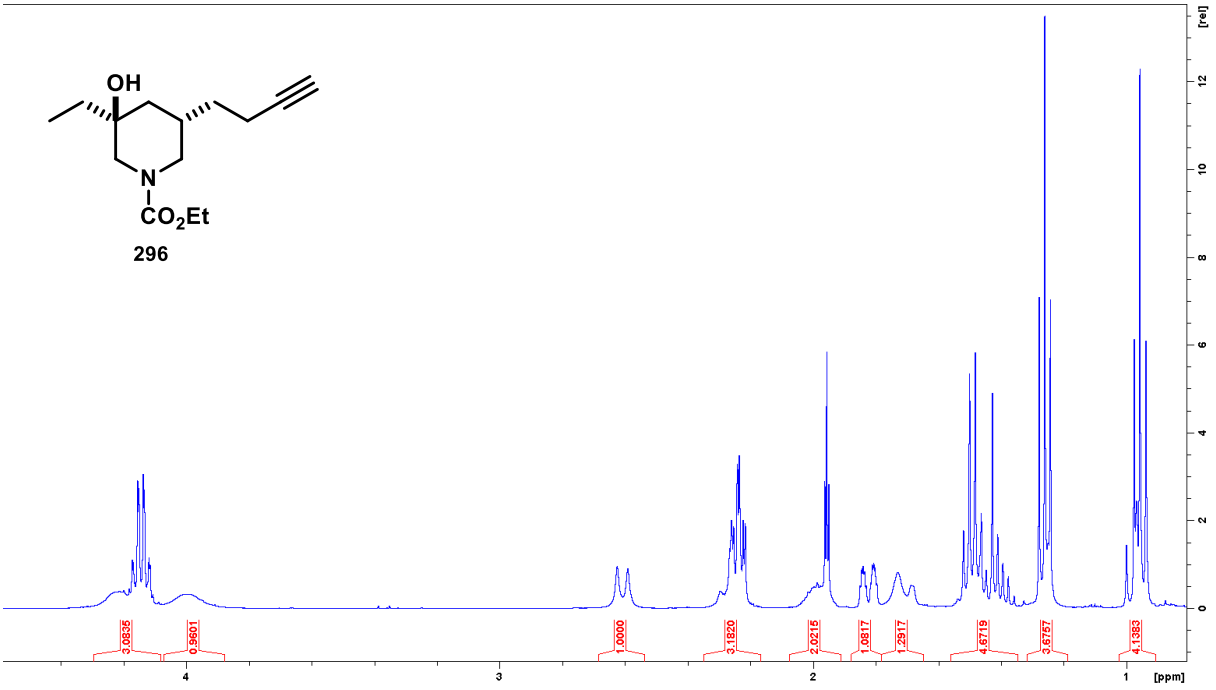
^{1}H NMR (400 MHz, $CDCl_3$)



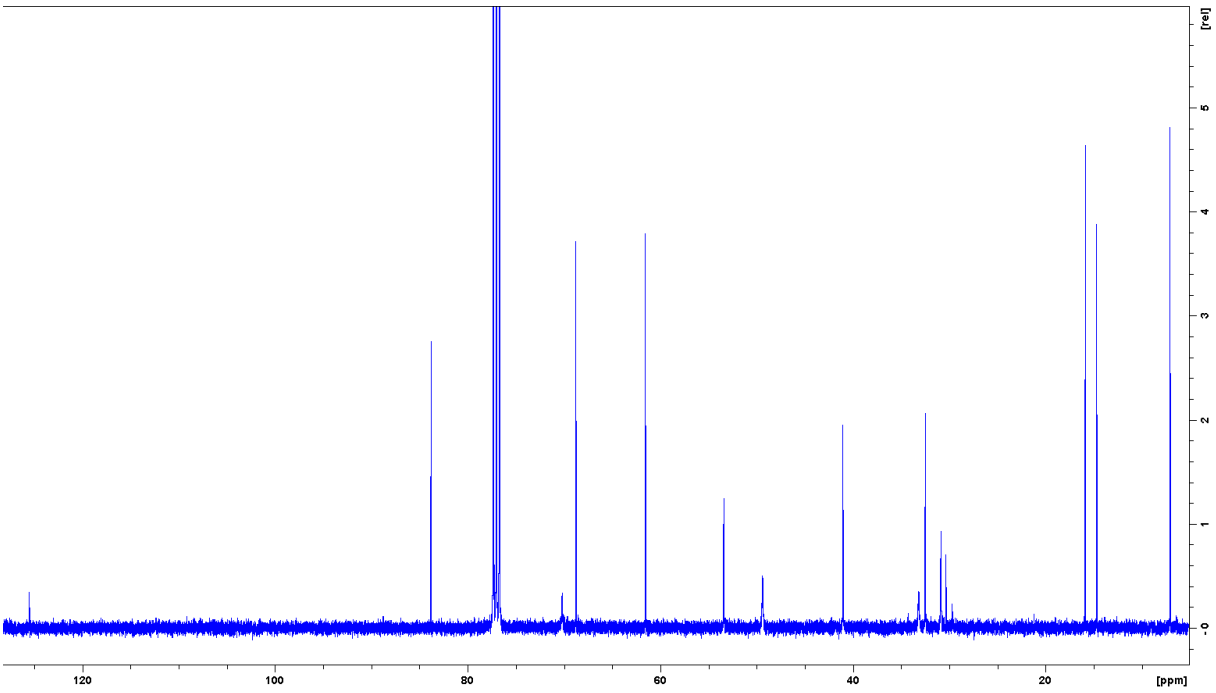
^{13}C NMR (100 MHz, $CDCl_3$)



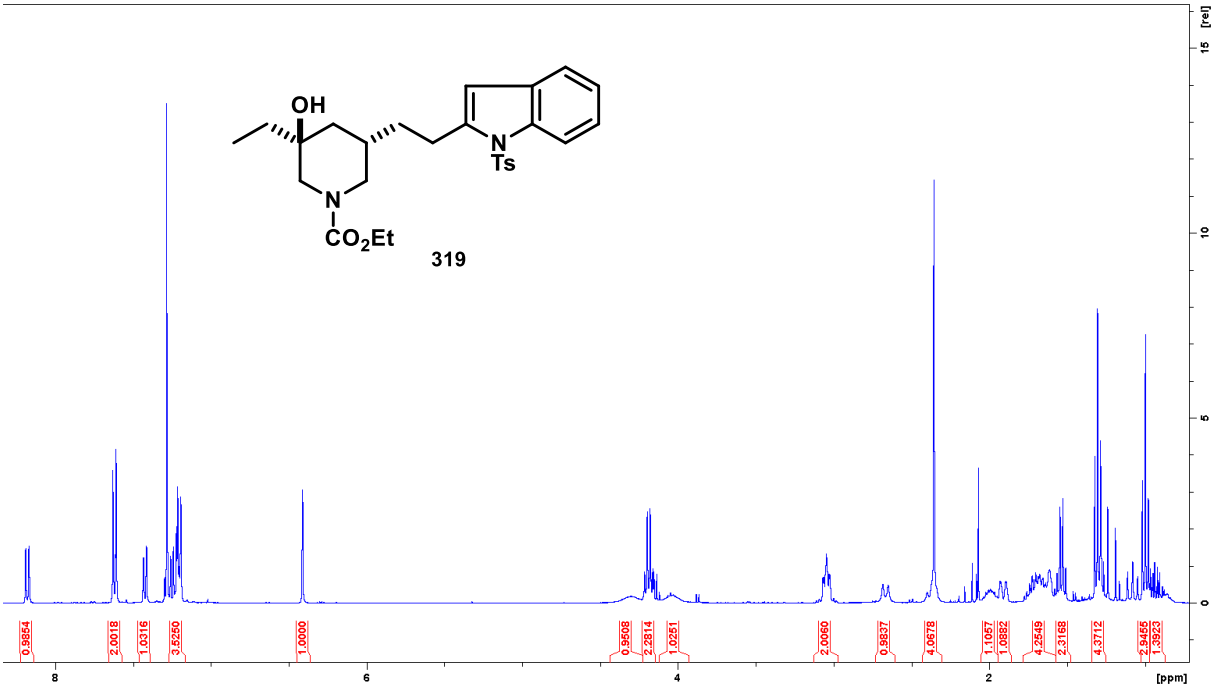
^{1}H NMR (400 MHz, $CDCl_3$)



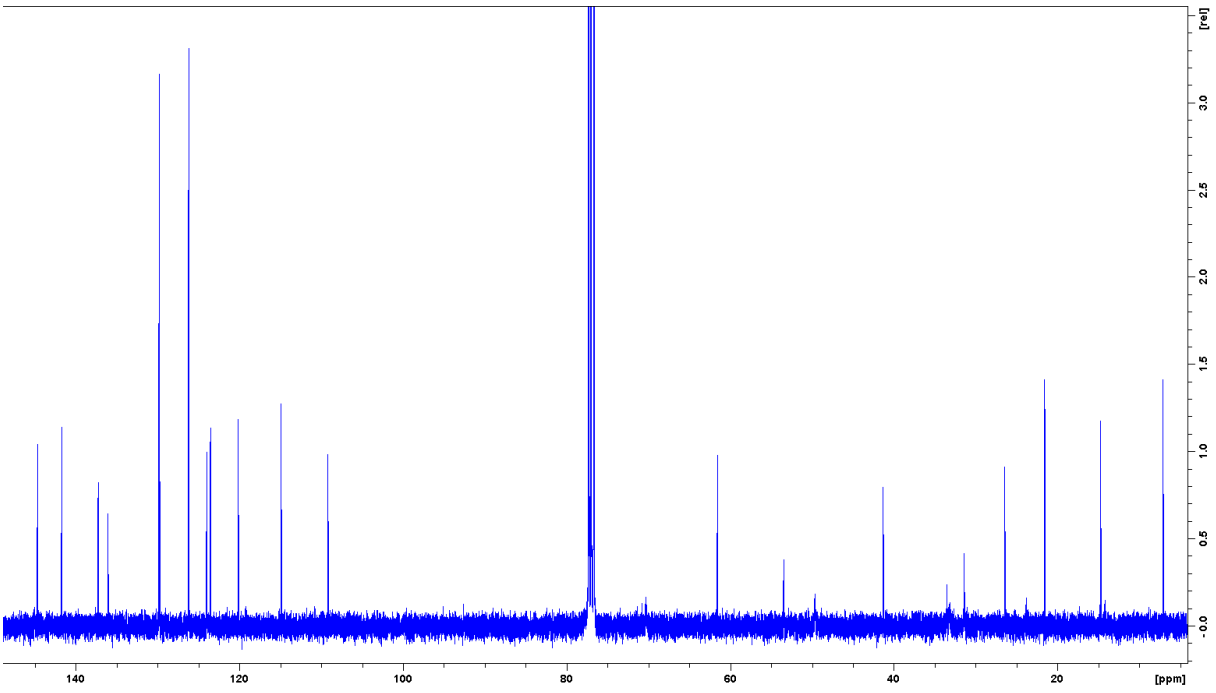
^{13}C NMR (100 MHz, $CDCl_3$)



^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)



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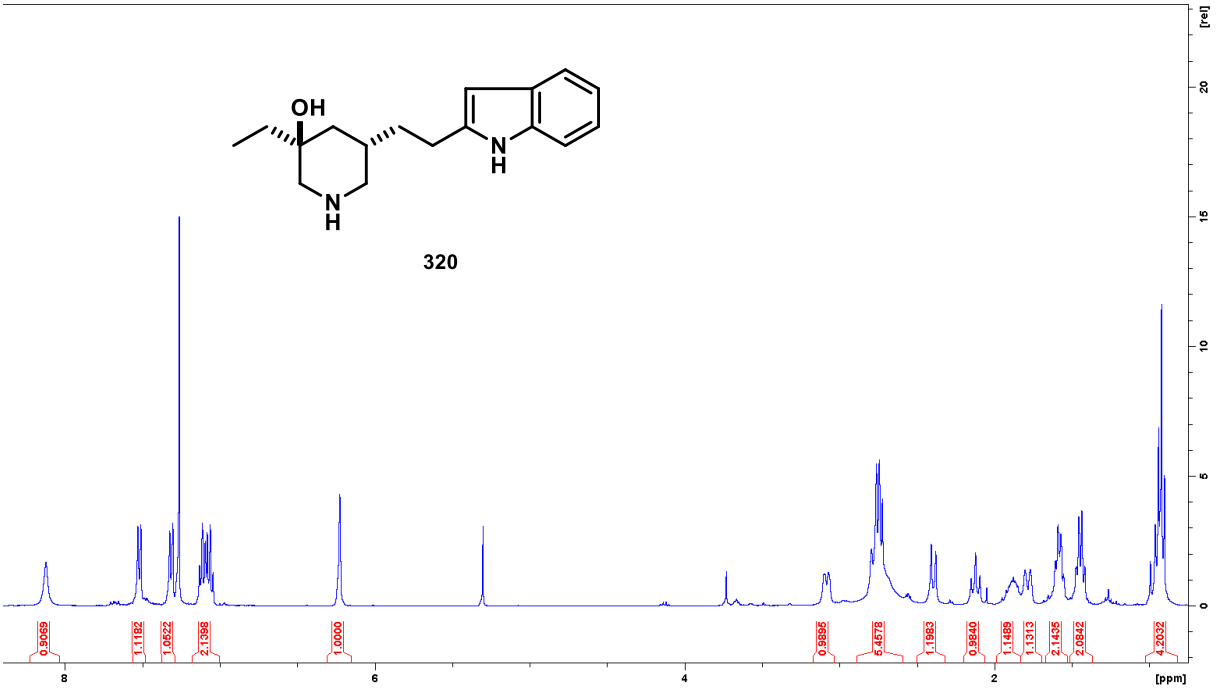

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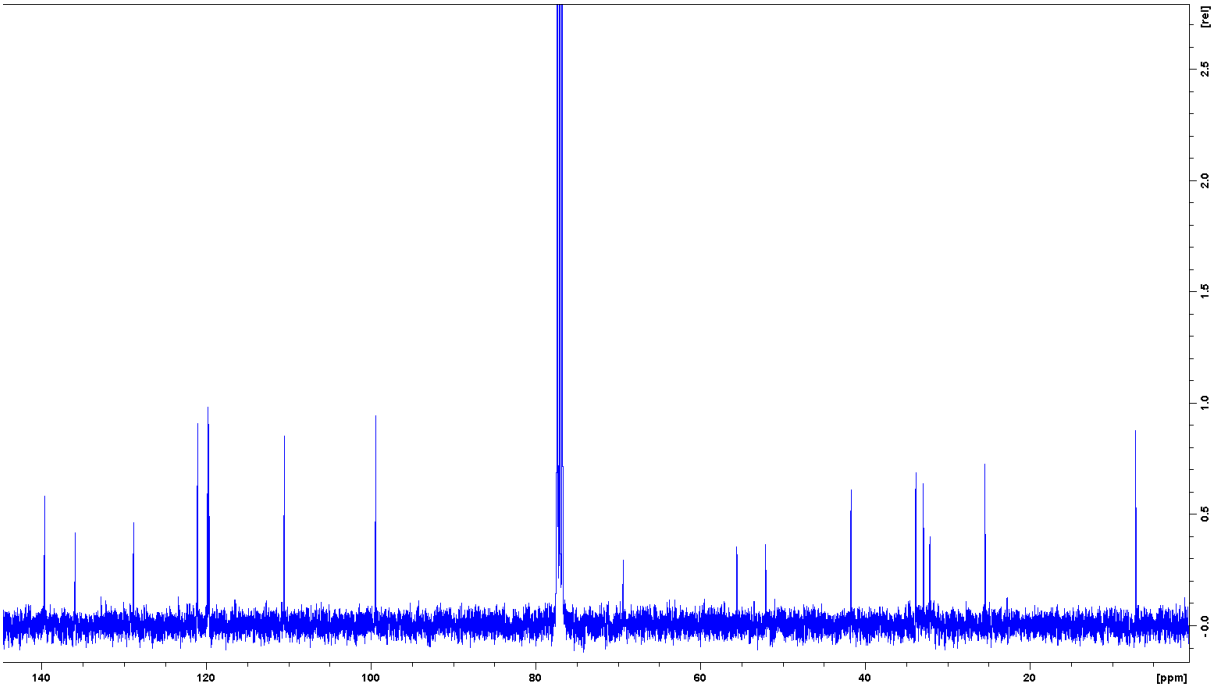
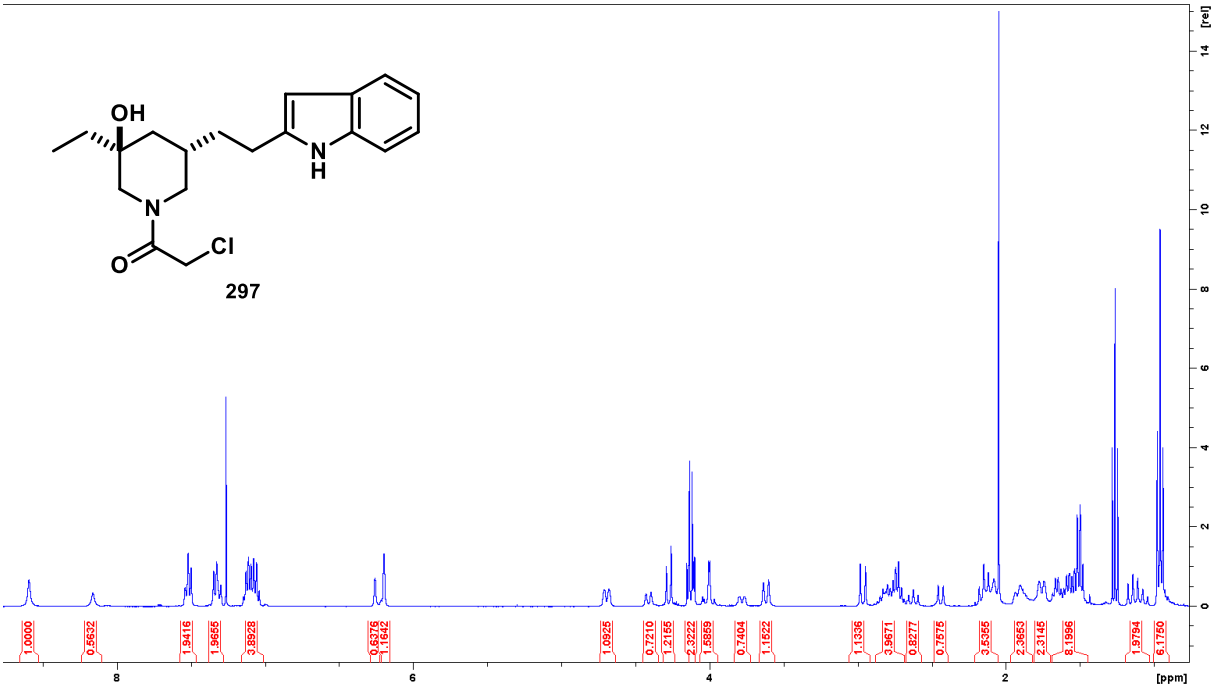


^{1}H NMR (400 MHz, $CDCl_3$, two rotamers)



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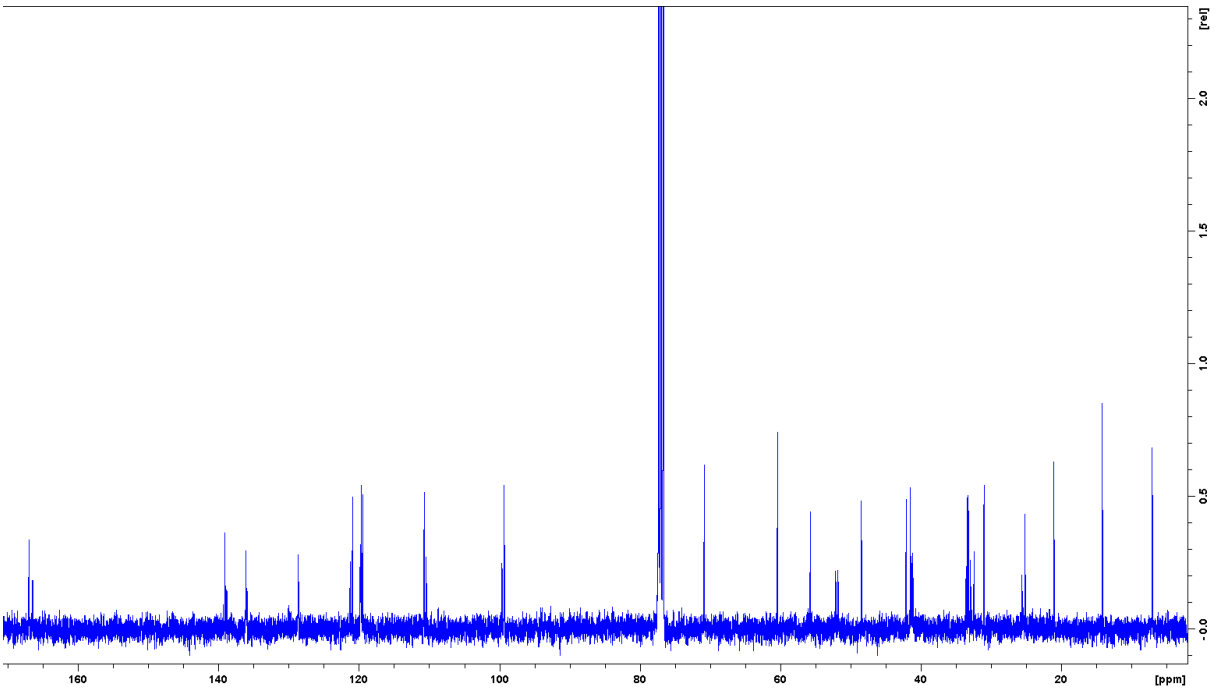

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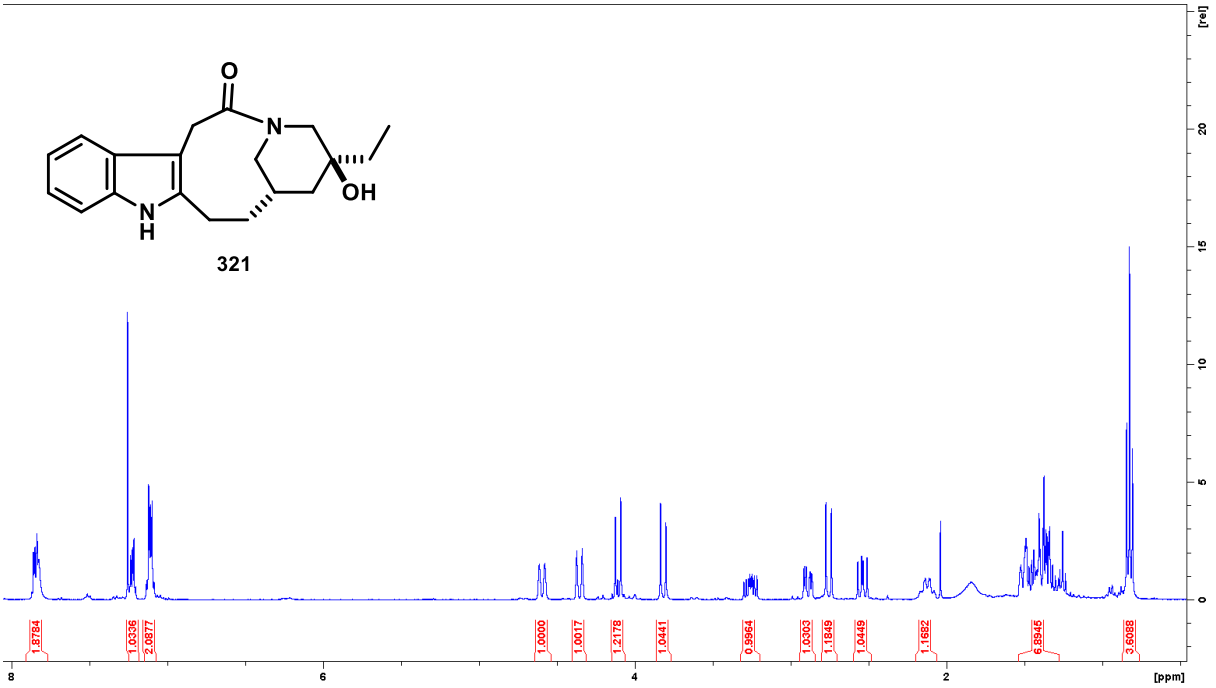

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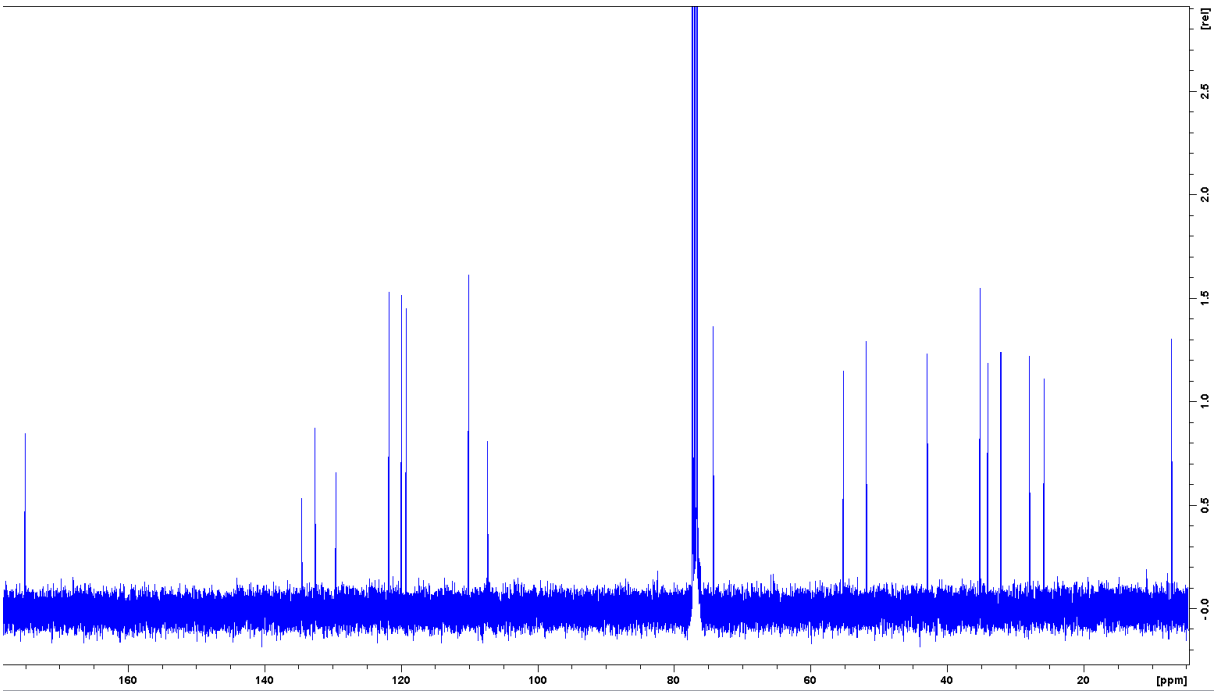

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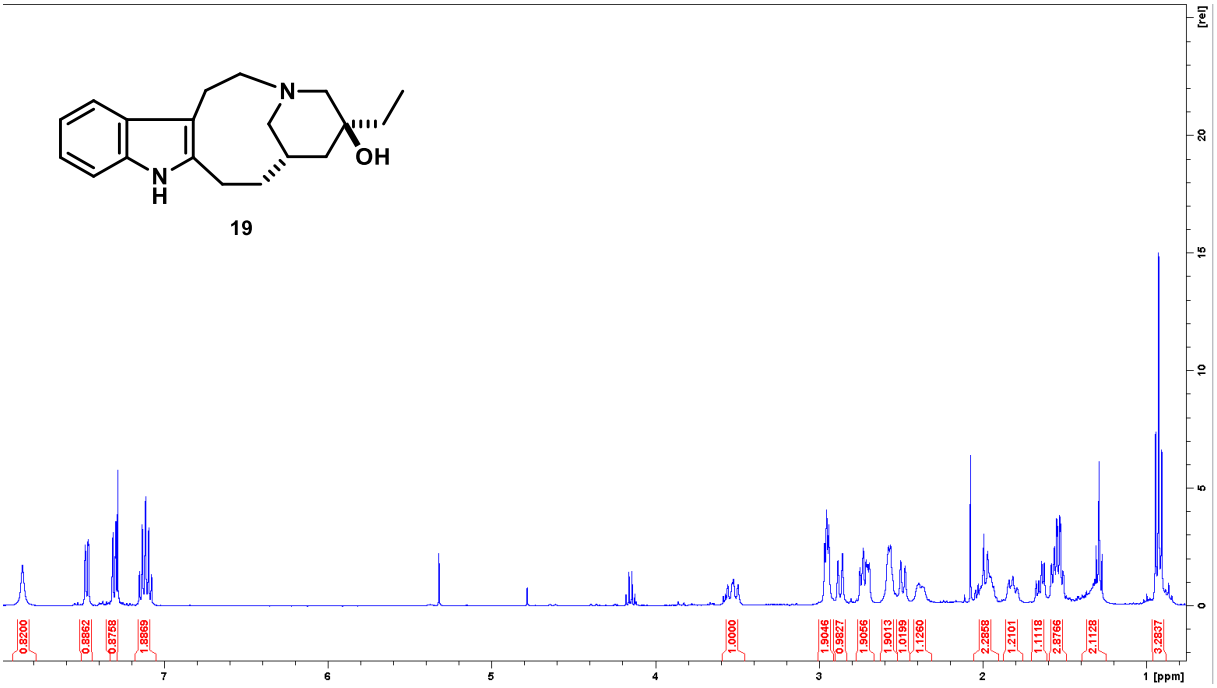

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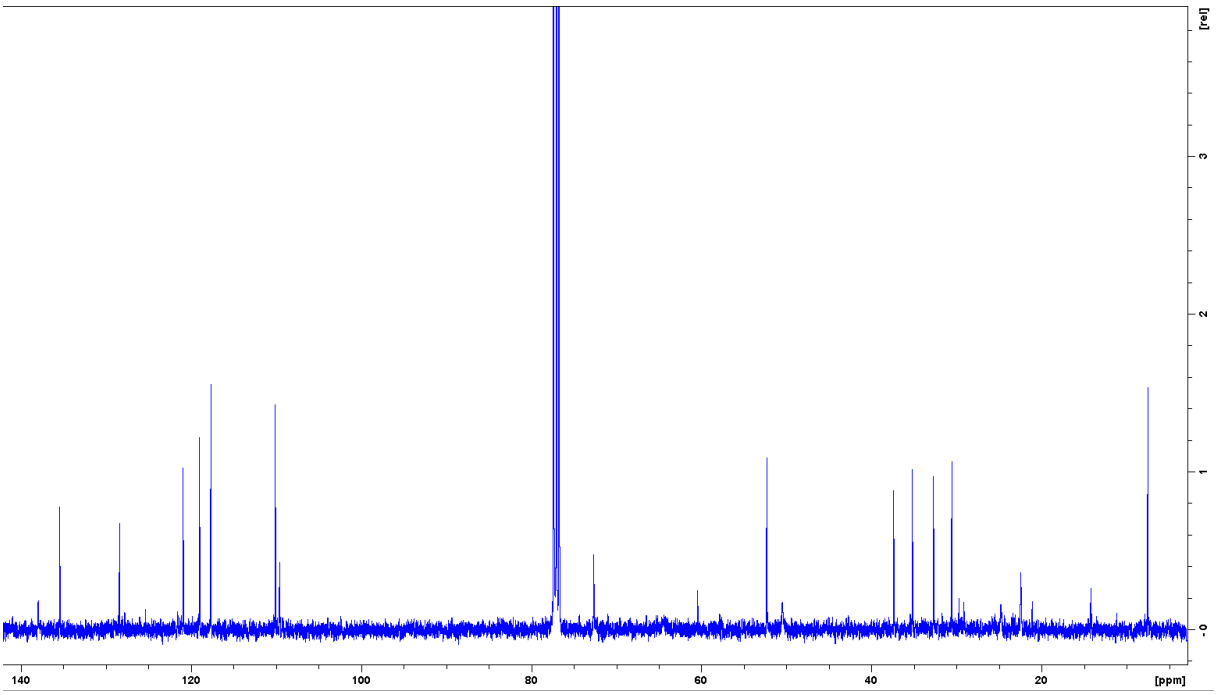

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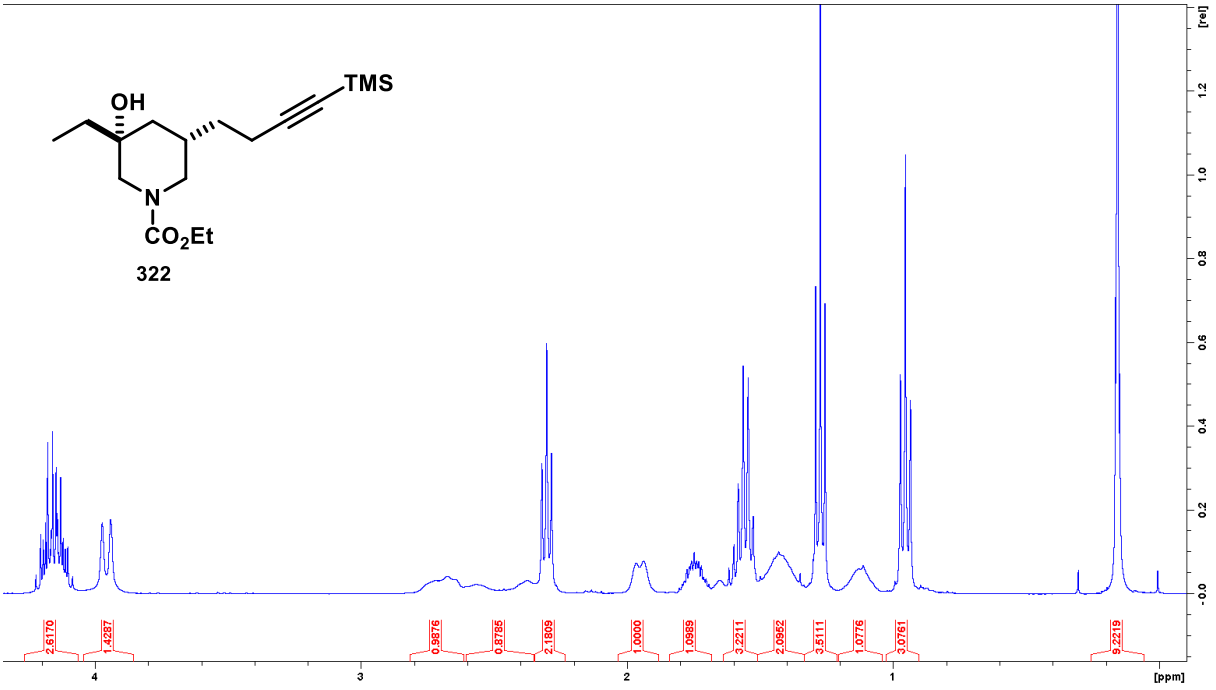

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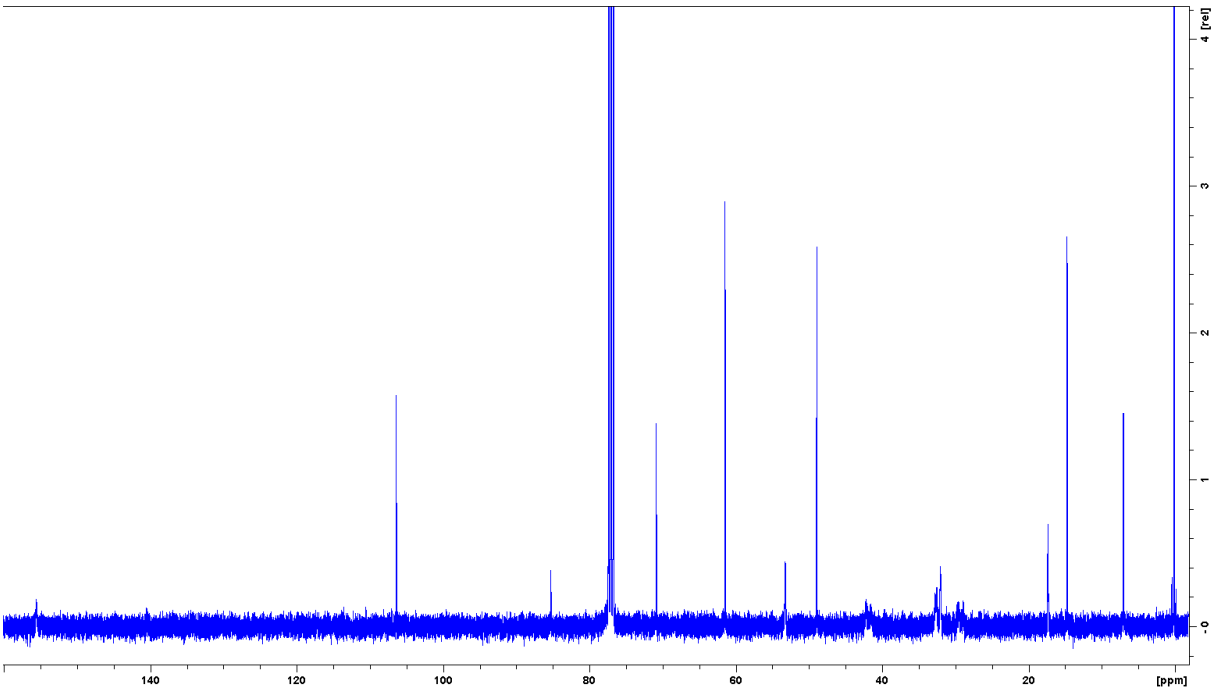

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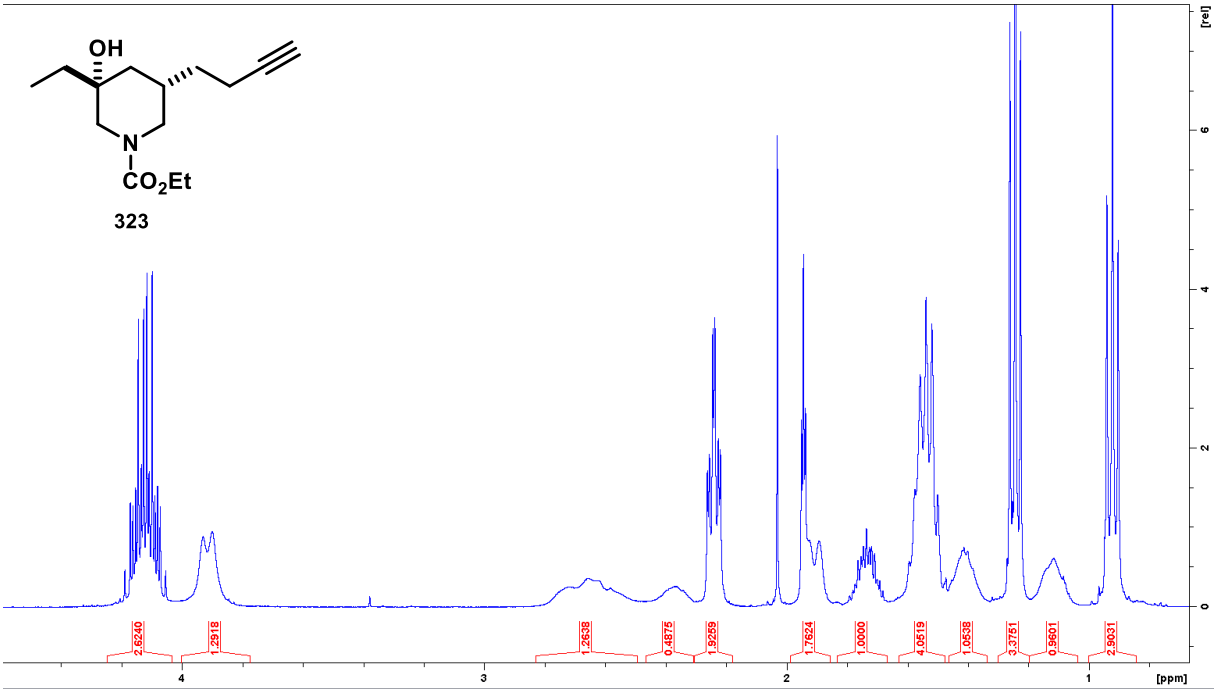

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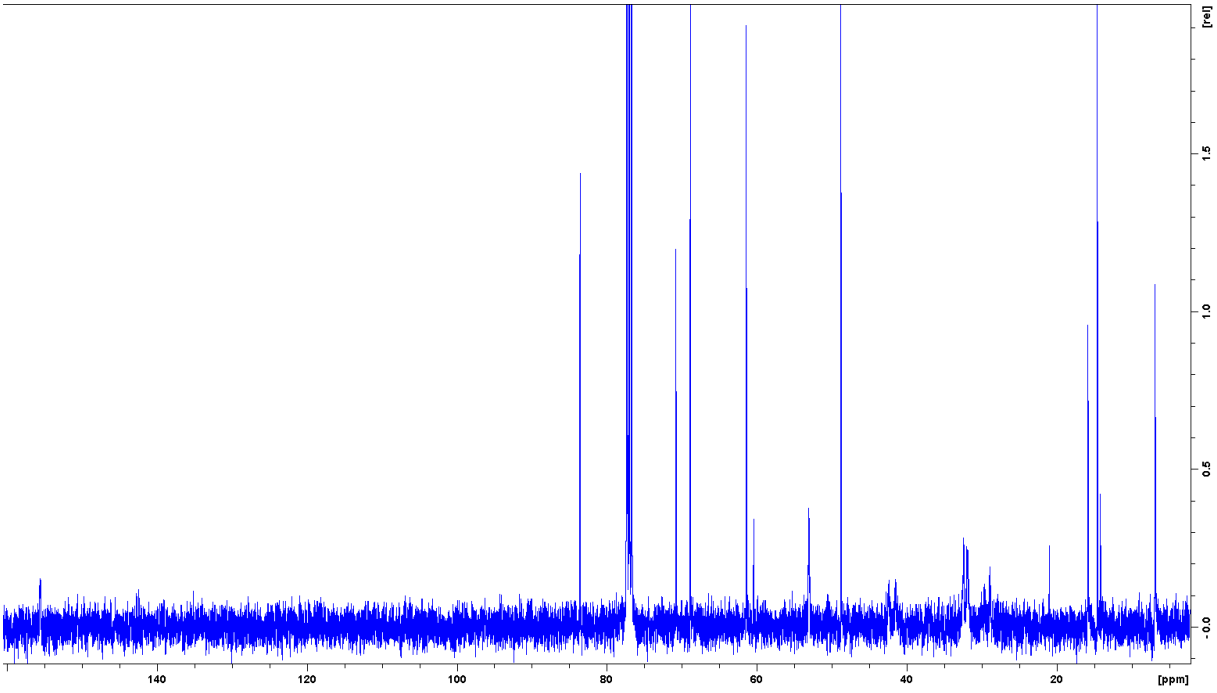

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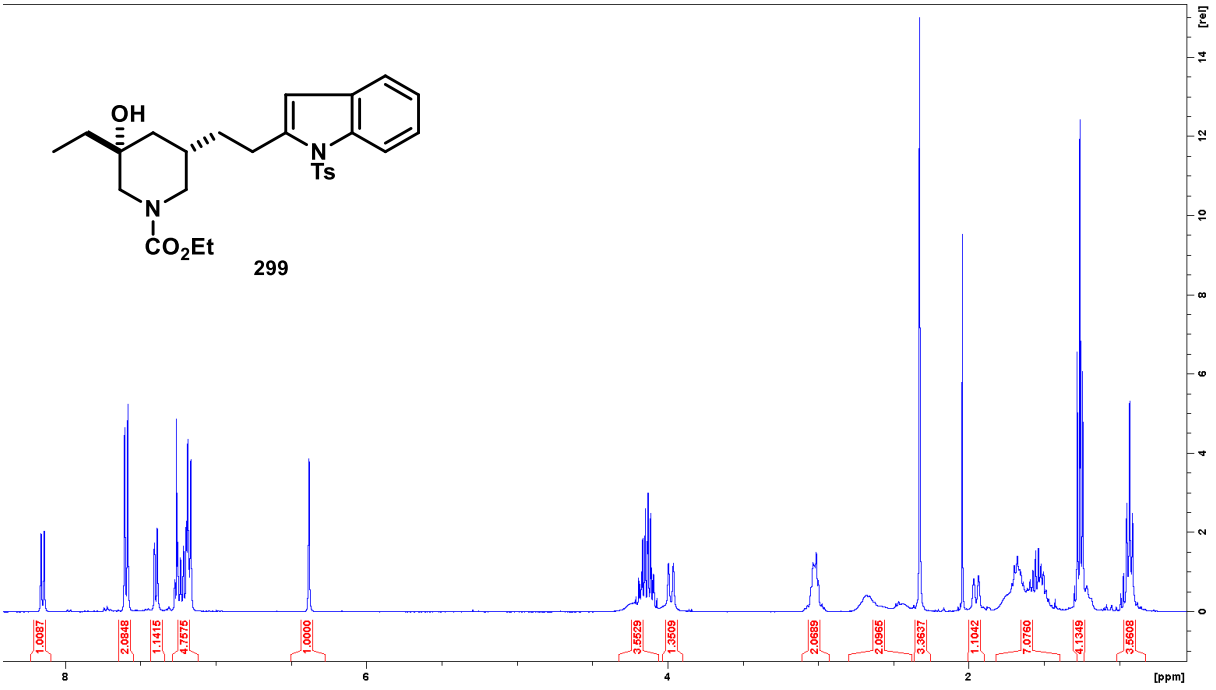

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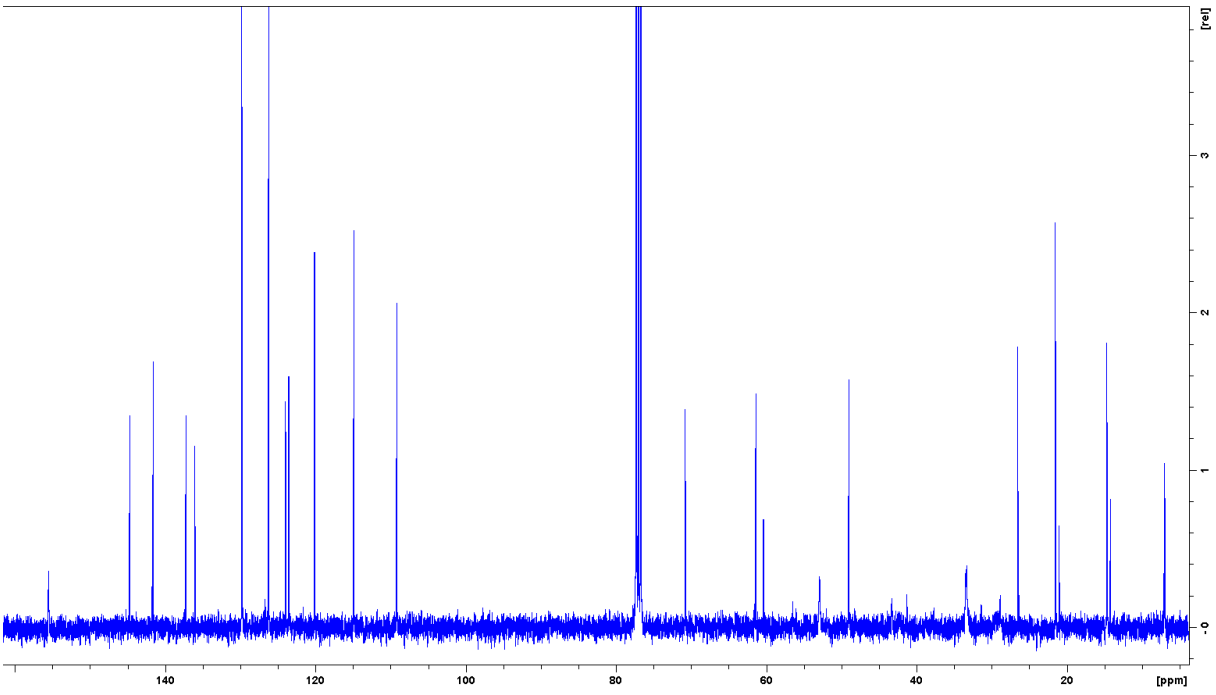

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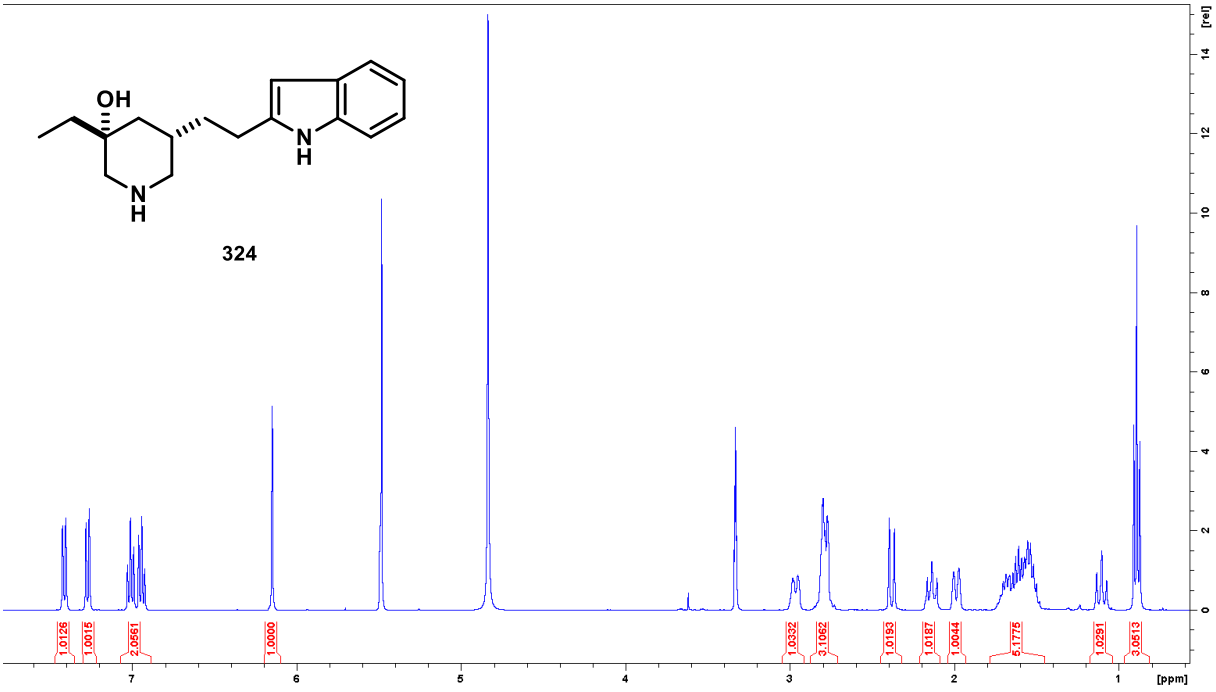
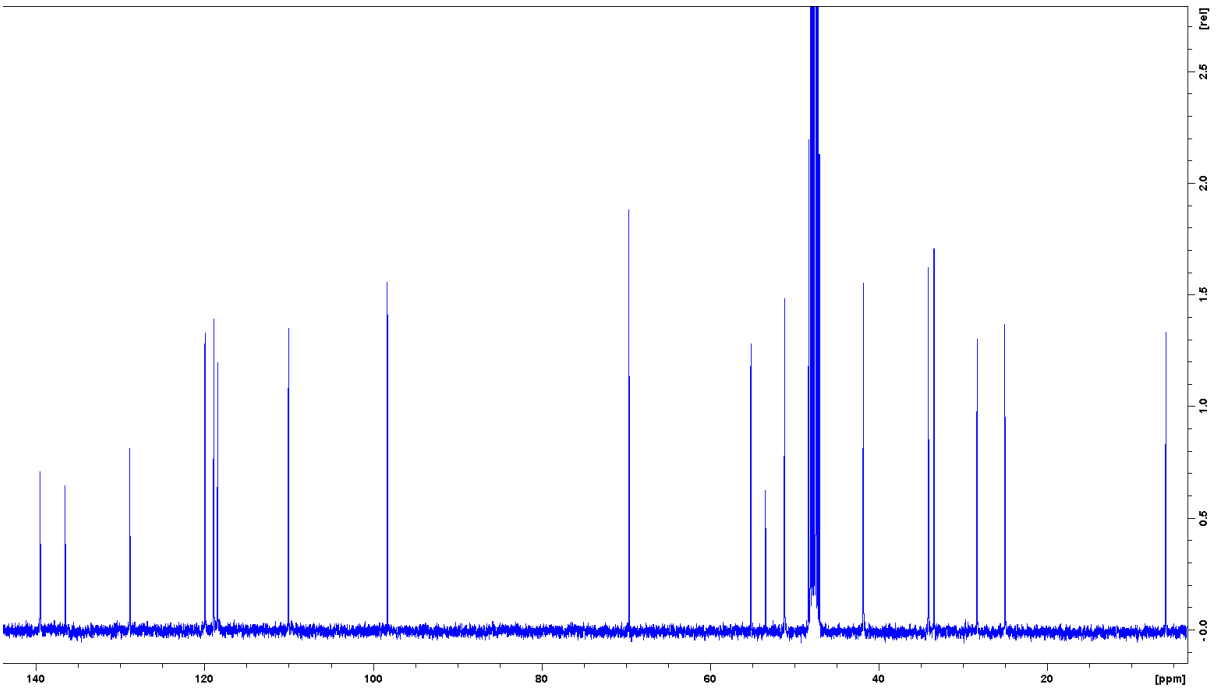
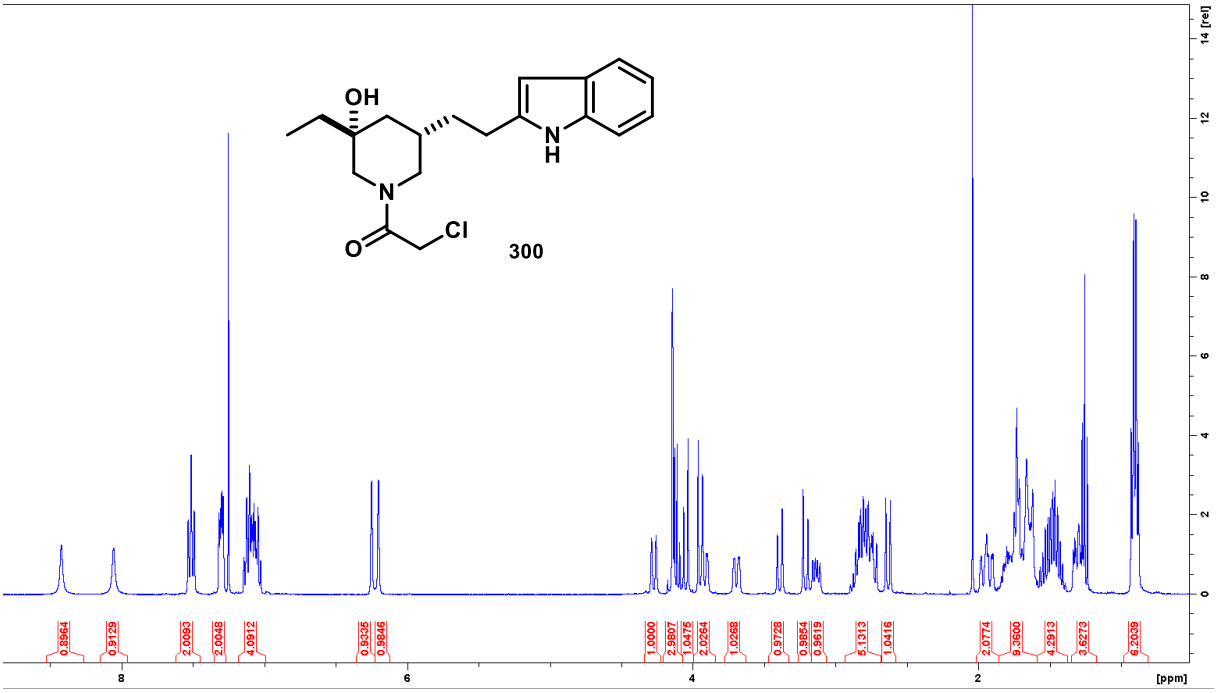


^{13}C NMR (100 MHz, CD_3OD)



^{1}H NMR (400 MHz, $CDCl_3$, two rotamers)



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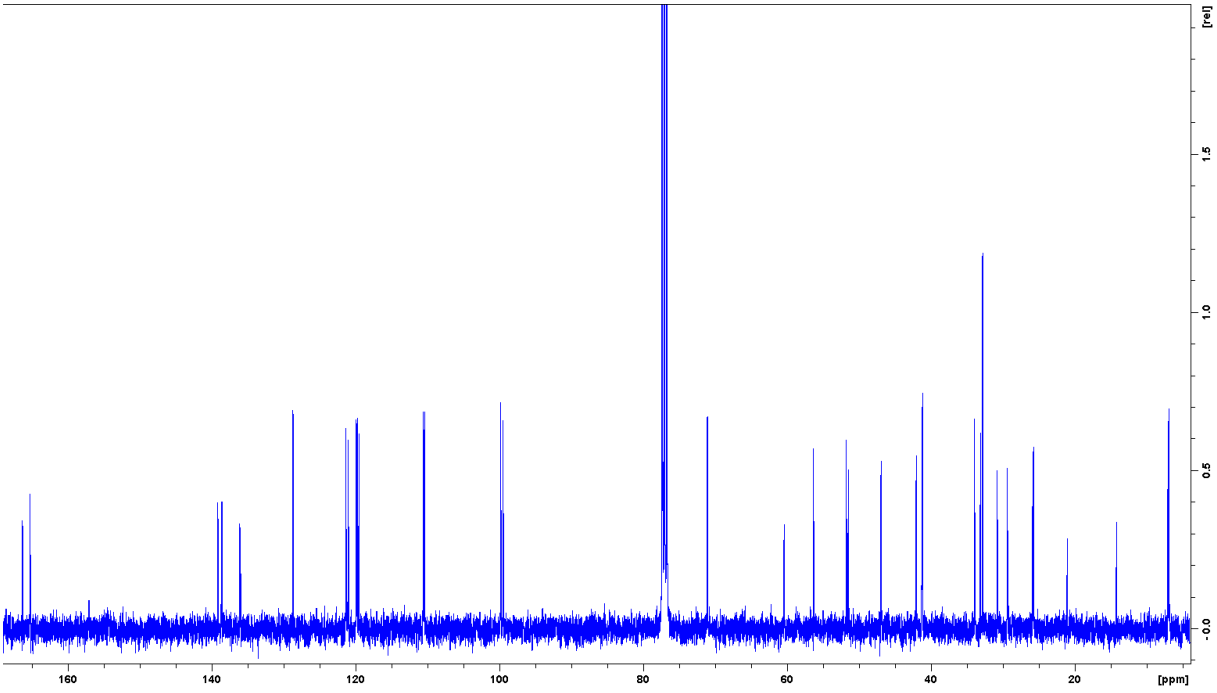
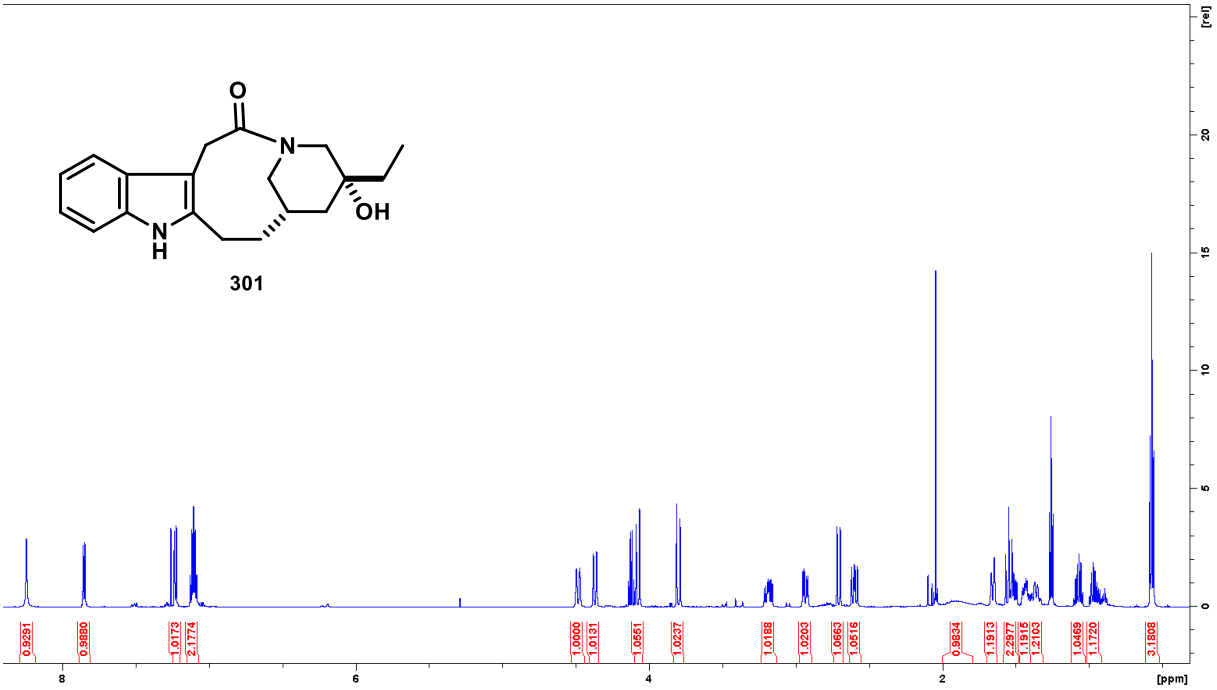


^{1}H NMR (600 MHz, $CDCl_3$)



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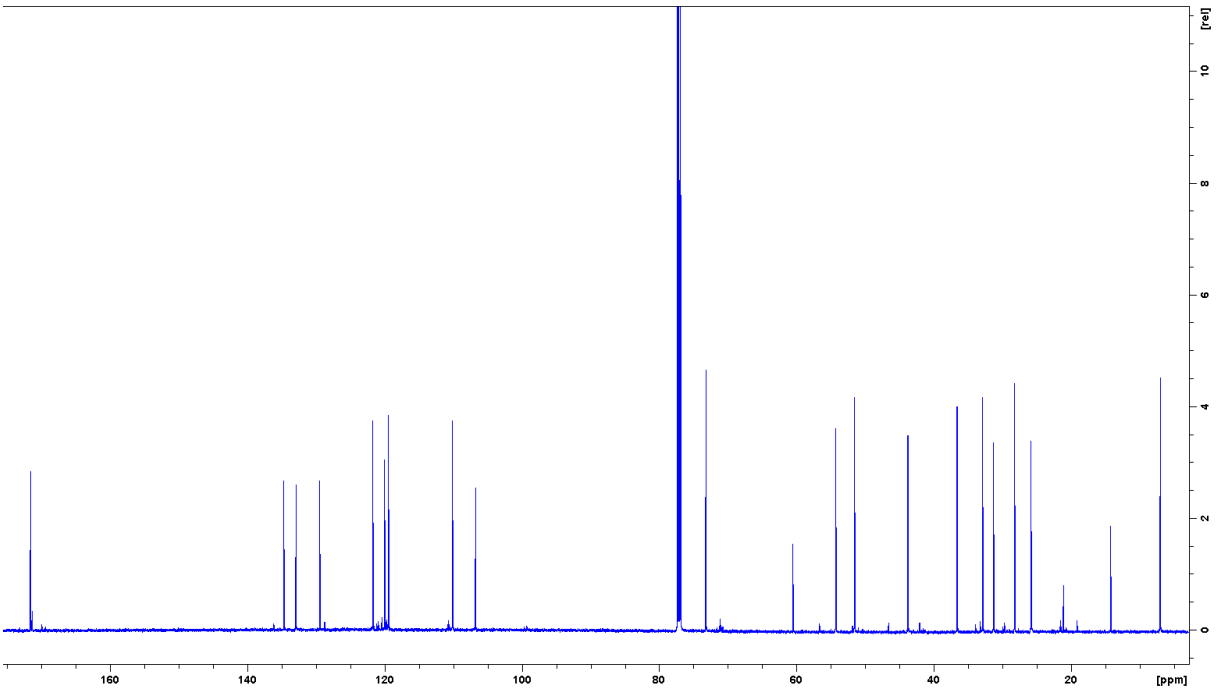

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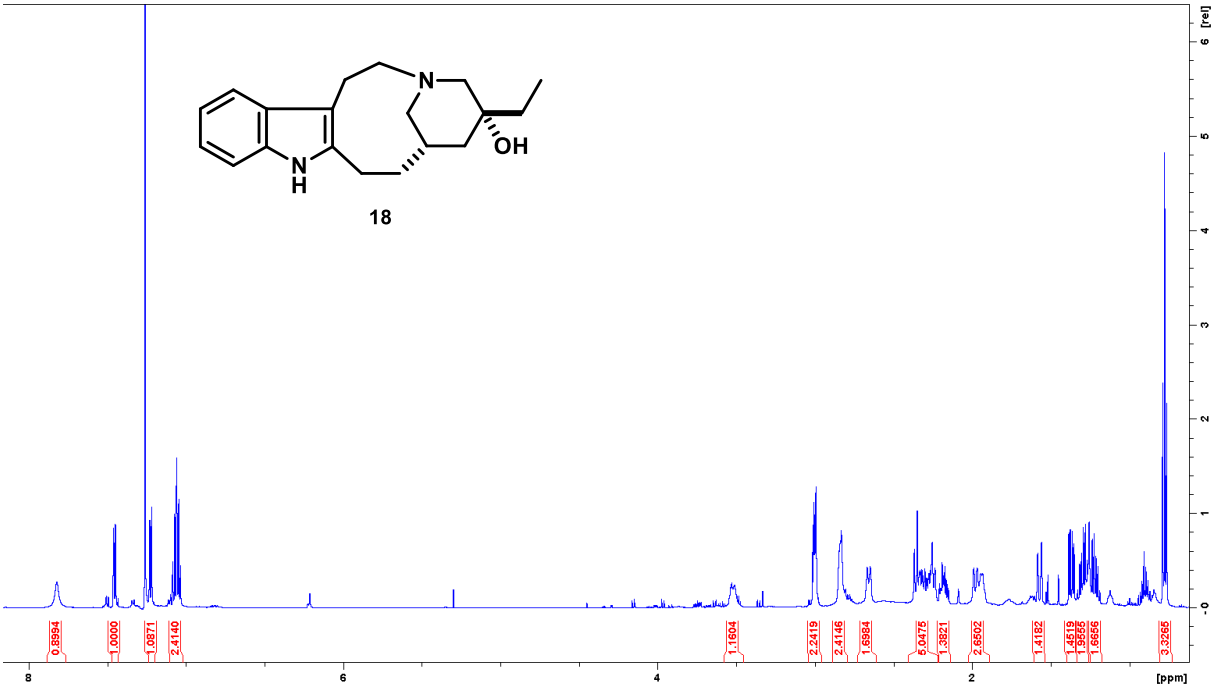

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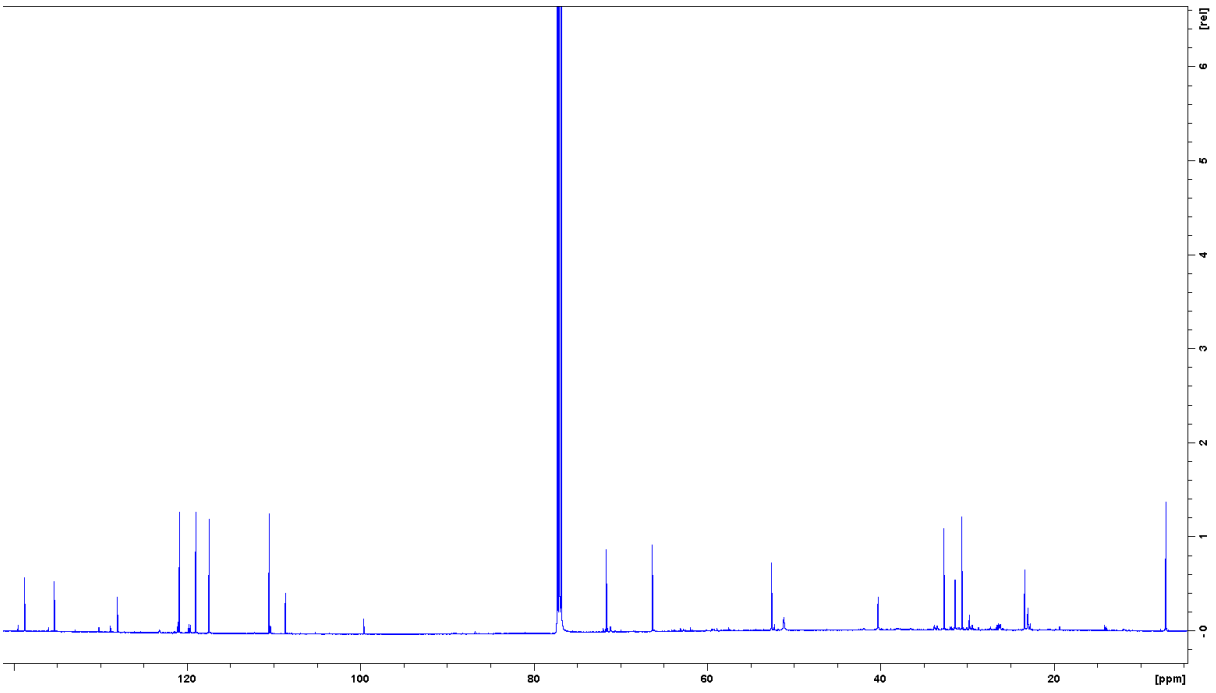

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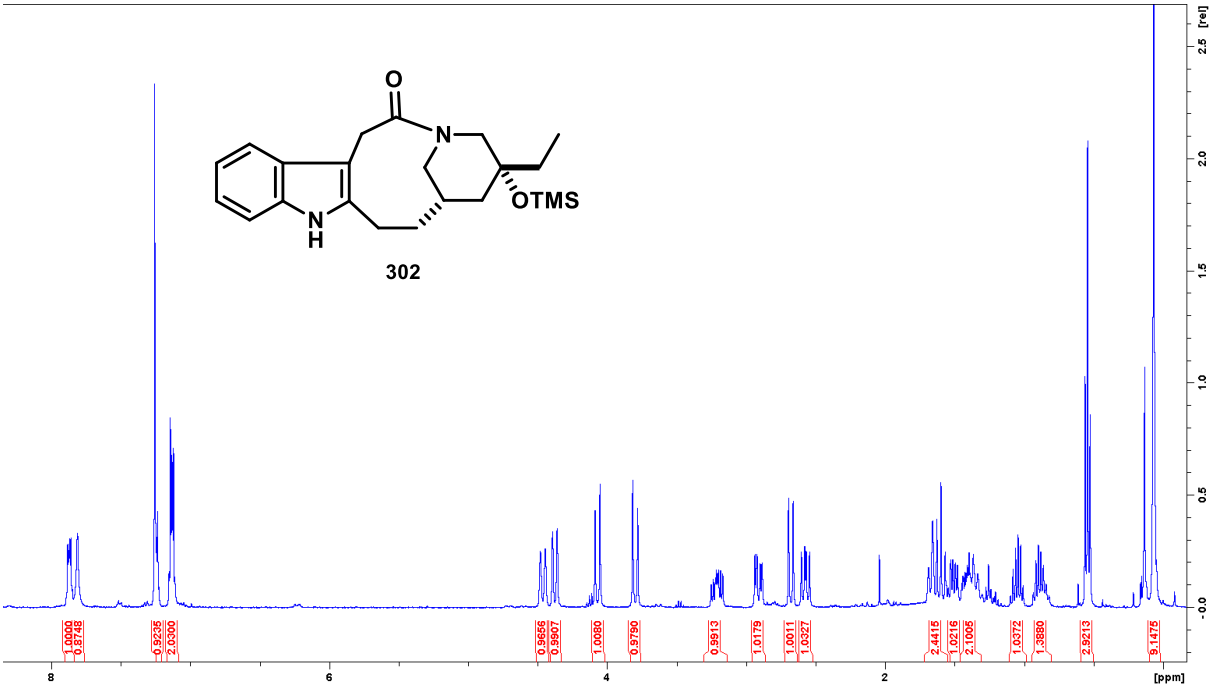
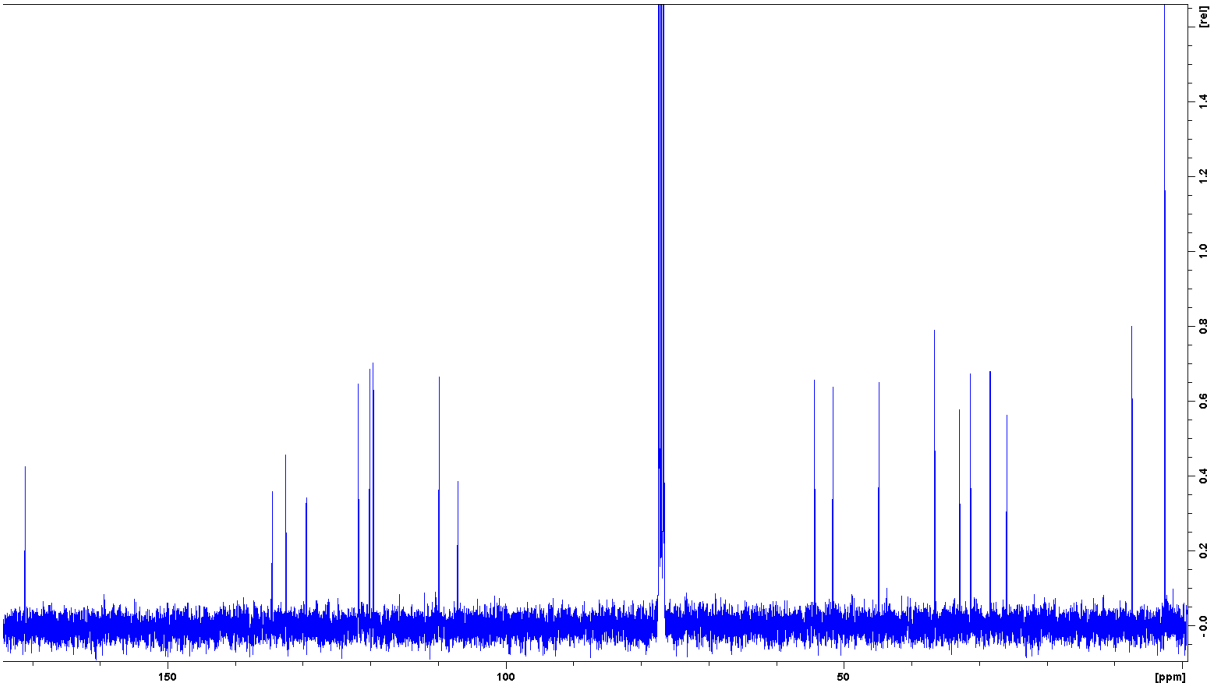


^{13}C NMR (100 MHz, $CDCl_3$)



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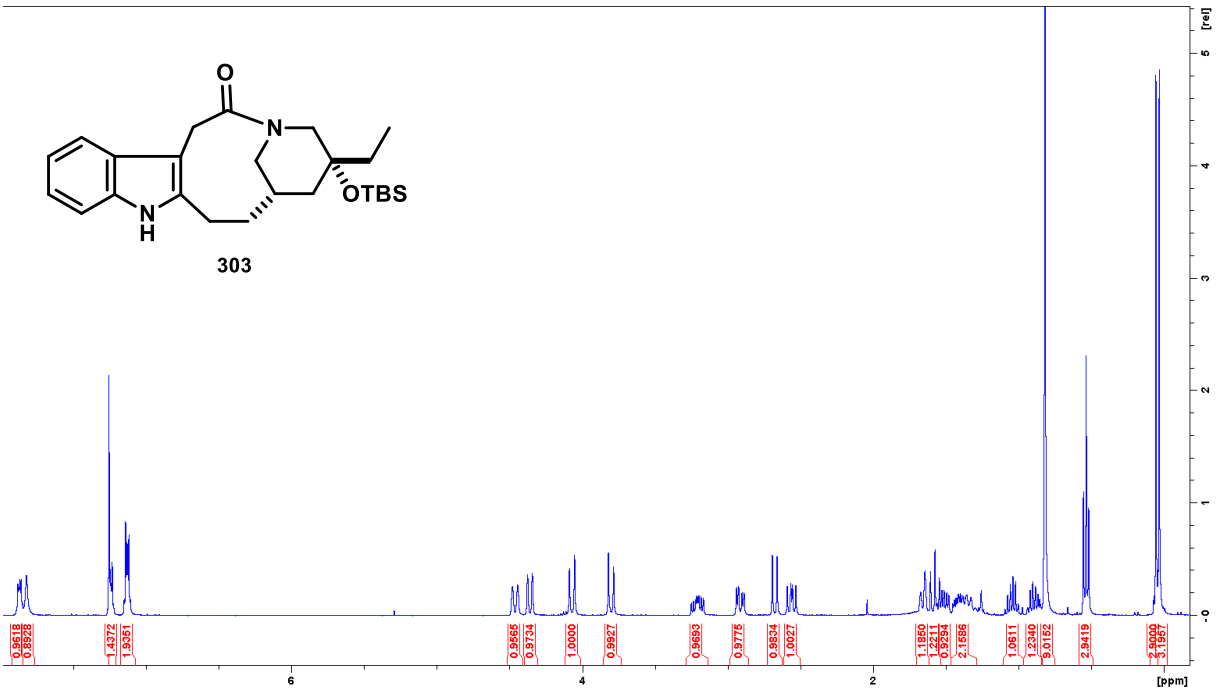

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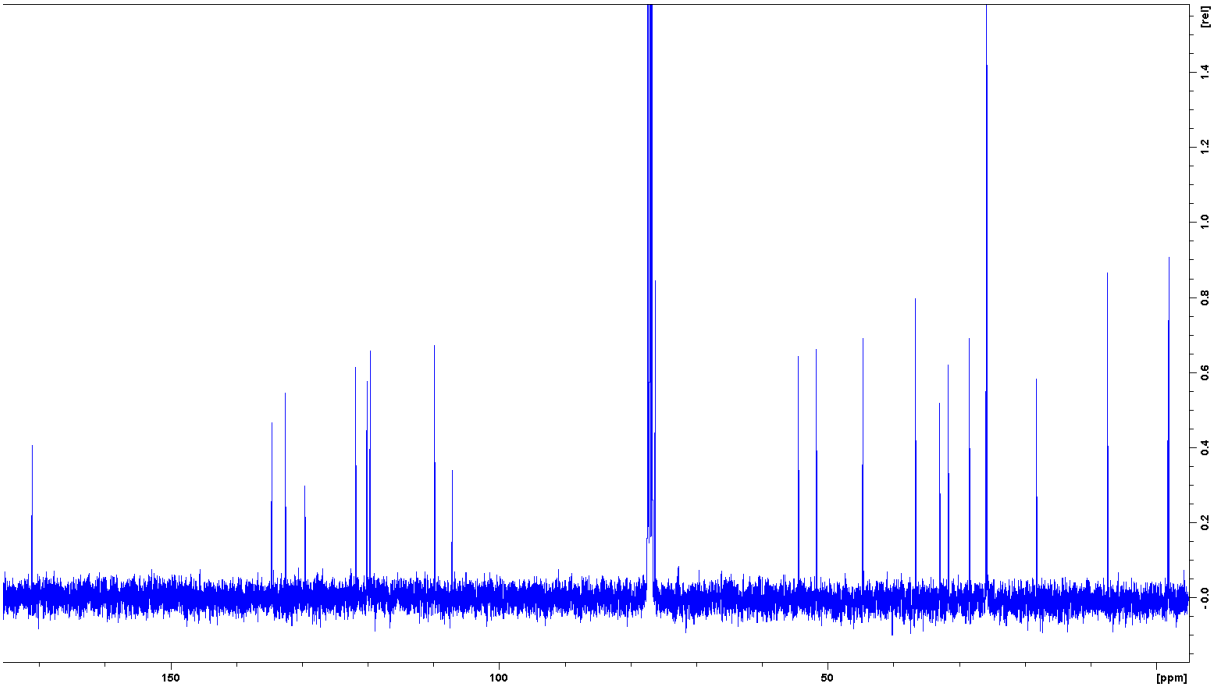

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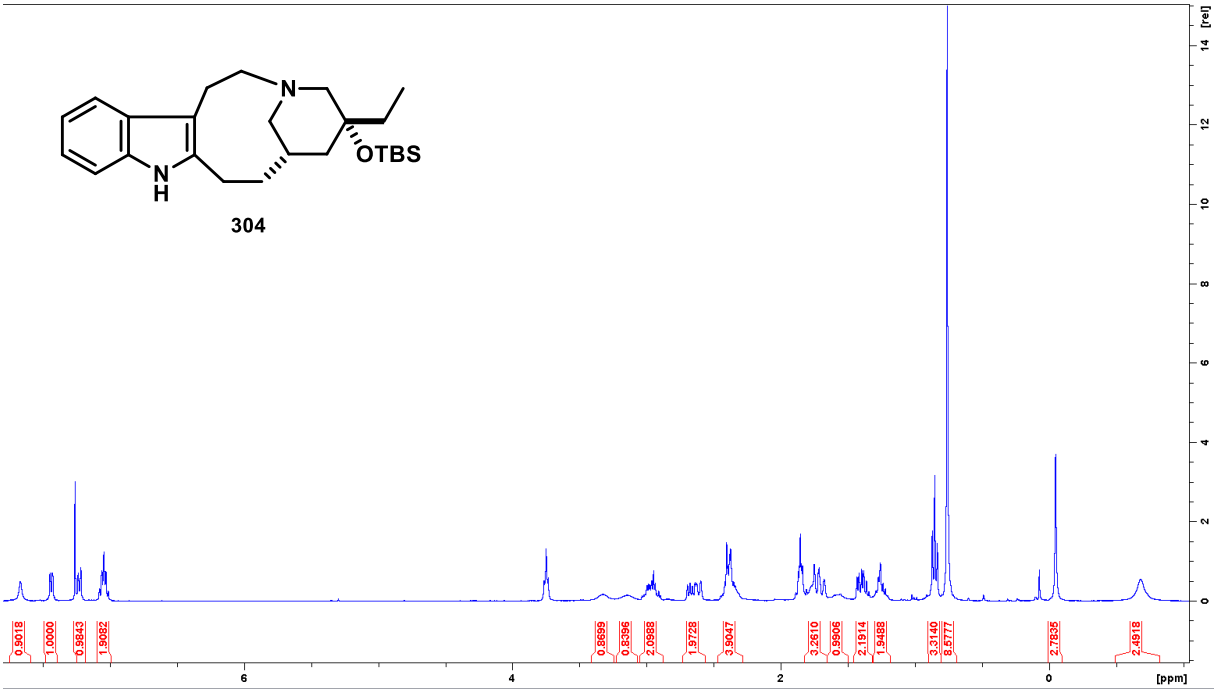

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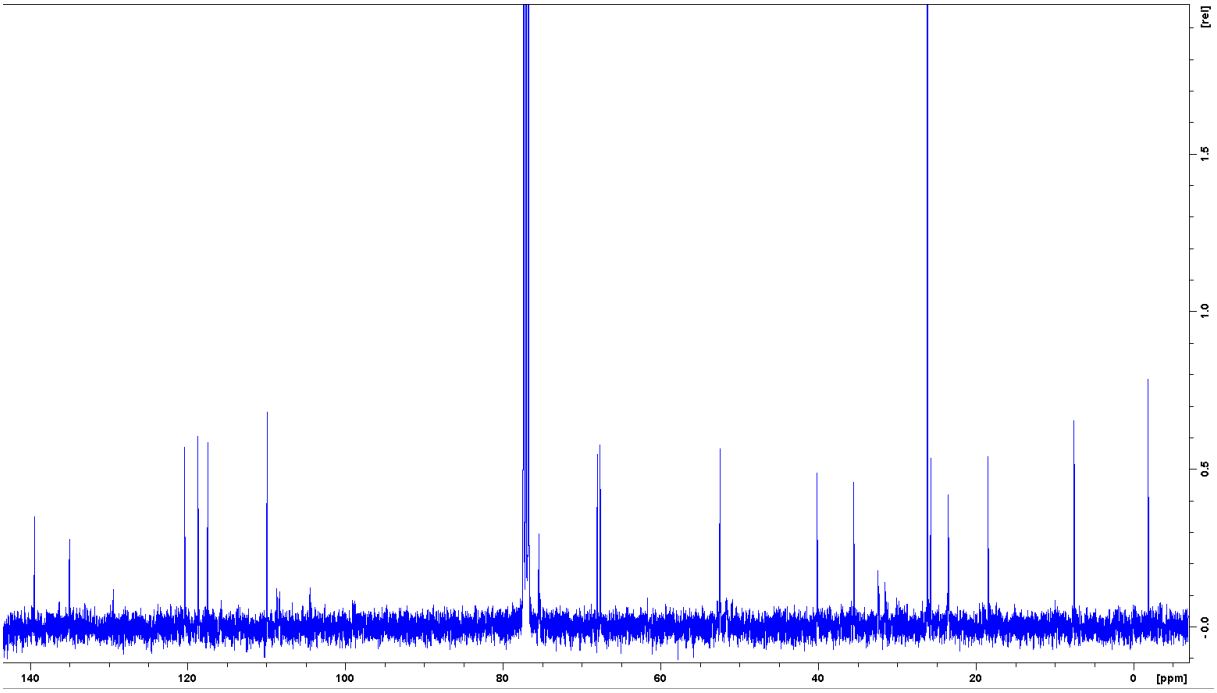

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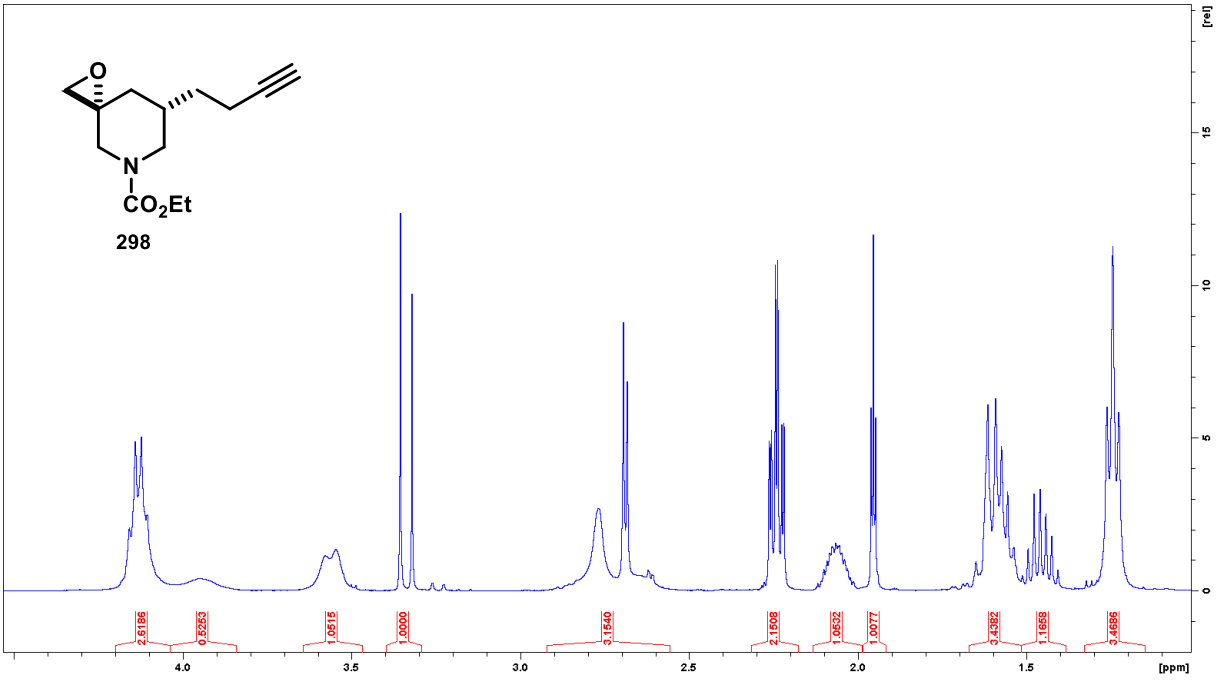

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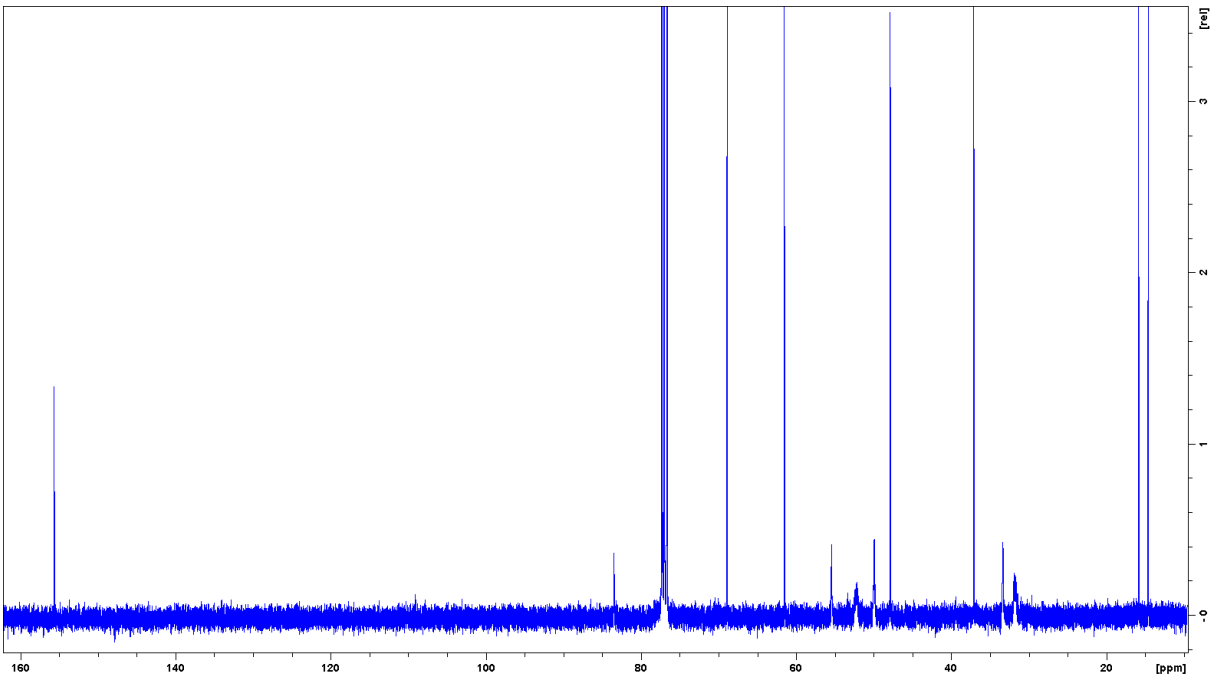

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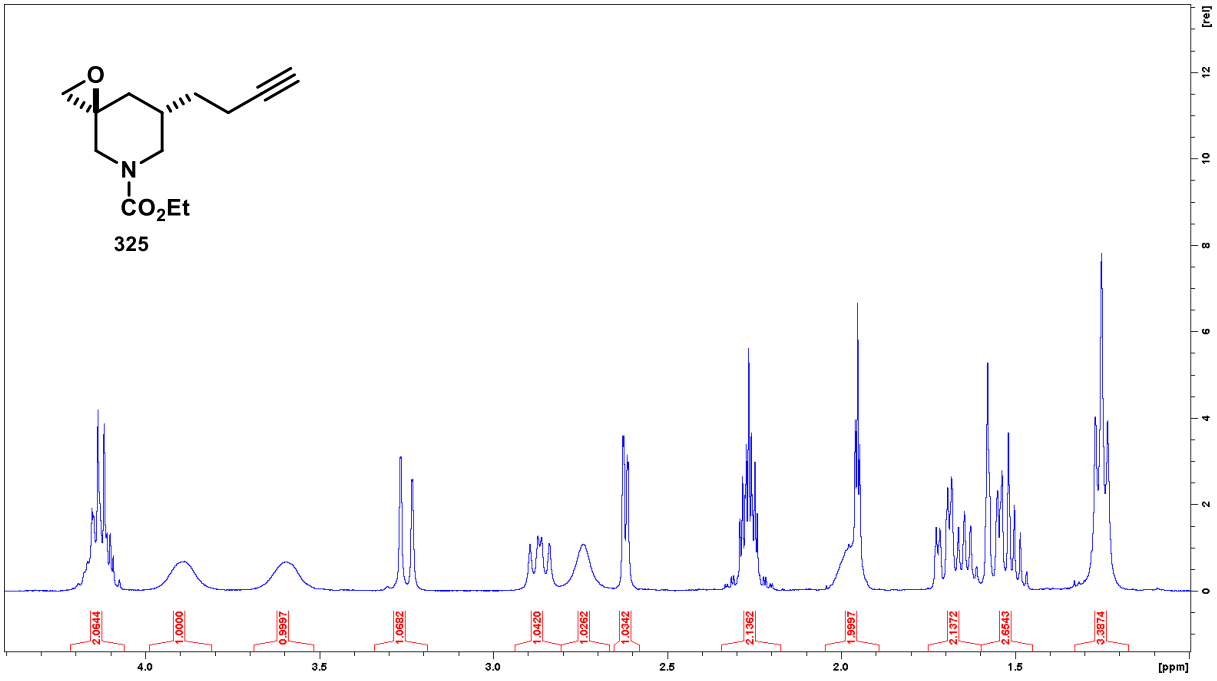

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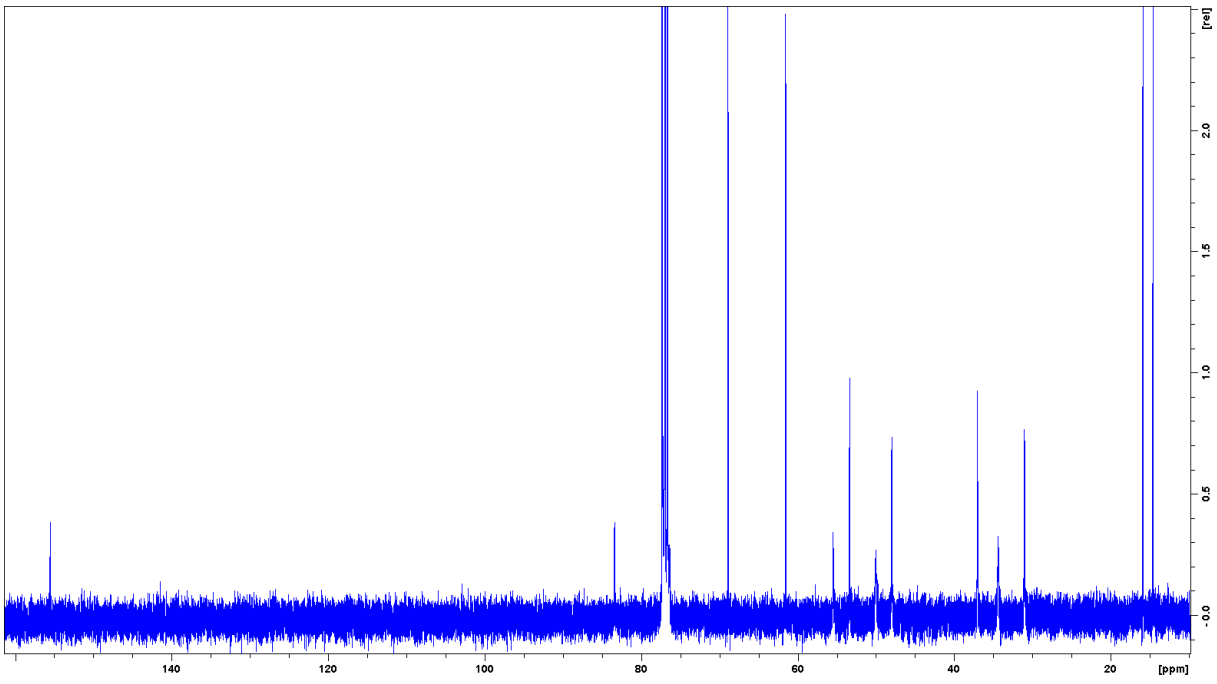

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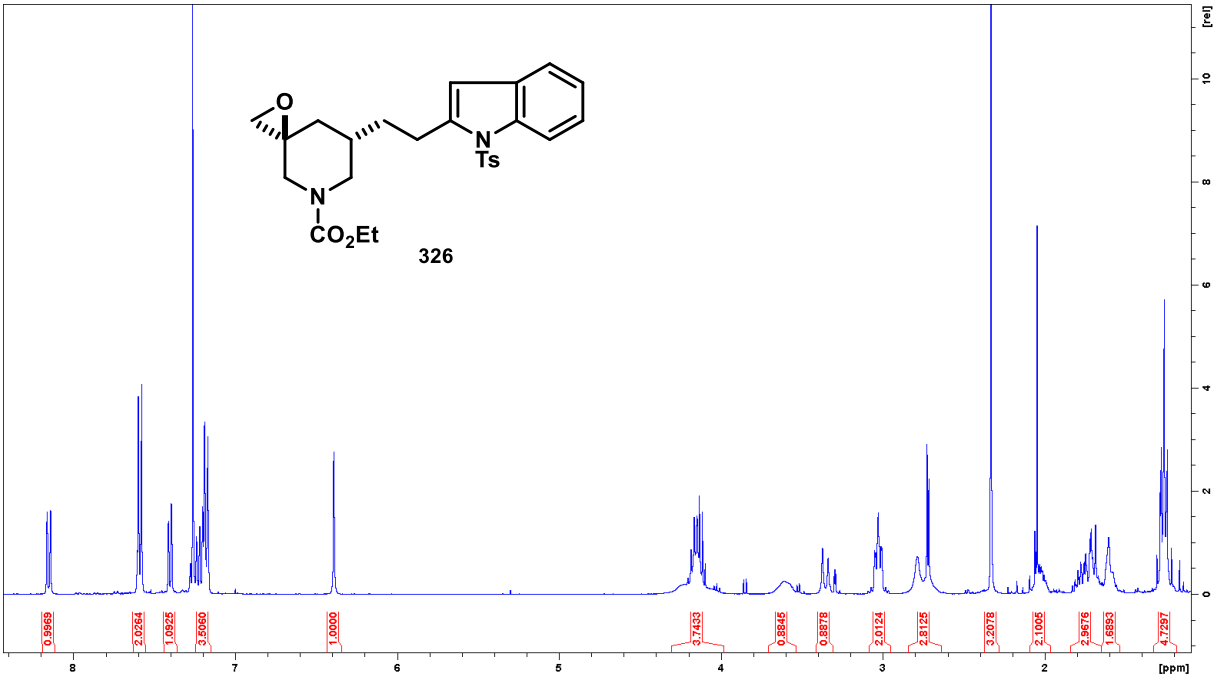

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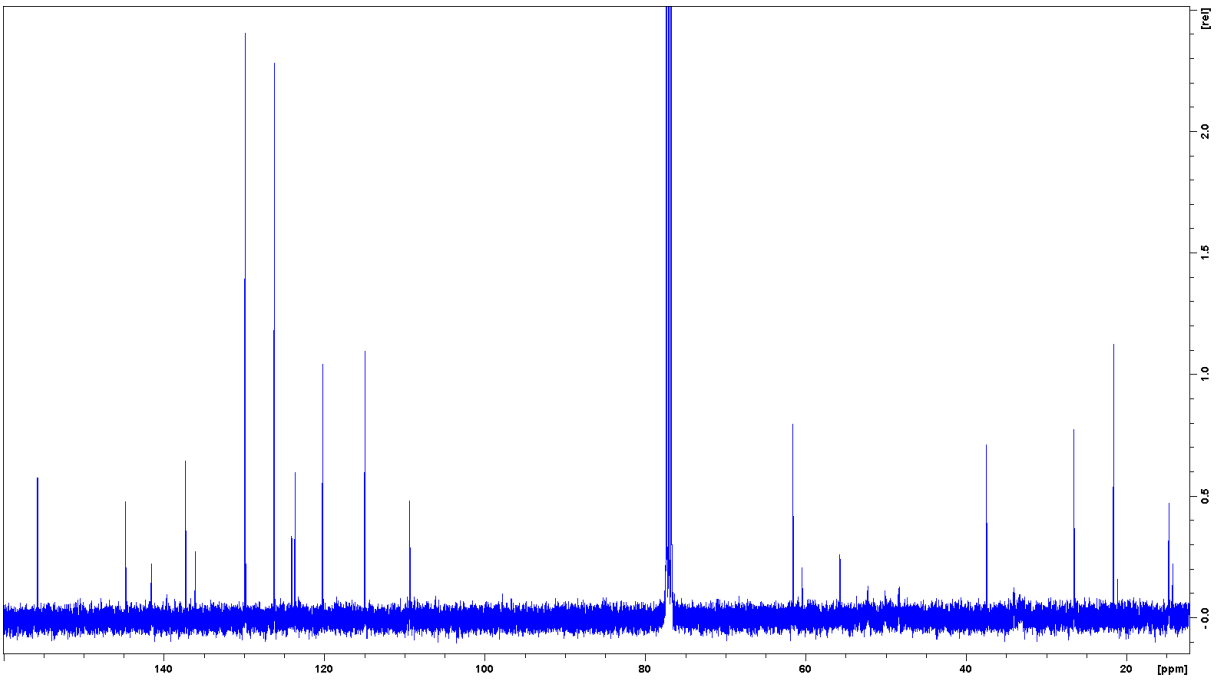

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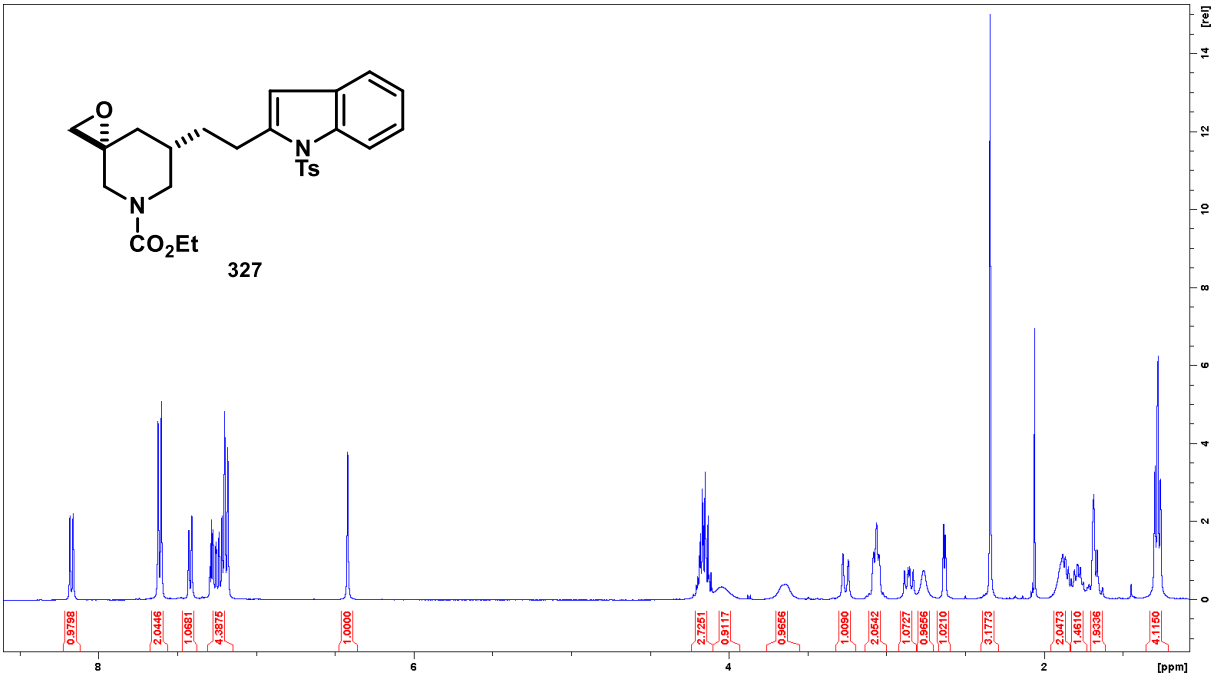

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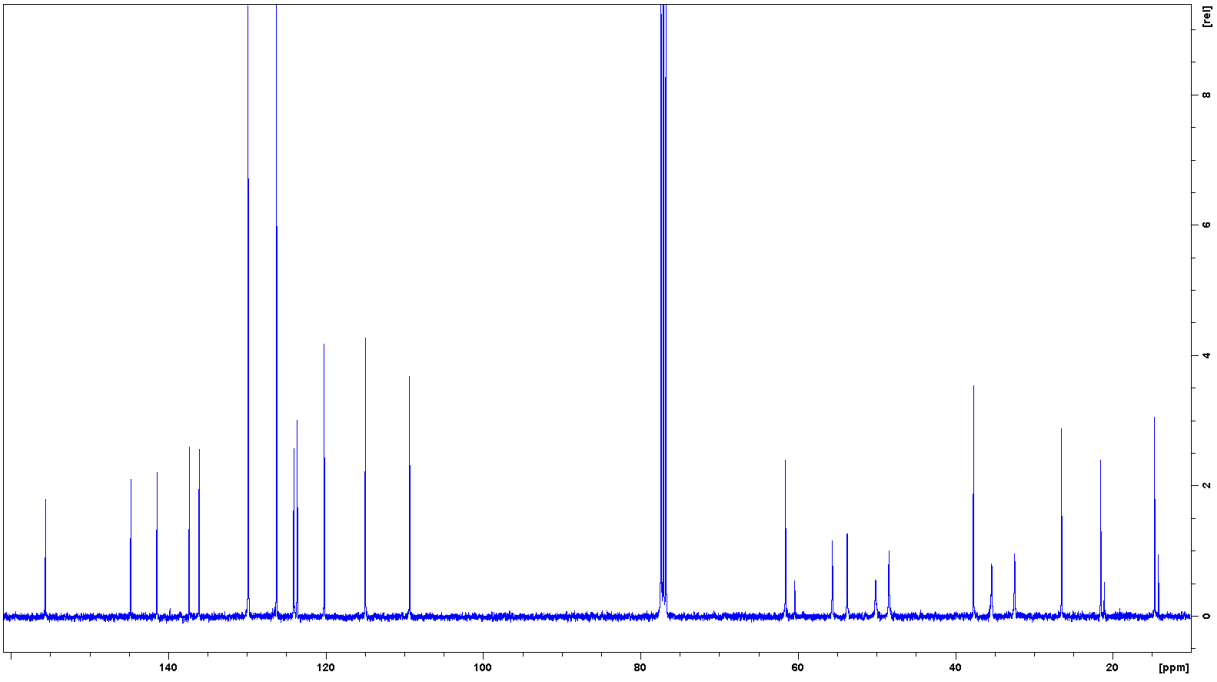

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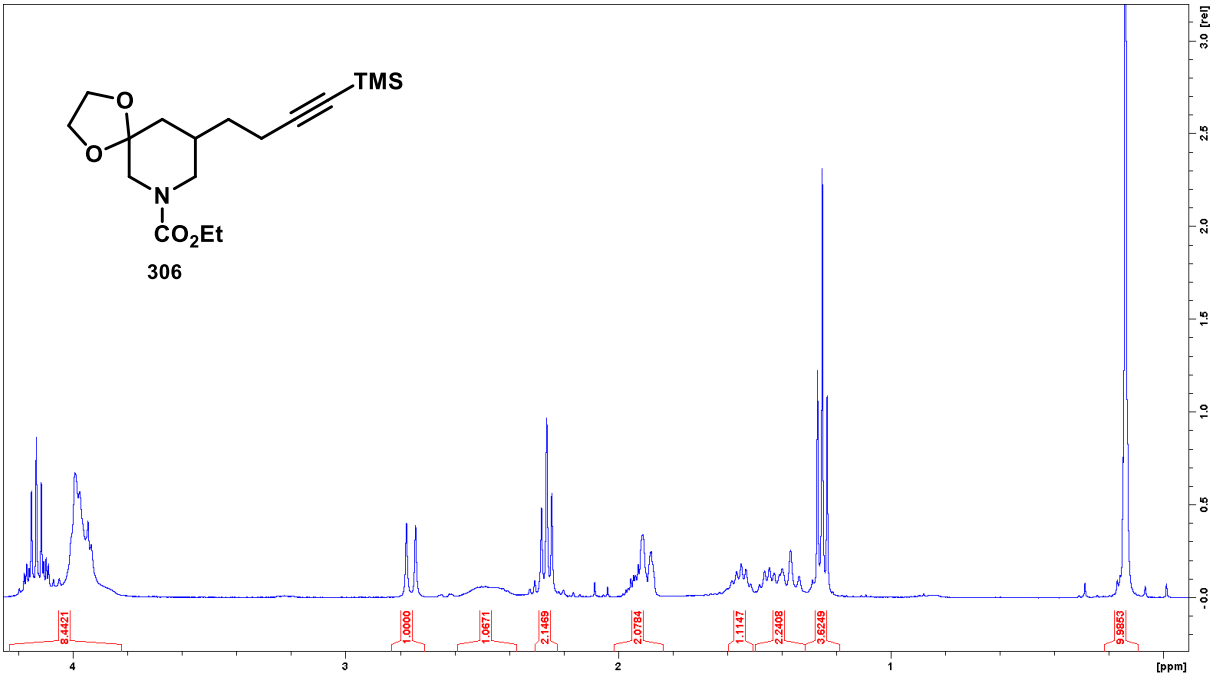

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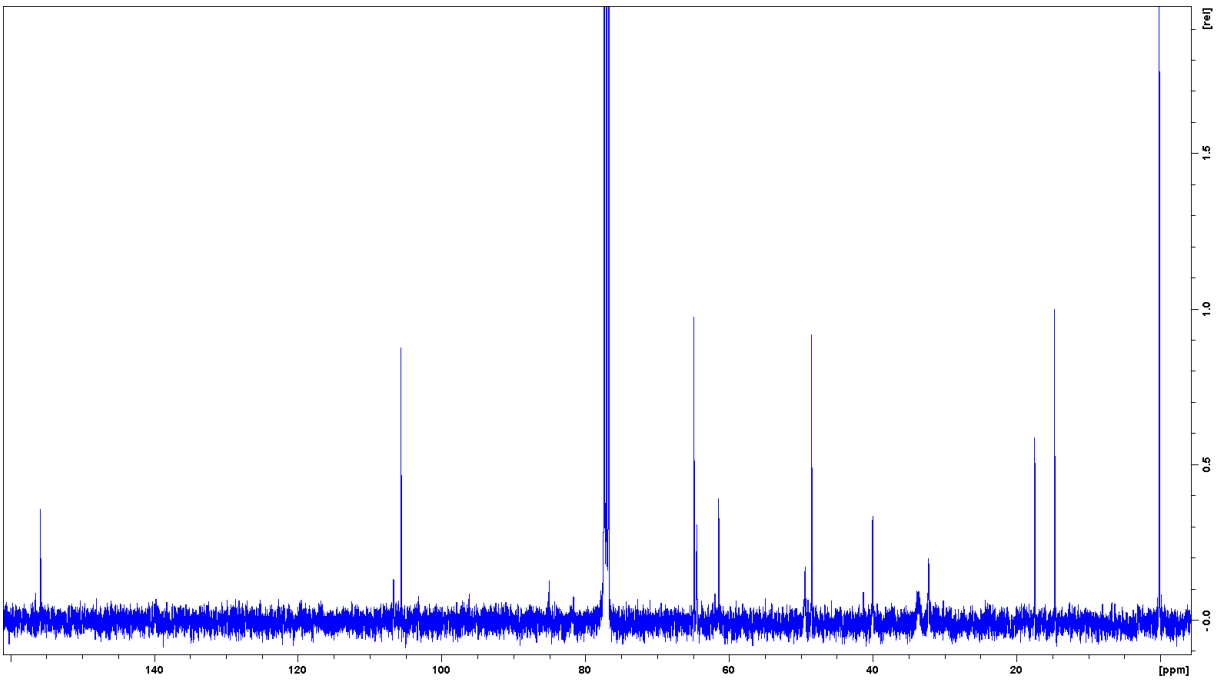

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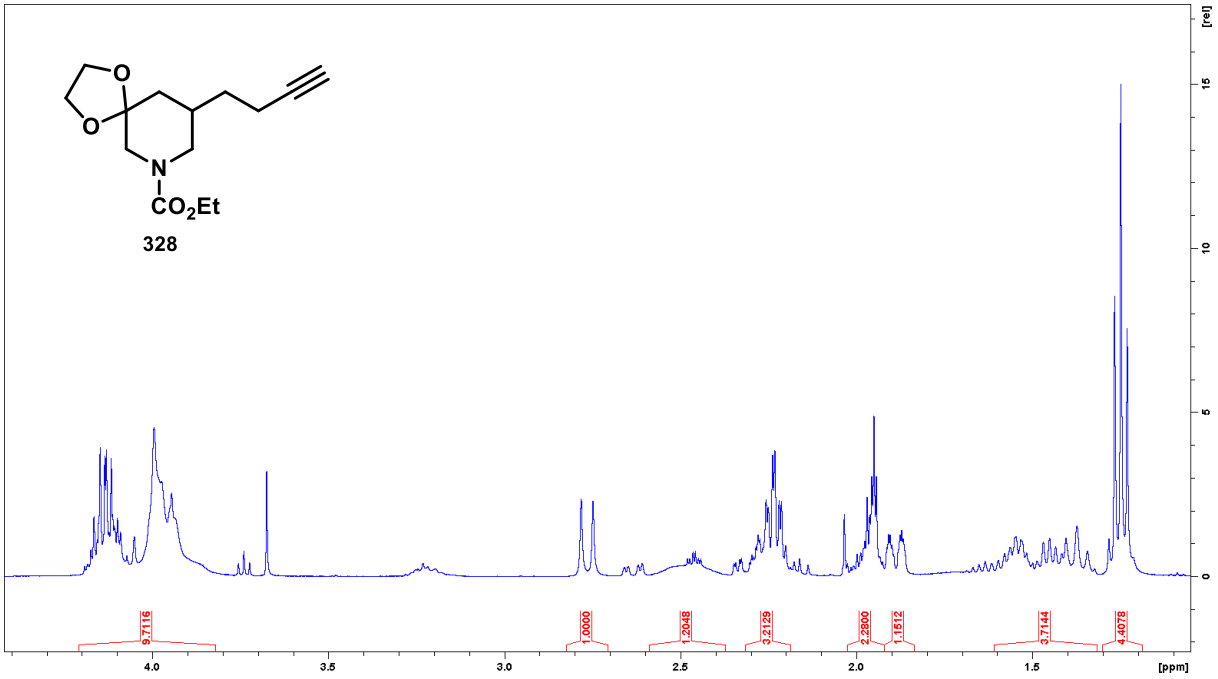

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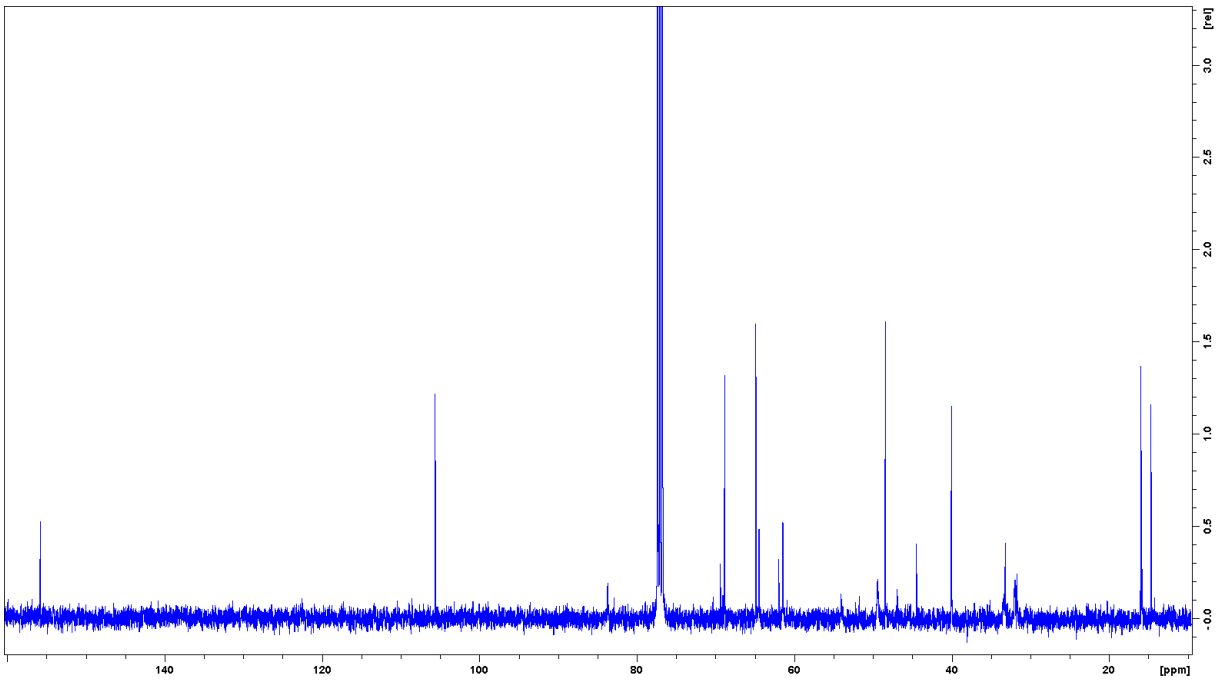

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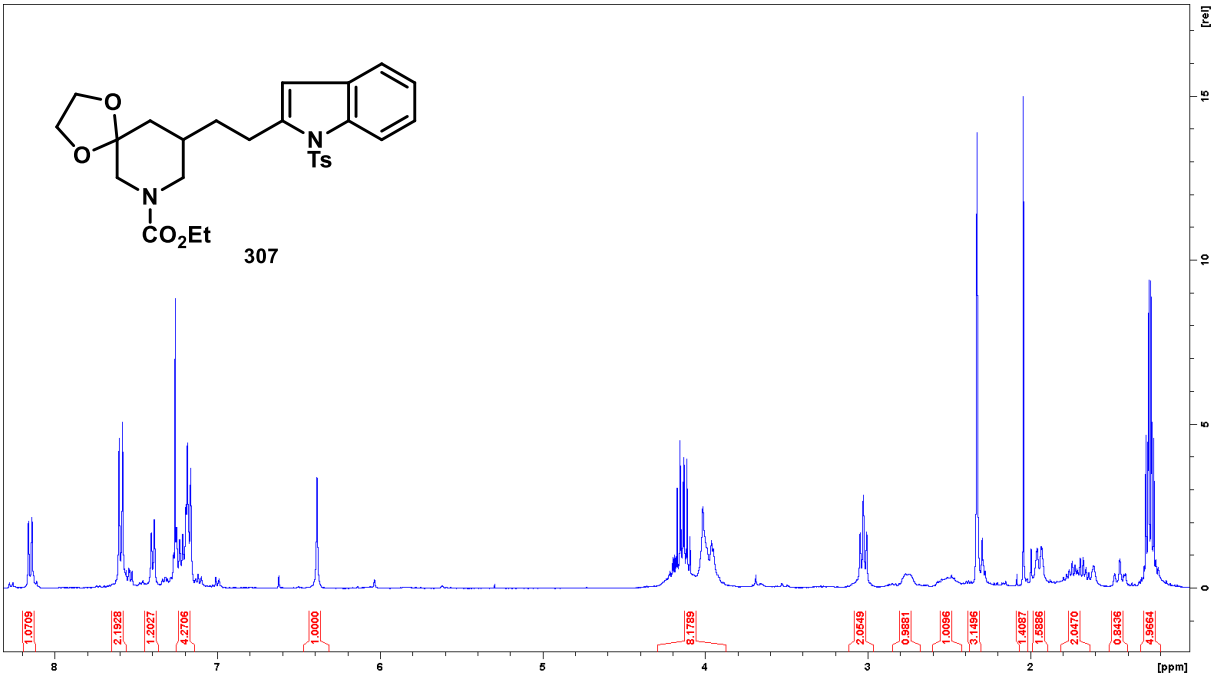

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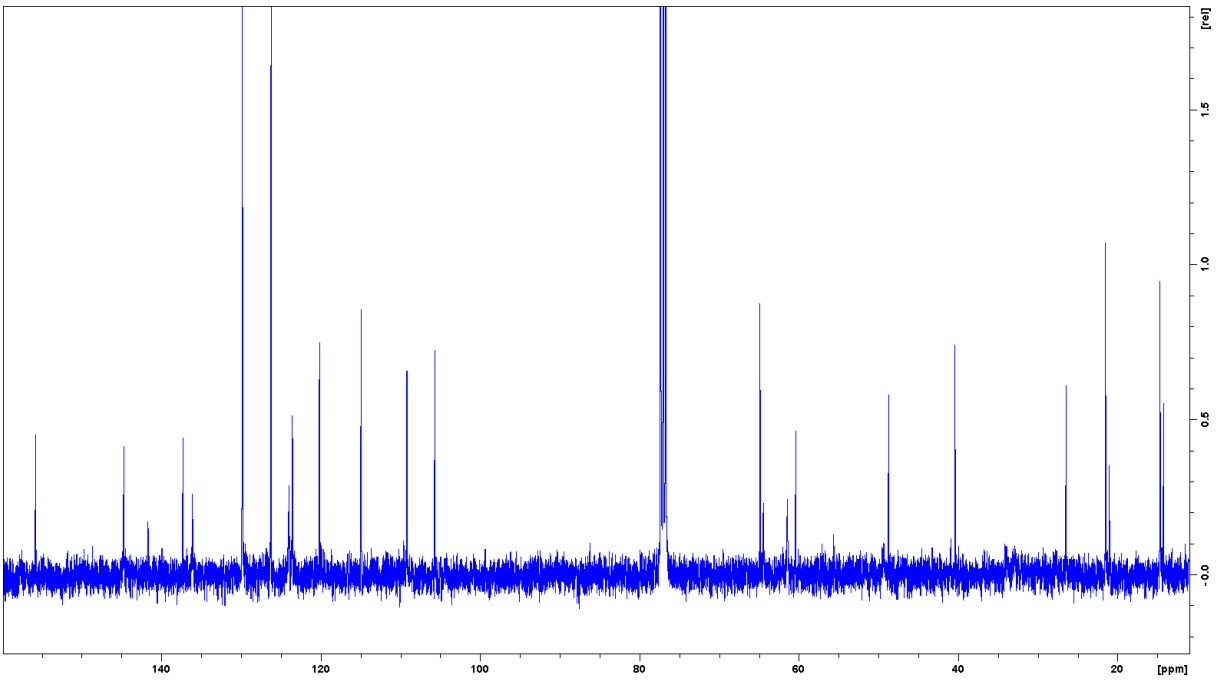

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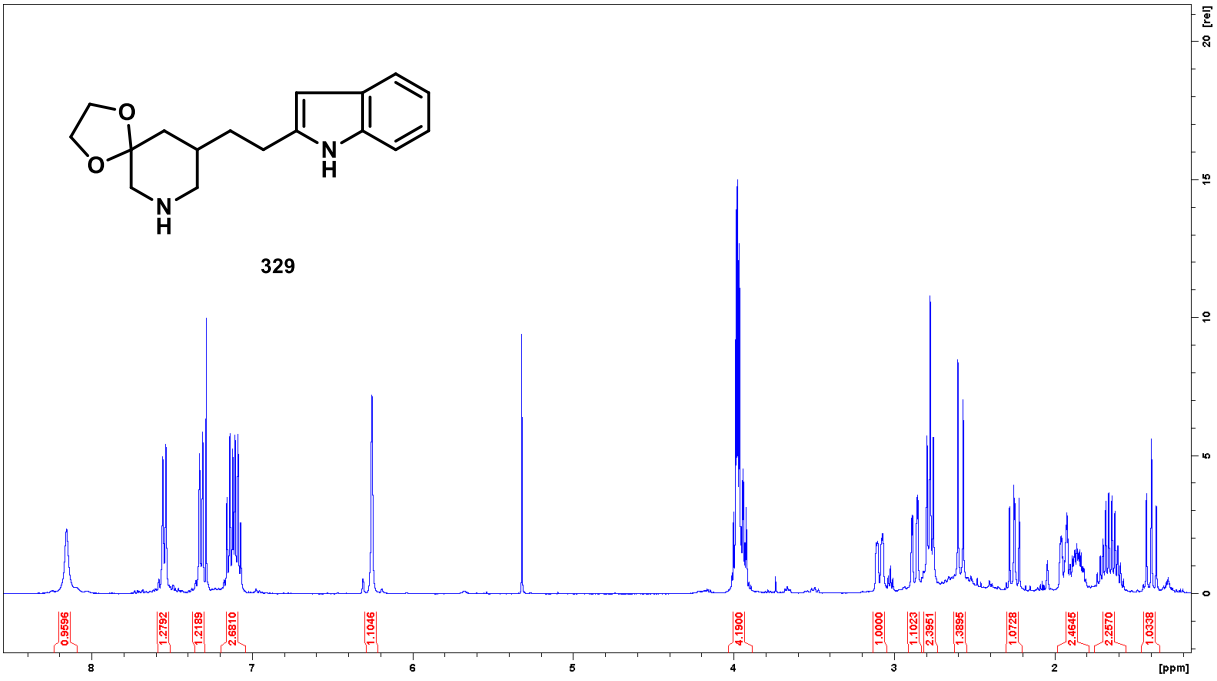

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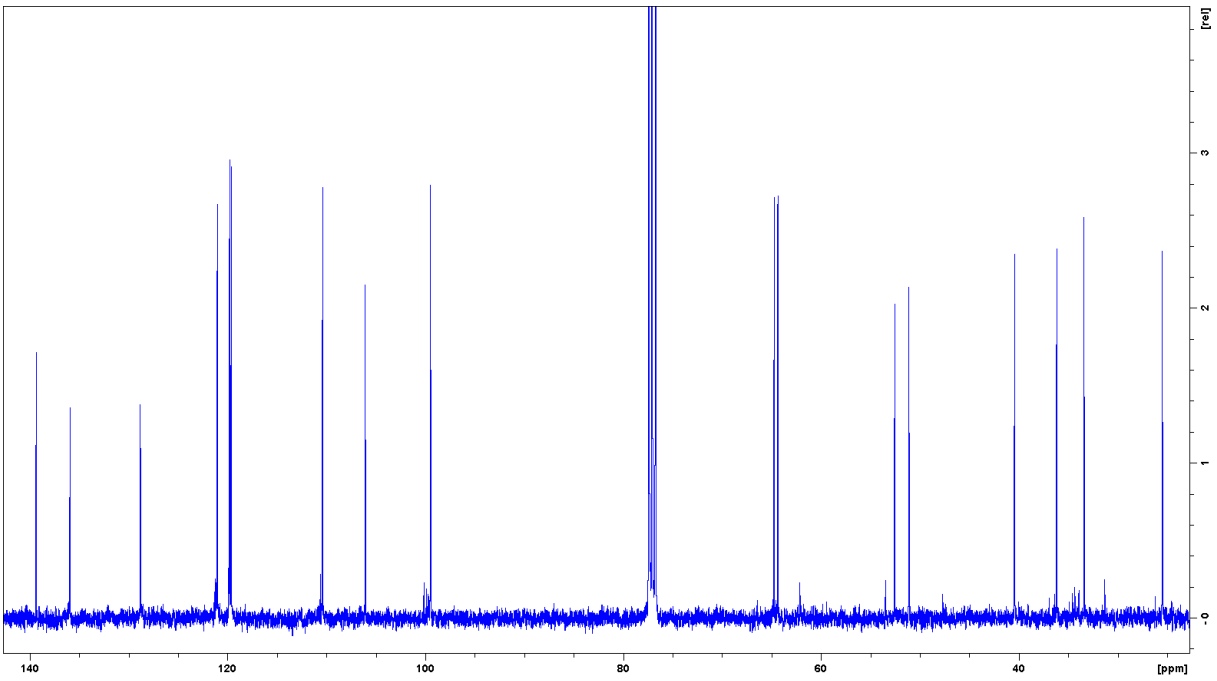
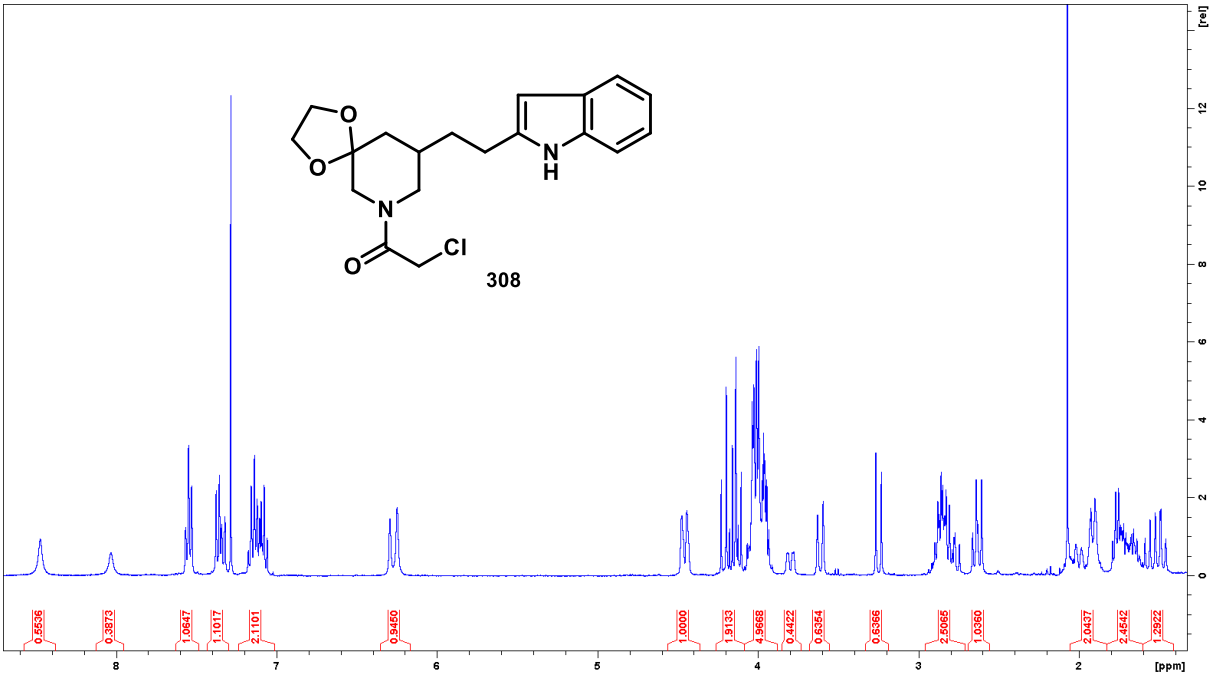
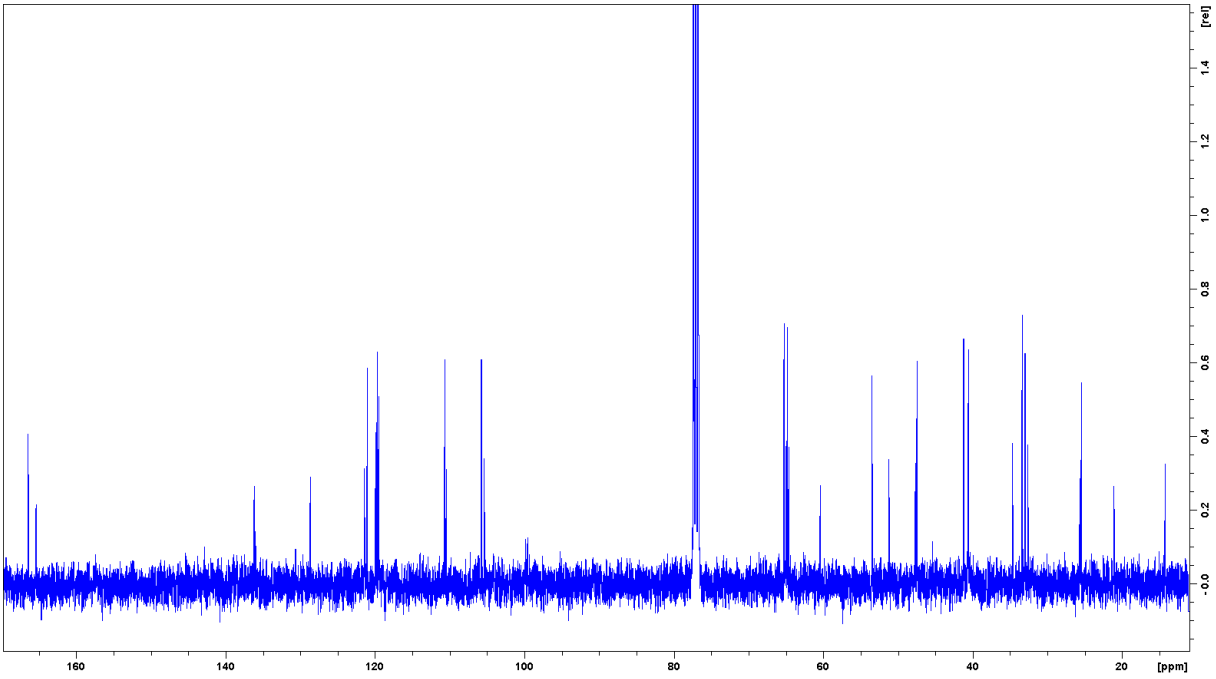


^{1}H NMR (400 MHz, $CDCl_3$, two rotamers)



^{13}C NMR (100 MHz, $CDCl_3$, two rotamers)



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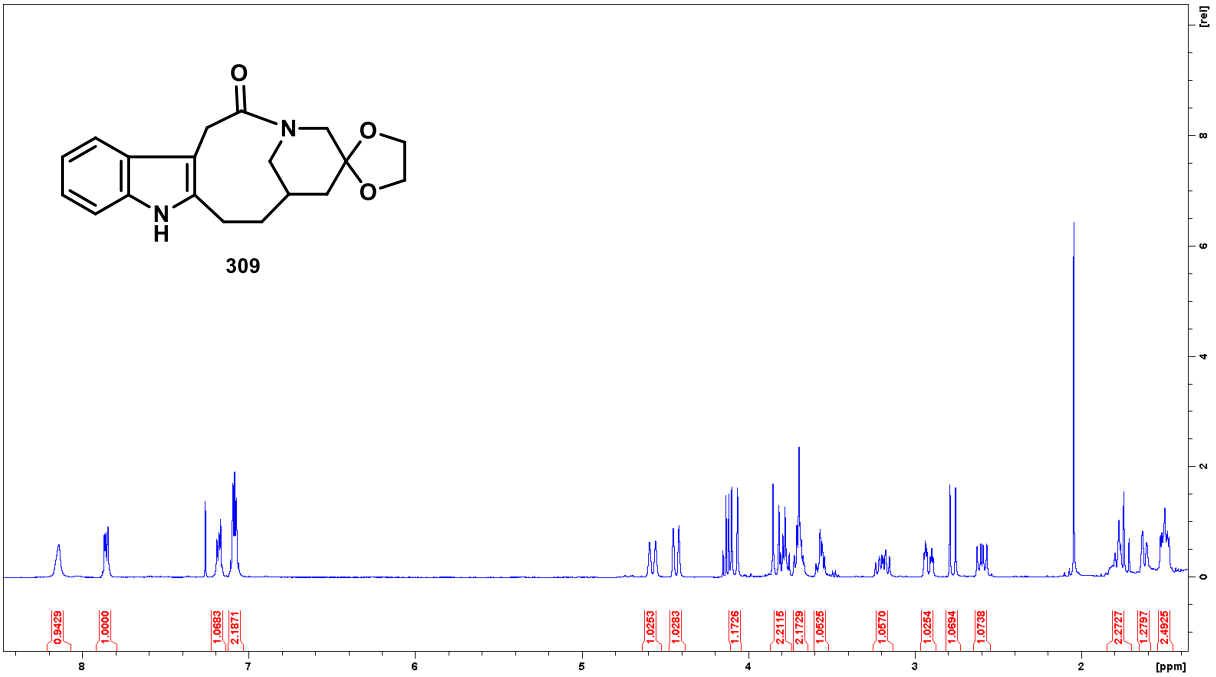

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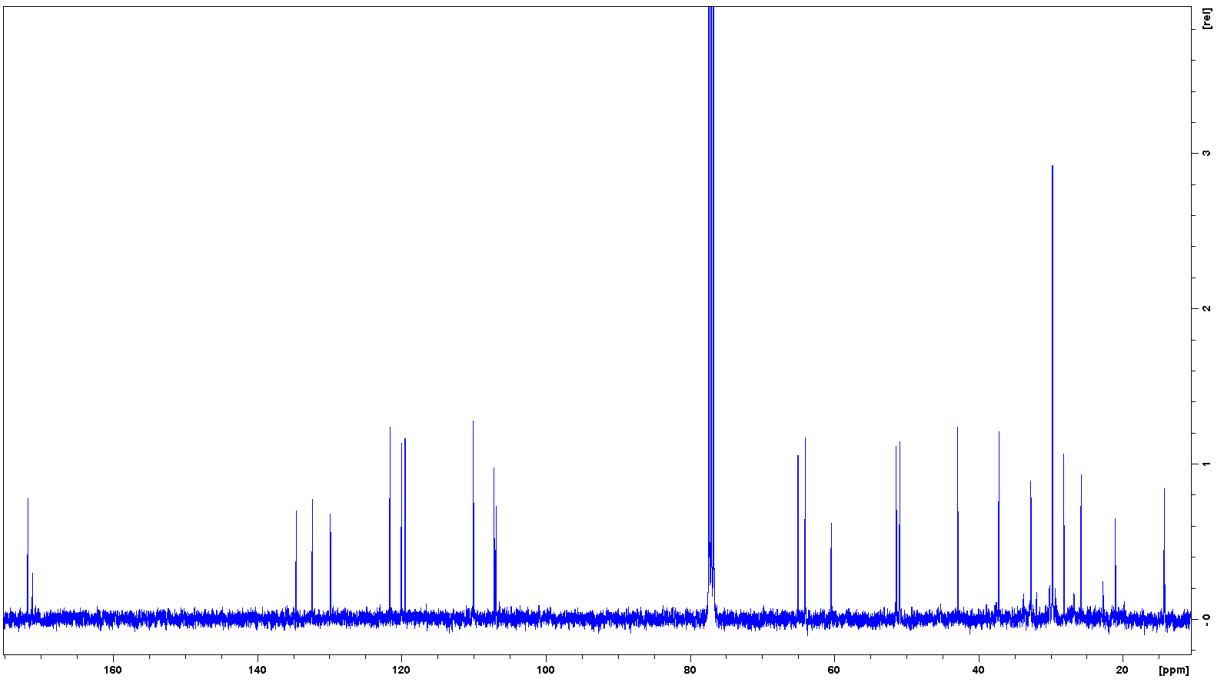

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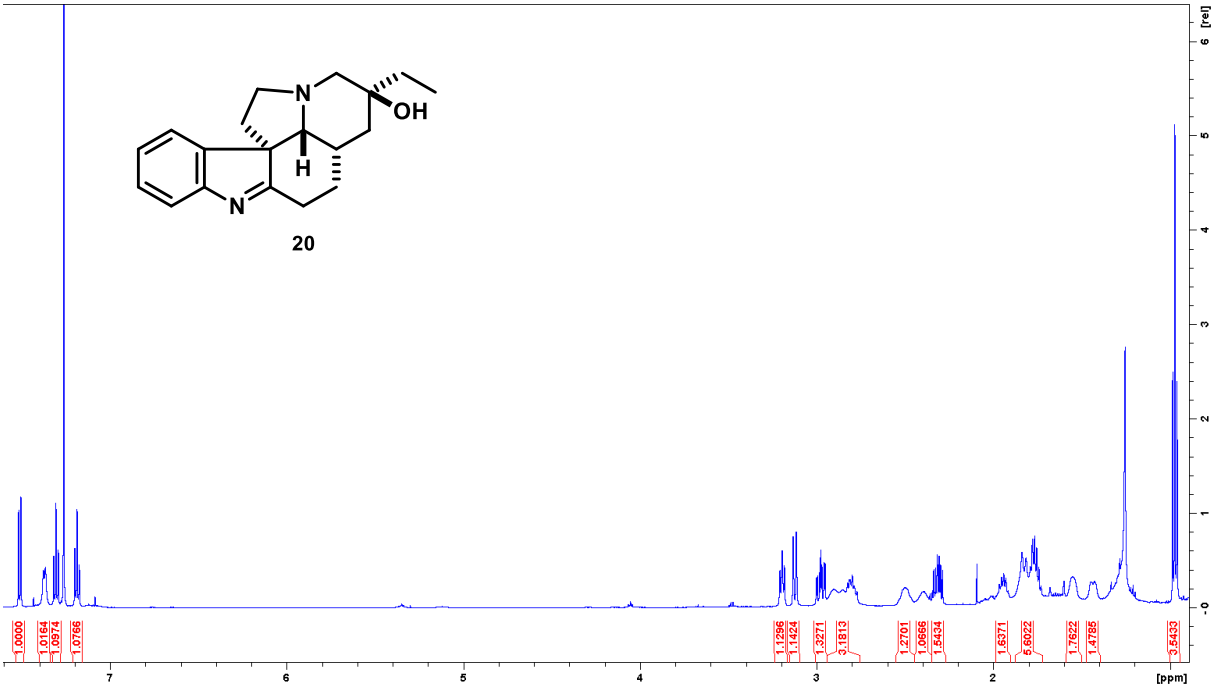
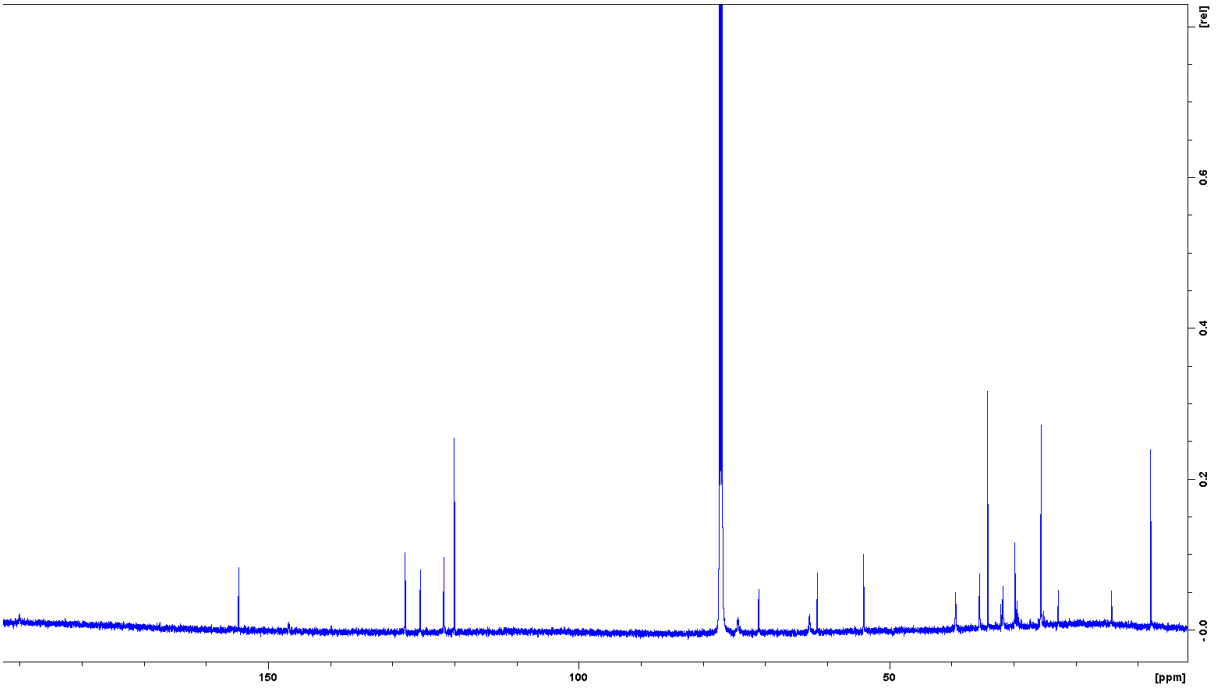


^{13}C NMR (150 MHz, $CDCl_3$)



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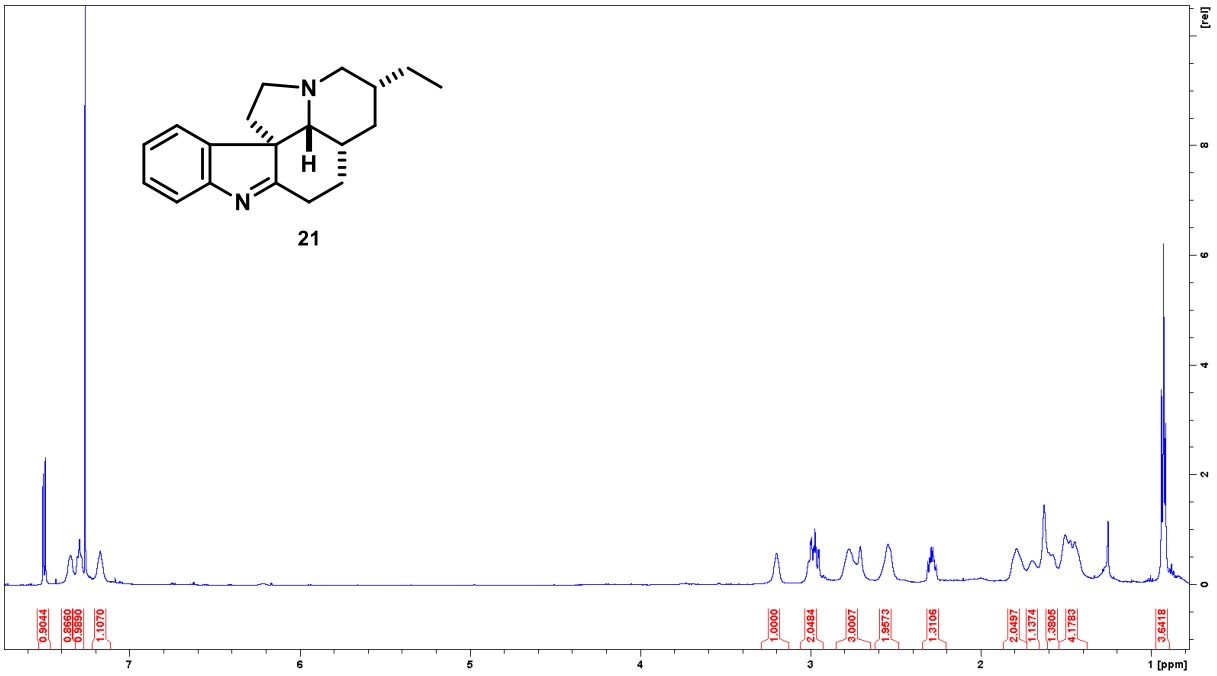

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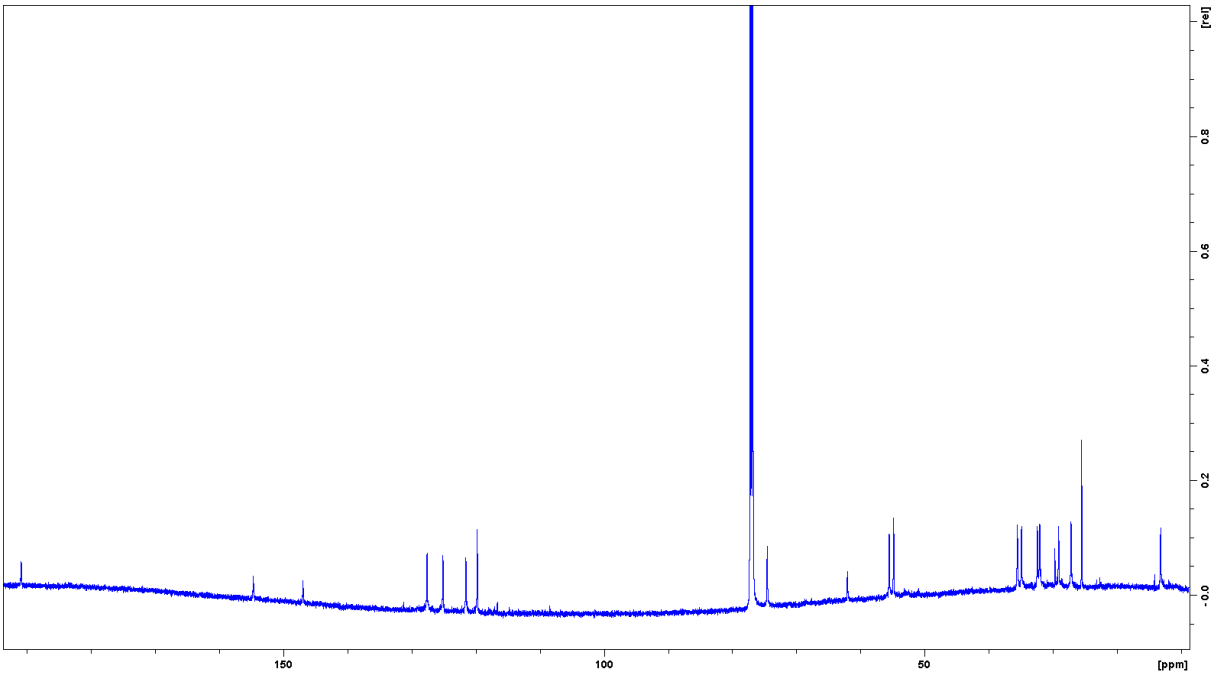

7.2. List of Figures

7.3. List of Schemes

7.4. List of Tables

7.5. References

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Danksagung

Ich bedanke mich bei Prof. Tanja Gaich dass Sie mir die Chance gegeben hat an so einem interessanten und komplexen Thema zu arbeiten. Weiteres bedanke ich mich für die hervorragende Betreuung und die Möglichkeit auch meine eigenen Ideen zu verfolgen.

Mein Dank gilt auch ganz besonders meinen ehemaligen Langzeitlaborkollegen Philipp Gritsch und Ruben Eckermann für die unglaublich tolle Zeit im Labor (Bf4e).

Herzlichen Dank auch an alle Kollegen und ehemaligen Kollegen im Labor: Michael Breunig für deinen erlesenen Weingeschmack, Christa Gerlinger dafür dass du eine Frau bist, Thomas Huhn für dein diplomatisches Geschick, Mikhail Kabdulov für die Arbeitsmoral, Sebastian Krüger für deinen Softwaresupport, Peng Peng für die Hintergrundgeräusche, Magnus Pfaffenbach für deine Kontinuität, Konstantin Samarin für das näherbringen der russischen Kultur, Birte Schröder für die Erinnerungen an Ruben, Darius Schwarzer für die Picdumps, Erik Stempel für die Laboratmosphäre, Dmytro Sysoiev für die Schokolade und Tiankun Zhao für die unzähligen Disskusionen.

Mein Dank gilt auch den Service-Teams in Hannover: NMR (Jörg Fohrer, Dagmar, Körtje, Monika Rettstadt), MS (Roswitha Reichel), Chemikalienausgabe (Mihail Astratov), Sekretariat (Monika Griese) als auch jenen in Konstanz: NMR (Ulrich Haunz, Anke Friemel), CTA (Angelika Früh, Malin Bein), Chemikalienausgabe (Uwe Kunze, Armin Schauren, Oliver Bahm), Sekretariat (Milena Quentin) für Ihre tatkräftige und zuvorkommende Unterstützung.

Ein ganz herzliches Dankeschön geht an meine Langzeitlebensabschnittsgefährtin Bettina Werner für ein erfülltes und glückliches Privatleben.

Zuletzt danke ich jenen denen ich nicht gedankt habe (hoffe es sind nicht zu viel).

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