Studies towards the total synthesis of dichomine

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

Presented by

Christian Leitner

At the

Universität
Konstanz

Faculty of Science
Department of Chemistry

Date of oral examination: 17.10.2016
1. Referee: Prof. Dr. Tanja Gaich
2. Referee: Prof. Dr. Andreas Marx
3. Referee: Prof. Dr. Rainer Winter
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, 20S-hydroxy-1,2-dehydro-pseudoaspidospermidine and 20R-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 20S-hydroxy-1,2-dehydro-pseudoaspidospermidine and 20R-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, 20S-Hydroxy-1,2-dehydro-pseudoaspidospermidine und 20R-1,2-Dehydro-pseudoaspidospermidine.


Graphical Abstract
Table of Contents

1. Introduction .................................................................................................................. 1

2. Related indole alkaloids isolated from the genus Tabernaemontana .................. 3
   2.1. The corynanthe class ............................................................................................. 3
   2.2. The aspidosperma class ....................................................................................... 5
   2.3. The iboga class .................................................................................................... 6
   2.4. Biosynthesis ......................................................................................................... 8

3. Previous synthetic work on related iboga alkaloids ............................................ 14
   3.1. Total synthesis of (±)-cleavamine by Hanaoka et al. 1981 ............................ 14
   3.2. Total synthesis of (±)-cleavamine by Bennasar et al. 2011 ......................... 16
   3.3. Total syntheses of (±)-dihydrocleavamines by Kutney et al. 1970 .............. 18
   3.4. Total synthesis of (+)-dihydrocleavamine by Lesma et al. 2000 ................. 19
   3.5. Total synthesis of (+)-dihydrocleavamine by Ogasawara et al. 2001 .......... 21
   3.6. Total synthesis of (-)-20S-dihydrocleavamine by Bosh et al. 2003 ............... 24
   3.7. Total synthesis of (±)-velbanamine by Büchi et al. 1968 ............................... 25
   3.8. Total synthesis of velbanamine and isovelbanamine by Narisada et al. 1971 28
   3.9. Total synthesis of (+)-velbanamine, (-)-isovelbanamine and (+)-cleavamine by Takano et al. 1982 ................................................................. 29
   3.10. Total synthesis of (±)-pandoline by Kuehne et al. 1980 .............................. 32
   3.11. Previous synthetic work on related alkaloid scaffolds using the Witkop photocyclization as a key step ............................................................... 33

4. Results and Discussion ............................................................................................... 37
   4.1. Retrosynthetic analysis ......................................................................................... 37
   4.2. First approach towards dichomine .................................................................... 38
       4.2.1. Conclusions of the first synthetic approach .............................................. 46
   4.3. Second approach towards dichomine ................................................................ 47
       4.3.1. Conclusions of the second synthetic approach ........................................ 52
   4.4. Third approach towards dichomine .................................................................... 53
4.4.1. Conclusions of the third synthetic approach ........................................ 56
4.5. Fourth approach towards dichomine ...................................................... 56
  4.5.1. Conclusions of the fourth synthetic approach .................................. 77
5. Summary and Conclusions ....................................................................... 78
6. Experimentals ............................................................................................ 80
  6.1. General information ........................................................................... 80
  6.2. Experimental procedures .................................................................... 81
    6.2.1. Experimentals of the first approach ............................................. 81
    6.2.2. Experimental procedures of the second approach ....................... 105
    6.2.3. Experimental procedures of the third approach ......................... 117
    6.2.4. Experimental procedures of the fourth approach ....................... 126
7. Appendix .................................................................................................... 190
  7.1. Spectra ................................................................................................. 190
  7.2. List of Figures ..................................................................................... 253
  7.3. List of Schemes ................................................................................... 253
  7.4. List of Tables ....................................................................................... 256
  7.5. References ........................................................................................... 257
Danksagung .................................................................................................... 261
Lebenslauf ..................................................................................................... 262
## List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>acac</td>
<td>acetylacetone</td>
</tr>
<tr>
<td>ATR</td>
<td>attenuated total reflection</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>t-butoxycarbonyl</td>
</tr>
<tr>
<td>Bu (nBu)</td>
<td>butyl</td>
</tr>
<tr>
<td>Cbz</td>
<td>carboxybenzyl</td>
</tr>
<tr>
<td>dba</td>
<td>dibenzylideneacetone</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DCC</td>
<td>N,N’-dicyclohexylcarbodiimide</td>
</tr>
<tr>
<td>DDQ</td>
<td>2,3-dichloro-5,6-dicyano-1,4-benzoquinone</td>
</tr>
<tr>
<td>DIBAL</td>
<td>diisobutylaluminum hydride</td>
</tr>
<tr>
<td>DIC</td>
<td>N,N’-diisopropylcarbodiimide</td>
</tr>
<tr>
<td>DIPEA</td>
<td>diisopropylethylamine</td>
</tr>
<tr>
<td>DMAP</td>
<td>N,N-4-dimethylaminopyridine</td>
</tr>
<tr>
<td>DME</td>
<td>dimethoxyethane</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>DMS</td>
<td>dimethyl sulfide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
</tr>
<tr>
<td>dpff</td>
<td>1,1’-bis(diphenylphosphino)ferrocene</td>
</tr>
<tr>
<td>dppp</td>
<td>1,3-bis(diphenylphosphino)propane</td>
</tr>
<tr>
<td>dr</td>
<td>diastereomeric ratio</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>EDC-HCl</td>
<td>1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride</td>
</tr>
<tr>
<td>EE</td>
<td>ethyl acetate</td>
</tr>
<tr>
<td>Enz</td>
<td>enzyme</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>FGI</td>
<td>functional group interconversion</td>
</tr>
<tr>
<td>Glc</td>
<td>glucosyl</td>
</tr>
<tr>
<td>H.E.</td>
<td>Hantzsch ester</td>
</tr>
<tr>
<td>HRMS</td>
<td>high resolution mass spectrometry</td>
</tr>
<tr>
<td>Im</td>
<td>imidazole</td>
</tr>
</tbody>
</table>
IR
KHMDS
LDA
LHMDS
mCPBA
Me
Ms
MS
MVK
NaHMDS
NMO
NMR
PET
Ph
PhthNH
PIDA
PPA
py.
Red-Al
r.t.
SAM
TBAF
TBAI
TBHP
TBS
TES
Tf
TFA
TFAA
THF
TIPS
TMS
Tr
p-Ts

infrared spectroscopy
potassium bis(trimethylsilyl)amide
lithium diisopropylamide
lithium bis(trimethylsilyl)amide
meta chloroperbenzoic acid
methyl
mesyl (methansulfonyl)
mass spectrometry
methyl vinyl ketone
sodium bis(trimethylsilyl)amide
N-methylmorpholine oxide
nuclear magnetic resonance
photon-induced electron transfer
phenyl
phthalimide
phenyliodonium diacetate
polyphosphonic acid
pyridine
sodium bis(2-methoxyethoxy)aluminumhydride
room temperature
S-adenosylmethionine
tetra-\(n\)-butylammonium fluoride
tetra-\(n\)-butylammonium iodide
\(\text{tert}\)-butylhydroperoxide
\(t\)-dibutyldimethylsilyl
triethylsilyl
trifluoromethanesulfonfyl
trifluoracetic acid
trifluoracetic anhydride
tetrahydrofuran
triisopropylsilyl
trimethylsilyl
trityl
\(p\)-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](image)

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).\textsuperscript{6} This natural compound was isolated from the leaves and fruits of *Tabernaemontana dichotoma*.\textsuperscript{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.\textsuperscript{8}

![Figure 2: Structure of dichomine (1) and carbon atom numbering.](image)

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 \( \mu \)g of dichomine gave the same response as 0.14 \( \mu \)g succinylcholine (3), 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 \( \mu \)g/ml dichomine lowers the amplitude of contractions of the stimulated rat diaphragm-phrenic nerve preparation by 50\%. A concentration of 28 \( \mu \)g/ml caused complete blockage of the contractions.\textsuperscript{10} Based on these properties this natural product could be interesting for the development of new narcotics in medicine.

![Figure 3: Structures of stemmadenine (2), succinylcholine (3) and neostigmine (4).](image)
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.\textsuperscript{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 reserpinline (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 dihydropyran 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.

![Chemical structures of alkaloids](image)

**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

![Chemical structures of aspidosperma alkaloids]

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 tubotauiwine (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

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.

A further subclass of the *iboga* family are the pseudotabernosines (Figure 8). In principle, the scaffold of 20S-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 vinlylogous carbamate functionality in both 20R-pandoline (22) and 20S-pseudovincadifformine (23).
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.

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. 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 $\alpha,\beta$-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).](image)

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).\textsuperscript{13}

\textbf{Scheme 2:} Proposed mechanism towards secologanin (33).

It is also noteworthy that the biosynthesis of secologanin is quite atypical 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.

\textbf{Scheme 3:} Proposed biosynthesis of stemmadenine (2).
Next, a strictosidine synthase catalyzed condensation between secologanin (33) and tryptamine generates the tetrahydro-\(\beta\)-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).\textsuperscript{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).\textsuperscript{15}

\[ \text{Scheme 4: Proposed biosynthesis of} \textit{aspidosperma and iboga} \textit{alkaloids.} \]
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). In principle, this compound could undergo two different Diels-Alder reaction. In the first case, the indole enamine in combination with the $\alpha,\beta$-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 $\alpha,\beta$-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 $\alpha,\beta$-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. 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). 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.](image)

As depicted in Scheme 6, the biosynthetic proposal of dichomine (1) leads back to 20R-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 pyrroloidine 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 $14S,20R$-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 $20S$-Hydroxy-1,2-dehydro-pseudoaspidospermidine (20) from *Tabernaemontana dichotoma* and not the $20R$ 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).](image)

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 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 16S-hydroxy cleavamine 67.

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). 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.

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 Boc₂O 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 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 20R-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). 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.

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. 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 (±)-20S- and 20R-dihydrocleavamine.\textsuperscript{33}

![Scheme 13](image_url)

\textbf{Scheme 13}: Kutney’s total synthesis of (±)-dihydrocleavamines.

In summary, the total synthesis of 20S- and 20R-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.

\textbf{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).\textsuperscript{34} This building block is accessible in 7 steps from the \textit{meso} diester 83.\textsuperscript{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 (+)-20R-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 (+)-20R-dihydrocleavamine (17).
The indole moiety is synthesized by the use of a Sonogashira coupling and cyclization protocol, which was developed by Yamanaka and coworkers.\textsuperscript{38} Moreover, introduction of the alkyne is achieved \textit{via} nucleophilic addition onto an acyliminium species. The caprolactam key structural motif is generated by utilizing a lactamization reaction between the \textit{in situ} generated amine from the primary azide \textsuperscript{89} and the adjacent \(\gamma\)-lactone. Further functional group interconversions and a photoinduced [2+2] cycloreversion reaction lead back to chiral bicycle \textsuperscript{90}. This optically active starting material is accessible in 5 steps from cyclopentadiene.\textsuperscript{39,40}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Scheme_17.png}
\caption{Ogasawara’s total synthesis of \textit{(+)-20R-}dihydrocleavamine (17).}
\end{figure}

The first step in the synthesis is a stereospecific dihydroxylation of the double bond in bicycle \textsuperscript{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.\textsuperscript{41} It is also noteworthy that the \textit{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 \( \gamma \)-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\(_2\)O 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 alkylation of an acyliminium species of compound 88 providing the introduction of the indole moiety later in the synthesis.
3.6. Total synthesis of \((-\text{20S})\)-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.\(^ {19}\)

\[
\begin{align*}
\text{(-)-20S-dihydrocleavamine (74)} & \quad \text{Friedel-Crafts acylation} \quad \overset{\text{Amide formation}}{\longrightarrow} \quad \overset{\text{OPiv}}{\text{CO}_2\text{H}} \quad \overset{\text{trans}}{\longrightarrow} \quad \overset{\text{OPiv}}{\text{CO}_2\text{H}} \\
\text{94} & \quad \text{95} \\
\text{97} & \quad \overset{\text{BuO}_2\text{C}}{\text{Ph}} \quad \overset{\text{alkylation}}{\longrightarrow} \quad \overset{\text{Ph}}{\text{Ph}} \quad \overset{\text{N,O-ketal}}{\text{N}} \quad \overset{\text{cis}}{\longrightarrow} \quad \overset{\text{Ph}}{\text{Ph}} \quad \overset{\text{N,O-ketal}}{\text{N}} \\
\text{96} & 
\end{align*}
\]

\textbf{Scheme 18:} Retrosynthetic approach of Bosh and coworkers towards \((-\text{20S})\)-dihydrocleavamine (74).

Cyclocondensation 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 \textit{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 \textit{cis} compound with an overall yield of 60%. The alkylation reaction between the lithium enolate of the \textit{trans} product 97 and \textit{tert}-butyl bromoacetate furnishes the second side chain in an almost 1:1 ratio of \textit{cis}/\textit{trans} diastereomers. In the next step, the use of borane enables the simultaneous reduction of the lactam and the \textit{N,O}-ketal to obtain piperidine 96. Cleavage of the benzyl moiety of \textit{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 (-)-20S-
dihydrocleavamine (17).

![Chemical structure](image)

**Scheme 19:** Bosh’s total synthesis of (-)-20S-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). 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).
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.\(^{51}\)

In the next step, a hydroxyl functionality is installed in \(\alpha\)-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. 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.

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. 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. 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.

![Scheme 23: Narisada’s retrosynthetic analysis of (±)-velbanamine (18) and (±)-isovelbanamine (19).](image)

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). 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 $t$-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 azabicycle 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.
The first steps in the synthesis deals with the preparation of the already known chiral \(\gamma\)-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.

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 mCPBA 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).\(^6\) Starting material of this synthesis is compound 122, which could be prepared in three steps from tryptamine.\(^5\) 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\(^6\) provides ionic intermediate 125 via a condensation reaction and a subsequent nucleophilic epoxide-opening. A following deprotonation in \(\alpha\)-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 \(\alpha,\beta\)-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's total synthesis of pandoline (22) and 20-epipandoline (127).](image)

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

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. Since its discovery in 1966, the most important application is the direct formation of medium-sized lactams across indole heterocycles. 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 electron rich 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](image)

Bosch and co-workers applied the Witkop cyclization to their enantioselective synthesis of the *strychnos* alkaloid (-)-tubifoline (139), as depicted in Scheme 30. 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%. Reduction of the double bond to an ethyl group and subsequent irradiation resulted in 20% yield of cyclized product. 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).](image)

The total synthesis of (±)-quebrachamine (142) by Pagenkopf and Bajtos comprises an example for a high yielding photocyclization process (Scheme 31). 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.

\[ \text{Scheme 31: Pagenkopf's total synthesis of } (\pm)\text{-quebrachamine (142).} \]

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.

\[ \text{Scheme 32: Photocyclization studies towards the total synthesis of catharanthine (43).} \]

The inverted indole substitution pattern required a \(\alpha\)-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 \(\alpha\)-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.
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

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.
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).

![Figure 11: Structure of velbanamine (18) and cleavamine (49).](image)

The indole moiety in compound 166 should be synthesized via a condensation reaction between tetrahydropyridine 167 and aromatic compound 168. 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). 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. 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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents</th>
<th>Solvent</th>
<th>Temp.</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaBH₄</td>
<td>MeOH</td>
<td>r.t.</td>
<td>no reaction</td>
</tr>
<tr>
<td>2</td>
<td>NaBH₄</td>
<td>MeOH</td>
<td>reflux</td>
<td>decomposition</td>
</tr>
<tr>
<td>3</td>
<td>LiBH₄</td>
<td>THF</td>
<td>0 °C</td>
<td>decomposition</td>
</tr>
<tr>
<td>4</td>
<td>DIBAL</td>
<td>THF</td>
<td>-78 to r.t.</td>
<td>decomposition</td>
</tr>
<tr>
<td>5</td>
<td>LiHBEt₃</td>
<td>THF</td>
<td>-78 to 0 °C</td>
<td>decomposition</td>
</tr>
</tbody>
</table>

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 nBuLi 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). 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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Solvent</th>
<th>Temp.</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LDA</td>
<td>THF</td>
<td>-78 to -20 °C</td>
<td>190 + recov. 181</td>
</tr>
<tr>
<td>2</td>
<td>LHMDS</td>
<td>THF</td>
<td>-78 to 0 °C</td>
<td>190 + recov. 181</td>
</tr>
<tr>
<td>3</td>
<td>NaHMDS</td>
<td>THF</td>
<td>-78 to 0 °C</td>
<td>190 + recov. 181</td>
</tr>
<tr>
<td>4</td>
<td>NaHMDS</td>
<td>Et2O</td>
<td>-78 to 0 °C</td>
<td>190 + recov. 181</td>
</tr>
</tbody>
</table>
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>
<thead>
<tr>
<th>Entry</th>
<th>Reagents</th>
<th>Solvent</th>
<th>Temp.</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LDA</td>
<td>THF</td>
<td>-78 to -20 °C</td>
<td>decomp. 191 + recov. 181</td>
</tr>
<tr>
<td>2</td>
<td>LHMDS</td>
<td>THF</td>
<td>-78 to 0 °C</td>
<td>decomp. 191 + recov. 181</td>
</tr>
<tr>
<td>3</td>
<td>NaHMDS</td>
<td>THF</td>
<td>-78 to 0 °C</td>
<td>decomp. 191 + recov. 181</td>
</tr>
<tr>
<td>4</td>
<td>NaHMDS</td>
<td>Et2O</td>
<td>-78 to 0 °C</td>
<td>decomp. 191 + recov. 181</td>
</tr>
<tr>
<td>5</td>
<td>NaHMDS, BF3•OEt2</td>
<td>THF</td>
<td>-78 °C</td>
<td>decomp. 191 + recov. 181</td>
</tr>
</tbody>
</table>
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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents</th>
<th>Solvent</th>
<th>Temp.</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LDA</td>
<td>THF</td>
<td>-78 °C to r.t.</td>
<td>29% 193</td>
</tr>
<tr>
<td>2</td>
<td>LHMDS</td>
<td>THF</td>
<td>-78 °C</td>
<td>Decomp. 191 + recov. 183</td>
</tr>
<tr>
<td>3</td>
<td>NaHMDS</td>
<td>THF</td>
<td>-78 °C</td>
<td>15-39% 193</td>
</tr>
<tr>
<td>4</td>
<td>NaHMDS, BF₃·OEt₂</td>
<td>THF</td>
<td>-78 to -25 °C</td>
<td>31% 194</td>
</tr>
<tr>
<td>5</td>
<td>KHMDS</td>
<td>THF</td>
<td>-78 °C to r.t.</td>
<td>Decomp.</td>
</tr>
<tr>
<td>6</td>
<td>KOtBu</td>
<td>THF</td>
<td>-78 °C</td>
<td>24% 194</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents</th>
<th>Solvent</th>
<th>Temp.</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TiCl₄</td>
<td>CH₂Cl₂</td>
<td>-78 °C</td>
<td>decomp. 191 + recov. 183</td>
</tr>
<tr>
<td>2</td>
<td>TiCl₄</td>
<td>THF</td>
<td>-78 °C to r.t.</td>
<td>decomp. 191 + recov. 183</td>
</tr>
<tr>
<td>3</td>
<td>BF₃•OEt₂</td>
<td>CH₂Cl₂</td>
<td>-78 to -40 °C</td>
<td>decomp. 191 + recov. 183</td>
</tr>
<tr>
<td>4</td>
<td>BF₃•OEt₂</td>
<td>THF</td>
<td>-78 °C to r.t.</td>
<td>decomposition</td>
</tr>
<tr>
<td>5</td>
<td>Sc(OTf)₃</td>
<td>CH₂Cl₂</td>
<td>-78 °C</td>
<td>decomposition</td>
</tr>
<tr>
<td>6</td>
<td>TMSOTf</td>
<td>CH₂Cl₂</td>
<td>-78 °C</td>
<td>decomposition</td>
</tr>
</tbody>
</table>

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.](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents</th>
<th>Solvent</th>
<th>Temp.</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LDA</td>
<td>THF</td>
<td>-78 °C</td>
<td>18% 197</td>
</tr>
<tr>
<td>2</td>
<td>NaHMDS</td>
<td>THF</td>
<td>-78 °C</td>
<td>13% 197</td>
</tr>
<tr>
<td>3</td>
<td>NaH</td>
<td>THF</td>
<td>reflux</td>
<td>28% 197</td>
</tr>
<tr>
<td>4</td>
<td>KOtBu</td>
<td>THF</td>
<td>-78 °C</td>
<td>21% 197 + 19% 198</td>
</tr>
<tr>
<td>5</td>
<td>KOtBu</td>
<td>THF</td>
<td>0 °C</td>
<td>30% 197 + 13% 198</td>
</tr>
<tr>
<td>6</td>
<td>KOtBu</td>
<td>THF</td>
<td>r.t.</td>
<td>30-62% 197 + 14-38% 198</td>
</tr>
</tbody>
</table>

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.

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

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.](image)

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 \( \alpha \)-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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Wittig Salts</th>
<th>Base</th>
<th>Solvent</th>
<th>Temp.</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtPPh₃Br</td>
<td>NaHMDS</td>
<td>THF</td>
<td>-78 °C to r.t.</td>
<td>decomposition</td>
</tr>
<tr>
<td>2</td>
<td>EtPPh₃Br</td>
<td>NaHMDS</td>
<td>Toluene</td>
<td>-78 °C to r.t.</td>
<td>decomposition</td>
</tr>
<tr>
<td>3</td>
<td>EtPPh₃Br</td>
<td>KHMDS</td>
<td>THF</td>
<td>-78 °C to r.t.</td>
<td>decomposition</td>
</tr>
<tr>
<td>4</td>
<td>BrPPh₃(CH₂)₃OTIPS</td>
<td>NaHMDS</td>
<td>THF</td>
<td>-78 °C to r.t.</td>
<td>decomposition</td>
</tr>
<tr>
<td>5</td>
<td>BrPPh₃(CH₂)₃OTIPS</td>
<td>KHMDS</td>
<td>THF</td>
<td>-78 °C to r.t.</td>
<td>decomposition</td>
</tr>
</tbody>
</table>

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 nBuLi 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 $\alpha$-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 glycine 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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Base</th>
<th>Solvent</th>
<th>Temp.</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NH₂CH₂CO₂tBu</td>
<td>K₂CO₃</td>
<td>MeOH</td>
<td>60 °C</td>
<td>no reaction</td>
</tr>
<tr>
<td>2</td>
<td>NH₂CH₂CO₂tBu</td>
<td>K₂CO₃</td>
<td>DMF</td>
<td>60 °C</td>
<td>decomposition</td>
</tr>
<tr>
<td>3</td>
<td>PhthNH</td>
<td>NaH</td>
<td>DMF</td>
<td>r.t.</td>
<td>decomposition</td>
</tr>
<tr>
<td>4</td>
<td>BnNH₂</td>
<td>py.</td>
<td>DMF</td>
<td>65 °C</td>
<td>36%; R = Bn</td>
</tr>
<tr>
<td>5</td>
<td>NH₂CH₂SnBu₃</td>
<td>py.</td>
<td>DMF</td>
<td>65 °C</td>
<td>decomposition</td>
</tr>
<tr>
<td>6</td>
<td>NH₂CH₂SnBu₃</td>
<td>NEt₃</td>
<td>DMF</td>
<td>70 °C</td>
<td>decomposition</td>
</tr>
</tbody>
</table>
Due to the poor yields of the substitution reaction, an alternative literature known procedure to synthesize aziridines from \( \alpha \)-hydroxy azides with triphenylphosphine was envisioned (Scheme 54).\(^9\) 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.](image)

**Table 10:** Conditions for the Staudinger mediated aziridine formation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Additives</th>
<th>Solvent</th>
<th>Temp.</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PPh(_3)</td>
<td>none</td>
<td>PhMe</td>
<td>reflux</td>
<td>decomposition</td>
</tr>
<tr>
<td>2</td>
<td>PPh(_3)</td>
<td>MS 3Å</td>
<td>PhMe</td>
<td>100 °C</td>
<td>decomposition</td>
</tr>
<tr>
<td>3</td>
<td>P((n)Bu)(_3)</td>
<td>none</td>
<td>PhMe</td>
<td>r.t. to 50 °C</td>
<td>decomposition</td>
</tr>
</tbody>
</table>

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.
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 $\alpha$-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.](image-url)
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.\textsuperscript{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.\textsuperscript{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 $\gamma$-lactone. A subsequent substitution reaction of the iodine with sodium azide afforded product 246.

![Scheme 58](image)

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

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Additives</th>
<th>Solvent</th>
<th>Temp.</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph$_3$</td>
<td>none</td>
<td>THF/H$_2$O</td>
<td>r.t.</td>
<td>20% 145</td>
</tr>
<tr>
<td>2</td>
<td>H$_2$</td>
<td>Pd/C</td>
<td>MeOH</td>
<td>r.t.</td>
<td>78% 145</td>
</tr>
</tbody>
</table>

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](image)

**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 \textit{in situ} generated amine and the \(\gamma\)-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 \(\gamma\)-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 \textit{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.\textsuperscript{97}

\begin{center}
\textbf{Scheme 60}: Fourth retrosynthetic approach towards Witkop precursor 166.
\end{center}
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. Installation of the carbamate by treatment of the tertiary amine with ethyl chloroformate followed by an epoxidation of the double bond with mCPBA 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 dihydropyridone 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 nBuLi under the same conditions again provided the protonated equivalent together with the unreacted iodine 248. Based on this result, tBuLi was used to guarantee a quantitatively halogen metal exchange. However, treatment of iodine 248 with tBuLi 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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Additives</th>
<th>Solvent</th>
<th>Temp.</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mg</td>
<td>CuBr•DMS</td>
<td>THF</td>
<td>-78 °C</td>
<td>protonation of 248</td>
</tr>
<tr>
<td>2</td>
<td>nBuLi</td>
<td>CuBr•DMS</td>
<td>THF</td>
<td>-78 °C</td>
<td>protonation of 248 + SM</td>
</tr>
<tr>
<td>3</td>
<td>tBuLi</td>
<td>CuBr•DMS</td>
<td>THF</td>
<td>-78 °C</td>
<td>decomposition</td>
</tr>
</tbody>
</table>

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 nBuLi 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, PhNTf2 or Tf2O yielded only in decomposition.

Parallel to the Michael addition approach, the feasibility of a SN2’ 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 SN2’ 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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Base</th>
<th>Solvent</th>
<th>Temp.</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MsCl</td>
<td>2,6-lutidine</td>
<td>CH₂Cl₂</td>
<td>0 °C</td>
<td>83% 276</td>
</tr>
<tr>
<td>2</td>
<td>TsCl</td>
<td>NEt₃</td>
<td>CH₂Cl₂</td>
<td>reflux</td>
<td>no reaction</td>
</tr>
<tr>
<td>3</td>
<td>Boc₂O</td>
<td>DMAP</td>
<td>CH₂Cl₂</td>
<td>r.t.</td>
<td>no reaction</td>
</tr>
<tr>
<td>4</td>
<td>CbzCl</td>
<td>NEt₃</td>
<td>CH₂Cl₂</td>
<td>reflux</td>
<td>no reaction</td>
</tr>
<tr>
<td>5</td>
<td>ClCO₂Me</td>
<td>py.</td>
<td>CH₂Cl₂</td>
<td>reflux</td>
<td>no reaction</td>
</tr>
<tr>
<td>6</td>
<td>AcCl</td>
<td>NEt₃</td>
<td>CH₂Cl₂</td>
<td>reflux</td>
<td>62% 276</td>
</tr>
<tr>
<td>7</td>
<td>AcCl</td>
<td>py.</td>
<td>CH₂Cl₂</td>
<td>r.t.</td>
<td>33% 274</td>
</tr>
<tr>
<td>8</td>
<td>TFAA</td>
<td>none</td>
<td>CH₂Cl₂</td>
<td>r.t.</td>
<td>80% 275</td>
</tr>
<tr>
<td>9</td>
<td>ClAcCl</td>
<td>py.</td>
<td>CH₂Cl₂</td>
<td>r.t.</td>
<td>65% 276</td>
</tr>
</tbody>
</table>

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 trifluoracetate 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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Solvent</th>
<th>Temp.</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeLi</td>
<td>THF</td>
<td>-40 °C</td>
<td>46% 283</td>
</tr>
<tr>
<td>2</td>
<td>HBr</td>
<td>AcOH</td>
<td>reflux</td>
<td>decomposition</td>
</tr>
<tr>
<td>3</td>
<td>KOtBu</td>
<td>MeOH</td>
<td>r.t.</td>
<td>no reaction</td>
</tr>
<tr>
<td>4</td>
<td>LiAlH₄</td>
<td>THF</td>
<td>r.t.</td>
<td>45% 284</td>
</tr>
<tr>
<td>5</td>
<td>DIBAL</td>
<td>THF</td>
<td>r.t.</td>
<td>no reaction</td>
</tr>
<tr>
<td>6</td>
<td>Red-Al</td>
<td>THF</td>
<td>r.t.</td>
<td>85% 284</td>
</tr>
<tr>
<td>7</td>
<td>KOH</td>
<td>EtOH</td>
<td>reflux</td>
<td>no reaction</td>
</tr>
<tr>
<td>8</td>
<td>hydrazine, KOH</td>
<td>ethylene glycol</td>
<td>140 °C</td>
<td>95% 204</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Base</th>
<th>Solvent</th>
<th>Temp.</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ClAcCl</td>
<td>py.</td>
<td>CH₂Cl₂</td>
<td>0 °C</td>
<td>decomposition</td>
</tr>
<tr>
<td>2</td>
<td>ClAcOH</td>
<td>DIC, DMAP</td>
<td>CH₂Cl₂</td>
<td>r.t.</td>
<td>44%</td>
</tr>
<tr>
<td>3</td>
<td>(ClAc)₂O</td>
<td>NEt₃, DMAP</td>
<td>CH₂Cl₂</td>
<td>0 °C</td>
<td>61%</td>
</tr>
<tr>
<td>4</td>
<td>(ClAc)₂O</td>
<td>NEt₃</td>
<td>CH₂Cl₂</td>
<td>0 °C</td>
<td>79%</td>
</tr>
</tbody>
</table>

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\textsuperscript{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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst/Reagent</th>
<th>Solvent</th>
<th>Temp.</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rh(PPh₃)₃Cl</td>
<td>EtOH</td>
<td>reflux</td>
<td>no reaction</td>
</tr>
<tr>
<td>2</td>
<td>RhCl₃</td>
<td>EtOH</td>
<td>reflux</td>
<td>no reaction</td>
</tr>
<tr>
<td>3</td>
<td>HRh(CO)(PPh₃)₃</td>
<td>xylene</td>
<td>reflux</td>
<td>no reaction</td>
</tr>
<tr>
<td>4</td>
<td>PdCl₂</td>
<td>toluene</td>
<td>reflux</td>
<td>no reaction</td>
</tr>
<tr>
<td>5</td>
<td>Pd(OAc)₂, dppp</td>
<td>DMF</td>
<td>reflux</td>
<td>no reaction</td>
</tr>
<tr>
<td>6</td>
<td>Pd(PPh₃)₄</td>
<td>AcOH</td>
<td>reflux</td>
<td>no reaction</td>
</tr>
<tr>
<td>7</td>
<td>NaI, TMSCl</td>
<td>CH₃CN</td>
<td>r.t.</td>
<td>decomposition</td>
</tr>
<tr>
<td>8</td>
<td>pTsOH</td>
<td>toluene</td>
<td>reflux</td>
<td>decomposition</td>
</tr>
<tr>
<td>9</td>
<td>Pd/C, H₂</td>
<td>EtOAc</td>
<td>r.t.</td>
<td>18% 293 + 35% 294</td>
</tr>
<tr>
<td>10</td>
<td>Pd/C</td>
<td>MeOH</td>
<td>reflux</td>
<td>no reaction</td>
</tr>
<tr>
<td>11</td>
<td>Pd(OH)₂/C, H₂</td>
<td>EtOAc</td>
<td>r.t.</td>
<td>18% 293 + 29% 294</td>
</tr>
<tr>
<td>12</td>
<td>Rh(PPh₃)₃Cl, H₂</td>
<td>CH₂Cl₂</td>
<td>r.t.</td>
<td>no reaction</td>
</tr>
<tr>
<td>13</td>
<td>PtO₂, H₂</td>
<td>EtOAc</td>
<td>r.t.</td>
<td>90% hydrated product</td>
</tr>
</tbody>
</table>

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)(PPh₃)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 pTsOH 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).

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 (±)-20R-dihydrocleavamine (17).

Scheme 75: Synthesis of (±)-20R-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).

\[ \text{(±)-velbanamine (18)} \rightarrow \text{[O]} \rightarrow \text{52} \rightarrow \text{(±)-dichomine (1)} \]

\[ \text{(±)-velbanamine (18)} \rightarrow \text{53} \]

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

It is also mentionable that this reaction could only proceed with the (20R,14S)-relative stereochemistry, which is present in velbanamine (18). Because in case of the (20S,14S)-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 (20S)-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 (20R)-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 (20S)-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\textsuperscript{107} were fruitless.

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

Nevertheless, based on the preferential (20S)-configuration in the Corey Chaykovsky reaction, a new approach to obtain the desired (20R)-alcohol was envisioned. After several attempts, the epoxidation of compound 279 with mCPBA 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 (20R)-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 chloroaetic anhydride to intermediate 300. Using the same reaction conditions as in the cyclization reaction of the (20S)-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. Fortunately, 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 and the sodium borohydride supported reduction. 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. A different method, which was developed by the Beller group, utilizes zinc acetate in combination with triethoxy silane to reduce amide moieties. However, also this protocol proved to be unsuitable
(Entry 12). Furthermore, the use of a stronger Lewis acid did not improve 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.\footnote{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).}

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Solvent</th>
<th>Temp.</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LiAlH₄, AlCl₃</td>
<td>THF</td>
<td>-20 °C</td>
<td>decomp.</td>
</tr>
<tr>
<td>2</td>
<td>LiAlH₄, MgBr₂•OEt₂</td>
<td>THF</td>
<td>r.t.</td>
<td>10%</td>
</tr>
<tr>
<td>3</td>
<td>LiAlH₄, LiCl</td>
<td>THF</td>
<td>reflux</td>
<td>30%</td>
</tr>
<tr>
<td>4</td>
<td>DIBAL</td>
<td>THF</td>
<td>0 °C</td>
<td>20%</td>
</tr>
<tr>
<td>5</td>
<td>Ti(OiPr)₄, DIBAL</td>
<td>CH₂Cl₂</td>
<td>50 °C</td>
<td>decomp.</td>
</tr>
<tr>
<td>6</td>
<td>Red-Al</td>
<td>THF</td>
<td>r.t.</td>
<td>20%</td>
</tr>
<tr>
<td>7</td>
<td>BF₃•OEt₂, NaBH₄</td>
<td>THF</td>
<td>r.t.</td>
<td>decomp.</td>
</tr>
<tr>
<td>8</td>
<td>BH₃•DMS</td>
<td>THF</td>
<td>reflux</td>
<td>decomp.</td>
</tr>
<tr>
<td>9</td>
<td>BH₃•DMS, NaBH₄</td>
<td>THF</td>
<td>50 °C</td>
<td>decomp.</td>
</tr>
<tr>
<td>10</td>
<td>Tf₂O, H.E.</td>
<td>CH₂Cl₂</td>
<td>r.t.</td>
<td>decomp.</td>
</tr>
<tr>
<td>11</td>
<td>Tf₂O, LiBH₄</td>
<td>CH₂Cl₂</td>
<td>r.t.</td>
<td>no reaction</td>
</tr>
<tr>
<td>12</td>
<td>Zn(OAc)₂, (EtO)₃SiH</td>
<td>THF</td>
<td>r.t.</td>
<td>no reaction</td>
</tr>
<tr>
<td>13</td>
<td>Ti(OiPr)₄, (EtO)₃SiH</td>
<td>THF</td>
<td>r.t.</td>
<td>no reaction</td>
</tr>
<tr>
<td>14</td>
<td>HRh(CO)(PPh₃)₃, PhSiH₃</td>
<td>THF</td>
<td>r.t.</td>
<td>decomp.</td>
</tr>
<tr>
<td>15</td>
<td>HRh(CO)(PPh₃)₃, PhSiH₃</td>
<td>THF</td>
<td>50 °C</td>
<td>53%</td>
</tr>
</tbody>
</table>
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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Solvent</th>
<th>Temp.</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LiAlH₄</td>
<td>THF</td>
<td>reflux</td>
<td>decomp.</td>
</tr>
<tr>
<td>2</td>
<td>DIBAL</td>
<td>THF</td>
<td>0 °C</td>
<td>decomp.</td>
</tr>
<tr>
<td>3</td>
<td>Tf₂O, H.E.</td>
<td>CH₂Cl₂</td>
<td>r.t.</td>
<td>decomp.</td>
</tr>
<tr>
<td>4</td>
<td>HRh(CO)(PPh₃)₃, PhSiH₃</td>
<td>THF</td>
<td>50 °C</td>
<td>25% of (18)</td>
</tr>
</tbody>
</table>

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 \textit{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.](image)

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.

![Scheme 83: Synthesis of thioamide 305 by the use of Lawesson’s reagent.](image)

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.\textsuperscript{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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Solvent</th>
<th>Temp.</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LiAlH₄</td>
<td>THF</td>
<td>50 °C</td>
<td>decomp.</td>
</tr>
<tr>
<td>2</td>
<td>Zn(OAc)₂, (EtO)₃SiH</td>
<td>THF</td>
<td>r.t.</td>
<td>no reaction</td>
</tr>
<tr>
<td>3</td>
<td>HRh(CO)(PPh₃)₃, PhSiH₃</td>
<td>THF</td>
<td>50 °C</td>
<td>decomp.</td>
</tr>
<tr>
<td>4</td>
<td>Lawesson’s reagent</td>
<td>PhMe</td>
<td>100 °C</td>
<td>30%</td>
</tr>
</tbody>
</table>

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.

![Scheme 85: Oxidation attempts of (±)-velbanamine (18) to (±)-dichomine (1).](image)

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Solvent</th>
<th>Temp.</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Silver(II) picolinate</td>
<td>H₂O/TFA</td>
<td>0 °C</td>
<td>decomp.</td>
</tr>
<tr>
<td>2</td>
<td>mCPBA, TFAA</td>
<td>CH₂Cl₂</td>
<td>0 °C</td>
<td>decomp.</td>
</tr>
<tr>
<td>3</td>
<td>PIDA, MS 4Å</td>
<td>DME</td>
<td>r.t.</td>
<td>no reaction</td>
</tr>
<tr>
<td>3</td>
<td>PIDA, MS 4Å</td>
<td>CH₃CN</td>
<td>50 °C</td>
<td>decompos.</td>
</tr>
<tr>
<td>4</td>
<td>DDQ</td>
<td>MeOH</td>
<td>r.t.</td>
<td>decompos.</td>
</tr>
<tr>
<td>5</td>
<td>K₃[Fe(CN)₆]</td>
<td>MeOH/H₂O</td>
<td>r.t.</td>
<td>decompos.</td>
</tr>
<tr>
<td>6</td>
<td>Co(acac)₂, O₂</td>
<td>CH₃CN</td>
<td>50 °C</td>
<td>decompos.</td>
</tr>
<tr>
<td>7</td>
<td>RuCl₃, O₂</td>
<td>MeOH</td>
<td>reflux</td>
<td>no reaction</td>
</tr>
</tbody>
</table>

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 mCPBA 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.\textsuperscript{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).\textsuperscript{120} Moreover, a ruthenium catalyzed oxidation of the natural product provided, even under reflux, no conversion of the starting material.\textsuperscript{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\textsubscript{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.\textsuperscript{122}

\textbf{Scheme 86:} Retro-biomimetic oxidation of (±)-isovelbanamine (19).

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

\textbf{Scheme 87:} Retro-biomimetic oxidation of (±)-20\textsubscript{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 Negishhi 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 commenced 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 mCPBA 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 (±)-20S-hydroxy-1,2-dehydro-pseudoaspidospermidine (20). Moreover, this conditions could also be used to synthesize the related alkaloid (±)-20R-1,2-dehydro-pseudoaspidospermidine (21) from (±)-20R-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 \( \gamma \)-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 (20S)-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 (±)-20S-hydroxy-1,2-dehydro-pseudoaspidospermidine (20) and (±)-20R-dihydro-cleavamine (17) to the related alkaloid (±)-20R-1,2-dehydro-pseudoaspidospermidine (21).
6. Experimental

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 (CDCl₃ ¹H, δ= 7.26 ppm, ¹³C, δ= 77.00 ppm; methanol-d₄ ¹H, δ= 3.31 ppm, ¹³C, δ= 49.00 ppm; DMSO-d₆ ¹H, δ= 2.50 ppm, ¹³C, 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 Aqutity Ultra Performance, electron spray ionization)
6.2. Experimental procedures

6.2.1. Experimentals of the first approach

Ethyl 5-bromonicotinate 203

Thionyl chloride (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 chloride 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. NaHCO₃, the aqueous layer was extracted with CH₂Cl₂ (3x), the organic layer was washed with brine and dried over MgSO₄. 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.

¹H NMR (400 MHz, CDCl₃): 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.

¹³C NMR (100 MHz, CDCl₃): 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 C₈H₈O₂N₁Br₁H⁺: 229.9817; found: 229.9817;
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$_3$): $\delta$ = 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$_3$): $\delta$ = 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, 1696, 1422, 1311, 1261, 1207, 1018, 805 cm$^{-1}$

HRMS: m/z calculated for C$_{10}$H$_{10}$O$_3$N$_1$Br$_1$H$: 270.9922; found: 270.9922,
1-(5-Bromopyridin-3-yl) ethan-1-one **175**

![Chemical Structure](image)

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 MgSO₄ 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.

**¹H NMR** (400 MHz, CDCl₃): \( \delta = 9.06 \) (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.

**¹³C NMR** (100 MHz, CDCl₃): \( \delta = 195.2, 154.5, 147.7, 138.1, 133.5, 121.3, 26.8 \); ppm.

**IR**: 3034, 1677, 1572, 1421, 1356, 1275, 1172, 1011, 897, 799 cm⁻¹
3-Bromo-5-ethylpyridine 176

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$_3$): $\delta = 8.50$ (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$_3$): $\delta = 148.2$, 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$_7$H$_8$N$_1$Br$_1$H$^+$: 185.9918; found: 185.9917;
Methyl (E)-3-(5-ethylpyridin-3-yl) acrylate 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 NEt₃ (1.6 mL, 2 eq., 11.5 mmol). The mixture was degassed followed by addition of Pd(dppf)Cl₂ (465 mg, 0.1 eq., 0.57 mmol). After stirring for 48 h at 105 °C, the resulting solution was poured into sat. NH₄Cl, the aqueous layer was extracted with diethyl ether (3x), the combined organic phases were washed with brine, dried over MgSO₄ 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.

¹H NMR (200 MHz, CDCl₃): 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.

¹³C NMR (100 MHz, CDCl₃): 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 C₁₁H₁₃O₂N₁H⁺: 192.1025; found: 192.1024;
Methyl 3-(5-ethylpyridin-3-yl) propanoate 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$_3$): $\delta = 8.31$ (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$_3$): $\delta = 172.8, 147.5, 147.1, 139.0, 135.4, 135.4, 51.7, 35.3, 28.0, 25.9, 15.3$; ppm.

HRMS: m/z calculated for C$_{11}$H$_{15}$O$_2$N$_1$H$: 194.1181$; found: 194.1177;
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.

**1H NMR** (400 MHz, CD$_3$OD): $\delta = 8.87$ (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.

**13C NMR** (100 MHz, CD$_3$OD): $\delta = 173.9$, 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$_2$N$_1$$^+$: 284.1646; found: 284.1640;
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.

\textbf{\textsuperscript{1}H NMR} (400 MHz, CDCl$_3$): $\delta$ = 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

![Chemical Structure](image)

To a solution of 168 (120 mg, 1.3 eq., 0.67 mmol) in hexane (5 mL) was added nBuLi (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. NH₄Cl. The aqueous layer was extracted with diethyl ether (3x), the combined organic phases were washed with brine and dried over MgSO₄. 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.

**¹H NMR** (200 MHz, CDCl₃): 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 C₁₇H₁₈N₂H⁺: 251.1548; found: 251.1548;
Dimethyl 3,3’-(benzylazanediyl) dipropionate 205

\[
\text{MeO}_2\text{C} \quad \text{N} \quad \text{CO}_2\text{Me}
\]

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. NH₄Cl, the aqueous layer was extracted with diethyl ether (3x), the combined organic phases were washed with brine, dried over MgSO₄ 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, CDCl₃): \(\delta = 7.28 \text{ (m, 5H)}, 3.65 \text{ (s, 6H)}, 3.59 \text{ (s, 2H)}, 2.80 \text{ (t, } J = 7.1 \text{ Hz, 2H)}, 2.47 \text{ (t, } J = 7.1 \text{ Hz, 2H}); \text{ ppm.}

\(^1^3\)C NMR (100 MHz, CDCl₃): \(\delta = 172.9, 139.0, 128.7, 128.2, 127.0, 58.3, 51.5, 49.2, 32.6; \text{ ppm.}

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

HRMS: m/z calculated for C₁₁H₂₁O₄N₁H⁺: 280.1549; found: 280.1548;
Methyl 1-benzyl-4-oxopiperidine-3-carboxylate 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. NaHCO₃ until pH = 8-9. The mixture was extracted with ethyl acetate (3x), the combined organic phases were washed with brine and dried over MgSO₄. 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.

**¹H NMR** (400 MHz, CDCl₃): 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.

**¹³C NMR** (100 MHz, CDCl₃): 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 C₁₄H₁₇O₃N⁺: 248.1287; found: 248.1295;
Methyl 1-benzyl-3-ethyl-4-oxopiperidine-3-carboxylate 183

A mixture of 182 (35.1 g, 142 mmol) and K₂CO₃ (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 MgSO₄ 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.

¹H NMR (400 MHz, CDCl₃): 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.

¹³C NMR (100 MHz, CDCl₃): 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 C₁₆H₂₁O₃N₁H⁺: 276.1600; found: 276.1600;
1-Benzyl-3-ethylpiperidin-4-one 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 MgSO₄. 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.

**¹H NMR** (400 MHz, CDCl₃): 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.

**¹³C NMR** (100 MHz, CDCl₃): 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 C₁₄H₁₉O₁N₁H⁺: 218.1545; found: 218.1547;
(2-Aminobenzyl) triphenylphosphonium bromide **185**

![Chemical Structure](image)

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**

![Chemical Structure](image)

To a mixture of **185** (43.1 g, 96 mmol) in CH₂Cl₂ (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.

**¹H NMR** (200 MHz, CDCl₃): 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 C₂₉H₂₇O₃N₁P₁⁺: 468.1723; found: 468.1727;
Methyl 2-(1H-indol-2-yl) acetate 187

![Chemical structure of methyl 2-(1H-indol-2-yl) acetate 187](image)

To a mixture of 186 (30 g, 54.7 mmol) in toluene (270 mL) was added tBuOK (55 mL, 1 eq., 1 M in tBuOH, 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$_3$): $\delta =$ 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)-1H-indole-1-carboxylate 206

![Chemical structure of tert-butyl 2-(2-methoxy-2-oxoethyl)-1H-indole-1-carboxylate 206](image)

To a solution of 187 (7.66 g, 40.5 mmol) in CH$_2$Cl$_2$ (90 mL) was added Boc$_2$O (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$_3$): $\delta =$ 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.
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 MgSO₄. 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, CDCl₃): \(\delta = 8.07 \text{ (m, 1H)}, 7.48 \text{ (m, 1H)}, 7.22 \text{ (m, 2H)}, 6.46 \text{ (s, 1H)}\) 3.95 (t, \(J = 6.2 \text{ Hz}, 2\text{H}\)), 3.32 (t, \(J = 6.2 \text{ Hz}, 2\text{H}\)), 1.89 (bs, 1H), 1.69 (s, 9H); ppm.
tert-Butyl 2-(2-iodoethyl)-1H-indole-1-carboxylate 180

To a solution of 188 (700 mg, 2.68 mmol) in CH$_2$Cl$_2$ (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$_2$S$_2$O$_3$ 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$_3$): $\delta$ = 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$_3$): $\delta$ = 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$_2$N$_1$I$_1$Na$: 394.0280; found: 394.0276;
tert-Butyl 2-(2-oxoethyl)-1H-indole-1-carboxylate 191

![191](image)

To a stirred solution of 206 (4.5 g, 15.6 mmol) in CH₂Cl₂ (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 MgSO₄. 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.

¹H NMR (200 MHz, CDCl₃): 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-(1H-indol-2-yl) ethylidene)-1-benzyl-3-ethyl-4-oxopiperidine-3-carboxylate 193

\[
\text{To a mixture of NHMDS (65 }\mu\text{L, 1.2 eq., 2 M in THF, 0.13 mmol) in THF (1 mL) was added 183 (30 mg, 0.11 mmol) at -78 °C. After stirring for 1 h at the same temperature, a solution of 191 (28 mg, 1 eq., 0.11 mmol) in THF (0.5 mL) was added dropwise. The mixture was stirred for 1.5 h at -78 °C and afterwards quenched with MeOH. The reaction was warmed to r.t. and sat. NH}_4\text{Cl was added. The aqueous layer was extracted with diethyl ether (3x), the combined etheral phases were washed with brine and dried over MgSO}_4\text{. The solvent was removed by rotary evaporation and the residue was purified by column chromatography (hexane/EtOAc, 6:1) to give 193 (18 mg, 39%) as clear colorless oil.}
\]

\(^1\text{H NMR (400 MHz, CDCl}_3\text{): }\delta = 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}\text{C NMR (100 MHz, CDCl}_3\text{): }\delta = 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\text{\textsubscript{26}}H\text{\textsubscript{28}}O\text{\textsubscript{3}}N\text{\textsubscript{2}}H\textsuperscript{+}: 417.2178; found: 417.2175;
Methyl 1-benzyl-3-ethyl-4-((trimethylsilyl) oxy)-1,2,3,6-tetrahydropyridine-3-carboxylate 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. NaHCO₃, the aqueous layer was extracted with diethyl ether (3x), the combined etheral phases were washed with brine and dried over MgSO₄. 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.

¹H NMR (200 MHz, CDCl₃): $\delta = 7.28$ (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

To a solution of 183 (50 mg, 0.18 mmol) in THF (1 mL) was added KOtBu (0.27 mL, 1.5 eq., 1 M in tBuOH, 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. NH₄Cl. The aqueous layer was extracted with diethyl ether (3x), the combined etheral phases were washed with brine and dried over MgSO₄. 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)

¹H NMR (200 MHz, CDCl₃): 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)

¹H NMR (400 MHz, CDCl₃): 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.

¹³C NMR (100 MHz, CDCl₃): 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 C₁₉H₂₅O₃N⁺Na⁺: 338.1732; found: 338.1729;
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.

\( ^1\text{H NMR} \) (400 MHz, C\textsubscript{6}D\textsubscript{6}): \( \delta = 7.37 \) (d, \( J = 7.4 \text{ Hz} \), 2H), 7.16 (m, 2H), 7.08 (m, 1H), 4.20 (dd, \( J = 4.4 \), 2.3 Hz, 1H), 3.57 (d, \( J = 13.2 \text{ Hz} \), 1H), 3.38 (dd, \( J = 14.3 \), 4.5 Hz, 1H), 3.33 (d, \( J = 13.2 \text{ Hz} \), 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, \( J = 7.5 \text{ Hz} \), 3H); ppm.

\( ^{13}\text{C NMR} \) (100 MHz, C\textsubscript{6}D\textsubscript{6}): \( \delta = 146.0, 140.5, 129.6, 128.8, 127.5, 92.8, 63.5, 54.4, 53.2, 47.8, 40.8, 26.2, 25.1, 12.9 \); ppm.
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. NH₄Cl. The aqueous phase was extracted with diethyl ether (3x), the combined organic layers were washed with brine and dried over MgSO₄. 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.

**¹H NMR (400 MHz, CDCl₃):** 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 C₁₇H₂₃O₁N₁H⁺: 258.1858; found: 258.1861;
Methyl 3-(1-benzyl-5-ethyl-4-oxopiperidin-3-yl) propanoate 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. NH₄Cl, the mixture was extracted with diethyl ether (3x), the combined organic phases were washed with brine and dried over MgSO₄. 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%).

**¹H NMR** (400 MHz, CDCl₃): \( \delta = 7.34 \) (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.

**¹³C NMR** (100 MHz, CDCl₃): \( \delta = 213.2, 173.6, 138.5, 128.6, 128.3, 127.2, 61.9, 58.8, 58.0, 51.6, 51.0, 47.6, 31.7, 24.0, 22.6, 11.7 \); ppm.

**IR**: 2959, 2801, 1736, 1708, 1453, 1253, 1196, 1162, 737, 669 cm⁻¹

**HRMS**: m/z calculated for C₁₈H₂₅O₃N₁H⁺: 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 Et₂O (8 mL) was sonificated for 20 min. Then water (0.4 mL) and Na₂CO₃ (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 Boc₂O (4.15 g, 0.66 eq., 19 mmol) in Et₂O (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 Et₂O. 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.

¹H NMR (400 MHz, CDCl₃): 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 Et₂O (30 mL) was added a solution of NEt₃ (1.25 mL, 1 eq., 9 mmol) in Et₂O (5 mL) at 0 °C. After stirring at the same temperature for 1.5 h the precipitate was filtered and washed with Et₂O. 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.

¹H NMR (400 MHz, CDCl₃): 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 C₁₂H₁₇O₅N₁S₁Na⁺: 310.0725; found: 310.0727;
**tert-Butyl (S)-2-ethyl-2-formylaziridine-1-carboxylate 211**

![Structural formula](image)

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 MgSO₄. 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 a clear colorless liquid.

**¹H NMR (200 MHz, CDCl₃):** 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**

To a solution of the Wittig reagent (320 mg, 2.5 eq., 0.95 mmol) in CH$_2$Cl$_2$ (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$_2$Cl$_2$ (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$_3$): $\delta = 6.57$ (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

![Formula](image)

A mixture of powdered K$_2$CO$_3$ (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$_2$O, 10:1) to yield 216 (210 mg, 86%) as volatile colorless liquid.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 2.54$ (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$_3$): $\delta = 160.1$, 81.5, 81.1, 71.1, 38.0, 29.9, 28.9, 28.0, 10.1; ppm.
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 Et₂O, 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 MgSO₄ 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.

**¹H NMR** (400 MHz, CDCl₃): 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.

**¹³C NMR** (100 MHz, CDCl₃): δ = 150.7, 108.1, 66.0, 25.7, 12.2; ppm.
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 CH₂Cl₂ (65 mL) was added Ti(O-iPr)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 CH₂Cl₂ (3x), the combined organic layers were washed with brine and dried over MgSO₄. 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.

**¹H NMR** (400 MHz, CDCl₃): 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.

**¹³C NMR** (100 MHz, CDCl₃): δ = 62.7, 60.4, 49.4, 24.7, 8.6; ppm.
(R)-(2-Ethyloxiran-2-yl) methyl 4-methylbenzenesulfonate 226

To a solution of 225 (200 mg, 2 mmol) in CH₂Cl₂ (4 mL) were added NEt₃ (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. NaHCO₃. The aqueous phase was extracted with CH₂Cl₂ (3x), the combined organic layers were washed with brine and dried over MgSO₄. 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.

¹H NMR (400 MHz, CDCl₃): 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

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. NH₄Cl. The mixture was extracted with Et₂O (3x), the combined organic phases were washed with brine and dried over MgSO₄. 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.

¹H NMR (400 MHz, CDCl₃): 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

\[
\begin{align*}
\text{OH} & \quad \text{OH} \\
\text{N}_3 & \quad \text{235}
\end{align*}
\]

To a solution of 225 (300 mg, 2.94 mmol) in DME/H$_2$O (8:1, 15 mL) were added NaN$_3$ (0.96 g, 5 eq., 14.7 mmol) and NH$_4$Cl (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$_3$): $\delta = 3.52$ (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$_3$): $\delta = 74.4$, 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

To a solution of 235 (100 mg, 0.69 mmol) in CH₂Cl₂ (3.5 mL) were added NET₃ (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. NH₄Cl. The aqueous phase was extracted with CH₂Cl₂ (3x), the combined organic layers were washed with brine and dried over MgSO₄. 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.

¹H NMR (400 MHz, CDCl₃): 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.

¹³C NMR (100 MHz, CDCl₃): 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

To a solution of 225 (200 mg, 2 mmol) and thiophenol (2.6 ml, 1.3 eq., 1 M in Et₂O, 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 Et₂O (3x), the combined organic phases were washed with brine, dried over MgSO₄ 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.

¹H NMR (200 MHz, CDCl₃): 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.

¹³C NMR (100 MHz, CDCl₃): 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 C₁₁H₁₆O₂SNa⁺: 235.0769; found: 235.0769;
(R)-2-Hydroxy-2-((phenylthio) methyl) butyl 4-methylbenzenesulfonate 231

\[
\begin{align*}
\text{OH} & \quad \text{SPh} & \quad \text{OTs} \\
231
\end{align*}
\]

To a stirred solution of 230 (360 mg, 1.69 mmol), NEt₃ (0.7 mL, 3 eq., 5.06 mmol) and DMAP (21 mg, 0.1 eq., 0.17 mmol) in CH₂Cl₂ (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. NH₄Cl. The aqueous layer was extracted with diethyl ether (3x), the combined organic phases were washed with brine, dried over MgSO₄ 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, CDCl₃): \(\delta = 7.74\) (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, CDCl₃): \(\delta = 145.0, 135.9, 132.4, 129.9, 129.8, 129.1, 128.0, 126.6, 73.2, 72.3, 41.3, 28.8, 21.6, 7.1\); ppm.

IR: 3520, 2970, 1598, 1356, 1173, 1096, 977, 833, 739, 666 cm⁻¹

HRMS: m/z calculated for C₁₈H₂₂O₄S₂Na⁺: 389.0857; found: 389.0859;
To a mixture of 231 (490 mg, 1.34 mmol) and Na$_2$CO$_3$ (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 portion. The mixture was stirred for 18 h at 60 °C and afterwards poured into water. The mixture was extracted with Et$_2$O (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$_3$):  $\delta = 7.43$ (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$_3$): $\delta = 136.1$, 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-1H-indol-2-yl) ethan-1-ol 249

![Chemical structure of 249](image)

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), NEt₃ (1.1 mL, 6 eq., 8.0 mmol) and Cul (25 mg, 0.1 eq., 0.13 mmol). The mixture was degassed and PdCl₂(PPh₃)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 MgSO₄. 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.

¹H NMR (200 MHz, CDCl₃): 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-1H-indole 248

To a solution of 249 (800 mg, 2.54 mmol) in CH$_2$Cl$_2$ (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$_2$S$_2$O$_3$ 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$_3$): $\delta = 8.17$ (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-1H-indol-2-yl) ethyl) malonate 250

A mixture of dimethyl malonate (0.77 mL, 1.1 eq., 6.7 mmol) and K$_2$CO$_3$ (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$_3$): $\delta = 8.15$ (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$_3$): $\delta = 169.5$, 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$_6$N$_1$S$_1$H$: 430.1324$; found: 430.1317;
Dimethyl 2-allyl-2-(2-(1-tosyl-1H-indol-2-yl) ethyl) malonate 247

![Chemical Structure](image)

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. NH₄Cl, the aqueous layer was extracted with diethyl ether (3x), the combined organic phases were washed with brine, dried over MgSO₄ 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.

^1H NMR (400 MHz, CDCl₃): 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.

^13C NMR (100 MHz, CDCl₃): 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 C₂₅H₂₇O₆N₁S₁H⁺: 470.1637; found: 470.1620;
Methyl 2-(2-(1-tosyl-1H-indol-2-yl) ethyl) pent-4-enoate 251

![Chemical Structure](image)

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 MgSO₄. 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.

**¹H NMR** (400 MHz, CDCl₃): 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.

**¹³C NMR** (100 MHz, CDCl₃): 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 C₂₃H₂₅O₄N₁S₁H⁺: 412.1583; found: 412.1580;
2-(2-(1-Tosyl-1\textit{H}-indol-2-yl) ethyl) pent-4-enoic acid 254

![Chemical Structure](image)

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$_3$OD): $\delta$ = 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$_3$OD): $\delta$ = 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$_4$N$_1$S$_1^{-}$: 396.1270; found: 396.1270;
5-(Iodomethyl)-3-(2-(1-tosyl-1H-indol-2-yl) ethyl) dihydrofuran-2(3H)-one 255

To a mixture of 254 (1.63 g, 4.09 mmol) in MeCN (40 mL) and sat. NaHCO₃ (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. Na₂S₂O₃. The aqueous phase was extracted with diethyl ether (3x), the combined organic layers were washed with brine, dried over MgSO₄ 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):

**¹H NMR** (400 MHz, CDCl₃): 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.

**¹³C NMR** (100 MHz, CDCl₃): 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 C₂₂H₂₂O₄N₁S₁I₁Na⁺: 546.0212; found: 546.0211;

Fr. 2 (major):

**¹H NMR** (400 MHz, CDCl₃): 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.

**¹³C NMR** (100 MHz, CDCl₃): 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 C₂₂H₂₂O₄N₁S₁I₁Na⁺: 546.0212; found: 546.0211;
To a solution of 255 (major, Fr. 2) (200 mg, 0.38 mmol) in DMSO (4 mL) was added NaN₃ (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. NaHCO₃, the aqueous layer was extracted with diethyl ether (3x), the combined organic phases were washed with brine and dried over MgSO₄. 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.

**¹H NMR** (400 MHz, CDCl₃): 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.

**¹³C NMR** (100 MHz, CDCl₃): 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 C₂₂H₂₂O₄N₄S₁H⁺: 439.1440; found: 439.1436;
5-(Azidomethyl)-3-(2-(1-tosyl-1H-indol-2-yl) ethyl) tetrahydrofuran-2-ol **253**

To a stirred solution of **246** (23 mg, 0.05 mmol) in CH$_2$Cl$_2$ (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$_2$Cl$_2$ (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$_3$): $\delta = 8.15$ (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$_3$): $\delta = 144.8$, 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

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$_2$O (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$_2$O (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$_3$): $\delta$ = 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$_3$): $\delta$ = 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$_1$H$: 174.1283$; found: 174.1283;
Ethyl 3,6-dihydropyridine-1(2H)-carboxylate 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. NaHCO₃. The mixture was extracted with ethyl acetate (3x), the organic layer was washed with brine and dried over MgSO₄. 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.

1H NMR (400 MHz, CDCl₃): δ = 5.82 (m, 1H), 5.64 (m, 1H), 4.14 (q, J = 7.1 Hz, 2H), 3.92 (q, 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.

13C NMR (100 MHz, CDCl₃): 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 C₈H₁₃O₂N₁H⁺: 156.1025; found: 156.1024;
Ethyl 7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate 266

To a solution of 256 (33 g, 215 mmol) in CHCl₃ (540 mL) was added mCPBA (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. NaHCO₃ and quenched with aq. Na₂S₂O₅, the aqueous layer was extracted with CH₂Cl₂ (3x), the combined organic phases were washed with brine and dried over MgSO₄. 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.

¹H NMR (400 MHz, CDCl₃): 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.

¹³C NMR (100 MHz, CDCl₃): 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 C₈H₁₃O₃N⁺Na⁺: 194.0793; found: 194.0788;
Ethyl 4-bromo-3-hydroxypiperidine-1-carboxylate 257

To a solution of 266 (32.7 g, 191 mmol) in CHCl₃ (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 CH₂Cl₂ (3x), neutralized with sat. NaHCO₃, washed with brine and dried over MgSO₄. 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.

¹H NMR (400 MHz, CDCl₃): 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.

¹³C NMR (100 MHz, CDCl₃): 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 C₈H₁₄O₃N₁Br₁Na⁺: 274.0055; found: 274.0053;
Ethyl 3-acetoxy-4-bromopiperidine-1-carboxylate 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 NaHSO₄. The aqueous layer was extracted with diethyl ether (3x), the ethereal phase was washed with NaHCO₃ and brine and dried over MgSO₄. 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.

^1H NMR (400 MHz, CDCl₃): 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.

^13C NMR (100 MHz, CDCl₃): 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 C₁₀H₁₅O₄N₁Br₁H⁺: 294.0341; found: 294.0338;
Ethyl 3-acetoxy-3,6-dihydropyridine-1(2H)-carboxylate 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. NH₄Cl, the aqueous phase was extracted with diethyl ether (3x), the combined organic phases were washed with brine and dried over MgSO₄. 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.

¹H NMR (400 MHz, CDCl₃): 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.

¹³C NMR (100 MHz, CDCl₃): 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 C₁₀H₁₅O₄N⁺: 236.0899; found: 236.0897;
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. NH₄Cl, the mixture was extracted with diethyl ether (3x), the combined organic layers were washed with brine and dried over MgSO₄. 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.

**¹H NMR** (400 MHz, CDCl₃): 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.

**¹³C NMR** (100 MHz, CDCl₃): 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 C₈H₁₃O₃N₁Na⁺: 194.0793; found: 194.0795;
Ethyl 3-oxo-3,6-dihydropyridine-1(2H)-carboxylate 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$_2$Cl$_2$ (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$_3$): $\delta = 7.03$ (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

To a solution of but-3-yn-1-ol (10 g, 143 mmol) in CH₂Cl₂ (240 mL) were added NEt₃ (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. NH₄Cl. The mixture was extracted with CH₂Cl₂ (3x), the combined organic layers were neutralized with sat. NaHCO₃, washed with brine and dried over MgSO₄. 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.

¹H NMR (400 MHz, CDCl₃): 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.

¹³C NMR (100 MHz, CDCl₃): δ = 145.0, 132.8, 129.9, 128.0, 78.4, 70.7, 67.4, 21.6, 19.4; ppm.

IR: 3290, 1598, 1356, 1096, 976, 902, 814, 764, 661 cm⁻¹

HRMS: m/z calculated for C₁₁H₁₂O₃S¹Na⁺: 247.0405; found: 247.0400;
4-(Trimethylsilyl) but-3-yn-1-yl 4-methylbenzenesulfonate 260

\[
\text{TMS} \xrightarrow{260} \text{OTs}
\]

To a solution of 259 (30 g, 134 mmol) in THF (80 mL) was added \(n\text{BuLi}\) (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. NH₄Cl. The aqueous layer was extracted with diethyl ether (3x), the combined organic phases were washed with brine and dried over MgSO₄. 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.

\(^1\text{H NMR}\) (400 MHz, CDCl₃): \(\delta = 7.79\) (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.

\(^{13}\text{C NMR}\) (100 MHz, CDCl₃): \(\delta = 144.9, 132.9, 129.9, 127.9, 100.3, 87.4, 67.5, 21.6, 20.7, -0.2\); ppm.

IR: 2960, 2181, 1599, 1362, 1250, 1175, 978, 905, 840, 760 cm\(^{-1}\)

HRMS: m/z calculated for C\(_{14}\)H\(_{20}\)O\(_3\)Si\(_1\)S\(_1\)Na\(^+\): 319.0800; found: 319.0798;
(4-Bromobut-1-yn-1-yl) trimethyilsilane **270**

![TMS-Br](image)

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. NaHCO₃. The mixture was extracted with diethyl ether (3x), the combined organic layers were washed with brine, dried over MgSO₄ 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.

**¹H NMR** (400 MHz, CDCl₃): δ = 3.43 (t, J = 7.5 Hz, 2H), 2.77 (t, J = 7.5 Hz, 2H), 0.16 (s, 9H); ppm.

**¹³C NMR** (100 MHz, CDCl₃): 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

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 NH₄Cl/NH₃ (8:1). The aqueous phase was extracted with diethyl ether (3x), the combined organic layers were washed with brine and dried over MgSO₄. 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.

¹H NMR (400 MHz, CDCl₃): 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.

¹³C NMR (100 MHz, CDCl₃): 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 C₁₅H₂₅O₃N₁S₁H⁺: 296.1687; found: 296.1682;
To a solution of 62 (1.71 g, 10.1 mmol) in Et₂O (51 mL) was added dropwise EtMgBr (8.1 mL, 2.4 eq., 3 M in Et₂O, 24.2 mmol) at -20 °C. The suspension was stirred for 40 min at the same temperature and then quenched with sat. NH₄Cl. The mixture was extracted with diethyl ether (3x), the combined organic layers were washed with brine, dried over MgSO₄ 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.

¹H NMR (400 MHz, CDCl₃): 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.

¹³C NMR (100 MHz, CDCl₃): 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 C₁₀H₁₇O₃N⁺Na⁺: 222.1106; found: 222.1105;
Ethyl 3-ethyl-3-(2,2,2-trifluoroacetoxy)-3,6-dihydropyridine-1(2H)-carboxylate 275

To a solution of 273 (85 mg, 0.43 mmol) in CH₂Cl₂ (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. NaHCO₃, the mixture was extracted with CH₂Cl₂ (3x), the combined organic layers were washed with brine and dried over MgSO₄. 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.

¹H NMR (400 MHz, CDCl₃): 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.

¹³C NMR (100 MHz, CDCl₃): 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 C₁₂H₁₆O₄N₁F₃Na⁺: 318.0929; found: 318.0929;
Ethyl 3-methylene-5-(4-(trimethylsilyl) but-3-yn-1-yl) piperidine-1-carboxylate 278

A mixture of MePPh₃Br (3.6 g, 3 eq., 10.1 mmol) in THF (34 mL) was placed in an ultrasonic bath for 10 min. Afterwards, KOtBu (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. NH₄Cl, the aqueous layer was extracted with diethyl ether (3x), the combined organic phases were washed with brine, dried over MgSO₄ 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.

¹H NMR (400 MHz, CDCl₃): 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.

¹³C NMR (100 MHz, CDCl₃): 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 C₁₆H₂₇O₂N₁Si₁Na⁺: 316.1709; found: 316.1710;
Ethyl 3-(but-3-yn-1-yl)-5-methyleneepiperidine-1-carboxylate 279

![Structure of 279](image)

To a solution of 278 (720 mg, 2.45 mmol) in MeOH (25 mL) was added K₂CO₃ (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 MgSO₄. 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.

**¹H NMR** (400 MHz, CDCl₃): 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.

**¹³C NMR** (100 MHz, CDCl₃): 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 C₁₃H₁₉O₂N₁Na⁺: 244.1313; found: 244.1318;
N-(2-iodophenyl)-4-methylbenzenesulfonamide 280

\[
\begin{array}{c}
\text{\includegraphics[width=0.1\textwidth]{image}} \\
280 \\
\end{array}
\]

To a solution of o-iodoaniline (15 g, 68.5 mmol) in CH$_2$Cl$_2$ (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$_2$Cl$_2$ (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$_3$): \( \delta = 7.64 \text{ (m, 4H)}, 7.30 \text{ (m, 1H)}, 7.21 \text{ (m, 2H)}, 6.82 \text{ (ddd, \( J = 15.4, 7.4, 1.6 \text{ Hz, 1H}\)}, 6.80 \text{ (bs, 1H)}, 2.38 \text{ (s, 3H)}; \text{ppm.}

$^{13}$C NMR (100 MHz, CDCl$_3$): \( \delta = 144.2, 139.1, 137.5, 135.9, 129.6, 129.5, 127.4, 126.8, 122.4, 92.3, 21.6; \text{ppm.}

IR: 3301, 1473, 1395, 1336, 1162, 1091, 1015, 911, 813, 753 cm$^{-1}$

HRMS: m/z calculated for C$_{13}$H$_{12}$O$_2$N$_1$S$_1$I$_1$Na$^+$: 395.9531; found: 395.9537;
Ethyl 3-methylene-5-(2-(1-tosyl-1H-indol-2-yl) ethyl) piperidine-1-carboxylate 281

\[
\text{CO}_2\text{Et}
\]

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 NEt₃ (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 PdCl₂(PPh₃)₂ (79 mg, 0.05 eq., 0.11 mmol). After stirring for 3 h at 70 °C, the resulting solution was poured into sat. NH₄Cl, the aqueous layer was extracted with diethyl ether (3x), the combined organic phases were washed with brine, dried over MgSO₄ 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.

\(^1\text{H NMR}\) (400 MHz, CDCl₃): \(\delta = 8.15\) (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.

\(^{13}\text{C NMR}\) (100 MHz, CDCl₃): \(\delta = 155.5, 144.7, 141.7, 141.4, 137.2, 136.0, 129.8, 129.7, 126.2, 124.0, 123.6, 120.1, 114.9, 110.9, 109.1, 61.3, 50.3, 48.6, 38.9, 36.3, 32.3, 26.5, 21.6, 14.7\); ppm.

\textbf{IR}: 2934, 1695, 1452, 1369, 1222, 1175, 1119, 1092, 749, 667 cm\(^{-1}\)

\textbf{HRMS}: m/z calculated for C\(_{26}\)H\(_{30}\)O\(_4\)N\(_2\)S\(_1\)Na+: 489.1824; found: 489.1820;
2-(2-(5-methyleneepiperidin-3-yl) ethyl)-1H-indole 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 CH₂Cl₂ (3x), the combined organic layers were washed with brine and dried over MgSO₄. 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.

¹H NMR (400 MHz, CDCl₃): 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.

¹³C NMR (100 MHz, CDCl₃): 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 C₁₆H₂₀N₂H⁺: 241.1705; found: 241.1705;
1-(3-(2-(1H-indol-2-yl) ethyl)-5-methylenepiperidin-1-yl)-2-chloroethan-1-one 285

To a solution of 282 (245 mg, 1.02 mmol) in CH$_2$Cl$_2$ (3.5 mL) were added at 0 °C NEt$_3$ (0.14 mL, 1 eq., 1.02 mmol) and (ClAc)$_2$O (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$_2$Cl$_2$ (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$_6$): $\delta$ = 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): $\delta$ = 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$_1$N$_2$Cl$_1$Na$: 339.1240$; found: 339.1233;
A mixture of 285 (120 mg, 0.38 mmol) and Na₂CO₃ (120 mg, 3 eq., 1.14 mmol) in MeOH (42 mL) and water (21 mL) was placed in a quartz 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 NaHCO₃. The aqueous layer was extracted with diethyl ether (3x), the combined organic phases were washed with brine, dried over MgSO₄ 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:

**1H NMR** (600 MHz, CDCl₃): 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.

**13C NMR** (150 MHz, CDCl₃): 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 C₁₈H₂₀O₁N₂Na⁺: 303.1473; found: 303.1474;

Fr. 2:

**1H NMR** (600 MHz, CDCl₃): 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$_3$): $\delta = 170.1, 138.8, 137.3, 134.4, 129.6, 121.5, 119.9, 118.2, 113.3, 110.1, 105.1, 48.9, 47.7, 39.3, 35.8, 30.9, 29.3, 23.1$; ppm.

IR: 3249, 2933, 1611, 1466, 1345, 1266, 1230, 1093, 898, 736 cm$^{-1}$

HRMS: m/z calculated for C$_{18}$H$_{20}$O$_1$N$_2$H$^+$: 281.1654; found: 281.1654;

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

A mixture of EtPPh$_3$Br (4.2 g, 3 eq., 10.1 mmol) in THF (34 mL) was placed in an ultrasonic bath for 10 min. Afterwards, KOtBu (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$_4$Cl, 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$_3$): $\delta = 5.43$ (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$_3$): $\delta = 155.6, 155.5, 132.1, 119.8, 106.9, 106.7, 84.9, 84.8, 61.2, 61.1, 51.8, 48.9, 48.8, 39.9, 36.0, 31.4, 17.5, 17.4, 14.7, 12.8, 12.6, 0.1$; ppm.

IR: 2960, 2174, 1697, 1428, 1248, 1204, 1123, 839, 759, 697 cm$^{-1}$

HRMS: m/z calculated for C$_{17}$H$_{29}$O$_2$N$_1$Si$_1$Na$^+$: 330.1865; found: 330.1863;
Ethyl 3-(but-3-yn-1-yl)-5-ethylideneepiperidine-1-carboxylate 287

To a solution of 261 (777 mg, 2.53 mmol) in MeOH (25 mL) was added K₂CO₃ (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 MgSO₄. 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.

¹H NMR (400 MHz, CDCl₃): 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.

¹³C NMR (100 MHz, CDCl₃): 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 C₁₄H₂₁O₂N₁H⁺: 236.1651; found: 236.1651;
Ethyl 3-ethylidene-5-(2-(tosyl-1H-indol-2-yl) ethyl) piperidine-1-carboxylate 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 NEt₃ (1.34 mL, 4 eq., 9.7 mmol). The mixture was degassed followed by addition of Cul (46 mg, 0.1 eq., 0.24 mmol) and PdCl₂(PPh₃)₂ (85 mg, 0.05 eq., 0.12 mmol). After stirring for 3 h at 70 °C, the resulting solution was poured into sat. NH₄Cl, the aqueous layer was extracted with diethyl ether (3x), the combined organic phases were washed with brine, dried over MgSO₄ 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:

¹H NMR (400 MHz, CDCl₃): 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.

¹³C NMR (100 MHz, CDCl₃): 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 C₂₇H₃₂O₄N₂S₂H⁺: 481.2161; found: 481.2162;
2-(2-(5-Ethylidenepiperidin-3-yl) ethyl)-1H-indole 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$_2$Cl$_2$ (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$_3$): $\delta = 8.24$ (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$_3$): $\delta = 139.4$, 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$_2$H$^+$: 255.1861; found: 255.1859;
To a solution of 316 (1 g, 3.93 mmol) in CH₂Cl₂ (3.5 mL) were added NEt₃ (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 CH₂Cl₂ (3x), the combined organic phases were washed with brine and dried over MgSO₄. 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.

¹H NMR (400 MHz, CDCl₃, 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.

¹³C NMR (100 MHz, CDCl₃, 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, 1743, 1457, 1287, 1242, 1140, 784, 749 cm⁻¹

HRMS: m/z calculated for C₁₉H₂₃O₂N₂Cl₁H⁺: 353.1397; found: 353.1395;
(Z)-5-Ethylidene-1,4,5,6,7,8,9,10-octahydro-2H-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-2H-3,7-methano[1]azacycloundecino[5,4-b]indol-2-one 291

A mixture of 289 (250 mg, 0.76 mmol) and Na₂CO₃ (240 mg, 3 eq., 2.27 mmol) in MeOH (84 mL) and water (42 mL) was placed in a quartz 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 NaHCO₃. The aqueous layer was extracted with diethyl ether (3x), the combined organic phases were washed with brine, dried over MgSO₄ 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):

**1H NMR** (400 MHz, CDCl₃): 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.

**13C NMR** (100 MHz, CDCl₃): 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, 1342, 1240, 1018, 908, 735, 669 cm⁻¹

**HRMS**: m/z calculated for C₁₉H₂₂O₁N₂H⁺: 295.1810; found: 295.1815;
Fr. 2 (minor 291 (E)-DB):

**^1H NMR** (400 MHz, CDCl$_3$): $\delta$ = 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.

**^13C NMR** (100 MHz, CDCl$_3$): $\delta$ = 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$_1$N$_2$H$^+$: 295.1810; found: 295.1817;
(Z)-5-Ethylidene-1,4,5,6,7,8,9,10-octahydro-2H-3,7-methano[1]azacycloundecino[5,4-b]indole 292a and (E)-5-Ethylidene-1,4,5,6,7,8,9,10-octahydro-2H-3,7-methano[1]azacycloundecino[5,4-b]indole 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 CH₂Cl₂ (3x), the combined organic layers were washed with brine and dried over MgSO₄. 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:

¹H NMR (400 MHz, CDCl₃): 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.

¹³C NMR (100 MHz, CDCl₃): 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 C₁₉H₂₄N₂H⁺: 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 C₁₉H₂₄N₂H⁺: 281.2018; found: 281.2022;
(20R)-15,20-Dihydro-cleavamine (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.\textsuperscript{25,123}

\textbf{1H NMR} (600 MHz, CDCl\textsubscript{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.

\textbf{13C NMR} (150 MHz, CDCl\textsubscript{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.

\textbf{IR}: 3400, 2914, 2784, 1635, 1463, 1440, 1336, 1136, 909, 739 cm\textsuperscript{-1}

\textbf{HRMS}: m/z calculated for C\textsubscript{19}H\textsubscript{26}N\textsubscript{2}H\textsuperscript{+}: 283.2174; found: 283.2169;
5-Ethyl-1,6,7,8,9,10-hexahydro-2H-3,7-methano[1]azacycloundecino[5,4-b]indol-2-one 293 and 5-Ethyl-1,4,7,8,9,10-hexahydro-2H-3,7-methano[1]azacycloundecino [5,4-b]indol-2-one 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 Et₂O 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):

¹H NMR (600 MHz, CDCl₃): 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.

¹³C NMR (150 MHz, CDCl₃): 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 C₁₉H₂₂O₁N₂Na⁺: 317.1630; found: 317.1630;

Fr. 2 (major 294):

¹H NMR (600 MHz, CDCl₃): 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.
**13C NMR** (150 MHz, CDCl₃): 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 C₁⁹H₂₂O₁N₂⁺: 295.1810; found: 295.1806;

Cleavamine (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 Et₂O (3x), the combined organic layers were washed with brine and dried over MgSO₄. 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

**1H NMR** (400 MHz, CDCl₃): 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.

**13C NMR** (150 MHz, CDCl₃): δ = 140.8, 139.5, 135.3, 128.7, 122.4, 120.6, 118.7, 117.8, 109.5, 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 C₁⁹H₂₄N₂H⁺: 281.2012; found: 281.1999;

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. NH₄Cl, the mixture was extracted with diethyl ether (3x), the combined organic phases were washed with brine, dried over MgSO₄ 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 (3R,7S) 317):

1H NMR (400 MHz, CDCl₃): 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.

13C NMR (100 MHz, CDCl₃): 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 C₁₆H₂₇O₃N₁Si₁H⁺: 310.1838; found: 310.1843;

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

1H NMR (400 MHz, CDCl₃): 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.
13C NMR (100 MHz, CDCl3): 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 C16H27O3N1Si1H+: 310.1838; found: 310.1843;

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

![Structure of 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 Et2O, 1.13 mmol) was added. After stirring for 30 min at the same temperature, the reaction was quenched with sat. NH4Cl, the aqueous phase was extracted with diethyl ether (3x), the combined organic phases were washed with brine, dried over MgSO₄ 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.

1H NMR (400 MHz, CDCl₃): 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.

13C NMR (100 MHz, CDCl₃): 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 C17H31O3N1Si1H+: 326.2151; found: 326.2153;
Ethyl (3S,5S)-5-(but-3-yn-1-yl)-3-ethyl-3-hydroxy Piperidine-1-carboxylate 296

To a solution of 318 (770 mg, 2.37 mmol) in MeOH (24 mL) was added K2CO3 (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 MgSO4. 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.

1H NMR (400 MHz, CDCl3): 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.

13C NMR (100 MHz, CDCl3): 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 C14H23O3N1Na+: 276.1576; found: 276.1577;
Ethyl (3S,5S)-3-ethyl-3-hydroxy-5-(2-(1-tosyl-1H-indol-2-yl) ethyl) piperidine-1-carboxylate 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 NEt₃ (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 PdCl₂(PPh₃)₂ (70 mg, 0.05 eq., 0.1 mmol). After stirring for 3 h at 70 °C, the resulting solution was poured into sat. NH₄Cl, the aqueous layer was extracted with diethyl ether (3x), the combined organic phases were washed with brine, dried over MgSO₄ 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.

¹H NMR (400 MHz, CDCl₃): 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.

¹³C NMR (100 MHz, CDCl₃): 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 C₂₇H₃₄O₅S₂N₂H⁺: 499.2267; found: 499.2266;
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$_2$Cl$_2$ (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$_3$): $\delta = 8.12$ (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$_3$): $\delta = 139.6, 135.8, 128.8, 121.0, 119.7, 119.6, 110.5$, 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$_2$N$_2$H$^+$: 273.1967; found: 273.1965;
1-((3S,5S)-5-(2-(1H-indol-2-yl) ethyl)-3-ethyl-3-hydroxypiperidin-1-yl)-2-chloroethan-1-one 297

To a solution of 320 (690 mg, 2.54 mmol) in CH₂Cl₂ (25 mL) were added NEt₃ (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 CH₂Cl₂ (3x), the combined organic phases were washed with brine and dried over MgSO₄. 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.

¹H NMR (400 MHz, CDCl₃, 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, 2H (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, 3H (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.

¹³C NMR (100 MHz, CDCl₃, 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 C₁₉H₂₅O₂N₂ClH⁺: 349.1683; found: 349.1679;
A mixture of 297 (250 mg, 0.72 mmol) and Na₂CO₃ (304 mg, 4 eq., 2.87 mmol) in MeOH (72 mL) and water (48 mL) was placed in a quartz 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 NaHCO₃. The aqueous layer was extracted with diethyl ether (3x), the combined organic phases were washed with brine, dried over MgSO₄ 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.

**¹H NMR** (400 MHz, CDCl₃): 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.

**¹³C NMR** (100 MHz, CDCl₃): 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 C₁₉H₂₄O₂NaH⁺: 313.1916; found: 313.1913;
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 CH₂Cl₂ (3x), the combined organic layers were washed with brine and dried over MgSO₄. The solvent was removed by rotary evaporation and the residue was purified by column chromatography (CH₂Cl₂/MeOH 20:1) to give 19 (82 mg, 86%) as white solid. The analytical data matches the data in literature.¹²⁴,¹²⁵

¹H NMR (400 MHz, CDCl₃): 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.

¹³C NMR (100 MHz, CDCl₃): 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 C₁₉H₂₆O₁N₂H⁺: 299.2123; found: 299.2122;
Ethyl (3R,5S)-3-ethyl-3-hydroxy-5-(4-(trimethylsilyl) but-3-yn-1-yl) piperidine-1-carboxylate 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 Et₂O, 0.87 mmol) was added. After stirring for 1 h at the same temperature, the reaction was quenched with sat. NH₄Cl, the aqueous phase was extracted with diethyl ether (3x), the combined organic phases were washed with brine, dried over MgSO₄ 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.

**1H NMR** (400 MHz, CDCl₃): 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.

**13C NMR** (100 MHz, CDCl₃): 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 C₁₇H₃₁O₃N₁Si₁H⁺: 326.2151; found: 326.2153;
Ethyl (3R,5S)-5-(but-3-yn-1-yl)-3-ethyl-3-hydroxypiperidine-1-carboxylate 323

To a solution of 322 (150 mg, 0.46 mmol) in MeOH (4.5 mL) was added at r.t. K₂CO₃ (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 MgSO₄. 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.

**¹H NMR** (400 MHz, CDCl₃): 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.

**¹³C NMR** (100 MHz, CDCl₃): 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 C₁₄H₂₃O₃N₁H⁺: 254.1756; found: 254.1754;
Ethyl (3R,5S)-3-ethyl-3-hydroxy-5-(2-(1-tosyl-1H-indol-2-yl) ethyl) piperidine-1-carboxylate 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 Cul (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$_4$Cl, 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$_3$): $\delta$ = 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$_3$): $\delta$ = 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$_5$N$_2$S$_1$H$^+$. 499.2267; found: 499.2265;
(3R,5S)-5-(2-(1H-indol-2-yl) ethyl)-3-ethylpiperidin-3-ol 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 CH₂Cl₂ (3x), the combined organic layers were washed with brine and dried over MgSO₄. 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.

¹H NMR (400 MHz, CD₃OD): 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.

¹³C NMR (100 MHz, CD₃OD): 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 C₁₇H₂₄O₁N₂H⁺: 273.1967; found: 273.1963;
To a solution of 299 (454 mg, 1.67 mmol) in CH$_2$Cl$_2$ (16 mL) were added at 0 °C NEt$_3$ (0.23 mL, 1 eq., 1.67 mmol) and (ClAc)$_2$O (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$_2$Cl$_2$ (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): $\delta$ = 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): $\delta$ = 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$_2$N$_2$ClNa$: 371.1502; found: 371.1503;
(5R,7S)-5-Ethyl-5-hydroxy-1,4,5,6,7,8,9,10-octahydro-2H-3,7-methano[1]azacycloundecino[5,4-b]indol-2-one 301

A mixture of 300 (250 mg, 0.72 mmol) and Na₂CO₃ (304 mg, 4 eq., 2.87 mmol) in MeOH (72 mL) and water (48 mL) was placed in a quartz 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 NaHCO₃. The aqueous layer was extracted with diethyl ether (3x), the combined organic phases were washed with brine, dried over MgSO₄ and the solvent was removed by rotary evaporation. The residue was purified by column chromatography (CH₂Cl₂/MeOH, 25:1) to afford 301 (120 mg, 53%) as white solid.

¹H NMR (600 MHz, CDCl₃): 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.

¹³C NMR (150 MHz, CDCl₃): 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 C₁₉H₂₄O₂N₂H⁺: 313.1916; found: 313.1911;
Velbanamine (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)(PPh₃)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. NaHCO₃. The aqueous phase was extracted with Et₂O (3x), the combined organic layers were treated with 1 M HCl (2x). The acidic aqueous phases were treated with NaHCO₃ until pH ≥ 9 and then extracted with CH₂Cl₂ (3x), the combined organic layers were washed with brine and dried over MgSO₄. 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

¹H NMR (600 MHz, CDCl₃): 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.

¹³C NMR (150 MHz, CDCl₃): 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 C₁₉H₂₆O₁N₂Na⁺: 299.2123; found: 299.2122;
(5R,7S)-5-Ethyl-5-((trimethylsilyl)oxy)-1,4,5,6,7,8,9,10-octahydro-2H-3,7-methano[1]azacycloundecino[5,4-b]indol-2-one 302

To a solution of 301 (60 mg, 0.19 mmol) in CH₂Cl₂ (2 mL) were added NEt₃ (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 CH₂Cl₂ (3x), the combined organic layers were washed with brine and dried over MgSO₄. 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.

¹H NMR (400 MHz, CDCl₃): 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.

¹³C NMR (100 MHz, CDCl₃): 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 C₂₂H₃₂O₂N₂SiNa⁺: 407.2131; found: 407.2129;
To a solution of 301 (40 mg, 0.13 mmol) in CHCl₃ (1 mL) were added NEt₃ (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 CH₂Cl₂ (3x), the combined organic layers were washed with brine and dried over MgSO₄. 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.

**¹H NMR** (400 MHz, CDCl₃): 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.

**¹³C NMR** (100 MHz, CDCl₃): 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 C₂₅H₃₉O₂N₂SiNa⁺: 449.2600; found: 449.2599;
(5S,7R)-5-((tert-Butyldimethylsilyl)oxy)-5-ethyl-1,4,5,6,7,8,9,10-octahydro-2H-3,7-methano[1]azacycloundecino[5,4-b]indole 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 CH₂Cl₂ (3x), the combined organic layers were treated with 1 M HCl (2x). The acidic aqueous layers were treated with NaHCO₃ until pH ≥ 9 and then extracted with CH₂Cl₂ (3x), the combined organic phases were washed with brine and dried over MgSO₄. The solvent was removed by rotary evaporation to product 304 (6 mg, 50%) as clear colorless liquid.

¹H NMR (400 MHz, CDCl₃): 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.

¹³C NMR (100 MHz, CDCl₃): 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 C₂₅H₄₀O₁N₂Si₁H⁺: 413.2988; found: 413.2988;
(5R,7S)-5-Ethyl-5-((trimethylsilyl)oxy)-1,4,5,6,7,8,9,10-octahydro-2H-3,7-methano[1]azacycloundecino[5,4-b]indole-2-thione 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 MgSO₄ 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.

¹H NMR (400 MHz, CDCl₃): 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.

¹³C NMR (100 MHz, CDCl₃): 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 C₂₂H₃₂O₁N₂Si₂S₂Na⁺: 423.1902; found: 423.1908;
Ethyl (3R,7S)-7-(but-3-yn-1-yl)-1-oxa-5-azaspiro[2.5]octane-5-carboxylate 298 and Ethyl (3S,7S)-7-(but-3-yn-1-yl)-1-oxa-5-azaspiro[2.5]octane-5-carboxylate 324

To a solution of 279 (1.7 g, 7.68 mmol) in CHCl₃ (75 mL) was added mCPBA (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. NaHCO₃ and quenched with aq. Na₂S₂O₃, the aqueous layer was extracted with CH₂Cl₂ (3x), the combined organic phases were washed with brine and dried over MgSO₄. 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 (3R, 7S) 298:

¹H NMR (400 MHz, CDCl₃): 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.

¹³C NMR (100 MHz, CDCl₃): 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 C₁₃H₁₉O₃N₁Na⁺: 260.1263; found: 260.1260

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

¹H NMR (400 MHz, CDCl₃): 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.

¹³C NMR (100 MHz, CDCl₃): 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.

177
IR: 3271, 2920, 2361, 1688, 1427, 1216, 1117, 881, 768, 661 cm\(^{-1}\)

HRMS: calculated for C\(_{13}\)H\(_{19}\)O\(_3\)N\(_1\)Na\(^+\): 260.1263; found: 260.1266

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

![Chemical Structure](image)

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 NE\(_3\) (2 mL, 3 eq., 14.6 mmol). The mixture was degassed followed by addition of Cul (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\(_4\)Cl, 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\(_3\)): \(\delta = 8.15\) (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\(_3\)): \(\delta = 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, 109.3, 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\(_5\)N\(_2\)S\(_1\)Na\(^+\): 505.1773; found: 505.1776
Ethyl (3S,5S)-3-ethyl-3-hydroxy-5-(2-(1-tosyl-1H-indol-2-yl) ethyl) piperidine-1-carboxylate 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 Et₂O, 4.67 mmol) was added. After stirring for 1 h at the same temperature, the reaction was quenched with sat. NH₄Cl, the aqueous phase was extracted with diethyl ether (3x), the combined organic phases were washed with brine, dried over MgSO₄ 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 (3R,7S)-7-((2-(1-tosyl-1H-indol-2-yl) ethyl)-1-oxa-5-azaspiro[2.5]octane-5-carboxylate 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 NEt3 (1 mL, 3 eq., 7.43 mmol). The mixture was degassed followed by addition of Cul (47 mg, 0.1 eq., 0.25 mmol) and PdCl2(PPh3)2 (87 mg, 0.05 eq., 0.12 mmol). After stirring for 3 h at 70 °C, the resulting solution was poured into sat. NH4Cl, the aqueous layer was extracted with diethyl ether (3x), the combined organic phases were washed with brine, dried over MgSO4 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.

1H NMR (400 MHz, CDCl3): 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, 2H), 1.66 (m, 2H), 1.26 (t, J = 7.5 Hz, 3H); ppm.

13C NMR (100 MHz, CDCl3): 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 C26H30O5N2S1H+: 483.1954; found: 483.1957
Ethyl (3R,5S)-3-ethyl-3-hydroxy-5-(2-(1-tosyl-1H-indol-2-yl) ethyl) piperidine-1-carboxylate 299

To a solution of 327 (830 mg, 1.72 mmol) in THF (17 mL) was added Cul (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 Et₂O, 2.58 mmol) was added. After stirring for 45 min at the same temperature, the reaction was quenched with sat. NH₄Cl, the aqueous phase was extracted with diethyl ether (3x), the combined organic phases were washed with brine, dried over MgSO₄ 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

To a solution of 271 (1.9 g, 6.43 mmol) and (TMSOCH₂)₂ (2.65 g, 2 eq., 12.9 mmol) in CH₂Cl₂ (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. NaHCO₃. The aqueous phase was extracted with CH₂Cl₂ (3x), the combined organic phases were washed with brine and dried over MgSO₄. 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.

¹H NMR (400 MHz, CDCl₃): 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.

¹³C NMR (100 MHz, CDCl₃): 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 C₁₇H₂₉O₄N₁Si₁Na⁺: 362.1764; found: 362.1765;
Ethyl 9-(but-3-yn-1-yl)-1,4-dioxa-7-azaspiro[4.5]decane-7-carboxylate 328

![Chemical Structure](image)

To a solution of 306 (1.29 g, 3.79 mmol) in MeOH (35 mL) was added K$_2$CO$_3$ (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$_3$): $\delta$ = 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$_3$): $\delta$ = 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$_4$N$_1$Na$: 290.1368; found: 290.1367;
Ethyl 9-(2-(1-tosyl-1H-indol-2-yl) ethyl)-1,4-dioxo-7-azaspiro[4.5]decane-7-carboxylate 307

![Chemical Structure](image)

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$_4$Cl, 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$_3$): $\delta =$ 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$_3$): $\delta =$ 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$_6$N$_2$S$_1$Na$^+$: 535.1879; found: 535.1880
9-(2-(1H-Indol-2-yl) ethyl)-1,4-dioxo-7-azaspiro[4.5]decane 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 CH₂Cl₂ (3x), the combined organic layers were washed with brine and dried over MgSO₄. 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.

¹H NMR (400 MHz, CDCl₃): 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.

¹³C NMR (100 MHz, CDCl₃): 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 C₁₇H₂₂O₂N₂H⁺: 287.1760; found: 287.1760;
To a solution of 329 (450 mg, 1.57 mmol) in CH$_2$Cl$_2$ (15 mL) were added at 0 °C NEt$_3$ (0.22 mL, 1.0 eq., 1.57 mmol) and (ClAc)$_2$O (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$_2$Cl$_2$ (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): $\delta$ = 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 (dd, $J$ = 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): $\delta$ = 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, 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$_3$N$_2$Cl$_1$Na$^+$: 385.1295; found: 385.1297;
A mixture of 308 (60 mg, 0.17 mmol) and Na₂CO₃ (53 mg, 3 eq., 0.5 mmol) in MeOH (18 mL) and water (9 mL) was placed in a quarts vessel. The vessel was sonificated under a nitrogen atmosphere for 30 min and then irradiated (\(\lambda=254\) nm) for 1 h at r.t.. Afterwards, the methanol was evaporated under reduced pressure and the residue was diluted with NaHCO₃. The aqueous layer was extracted with diethyl ether (3x), the combined organic phases were washed with brine, dried over MgSO₄ 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, CDCl₃): \(\delta = 8.14\) (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, CDCl₃): \(\delta = 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\(^{-1}\)
To a solution of 19 (10 mg, 34 µmol) in EtOH (1 mL) was added PtO₂ (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 Et₂O and filtered through a pad of Celite. The solvent was removed under reduced pressure and the residue was purified by column chromatography (CH₂Cl₂ /MeOH 15:1) to give 20 (3 mg, 30%) as yellow oil. The analytical data matches the data in literature.¹²³

¹H NMR (600 MHz, CDCl₃): 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.

¹³C NMR (150 MHz, CDCl₃): 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, 35.4, 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 C₁₉H₂₄O₁N₂H⁺: 297.1967; found: 297.1965;
(20R)-1,2-Dehydro-pseudoaspidospermidine (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$_2$Cl$_2$ and filtered through a pad of Celite. The solvent was removed under reduced pressure and the residue was purified by column chromatography (CH$_2$Cl$_2$ /MeOH 10:1) to give 21 (7 mg, 28%) as brown oil. The analytical data matches the data in literature.\textsuperscript{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$_2$H$: 281.2018$; found: 281.2020;
7. Appendix

7.1. Spectra

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100 MHz, CDCl$_3$)
$^1\text{H NMR} \ (400 \text{ MHz, } \text{CDCl}_3)$

$^{13}\text{C NMR} \ (100 \text{ MHz, } \text{CDCl}_3)$
$^{1}H$ 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$_3$)
$^1\text{H NMR}$ (400 MHz, CDCl$_3$)

$^{13}\text{C NMR}$ (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, CDCl₃)

$^{13}$C NMR (100 MHz, CDCl₃)
$^{1}H$ NMR (400 MHz, CDCl$_{3}$)

$^{13}C$ NMR (100 MHz, CDCl$_{3}$)
$^1\text{H NMR}$ (400 MHz, CDCl$_3$)

$^{13}\text{C NMR}$ (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$_6$)
$^1$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)

![NMR Spectrum](image)

$^{13}C$ NMR (100 MHz, CDCl$_3$, two rotamers)

![NMR Spectrum](image)
$^1$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$_3$)

(Z)-292a

$^{13}$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$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100 MHz, CDCl$_3$)
$^1$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 (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, CD$_3$OD)

$^{13}$C NMR (100 MHz, CD$_3$OD)
$^1$H NMR (400 MHz, CDCl$_3$, two rotamers)

$^{13}$C NMR (100 MHz, CDCl$_3$, two rotamers)
$^{1}H$ 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$_3$)

$^{13}$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$_3$)
$\textbf{^1H NMR (400 MHz, CDCl}_3\text{)}$

$\textbf{^13C NMR (100 MHz, CDCl}_3\text{)}$
$^1$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$_3$)
\(^1\text{H NMR}\) (600 MHz, CDCl\(_3\))

\(^{13}\text{C NMR}\) (150 MHz, CDCl\(_3\))
$^1$H NMR (600 MHz, CDCl$_3$)

$^{13}$C NMR (150 MHz, CDCl$_3$)
7.2. List of Figures

Figure 1: *Tabernaemontana dichotoma* ........................................................................................................ 1
Figure 2: Structure of dichomine (1) and carbon atom numbering ................................................................. 2
Figure 3: Structures of stemmadenine (2), succinylcholine (3) and neostigmine (4). 2
Figure 4: Representative members of the *corynanthe* class of alkaloids .................................................. 4
Figure 5: Representative members of the *aspidosperma* class of alkaloids ................................................. 5
Figure 6: Representative members of the *iboga* class of alkaloids, part 1 .................................................. 6
Figure 7: Representative members of the *iboga* class of alkaloids, part 2 .................................................. 6
Figure 8: Representative members of the *iboga* class of alkaloids, part 3 .................................................. 7
Figure 9: Representative members of the *iboga* class of alkaloids, part 4 .................................................. 7
Figure 10: Substitution pattern of the Witkop reaction ............................................................................... 34
Figure 11: Structure of velbanamine (18) and cleavamine (49) ................................................................. 38
Figure 12: Electronic effect of the alkoxide towards the lactam moiety ......................................................... 73

7.3. List of Schemes

Scheme 1: Biosynthesis of loganin (31) ............................................................................................................ 8
Scheme 2: Proposed mechanism towards secologanin (33). ................................................................. 9
Scheme 3: Proposed biosynthesis of stemmadenine (2) ............................................................................. 9
Scheme 4: Proposed biosynthesis of *aspidosperma* and *iboga* alkaloids ........................................... 10
Scheme 5: Proposed biosynthesis of *iboga* alkaloids .......................................................................... 12
Scheme 6: Proposed biosynthesis of dichomine (1) .................................................................................. 13
Scheme 7: Reduction of dichomine (1) ......................................................................................................... 13
Scheme 8: Retrosynthetic analysis of Hanaoka´s approach to (±)-cleavamine (49) ................................. 14
Scheme 9: Hanaoka´s total synthesis of (±)-cleavamine (49) .............................................................. 15
Scheme 10: Retrosynthetic approach of Bennasar and coworkers ............................................................. 16
Scheme 11: Bennasar´s total synthesis of (±)-cleavamine (49) and (±)-dihydrocleavamine (17) ................. 17
Scheme 12: Kutney´s retrosynthetic analysis of (±)-dihydrocleavamines ................................................. 18
Scheme 13: Kutney´s total synthesis of (±)-dihydrocleavamines ............................................................... 19
Scheme 14: Lesma´s retrosynthetic analysis of (+)-dihydrocleavamine (17) ............................................. 20
Scheme 15: Lesma´s total synthesis of (+)-20R-dihydrocleavamine (17) ............................................... 20
**Scheme 16:** Retrosynthetic approach of Ogasawara et al. towards (+)-20R-dihydrocleavamine (17). ............................................................ 21

**Scheme 17:** Ogasawara’s total synthesis of (+)-20R-dihydrocleavamine (17). ........ 22

**Scheme 18:** Retrosynthetic approach of Bosh and coworkers towards (-)-20S-dihydrocleavamine (74). .............................................................. 24

**Scheme 19:** Bosh´s total synthesis of (-)-20S-dihydrocleavamine (74). ............... 25

**Scheme 20:** Retrosynthetic approach of Büchi and coworkers towards (±)-velbanamine (18). .......................................................................................... 26

**Scheme 21:** Büchi´s synthesis of compound 102. ............................................. 26

**Scheme 22:** Büchi´s total synthesis of (±)-velbanamine (18). ........................... 27

**Scheme 23:** Narisada´s retrosynthetic analysis of (±)-velbanamine (18) and (±)-isovelbanamine (19). .............................................................................. 28

**Scheme 24:** Narisada´s total synthesis of (±)-velbanamine (18) and (±)-isovelbanamine (19). ....................................................................................... 29

**Scheme 25:** Retrosynthetic analysis of Takano and coworkers. ......................... 30

**Scheme 26:** Synthesis of the cyclization precursor 117. .................................. 30

**Scheme 27:** Takano´s total synthesis of velbanamine (18), isovelbanamine (19) and cleavamine (49). ............................................................................. 31

**Scheme 28:** Kuehne´s total synthesis of pandoline (22) and 20-epipandoline (127). 32

**Scheme 29:** Accepted mechanism of the Witkop reaction ............................... 33

**Scheme 30:** Photocyclization of compound 137 towards Bosch´s total synthesis of (-)-tubifoline (139). ................................................................. 34

**Scheme 31:** Pagenkopf´s total synthesis of (±)-quebrachamine (142). ............... 35

**Scheme 32:** Photocyclization studies towards the total synthesis of catharanthine (43). ........................................................................................... 35

**Scheme 33:** Photocyclization of α-chloro esters to obtain regioisomeric catharanthine analogs. ...................................................................................... 36

**Scheme 34:** Retrosynthetic analysis of (±)-dichomine (1). .............................. 37

**Scheme 35:** Proposed mechanism of the envisioned biomimetic ring-closing reaction. .......................................................................................... 37

**Scheme 36:** Synthesis of pyridine 169 and pyridinium salt 177. ......................... 39

**Scheme 37:** Attempted reduction of pyridinium salt 177 to obtain tetrahydropyridine 178. ................................................................................................. 39

**Scheme 38:** Test reaction for the synthesis of indole 179. ................................. 40
Scheme 39: Alternative retrosynthetic approach to compound 166.

Scheme 40: Synthesis of piperidone building block 181.

Scheme 41: Synthesis of the indole fragment 180.

Scheme 42: Alkylation attempts between compound 180 and 181.

Scheme 43: Synthesis of the indole aldehyde 191.

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

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

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

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

Scheme 48: Enamine mediated side chain installation attempts.

Scheme 49: New retrosynthetic analysis towards building block 166.

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

Scheme 51: Several transformation attempts of aldehyde 211.

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

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

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

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

Scheme 56: Third retrosynthetic analysis towards Witkop precursor 166.

Scheme 57: Synthesis of azide compound 246.

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

Scheme 59: Synthesis of compound 245 via reductive amination.

Scheme 60: Fourth retrosynthetic approach towards Witkop precursor 166.

Scheme 61: Synthesis of dihydropyridon.

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

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

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

Scheme 65: Attempted substitution reaction towards compound 277.

Scheme 66: Synthetic sequence towards compound 281.

Scheme 67: One-step deprotection attempts to obtain compound 204.
Scheme 68: Acylation attempts towards α-chloro lactam 285. ........................................ 62
Scheme 69: Synthesis of the macrolactams 286 by utilizing a Witkop photocyclization.
........................................................................................................................................... 63
Scheme 70: Synthetic route towards Witkop precursor 289. .............................................. 63
Scheme 71: Witkop photocyclization of compound 289 to generate macrocycles 290 and 291........................................................................................................................................... 64
Scheme 72: Further steps to synthesize the biomimetic precursor 165............................. 64
Scheme 73: Isomerization attempts towards acyl enamine 293........................................... 65
Scheme 74: Reduction of lactam 294 to obtain (±)-cleavamine (49) ..................................... 66
Scheme 75: Synthesis of (±)-20R-dihydrocleavamine (17) via reduction of amines 292.
............................................................................................................................................. 66
Scheme 76: Alternative retro-biomimetic oxidation approach towards (±)-dichomine (1). ............................................................................................................................................. 67
Scheme 77: Corey Chaykovsky approach to epoxide 295 and synthesis of Witkop precursor 297............................................................................................................................................. 68
Scheme 78: Remaining steps from compound 297 to (±)-isovelbanamine (19)............. 69
Scheme 79: Epoxidation approach to compound 298 and synthesis of Witkop precursor 300............................................................................................................................................. 69
Scheme 80: Remaining steps from compound 300 to (±)-velbanamine (18). ............... 70
Scheme 81: Alternative reduction attempts form lactam 302 to (±)-velbanamine (18).
............................................................................................................................................. 72
Scheme 82: Synthesis and reduction of compound 303.................................................... 72
Scheme 83: Synthesis of thioamide 305 by the use of Lawesson´s reagent. ................. 73
Scheme 84: Synthesis of lactam 309 and reduction attempts to provide amine 310.
............................................................................................................................................. 74
Scheme 85: Oxidation attempts of (±)-velbanamine (18) to (±)-dichomine (1)........... 75
Scheme 86: Retro-biomimetic oxidation of (±)-isovelbanamine (19)............................. 76
Scheme 87: Retro-biomimetic oxidation of (±)-20R-dihydro-cleavamine (17).......... 76

7.4. List of Tables

Table 1: Conditions for the reduction of pyridinium salt 178........................................ 39
Table 2: Conditions for the alkylation attempts between compound 180 and 181. ... 41
Table 3: Conditions for the aldol condensation reaction between compound 191 and 181. ................................................................. 42
Table 4: Conditions for the aldol reactions between compound 181 and 183. ....... 43
Table 5: Conditions for the Lewis acid mediated aldol reaction approach to compound 110. .................................................................................................................. 44
Table 6: Conditions for the allylation attempts of piperidone 183 with allyl bromide. 45
Table 7: Conditions for the enamine mediated side chain installation attempts. ...... 46
Table 8: Condition for the Wittig olefination attempts towards compound 214. ...... 48
Table 9: Conditions for the substitution attempts to amine 227. ......................... 50
Table 10: Conditions for the Staudinger mediated aziridine formation. ............... 51
Table 11: Conditions for the ring-opening, ring-closing reaction. ....................... 55
Table 12: Conditions for the 1,4-addition towards compound 269. ..................... 58
Table 13: Conditions for the derivatization attempts of the allylic alcohol. .......... 60
Table 14: Conditions for the one-step deprotection attempts. ................................ 62
Table 15: Conditions for the acylation reactions. .............................................. 62
Table 16: Conditions for the isomerization attempts towards acyl enamine 293. .... 65
Table 17: Reduction conditions to (±)-velbanamine (18) .................................... 71
Table 18: Conditions for the reduction of lactam 302. ...................................... 72
Table 19: Conditions for the lactam reduction to provide amine 310. ................. 74
Table 20: Conditions for the oxidation of (±)-velbanamine (18) ....................... 75

7.5. References

1 E. Roberts, Vegetable Materia Medica of India and Ceylon 1931, Colombo Plate, Colombo, p. 364.
5 S. M. Kupchan, A. Bright, E. Macko, J. Pharm. Sci. 1963, 52, 598-599.
123. T. A. van Beek, R. Verpoorte, A. B. Svendsen, Tetrahedron 1984, 40, 737-748.
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 Langzeitalborkollegen 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 Diskusisionen.

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).
Lebenslauf

Persönliche Daten:

Name: Christian Leitner
Geburtsdatum: 31.08.1982
Geburtsort: Zams, Österreich
Adresse: Rheingutstr. 30, 78462 Konstanz, Deutschland

Promotion 2012 – 2016:

Ich begann meine Doktorarbeit im November 2012 am Institut für organische Chemie der Leibniz Universität Hannover im Umfeld von Frau Prof. Dr. Tanja Gaich. Ziel meiner Arbeit ist die synthetische Darstellung des Naturstoffes Dichomine. Im Juli 2015 erfolgte der Umzug an die Universität Konstanz und darauf die Fertigstellung meiner Arbeit im Juli 2016.

Masterarbeit 2011 – 2012:


Bachelorarbeit 2010:

Meine Bachelorarbeit an der Universität Wien im Arbeitskreis von Prof. Dr. Michael Widhalm befasste sich mit der „Synthese von Bishydrasonliganden“. Schwerpunkt der Arbeit lag in der Synthese von Bishydrasonliganden zur Herstellung neuartiger Palladiumkomplexe für die asymmetrische Suzuki Biarylkupplung.

Studium:

2010-2012: Masterstudium an der Universität Wien (Abschluss mit ausgezeichnetem Erfolg)
2007-2010: Bachelorstudium an der Universität Wien
Berufserfahrung:


Präsenzdienst:


Schulbildung:


Zusätzliche Kenntnisse:

Sprachen: Englisch in Wort und Schrift (sehr gut)

Kurse: Teilnahme am „Promotion plus qualifiziert“ Programm der Graduierten Akademie der Universität Hannover. Dabei wurden Grundkenntnisse im Bereich Teamführung, Geschäftsstrategien, Personal und Projektmanagement vermittelt.

Computerkenntnisse: (sehr gut)

Word, Excel, Power Point, Chemdraw, Topspin, Rhinoceros, AutoCAD, Photoshop.