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Novel synthetic approaches to 3-oxo-γ-carbolines and highly substituted β-carbolines

Katharina Thees

aus

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Erklärung

Diese Dissertation wurde im Sinne von § 7 der Promotionsordnung vom 28. November 2011 von Herrn Prof. Dr. Franz Bracher von der Fakultät für Chemie und Pharmazie vertreten.

Eidesstattliche Versicherung

Diese Dissertation wurde eigenständig und ohne unerlaubte Hilfe erarbeitet.

München, 12.03.2024

…….

Katharina Thees

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Acknowledgements and Dedication

A special thank you goes to Prof. Dr. Franz Bracher, for the opportunity and chance to do my doctorate in his working group, for the skilled professional and other support in research matters, with scientific publications and in writing this dissertation.

Another big thank you goes to all members of the doctoral committee, especially Prof. Dr. Franz Paintner for carrying out the second correction of this work.

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Lastly, I would like to thank my loved ones, who always supported me unconditionally and in every possible way during the good and bad times of my studies and this doctorate. Thanks to them, the dream of studying and getting this doctorate finally became possible. This dissertation is thereby dedicated to my loved ones.

Publications

"Novel Approaches to 1,4-Disubstituted and 1-Substituted β-Carbolines via 3-Substituted 2-Acylindoles" - **European Journal of Organic Chemistry** (status “submitted”, 31 Jan 2024, submission number: ejoc.202400124)

A second paper about a new synthetic pathways to highly substituted 3-oxo-γ-carbolines is currently in preparation.

List of abbreviations

abbreviation	definition
°C	degree Celsius
^{13}C-NMR	carbon-13 nuclear magnetic resonance
^{1}H-NMR	proton nuclear magnetic resonance
Å	Angstrom
alk/Alk	alkyl
ATR	attenuated total reflection
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
CDI	1,1'-carbonyldiimidazole
CI	chemical ionization
COSY	COSY (correlated spectroscopy)
d	doublet
D	deuterium
DBU	1,8-Diazabicyclo(5.4.0)undec-7-ene
DCM	dichloromethane
DCM	dichloromethane
DEPT	distortionless enhancement by polarization transfer (NMR)
DLP	dilauroyl peroxide
DMAC	*N*,*N*-dimethylacetamide
DMF	dimethylformamide
DMF-DMA	dimethyl formamide diethyl acetal
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DNA	deoxyribonucleic acid
dt	tripplett of doublett
$E_{1,2}$ or E_i	elimination (E_1 or E_i) mechanisms
EI	electron ionization
equiv./eq.	equivalent
ESI	electrospray ionization
Et	ethyl
et al.	et alii (and others)
Et	ethyl
EWG	electron withdrawing group
g	grams
GC	gas chromatography
h	hour
H_2O_d	destilled water
Hal / X	halogene residue / halo-
HATU	1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate
$HCl_{conc.}$	concentrated hydrochloric acid
HMBC	heteronuclear multiple bond correlation

HMQC	heteronuclear multiple quantum coherence
HPLC	high performance liquid chromatography
HPLC-MS	high performance liquid chromatography coupled with mass spectrometry
HRMS	high resolution mass spectrometry
Hz	hertz
IR	infra-red
J	coupling constant
KEX	potassium ethyl xanthogenate
KOtBu	potassium *tert*-butoxide
kV	kilovolt
L	liter
LAH	lithium aluminium hydride
LSD	lysine demethylase
m	multiplet
M	molar
m-	*meta*-
M.p.	melting point
m/z	mass-to-charge ration
Me	methyl
$Me_2NCH(OEt)_2$	Bredereck's reagent
mg	milligram
MHz	megahertz
min	minute
mol	mole
MS	mass spectrometry
MW	synthesis microwave reactor (method)
NBS	*N*-bromosuccinimide
n-BuLi	*n*-butyllithium
NER	nucleotide excision repair
NMR	nuclear magnetic resonance
o-	*ortho*-
$^{-}$OtBu	*tert-butoxide*
p-	*para*-
PG	protective group
Ph	phenyl
ppm	parts per million
q	quartet
R	residue
r.t./rt	room temperature
s	singulet
SEM-Cl	2-(trimethylsilyl)-ethoxymethyl chloride
S_N	nucleophilic substitution (S_N1 or S_N2)
t	tripplet
TBAB	tetrabutylammonium bromide
TEA / Et_3N / NEt_3	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran

TLC	thin layer chromatography
TLC-MS (TLC/CMS)	TLC-MS (TLC/CMS) analysis
TMDS	1,1,3,3-tetramethyldisiloxane
TMS	tetramethyl silane
UV	ultra violet (light / spectrum)
V	volt
W	watt
Z or *E*	*Z* and *E* isomers
δ	chemical shifts in parts per million
λ	wavelength
µg	microgram
µM	micromolar
ν	wavenumber

Table of contents

1 Introduction

1.1 XPD helicase as potential target in the treatment of cancer

DNA repair and binding proteins, like the XPD helicase, have become increasingly important as potential targets to treat cancer.[1] Human XPD mutations are associated with several inherited diseases such as Cockayne syndrome, xeroderma pigmentosum or trichothiodystrophy[2] or cancer[3]. As shown in Figure 1, the XPD helicase is part of a 10 subunits (XPB, XPD, p62, p52, p44, p34, p8, CDK7, Cyclin H and MAT1) containing protein complex named TFIIH, which plays an essential role in transcription processes (by RNA polymerase II) and the nucleotide excision repair (NER), that are two fundamental mechanisms in the area of DNA damage repair.[1-2]

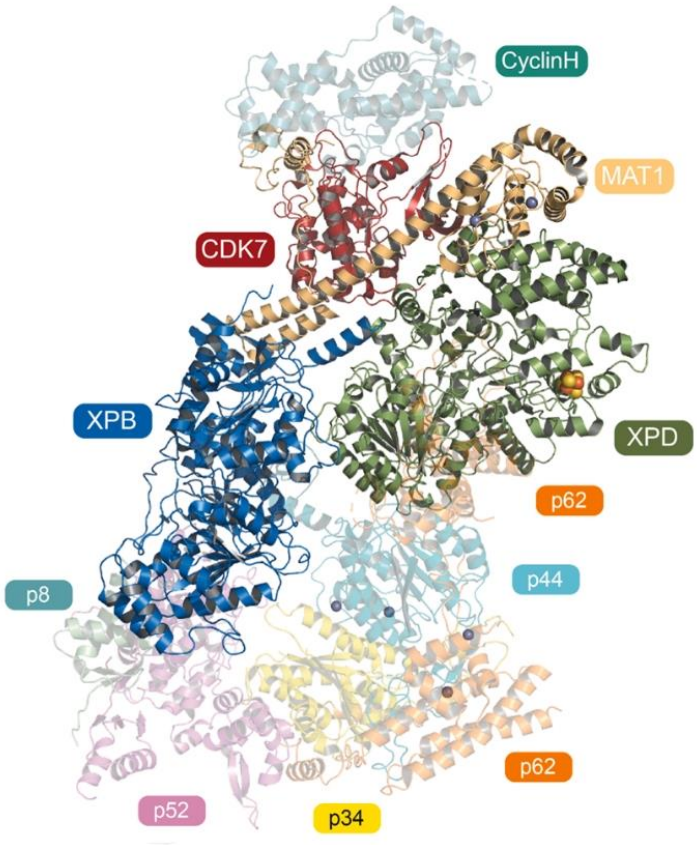


Figure 1: XPD helicase as part of the 10 subunits (XPB, XPD, p62, p52, p44, p34, p8, CDK7, Cyclin H and MAT1), the TFIIH complex consists of. (The 4Fe4S cluster in the XPD and the Zn atoms in p44 and p62 are shown as spheres.)[1]

The TFIIH fulfils several functions in the repair cascade as for example verifying the presence of lesions and takes part in the recruitment of other repair factors, like nucleases, which are required to excise the damage.[1] The TFIIH harbours three enzymatic activities, originating from the subunits CDK7 kinase, the XPB translocase, and the XPD helicase that all exert different impacts on the activities of the TFIIH complex.[1] While the CDK7 kinase is deeply and only involved in the transcription mechanism and the XPB translocase is involved in the transcription and the NER

mechanisms, the XPD solely takes part in the NER mechanism.[1] Due to the involvement in these two essential functions, the transcription and the NER, the TFIIH complex has become increasingly interesting as potential target for cancer therapies in the last few years, as already earlier stated.[1] Within the TFIIH complex, the XPD helicase functions as bridging factor between the core (consists of XPB, XPD, p62, p52, p44, p34, p8) and the CAK complex (containing CDK7, Cyclin H and MAT1).[1] The dissociation of the CAK module of the core TFIIH activates the XPD for the repair process.[1] In reality, the NER (initiation) process is more complicated of course, and all the specific subunits take a certain place in the mechanism. However, due to simplification reasons the specific subsequent processes are not elaborated further in this work. If anyone is interested in all specific functions of all the subunits that take part in the TFIIH induced NER cascade, the details are elaborated in the works[1-2, 4-6] of Prof. Dr. Kisker and co-workers, only to name a few examples of accompanying literature. *In vivo* and *in vitro* studies have recently shown, that mutations in the XPD's 4Fe4S cluster domains lead to inactivation of the NER function of the TFIIH function but did not impair the activity of the transcription processes, proving not only that the XPD has no active role in the transcription, but also that it can be inhibited without deactivating or even decreasing the TFIIH's transcriptional activities.[2] The XPD helicase, in conclusion, might represent a potential and very interesting target within the TFIIH that can be used to exclusively interfere with the NER, as potential means to treat cancer.[1] But how might we now treat cancer through interfering with the NER? Somatic tumour mutations which an inactivated XPD helicase function showed a positive response during cisplatin treatment in urothelial cancer[1, 7-8], which lead to the idea that XPD helicase inhibitors could open up new combinatorial treatment options to increase the success rate of the DNA interacting drugs, like for example platinum-based treatments. Cisplatin and it's successors have been successfully used in cancer treatment therapies for decades. However, apart from having severe side effects, there is another significant drawback of this drug class, which is the increasing drug resistance as consequence of each treatment cycle. Cisplatin, as a prodrug, is activated after entering the cell through the exchange of one chloro ligand to a H_2O ligand, turning the drug into a reactive water species (see Figure 2).[9] After entering the cell nucleus, the activated aqua platinum species preferentially forms intrastrand or interstrand bis-adducts with the DNA, while the preferred complexated position is the N-7 of guanine.[9] The difference between a healthy cell and a malignant cell is now, that the healthy cell can usually repair this type of drug induced damage, while a malignant cell would commit suicide. Technically this cellular process is called apoptosis. Potential reasons for an increasing drug resistance of tumour cells with an increasing number of treatment cycle can be loss of DNA mismatch repair, bypassing DNA adducts or a decrease in apoptosis of the tumour cells and tissue (see Figure 2 again).[9]

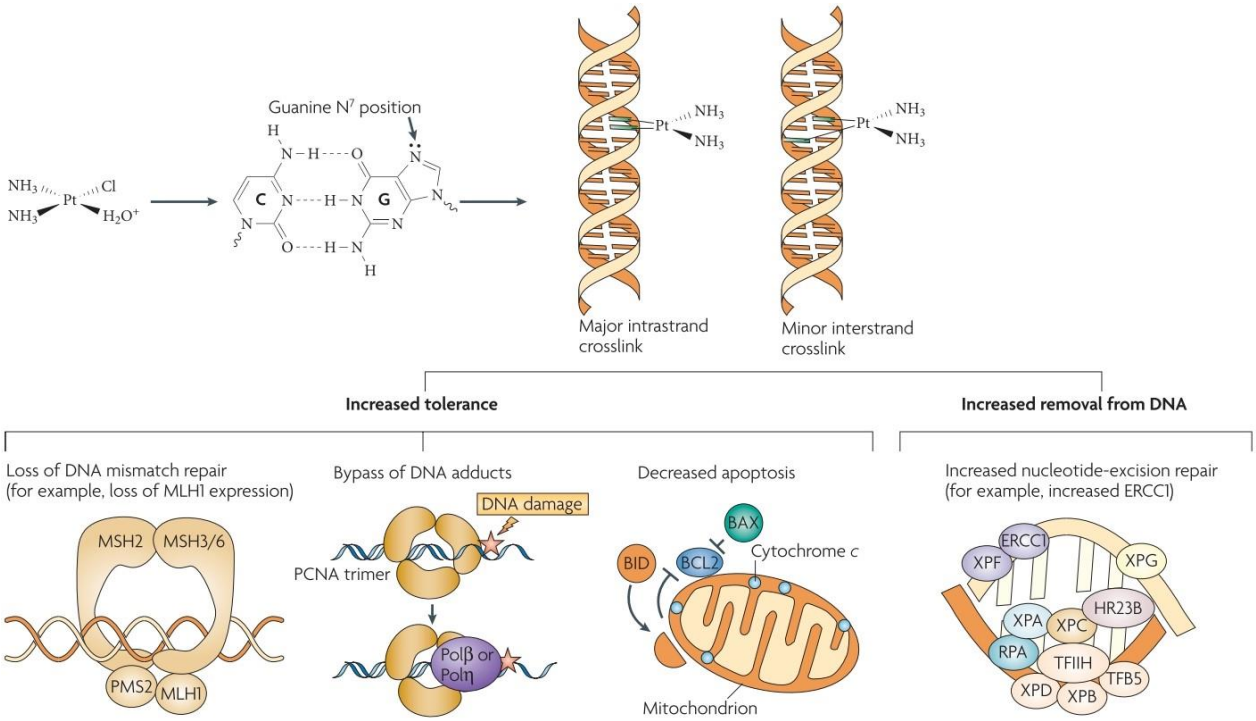
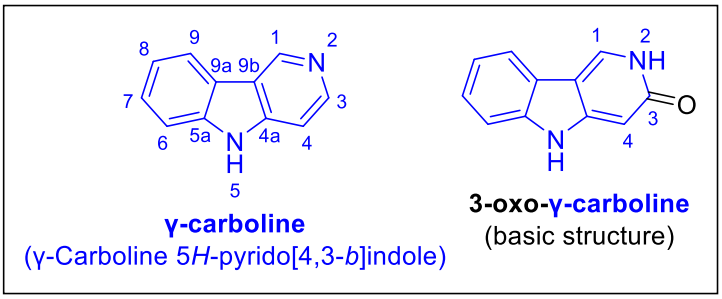


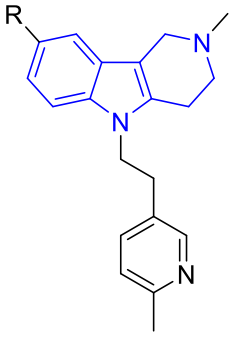
Figure 2: Cisplatin and it's successors' mechanism of action and the common mechanisms for developing a drug resistance with each additional treatment cycle.[9]

Why though is there a decrease in apoptosis of the tumour cells with the rising number of treatment cycles? The main repair mode for the DNA adducts is the NER, for which the activity can increase in tumour cells that consequently leads to an increased capability to repair DNA damages/lesions over time a – or differently phrased, in a drug resistance.[9] The activity of the NER is presumably increased as means to adapt to the repeated treatment cycles. Of course, if one could deactivate the NER during the treatments, the cells could not adapt and thereby the increasing drug resistance might probably be overcome - to get back to the topic of developing XPD helicase inhibitors!

1.2 The importance of γ-carbolines for pharmaceutical purposes and recent strategies for the synthesis of 3-oxo-γ-carbolines and their hyrogenated analogues

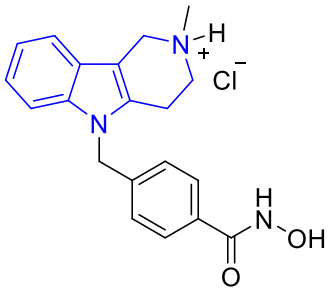
In the last few years, variously functionalised γ-carbolines (pyrido[4,3-*b*]indoles), dihydro-γ-carbolines, tetrahydro-γ-carbolines and other structure analogues have been subjects of research for treating pain[10], nausea[10], neurolepsy[10-11], allergies[11-13], Huntingtons' disease[14], cardiovascular[10-13] or Alzheimer's disease[10-12, 15], mental illness[11-13], irritable bowel syndrome (IBS)[10, 16-17], viral infections[13, 18-19] caused by for example Bovine Viral Diarrhea Virus (BVDV)[13, 19] or Herpes simplex type I virus[18], epigenetic targets[12], cancer[12, 18, 20], bacterial/fungal infections[21] and others[10].



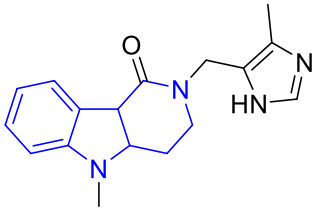


Dimebon (R = Me) (antihistamine)
Dorastine (R = Cl) (antiallergic)

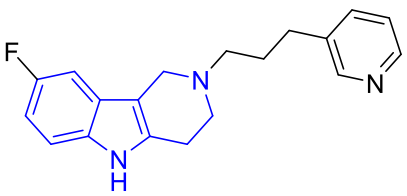
SK3M4M5M
(anti-BVDV activity,
EC_{50}: 0.0035 μM
Aoyama et al. (2009))



Tubastatin A hydrochloride
(HDAC6 inhibitor)



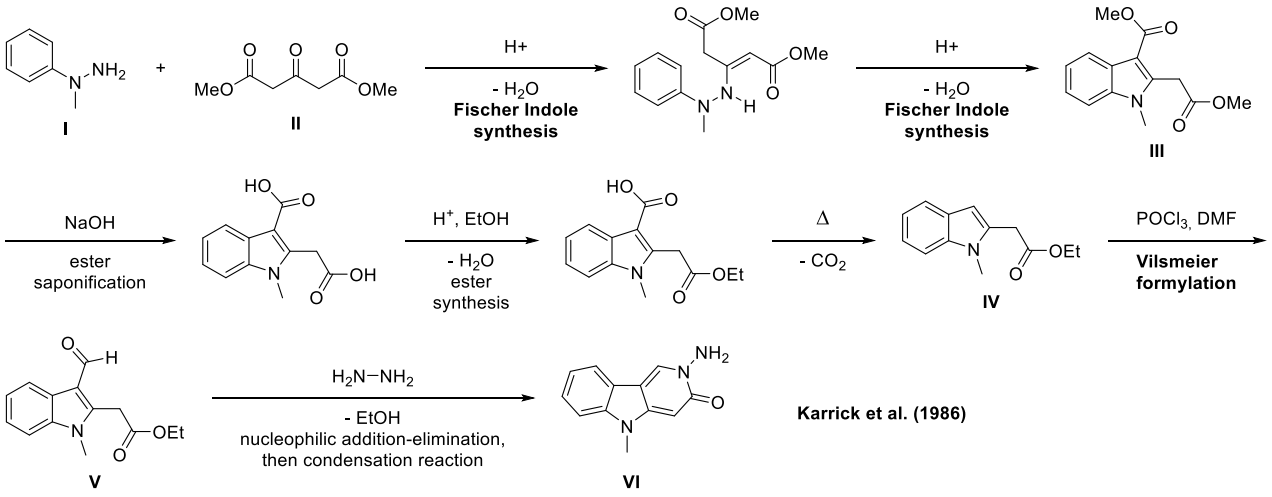
Alosetron, trading name: **Lotronex®**
(USA, Prometheus Laboratories Inc.;
irritable bowel syndrome (IBS))



Gevotroline (antipsychotic)

Figure 3: Potential applications for γ-carboline drugs - a few examples.[12-13, 16, 18-19]

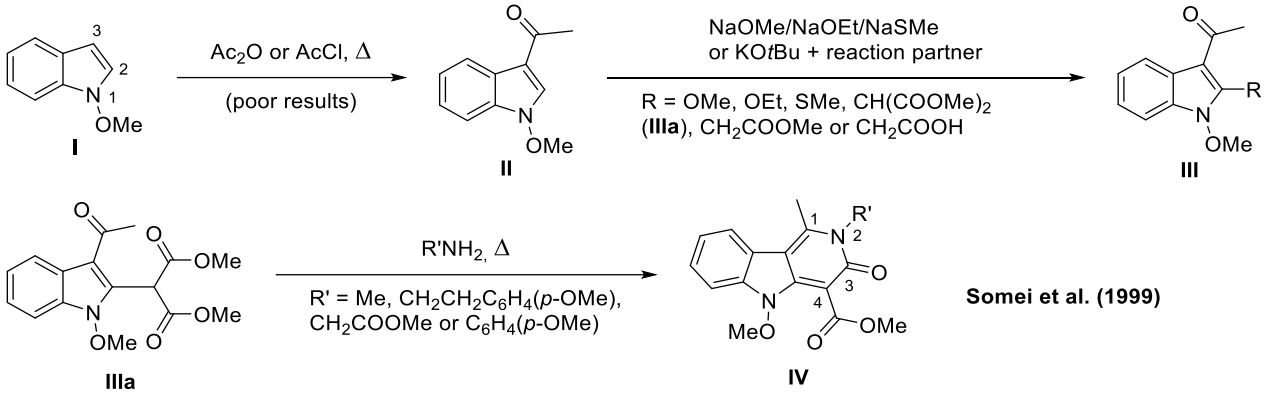
As shown in Figure 3, certain representatives have already been used in the treatment of patients, like the antihistamine drug Dimebon, which in Russia has been an approved drug against allergies since 1983[12, 14] or Alosetron (Lotronex®) which has been on the US market for years to treat the irritable bowel syndrome (IBS)[14, 15]. Dorastine also has shown potential in investigations as antiallergic while Gevotroline showed interesting results as potential antipsychotic drug.[11-13] Further, Dimebon has been investigated to be used in cardiovascular and neural systems treatment[12-14] and also showed inhibition of NMDA (*N*-methyl-D-asparate), acetylcholine-esterase (ACE), butyrylcholinesterase (BuCE) and proved to be a potent calcium-channel blocker in in vitro tests[22]. Tubastatin A in comparison, has been known to be a very potent histone deacetylase 6 inhibitor (HDAC6) for years.[12, 23] Aoyama et al.[19] have published results in 2009 that showed that SK3M4M5M (and other alkylated γ-carbolines), which were tested for efficacy against the BVDV (Anti-Bovine Viral Diarrhea Virus), showed very high anti-BVDV activity.[19] The last six substances are still subject of current investigations. Because of this broad spectrum of potential therapeutic applications, the importance of γ-carbolines for scientific research has increased steadily over the last years[13], compared to their β-carboline analogues, they are much less well studied though[24]. The substance class 3-oxo-γ-carbolines, also shown in Figure 3, will play a significant role in this work, therefore there is to be given some information about the current state of science about this specific subclass, especially concerning biological studies and chemical developments of the last years. However, the scientific review presented in this chapter should only give an overview over the, for this work, most important methods. Therefore, in the following only the most relevant examples are given.



Scheme 1: The first interesting total synthesis of a 3-oxo-γ-carboline, which was published in 1986.[25]

Until now and as far as is known to us, 3-oxo-γ-carbolines have not been heavily applied in drug therapy until today. This may be the case because until now, they have been synthetically poorly available.[21] Therefore, and as far as is known to us, there is also not very much known about the substance class in general. One of the most interesting pieces of literature was already published

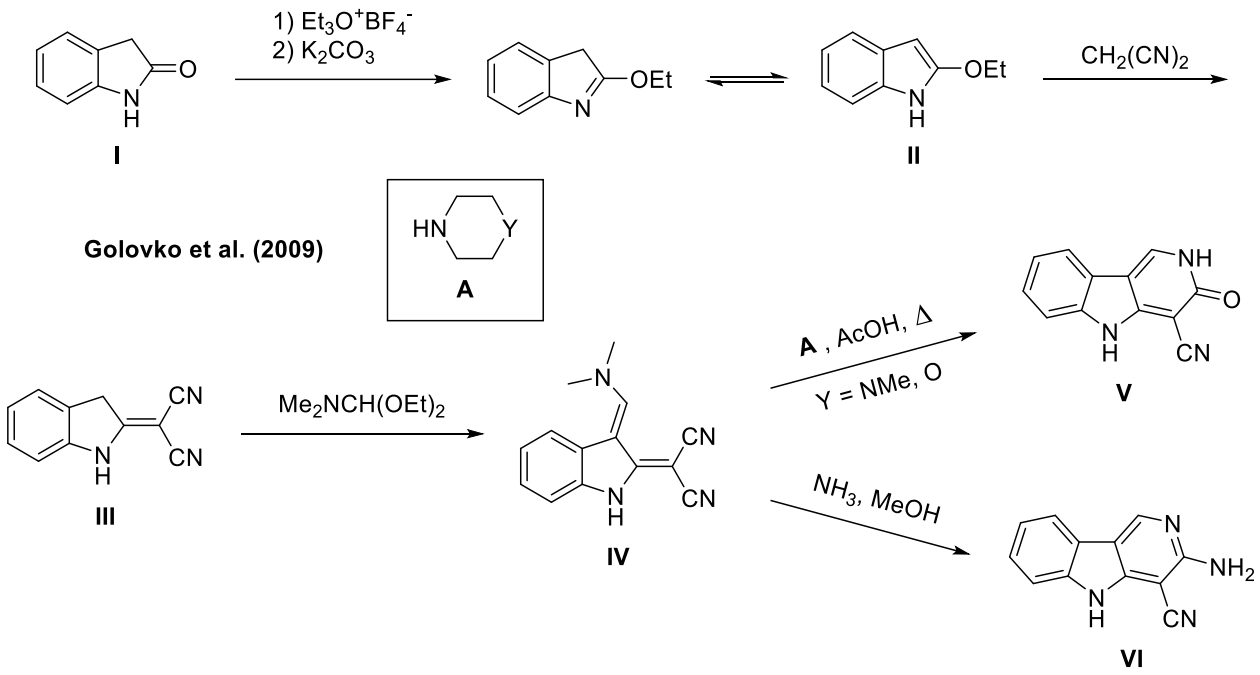
in 1986 by Karrick et al.[25] (see Scheme 1). They started the synthesis by building up the indole starting from a phenylhydrazine **I** and achieved the indole construction through the classical Fischer indole synthesis using the ketodiester **II**.[25] Deriving from **II**, through ester saponification, consecutive esterification and then decarboxylation they managed to obtain the C-3 unsubstituted indole **IV**.[25] Formylation of **IV** in a Vilsmeier reaction provided the aldehyde **V**.[25] Finally, the 3-oxo-γ-carboline **VI** could be obtained as a result of an addition-elimination-condensation cascade reaction.[25] Although this was surely an efficient method already, using already well known chemistry, the preparation way though surely suffered from lack of easy accessibility of differently functionalised ketodiesters (of type **II**), the insufficient chemoselectivity during the ester synthesis step and further problems. As shown Scheme 2, in the year 1999, Somei et al.[26] published a quite easy way to synthesise 1,4-disubstituted 3-oxo-γ-carbolines already starting from the *N*-substituted indole **I**.[26] They prepared **II** from **I** in an acylation reaction and proceeded with a nucleophilic substitution reaction under strong basic conditions to generate 2,3-disubstituted indoles of the type **III**.[26]



Scheme 2: Somei et al.'s method to synthesise 1,4-disubstituted 3-oxo-γ-carbolines starting from an *N*-substituted indole.[26]

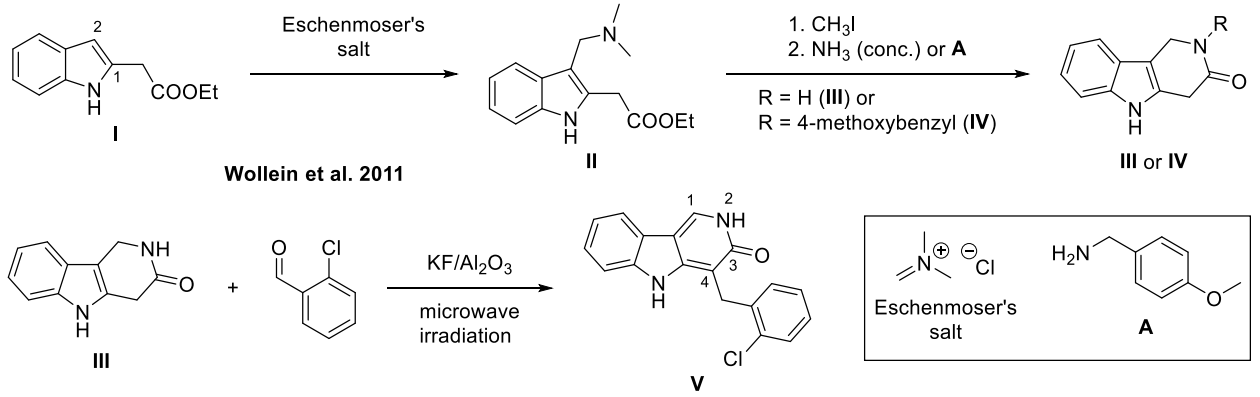
From **IIIa**, they managed to generate differntly 2-*N* substituted 1,4-disubstituted 3-oxo-γ-carbolines of the type **IV**.[26] Again, this seemed to be a neat method for synthesising multi-substituted 3-oxo-γ-carbolines, however when they exchanged the 2-acetyl group for other substituents, the following step (second synthesis step in Scheme 2) couldn't be reproduced successfully.[26] The next really interesting work in that substance class appeared not until ten years later, when Golovko et al.[27] managed to synthesise a 4-nitrile substituted 3-oxo-γ-carboline **V**, starting from oxindole **I** (2-indolone)[27], as schematically imaged in Scheme 3.[27] This impressively simple method shows, that it is possible to generate a 4-substituted 3-oxo-γ-carboline in only four steps.[27] Starting from **I**, they managed to transform the lactam group to 2-ethoxy-3*H*-indole which tautomerizes to the 1*H*-indole derivative **II**, that was further reacted with malononitrile, in the second synthesis step, to **III**.[27] From there they substituted the hydrogen with an enamine group using DMF-DMA (dimethyl formamide diethyl acetal or $Me_2NCH(OEt)_2$).[27] Finally, using acetic acid

and **A** (see Scheme 3) they reportedly succeeded in the preparation of **V**, while using ammonia in methanol brought the 3-amino 4-nitrile substituted γ-carboline **VI**.[27]



Scheme 3: Golovko et al.[27]'s method to synthesise 4-nitrile substituted 3-oxo-γ-carbolines starting from oxindole **I** (2-indolone).[27]

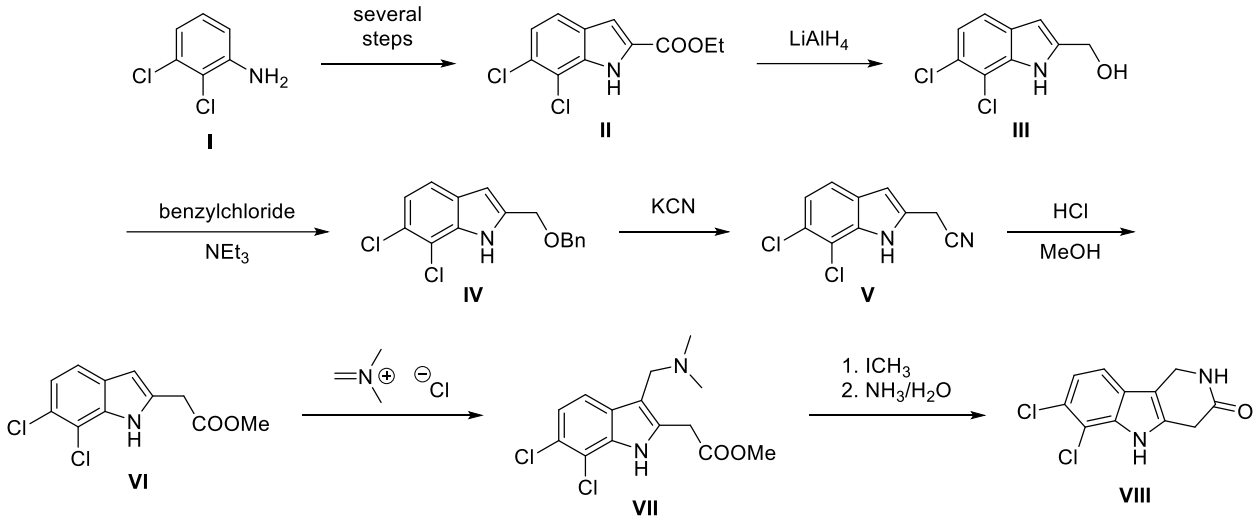
One of the, for this work, most mentionable preliminary works were dealt with by Dr. Uwe Wollein in the Bracher group, whose research inspired the research project, which has been worked on for this thesis.



Scheme 4: Dr. Wollein's work on 3-oxo-γ-carbolines.[21]

As shown in Scheme 4, Wollein as the first did try to introduce more complex substituents onto this molecular structure (**V**), at the C-4 to be exact.[21] starting from the indole ester **I**, he used the Eschenmoser salt to gain the gramine analogue **II**.[21] Then in the second reaction step, he generated a leaving group from the *N*,*N*-dimethylamine group by *N*-methylation and through the addition of an amine of choice, he gained the elimination- addition cascade products **III** or **IV**.[21]

Using educt **III** in the following reaction, he claimed to have obtained the desired product **V** through reacting it with 2-chlorobenzaldehyde and KF/Al_2O_3 under microwave irradiation.[21] As intriguing as this approach is, this approach only would in theory allow us to introduce substituents on C-4 of the 3-oxo-γ-carboline and to anticipate that, we wanted to develop a more flexible approach, which would allow us to variate the structure also in the C-1 position of **V** eventually. Also, the educt ester **I**, from our earlier experience, cannot be easily achieved and it is further to mention, that every single step of Wollein's total synthesis did not produce a higher than fair yield at best[21], which is not bad, but might still be improved if the synthesis approach is changed. One other relevant preliminary research was processed by Dr. Anne Wurzlbauer. In her dissertation in the Bracher group, she worked on the total synthesis of substance **VIII** (see Scheme 5), starting from 2,3-dichloroaniline (**I**).[20]

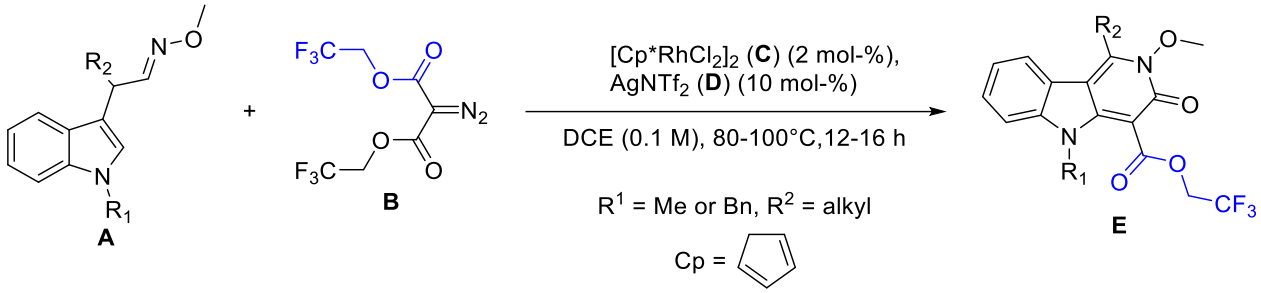


Scheme 5: Dr. Wurzlbauer's approach to substance **VIII**.[20]

Wurzlbauer prepared the C-2 substituted indole **II** from **I**, reduced it using lithium aluminium hydride ($LiAlH_4$) to the primary alcohol **III** and performed activation of the alcohol group through tranforming it into the benzyl ether **IV**.[20] Statring from **IV**, in an S_N reaction using KCN, **IV** was transposed to the nitrile **V**, which again was transformed to ester **VI** in an acidified methanol solution.[20] From there, the Eschenmoser salt enabled the introduction of the $-CH_2N(CH_3)_2$ group on the C-3 of the indole to obtain **VII**.[20] The successive addition of CH_3I and then concentrated ammonia solution induced the ring closure reaction to **VIII**.[20] Until the practical work started which is represented in this thesis, the for this project and in my perspective really relevant last work in this synthetic field was published by that Dr. Wurzlbauer. Later, in 2018 a piece of literature appeared after the beginning of my work with this project, which are also quite interesting as well. Since the work of Biswas et al.[28] (2018) had not been published at the time when I started to work on this project (2016), my research was not influenced through their work, but might maybe influence future researches and is therefore as a last method mentioned in the following. This was

the newest of all relevant found methods and it was published by Biswas et al.[28] in 2018. They performed experiments with the Rhodium(III) catalysts $[CpRhCl_2]_2$ (**C**) in combination with a silver bis(trifluoromethanesulfonyl)imide (**D**) additive, transforming 1,3-disubstituted indoles of the type **A** in the presence of bis(2,2,2-trifluoroethyl) 2-diazomalonate (**B**) to 1,2,4-trisubstituted 3-oxo-γ-carbolines in the style of **E** (see Scheme 6).[28]

Biswas et al. (2018):

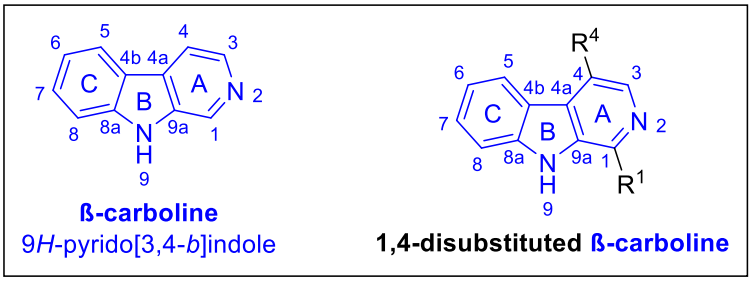


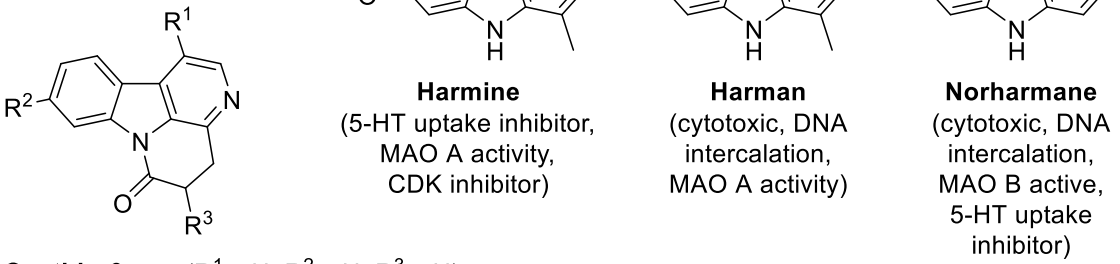
Scheme 6: The approach published by Biswas et al.[28] (2018).

All in all, it is to mention that all earlier published methods lacked either the accessibility of a satisfying variety of purchasable precursors, were to restricted with the importability of certain functional groups, or were simply inefficient when it came to the number of steps required to obtain the desired 3-oxo-γ-carbolines. Having not much literature to build up on, the opportunity presented itself to start from scratch with the synthesis route development.

1.3 β-Carbolines and their area of application & 1,4-disubstituted β-carbolines, their (potential) targets and recent synthesis strategies for their total synthesis

The total syntheses of β-carboline alkaloids and their efficacy for a variety of targets have been topic of research for decades now. β-Carbolines are natural substances, that in nature can be found in marine invertebrates[29], various plants[29] and mammals[29] including humans[30]. β-Carbolines have been in research to develop drugs for the treatment of cancer[31-35], reactive oxygen species induced illnesses[34], depressions[31, 33, 35-37], anxiety[35], muscular tension[37], Parkinson's disease (PD)[36], Alzheimer's disease[32-33], diabetes[33], inflammation[32-33], parasites and microbe infestation[31-33], HIV[31-32, 35], malaria[32]. Harmine alone (see Figure 4) not only showed efficacy against inflammation, Alzheimer's disease, diabetes, but also proved to be a potent several disease-relevant protein kinases (PLK, Haspin, DYRK1A) inhibitor and monoamine oxidase A (MAO A) inhibitor.[33]





Canthin-6-one (R^1 = H, R^2 = H, R^3 = H)
(cytotoxicity agains breast/lung/colon, cancer, lymphocytic leukemia)
1-Methoxycanthin-one (R^1=OCH_3 R^2=H R^3=H)
cytotoxicities against HCT-8, SK-MEL-2, CAK-1, KB, A 549, MCF-7
5-Methoxycanthin-one (R^1=H R^2=H R^3=OCH^3)
cytotoxicities against HCT-8, SK-MEL-2, CAK-1, KB, A 549, MCF-7

Figure 4: A few examples of natural occurring biological and pharmacological active β-carbolines.[36, 38-39]

Prof. Dr. Bracher (LMU Munich, Department of Pharmacy, Centre for Drug Research) and co-workers are specialized in the field of total synthesis of β- and γ-carbolines for many years now. There are already some known syntheses for multi-substituted β-carbolines published, and since over the last years my colleagues tended intensively to the development of total syntheses of

1-/3-/4-monosubstituted and 1,3-disubstututed β-carbolines – for their research outcomes see the PhD theses and publications of Dr. Martin Untergehrer[40-41], Dr. Alexandra Kamlah[31, 33, 38], Dr. Tim Tremmel[42], Dr. Anne Wurzlbauer[20] and the Bachelor Thesis of David Leix[43] – and out of this reason the history of the total syntheses of those will not be taken a look at in the introduction chapters of this work. However, since one of two main goals of this work was the development of a synthesis approach to 1,4-disubstituted β-carbolines, a history of their preparation methods which appeared over the last decades is given in the following. From what can be observed over the years, the common approach to build up the β-carbolines was originating from anilines or in nature pre-existing indole-based structures like tryptamines or tryptophanes[31, 33] for which a certain variety of natural analogues already exist (for a few examples see Figure 5). Since both molecule classes are popular precursors, by now a large quantity of artificial analogues are also available for purchase online.

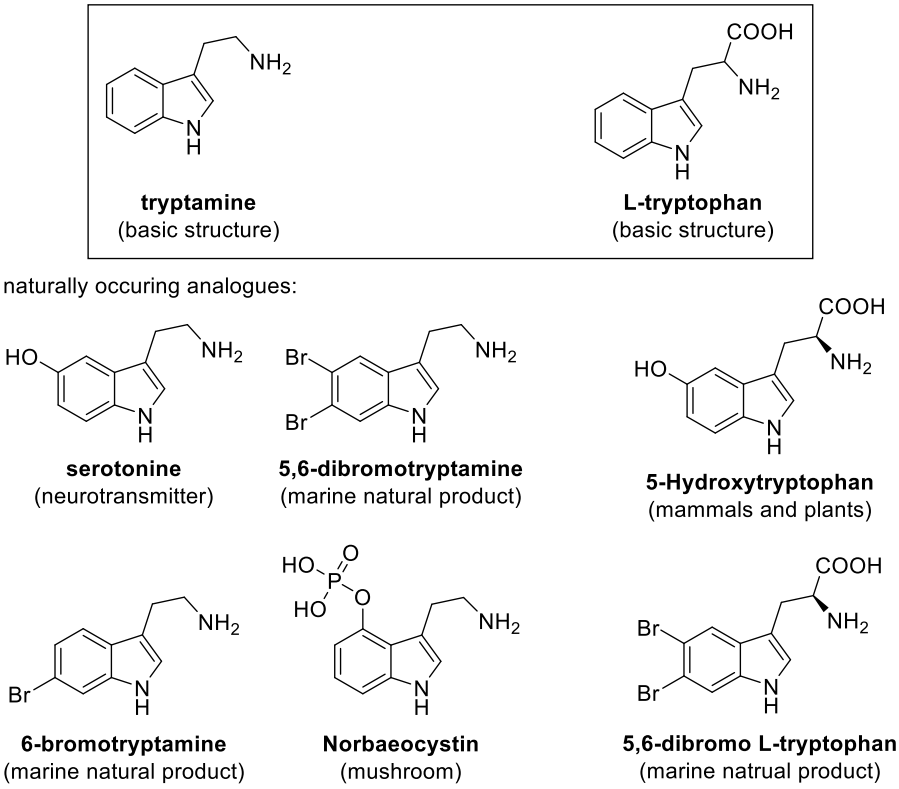
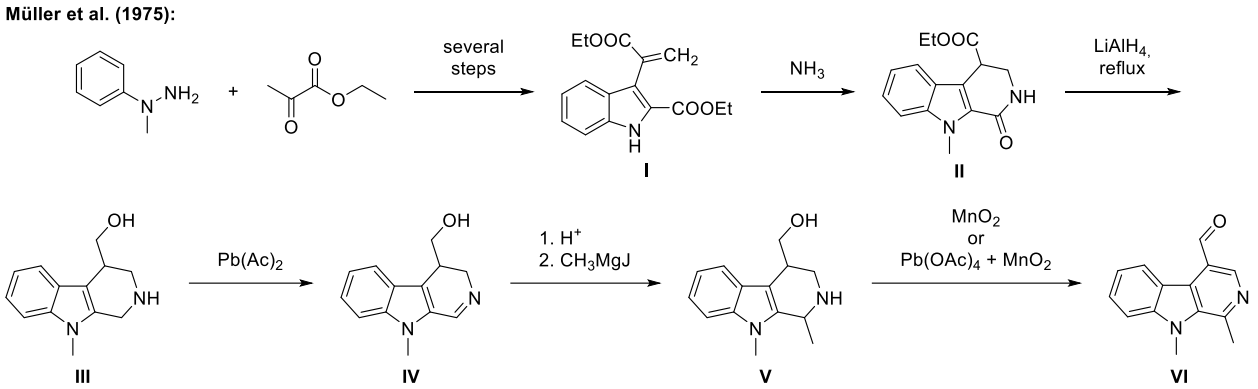


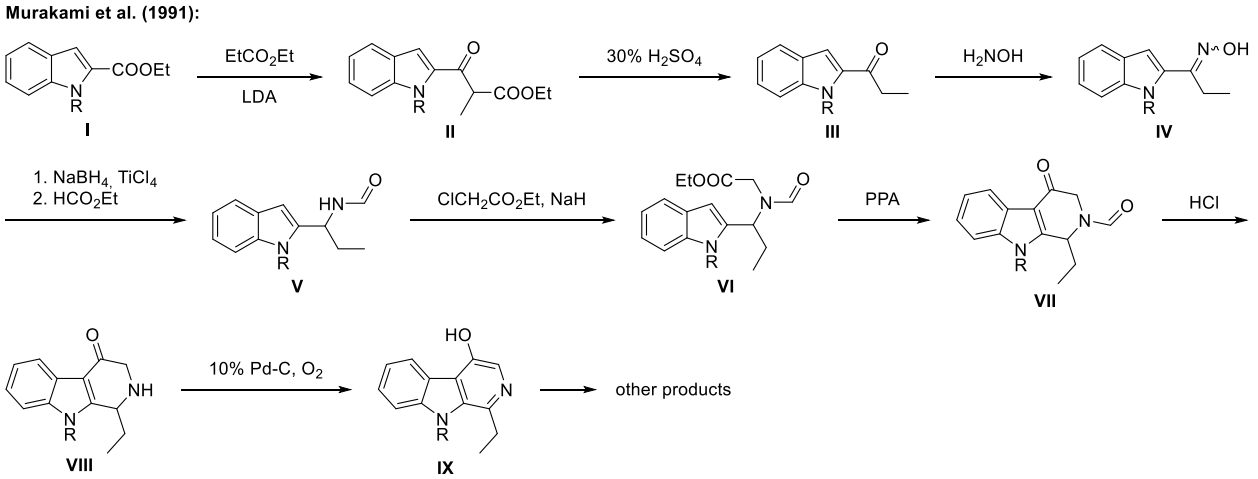
Figure 5: Tryptamine and L-tryptophan and a few examples of naturally occurring analogues.[44-46]

Since we, to pre-empt that, wanted to also be able to flexibly introduce substituents on the C-ring of the β-carboline (see Figure 4), we rather wanted to focus on the total syntheses starting from anilines or derivatives. But it was still important to know how other researchers build up the 1,4-disubstituted β-carboline. In the following, of course only an extract of the most interesting syntheses is given which appeared over the years.



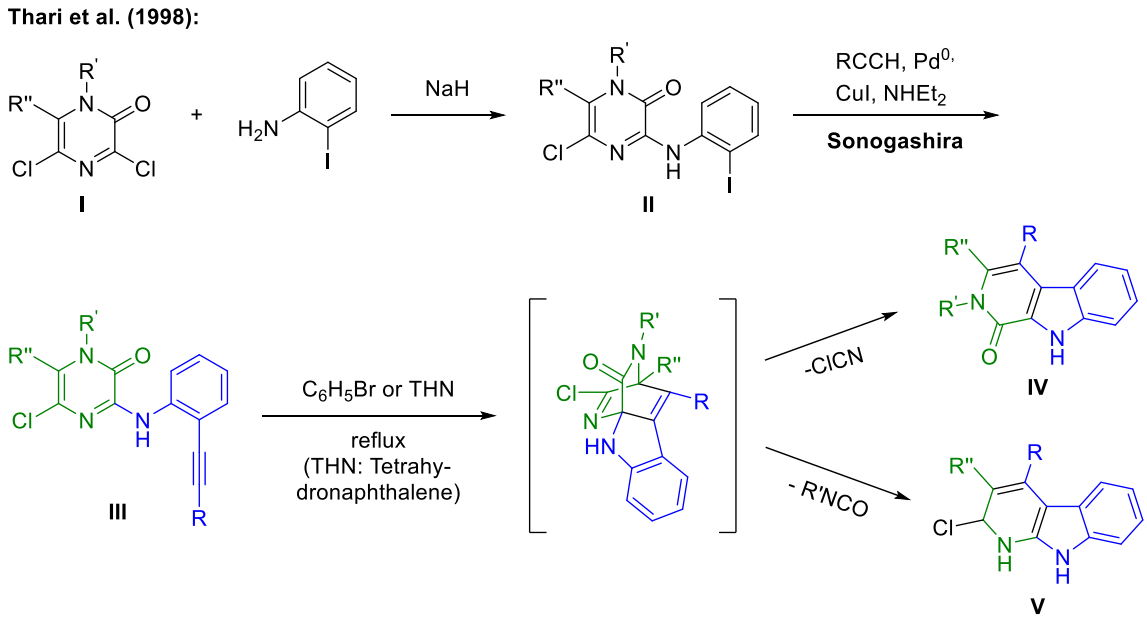
Scheme 7: Müller et al.[47]'s approach for the total synthesis of 1,4-disubstituted β-carbolines.[47]

The first really interesting synthesis appeared already in 1975 (see Scheme 7). The approach of Müller et al.[47] originated from a arylhydrazine and ethyl pyruvate, which in the first step in a Fischer-Indole synthesis and a subsequent condensation with another molecule ethyl pyruvate yielded the 2,3-disubstituted indole **I**.[47] The addition of ammonia induced a nucleophilic addition-elimination cascade, followed by a sigmatropic rearrangement that brought lactam **II**.[47] Using $LiAlH_4$, the ester and lactam moieties were reduced and through the usage of the oxidation agent $Pb(OAc)_2$, the dihydropyridine **IV** was allegedly obtained.[47] The residue later to become the 4-position substituent could very late in the synthesis be introduced through a Grignard reagent, which brought **V**.[47] The usage of oxidation agents in the last step, not only oxidised the alcohol group, but also aromatised the tetrahydropyridine (A-ring) to yield the fully aromatic β-carboline derivative **VI**.[47] This method in general has the drawback that through using the Grignard rection as means to introduce the residue on the C-4 of the β-carboline is, although the obvious choice at that point, not really the most fitting choice of reaction when it comes to tolerating a variety of functional groups which we, for our project ideas, would want the reaction to tolerate later.



Scheme 8: Murakami et al.[34] published an alternative method to prepare 1,4-disubstituted β-carbolines (R = Bn, Me, H).[34]

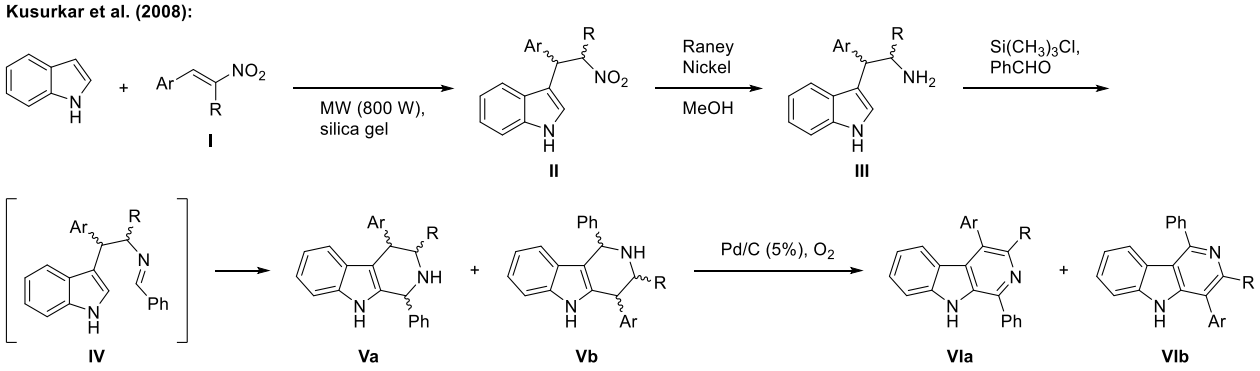
Since this was not a fitting method for our project, which is of course elaborated later in the synthesis planning chapters, we searched further for ideas. Murakami et al.[34], see Scheme 8, published a method a few years later in which 1,4-disubstituted β-carbolines of the type **IX** were prepared in six steps from 2-acylindoles of the type **III**, which themselves could be prepared in two steps from indole-2-carboxylates of the type **I**.[34] Ketones **III** were condensed with hydroxylamine to give oximes of type **IV**, which in the next step were reduced and in-situ reacted with ethyl formate to yield formamides of the type **V**.[34] After *N*-carboxymethylation to generate **VI**, in the next reaction step PPA (polyphosphoric acid) induced the cyclisation to **VII**.[34] Hydrochloric acid catalysed hydrolysis of **VII** gave the secondary amines of the type **VIII**, which could then be aromatised through Pd-C (and air) to yield 1,4-disubstituted β-carbolines of the type **IX**.[34] From there they modified **IX** further[34], but since these following proceedings are irrelevant for our purposes, I'm not going to elaborate further. This total synthesis appears really uncomplicated; however, the for **IX** C-1 alkyl substituent is very early introduced and appears not be varied easily. The C-4 substituent can only turn out to be a ketone or a hydroxy group, since the ester group and its chemical properties (of substance **VI**) is highly relevant for the A-ring formation, therefore **IX** could would always turn out to have a hydroxy- or keto group in position 4.



Scheme 9: The method of Thari et al. [37] to synthesise 1,4-disubstituted β-carbolines (R' = Ph, Bn; R'' = H, Me, Ph; R = TMS, Ph).[37]

One completely different approach piqued my interest since it, as a rare exception, started with the construction of the A-ring.[37] As imaged in Scheme 9, Thari et al.[37] showed, that starting from pyrazinones of the type **I**, which were coupled to 2-iodoaniline through a strong base to yield substances of type **II**, could in the following Sonogashira reaction (using an alkyne) be transformed to **III**. [37] In turn **III**, when refluxed with bromobenzene or THN (tetrahydronaphthalene) and under

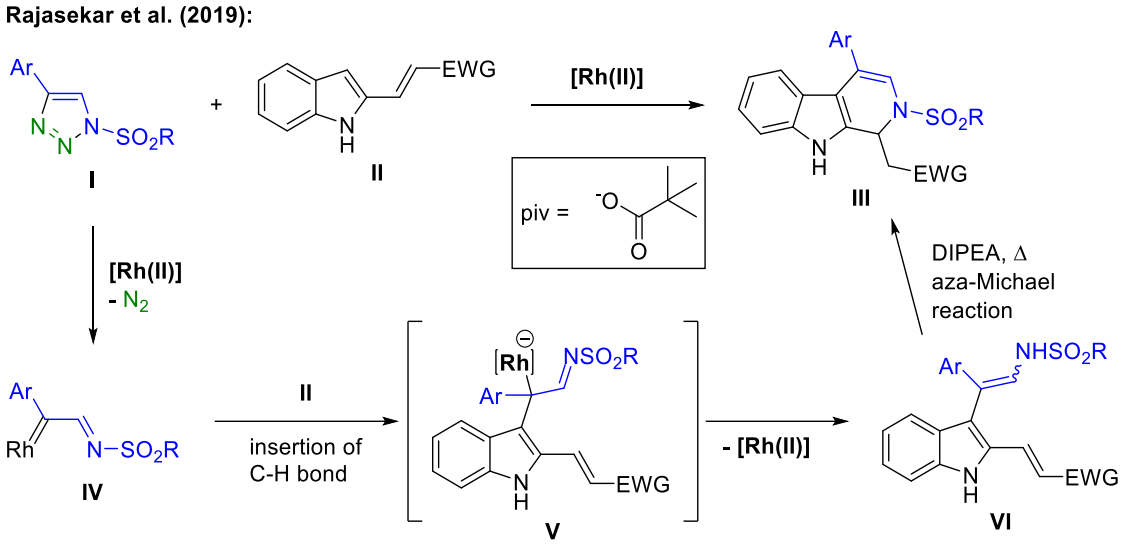
the secretion of chlorocyanide had delivered 1-oxo 2-4 variously functionalised β-carbolines **IV** as [4+2]-cycloaddition products, depending on the residues R',R'' and R of course.[37] Although this was a very interesting and only four preparation steps approach, in this paper no general preparation method is described for the preparation of the pyrazinones **I**. [37] Estimated, that these might not be easily synthetically accessible or purchasable in a huge variety, this might be one major drawback of this method. The other major drawback of this method is, that apart from the desired multi-substituted β-carbolines, in most of the reactions, α-carbolines of the type **V** were nearly always isolated after each reaction, in some cases with a side-product yield of over 50%, telling us, that in case the functional residues R, R' and R'' were altered, products of the type **V** instead of **IV** might become the major products for the last reaction step, which renders the method quite frankly not particularly reliable.



Scheme 10: The method of Kusurkar et al.[35] to prepare 1,4-disubstituted β-carbolines.[35]

A convenient method appeared, published by Kusurkar et al.[35] in the year 2008, who started the development from the unsubstituted indole. As can be seen in Scheme 10 at the first glace, the two key reactions in this approach are the microwave-assisted reaction (first synthesis step) to substitute at the indole's C-3 and the Pictet-Spengler condensation (third and fourth step) to close the A-ring.[35] The final substituents on the final substances of type **VIa** and **VIb** hold the substituents which had been introduced already in the first reaction step through an unsaturated nitro-olefin of the type **I**.[35] In the next reaction step, the alkylated indole of the type **II** was reduced to an amine **III** *via* a Raney-Nickel reduction and from there the authors prepared the tetrahydro-β-carbolines **Va** and **Vb** through an unusual variation of the Pictet-Spengler reaction, which is usually Brønsted acid catalysed.[35] The alteration was justified as an attempt to prevent the formation of diastereomers.[35] It was further stated, that the appearance of the two regiomers **Va** and **Vb**, resulted probably from a fife-membered spiro intermediate, which would then rearrange to a six-membered ring to form either **Va** or **Vb**.[35] Treatment with Pd/C and oxygen led to the aromatisation of **Va**/**Vb** and yielded β- and γ-carbolines of the type **VIa** and **VIb**.[35] In this specific paper, the authors only experimented with different aromatic and heteroaromatic residues for R.[35] It would have been interesting to know, if this particular approach is also compatible with other

substituents for R, like alkyl or specific functional groups. One of the last interesting synthesis strategies was published in 2019, as the practical works of my research project had already been in in motion. This method for a change is a metal catalysed method, using $Rh_2(OAc)_4$ or $Rh_2(piv)_4$ as a catalyst.[32] As can be seen in the following Scheme 11, the initial indoles of the type **II** need to have an unsaturated residue with a terminal EWG (electron withdrawing group) in the 2-position.[32] The other reaction partner needs to be a triazole of the type **I**.[32] The mechanism (see Scheme 11) is described by Rajasekar et al.[32], starting with the triazole type **I**, which under exclusion of nitrogen reacts to the organometal adduct **IV**.[32] The rhodium azavinyl compound **IV** is selectively inserted onto the C-3 position of the indole **II** and under rhodium catalyst elimination, the 2,3-disubstituted indole **VI** results.[32]



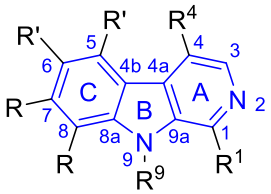
Scheme 11: Rajasekar et al.[32] development from 2019 (**[Rh(II)]** = $Rh_2(OAc)_4$ or $Rh_2(piv)_4$).[32]

Under basic conditions through DIPEA, NEt_3 or DBU and after heating, the dihydro-β-carboline **III** resulted. [32] This is a remarkably short approach to β-carbolines, which might again easily be obtained through oxidising the dihydro-β-carbolines of the type **III** using Pd/C in combination with O_2 for example. However again here, no information was given in the paper about varying the substituent in the 4-position of the dihydro-β-carbolines (of the type **III**), apart from substituted phenyls or heteroaromatic substituents. It would have been interesting to know, if this chemistry is chemistry also functions with other residues instead of aromatic rings. Also, there is no mentioning in the work on the accessibility of the substituted triazoles of the type **I**, which is of course an essential prerequisite. All in all, to monitor the development of this research is advisable in the future though. At last, and highly relevant for this thesis is the work of Dr. Martin Untergehrer, former member of the Bracher group. His research put forth preliminary findings, which have been important for the research of this work. His findings are mentioned at several points in this thesis

in the following chapters in any case, therefore it is skipped over it at this point to elaborate his research later – which leads me to explain the goals of this thesis.

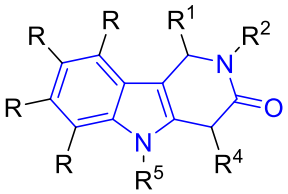
2 Objective of this work

The aim of this work was to develop new syntheses routes for two or rather tree molecule classes, 3-oxo-γ-carbolines, their dihydro precursors and highly substituted β-carbolines (see Figure 6).



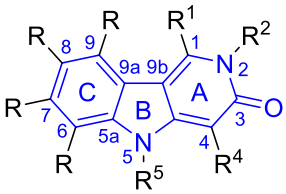
ß-carbolines

(R = H or Cl, R' = H or any R^4 = alkyl, aryl, hereroaryl, nitril, COAlk, COAr, COOAlk, etc.)



dihydro 3-oxo-γ-carboline
(basic structure)

$R^{1,4}$ = alkyl, aryl, hereroaryl, nitril, COAlk, COAr, COOAlk, etc.
$R^{2,5}$ = H, Alk; R = any



3-oxo-γ-carboline
(basic structure)

$R^{1,4}$ = alkyl, aryl, hereroaryl, nitril, COAlk, COAr, COOAlk, etc.
$R^{2,5}$ = H, Alk; R = any

Figure 6: Basic structures of highly substituted β-carbolines, 3-oxo-γ-carbolines and their dihydro precursors (from left to right).

2.1 Aims of the 3-oxo-γ-carbolines and dihydropyridone precursors project

The displayed lead structure **uwIND086** shown in Figure 7, resulted from a cooperation with Dr. J. Kuper (group of Prof. Dr. Kisker, Chair of Structural Biology, Rudolf Virchow Centre for Integrative and Translational Bioimaging, University of Würzburg, Germany). The Kisker group has been specialised in XPD Helicase research for years. Through testing the substance in a high-throughput screening, they had found that **uwIND086** shows XPD helicase inhibiting activity. This finding led to the need to develop a new, short and efficient access to structurally diverse 3-oxo-γ-carbolines with substituted 4-benzyl residues and their maybe also interesting dihydropyridone precursors.

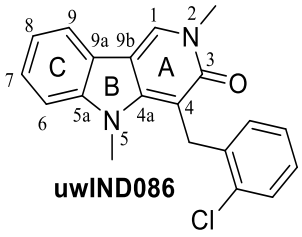


Figure 7: **uwIND086** - the lead structure, based on which the synthesis route development for the 3-oxo-γ-carboline project had been planned in this dissertation.

Concerning the 3-oxo-γ-carbolines project, we wanted to concentrate on developing a method which would allow us to synthesise 3-oxo-γ-carbolines quick, easy and cheap if possible. Further the goal was to design the synthesis route in a way that at all positions on the molecule might be substituted/varied according to the requirements later for structure-activity relationship analysis, briefly to be able to flexibly introduce any residue during the synthesis. In this work we focused on

structural variations on the A-ring (see Figure 7) of the 3-oxo-γ-carbolines. One also quite important criterium was to find a starting compound that is either easy and cheap to produce or purchasable for a reasonable prize. The C-ring variations that, to say it up front, would have required to synthesise 3-indole carbaldehyde analogues, have not been attended to in this work. For this work, I had planned therefore on assembling a selection of **uwIND086** (see Figure 7) variations, thereby proving the easy accessibility through my developed route. If successful, the synthesised compounds had been planned to get sent to the cooperation partners. Their task would be, with the help of an especially for this project developed assay, to determine the efficacy or inefficacy of the potential drugs by testing them on the XPD helicase.

2.2 Aims of the β-carbolines project

Another lead structure **AnnH-71** (imaged in Figure 8), which also resulted from a screening performed by the work group of Prof. Dr. Kisker (Chair of Structural Biology, Rudolf Virchow Centre for Integrative and Translational Bioimaging, University of Würzburg, Germany), led also to the necessity to find a new, quick and easy access for multi-substituted β-carbolines, with a special focus on flexible variations of the A-ring residues.

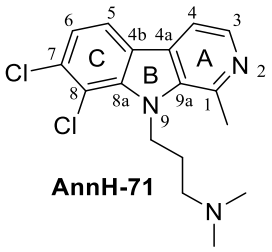
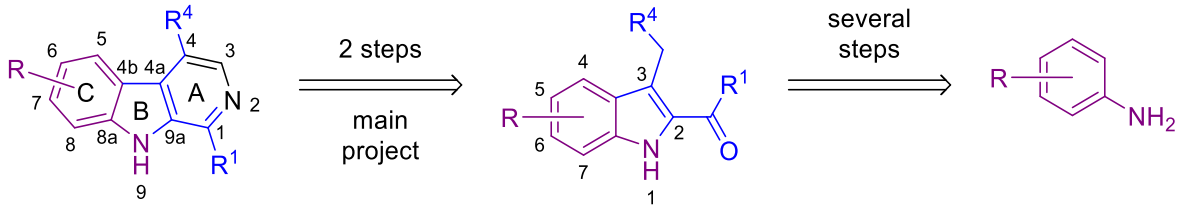


Figure 8: **AnnH-71** as lead structure for developing new synthetic pathways for multi-substituted β-carbolines.

Since the earlier published methods did not sufficiently meet our demands for functionally varying the A- and C-ring in the molecule, we decided to develop a new approach to synthesise β-carbolines deriving from suitably substituted aniline derivatives. The residues on the primary used anilines would that way become the C-ring functional groups of the β-carboline later (see Scheme 12). The advantages of using anilines have been mentioned before in this work, so it is not going to be elucidated again at this point.



Scheme 12: Comparison of the synthesised compounds of Kim et al.[48] and planned syntheses for this work.

When building up the indole basic structure starting from an aniline, one needs to consider at what point in the synthesis to introduce the functional groups, that would become the residues on the 1- and 4-positions of the β-carboline. We found a quite interesting method for the construction of suitably substituted indole intermediates, published by A. Kim et al.[48] in 2016, starting with substitution reactions on anilines, based on which we wanted to build up the indole intermediates (equated with the B- and C-ring of the β-carbolines in Scheme 12) and at the same time introduce the desired functional groups on the 2- and 3-positions of the indole intermediates. R^1 of the 2-COR^1 (acyl) residue and the residue R^4 on the 3-positioned -CH_2-R^4 of the indole would later become the 1- and 4-substituents of the β-carboline's A-ring (see Scheme 12). Using this method,

introducing 3-position substitutions on the β-carboline might only be possible shortly before the A-ring closure.

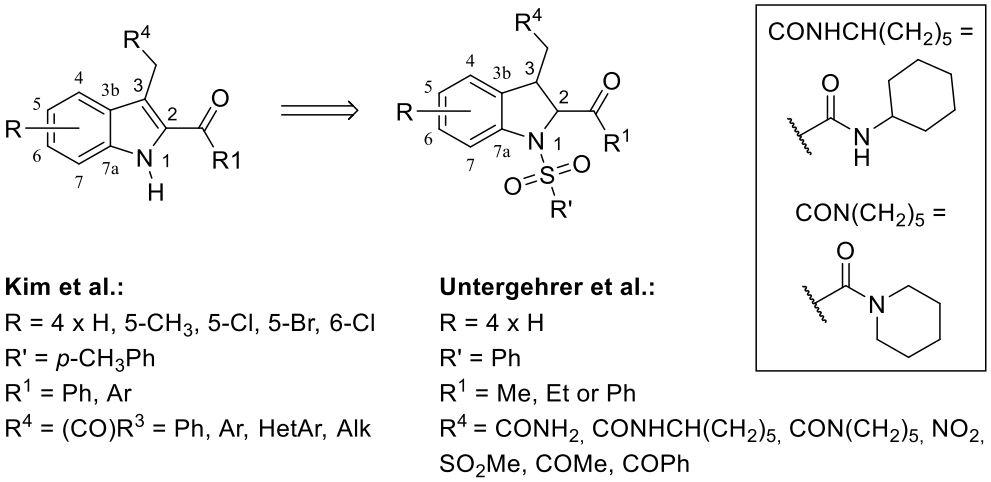
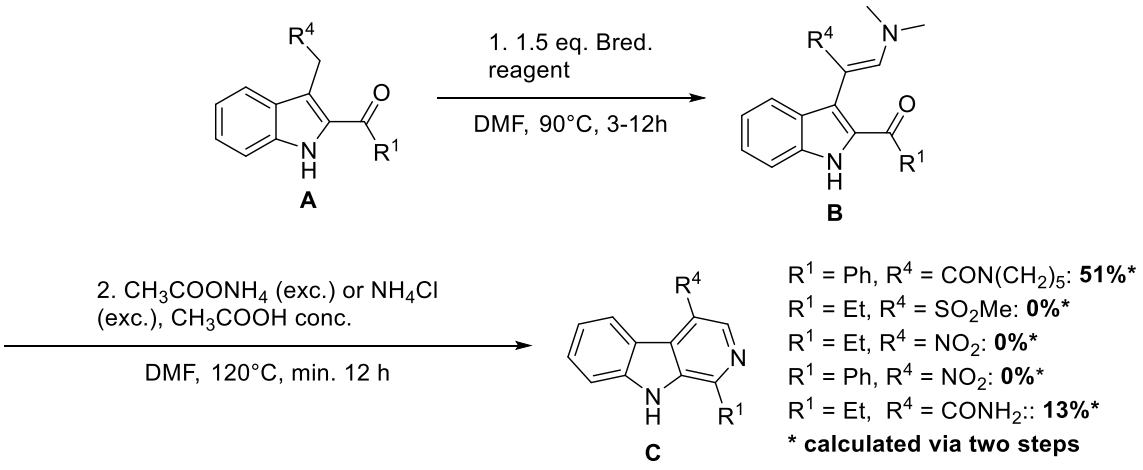


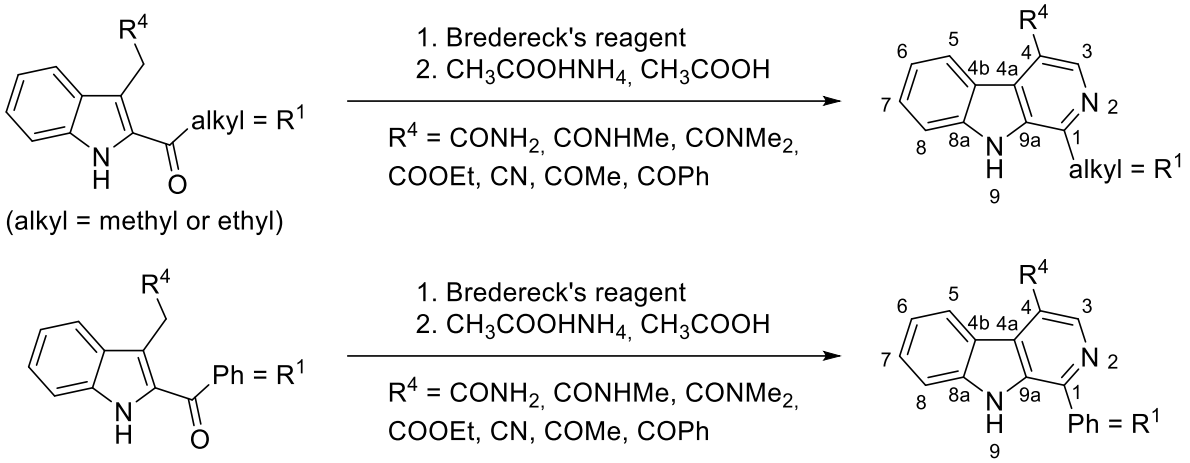
Figure 9: The different indoles, which have been prepared and were mentioned in the works of Kim et al.[48] and Untergehrer et al.[40-41].

As shown also in Figure 9, Kim et al.[48] though have only reported the preparation of indole intermediates holding 2-phenyl/2-arylacyl and 3-methylene phenyl/aryl/heteroaryl/alkyl-acyl residues. But we wanted to know, if this kind of chemistry functions with a wider range of functional groups as well. The research in this work, yet to mention that, did emerge from a collaboration with Dr. M. Untergehrer (former member of the group of Prof. Bracher), whose investigations[40-41] are complementary to this work. In his works, he used Kim's protocol[48] to prepare 2,3-disubstituted indoles with different functional groups (again see Figure 9), from which he then generated mainly 1,3- and 1-substituted β-carbolines by means of cyclocondensation reactions[40-41]. As a side project however, Untergehrer and a bachelor student (D. A. Leix), who was subjected to him by that time, have already performed a few exemplary syntheses to generate 1,4-disubstituted β-carbolines of the type **C**, though as can be seen in Scheme 13, only two of those went successfully.



Scheme 13: First 1,4-disubstituted beta-carboline exemplary syntheses, performed for the PhD thesis of M. Untergehrer.[41, 43] For $R^4 = CON(CH_2)_5$ – see Figure 9.

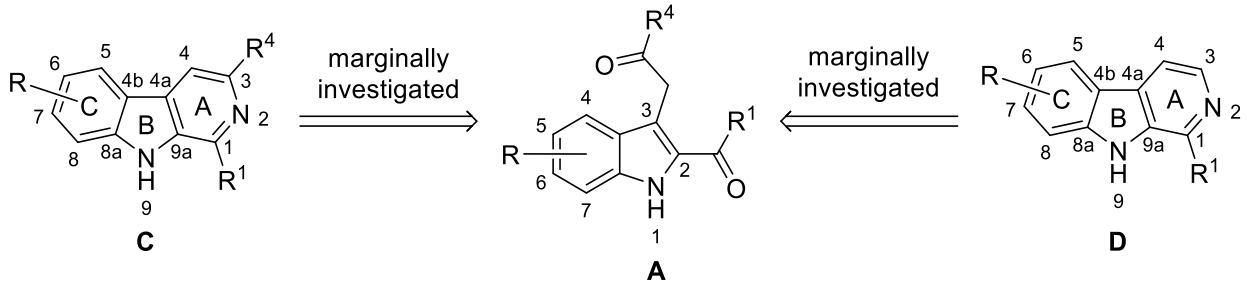
Based on these two positive results, we wanted to explore the versatility of the in Scheme 13 shown preparation method, or rather said, to check which functional groups for R^4 would be compatible with this specific method to prepare 1,4-disubstituted β-carbolines. The preparation of 1,4-disubstituted β-carbolines of type **C** in Scheme 13, to clarify that, was the main objective of this project.



Scheme 14: The for this dissertation planned indole intermediates (left) and 1,4-disubstituted β-carbolines (right), which should be prepared for this dissertation.

On these grounds and as shown in Scheme 14, for this project a selection of 2- and 3-substituted indoles should be prepared, holding a primary/secondary/tertiary amide, an ester, nitrile or ketone (with an aromatic or aliphatic residue) which equated the residue R^4, whereas for each functional group R^4, two indole intermediates should be prepared, one holding an alkyl residue for R^1, for which we chose methyl, and the other holding an aromatic group for R^1, for which as representative we simply chose the phenyl group. Having successfully synthesised those, the obtained indole intermediates should each be transposed to 1,4-disubstituted β-carbolines, using the same method that is already shown in Scheme 13. Since Untergehrer had already tried to prepare 1,4-disubstituted β-carbolines holding NO_2 and SO_2Me for the residue R^4,[41] these functional groups have not been investigated in this work again. However, he did not finish his investigations with the indoles holding primary/secondary/tertiary amides (for R^4), therefore the synthesis attempts to generate their 1,4-substituted β-carbolines derivatives and their precursors have been complementary performed for this project. Since some of the syntheses for this work started emanating from precursors, which had in some cases been prepared by Untergehrer already. For each by him received precursor, there will be an according comment in Chapter 4.2, where the conducted syntheses are elucidated. Untergehrer et al. as well as Kim et al. have used the same preparation protocol for the syntheses of their indole intermediates.[40-41, 48] Since their used method comes with certain restrictions and exposure to certain hazards, which are all elaborated in subchapter 3.2.1 and further, there were certain ideas to further improve the synthesis route in

terms of functional groups flexibility, temporal and financial efficiency, to increase the occupational safety and so forth, we decided to try a new approach to prepare these indole intermediates. If the preparation of the indole intermediates **A** succeeded, two brief side projects had also been planned as imaged in Scheme 15.



Scheme 15: Synthetic approaches to 1-, 3- and 1-substituted β-carbolines.

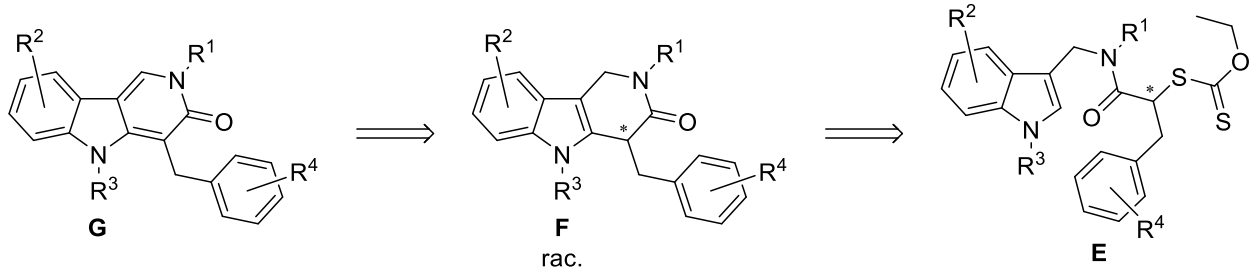
Exemplary, one 1,3- (of type **C**) and one 1-substituted β-carboline (of type **D**) should be prepared from one exemplary indole intermediate of the type **A** to show that these are equally suitable precursors for those. Since the approaches to 1-, 3-, 1,3- and 1,3,4-substituted β-carbolines were in detail already processed by Untergehrer et al.[40-41] and Kamlah et al.[31, 33], both former colleagues of mine, these structural variations were only investigated marginally in this work. From earlier works in the Bracher group it was known, that having substituents on C-4 to -7 of the indole might impede with certain synthesis steps. It was therefore decided to work only with C-4 to -7 unsubstituted indoles of the type **A** (see Scheme 15) in the route development phase. In case of having success with the synthesis development, it had been the plan to work later with 6,7-dichlorosubstituted indoles of the type **A** to receive 7- and 8-Cl substituted β-carbolines of the type **C** and **D**. These 7- and 8-Cl substituted β-carbolines would structurally be closer to the lead structure lead structure **AnnH-71** (imaged in Figure 8). In the final stages of this work, to anticipate that, it was tended to the preparation of 6- and 7-Cl substituted indoles, but deplorably synthesising the actual potential drugs, which could be tested on the XPD helicase, could not be finished during the time frame of this work. In conclusion, the aim of this project has not specifically been all along to get the generated β-carboline tested for efficacy on the XPD helicase, which has already been mentioned in subchapter 2.1. The main goal of this project was rather to accomplish the development of an efficient and improved synthesis route for multi-substituted β-carbolines. The findings of this work could of course later be used to prepare any desired 7- and 8-chloro substituted β-carboline, which could then further be tested in Würzburg (Germany) for efficacy or inefficacy on the XPD helicase. All the detailed synthesis planning is elaborated in Chapter 3.2.1.

3 Synthesis Plan

3.1 Project 3-oxo-γ-carbolines and their dihydropyridone analogues

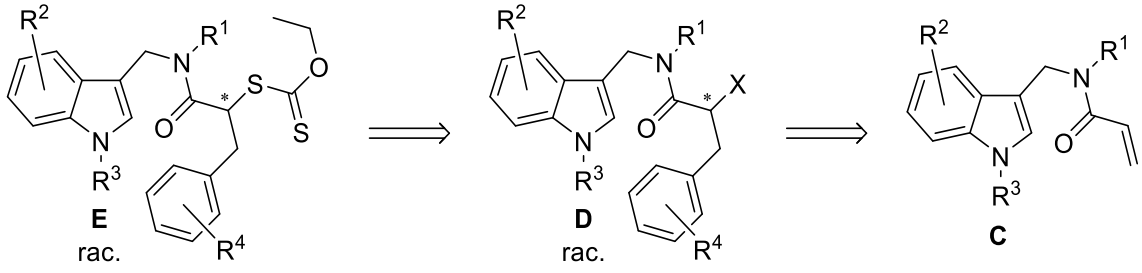
3.1.1 Approach 1 - building up the A-ring starting from 3-substituted indoles *via* an intramolecular radical substitution reaction

Scheme 16 to Scheme 18 outline the first envisaged way to approach the synthesis by building up the pyridone ring of the substituted 3-oxo-γ-carbolines of the type **G** starting with substitutions at the 3-position of the ((multi-)substituted) indole of ones choosing.



Scheme 16: Retrosynthesis of the substituted 3-oxo-γ-carbolines **G** from the dihydropyridones **F**, starting from xanthates of the type **E**. R^1 = H, Alk; R^2 = 4 x H, 4,5-H and 6,7-Cl (indole), any; R^3 = H, Alk, PG; R^4 = *o*-Cl, *m*-Cl, *p*-Cl, *p*-OCH_3.

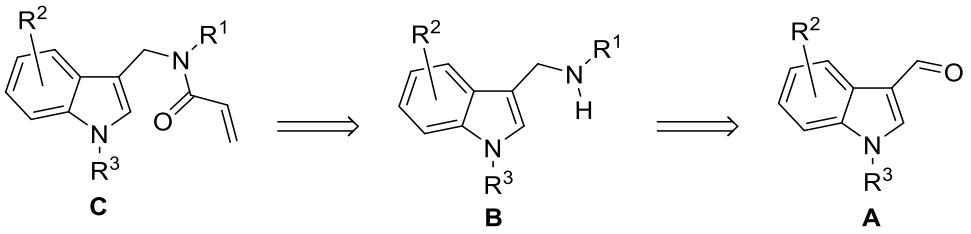
When looking backwards how one might synthesise the 3-oxo-γ-carbolines **G**, as seen in Scheme 16, one might easily get from the previously closed dihydropyridone precursor **F** to the pyridone final product **G** by any oxidation reaction. The precursor, the racemic dihydropyridone **F**, had been planned to be built up by an intramolecular radical substitution starting from a xanthate of type **E**. Substances of type **E** should be reacted with the radical initiator dilauroyl peroxide (DLP) to undergo an intramolecular substitution reaction that would yield type **F** dihydropyridones, using a method that was originally invented by Destarac et al.[49]. Radical substitutions on the 2-position of indole derivatives, amongst them intramolecular ones[50], had already been performed successfully before[50-53].



Scheme 17: Retrosynthesis from xanthate **E** to the halide **D** to the acrylamide precursor **C**. R^1 = H, Alk; R^2 = 4 x H, 4,5-H and 6,7-Cl (indole), any; R^3 = H, Alk, PG; R^4 = *o*-Cl, *m*-Cl, *p*-Cl, *p*-OCH_3, X = Cl, Br.

A xanthate of type **E** should be easily accessible through a S_N2 reaction of the α-haloamide of the type **D** with an *O*-ethyl dithiocarbonate salt (see Scheme 17). This kind of derivatisation also has

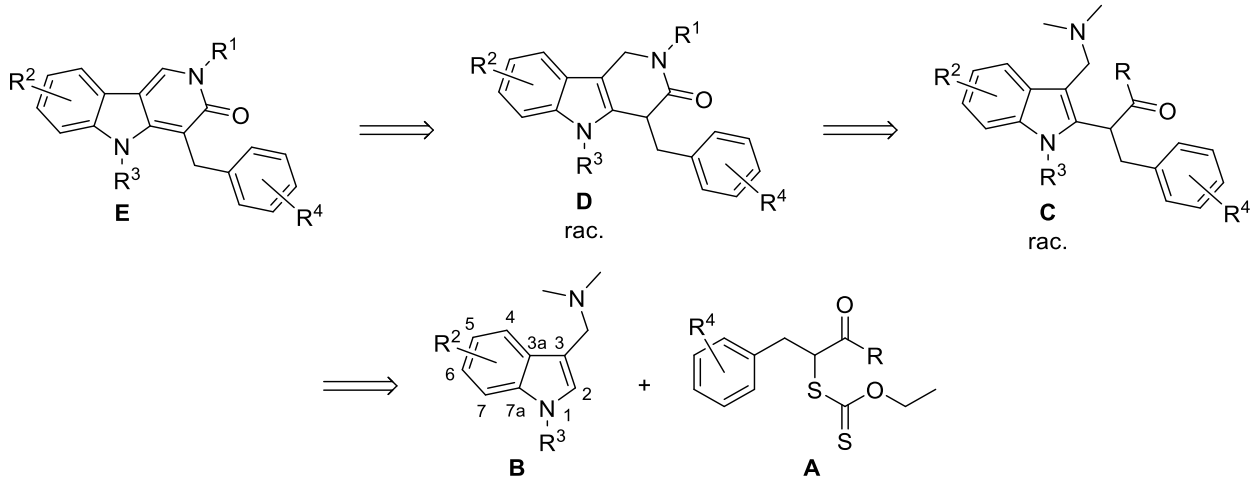
been performed on related substrates several times before.[51, 54-55] Several general options to generate a type **D** halide have been published in literature before. Performing a Meerwein arylation from *N*-(indoylmethyl)acrylamide analogues **C** using different diazotated anilines, to gain variably substituted benzyl residues, appeared to be the perfect approach to get to the desired intermediate **D** (Scheme 17).



Scheme 18: Retrosynthesis from a type **C** acrylamide to a type **A** 3-indole carbaldehyde. R^1 = H, Alk; R^2 = 4 x H or 4,5-H and 6,7-Cl (indole), any; R^3 = H, Alk, PG.

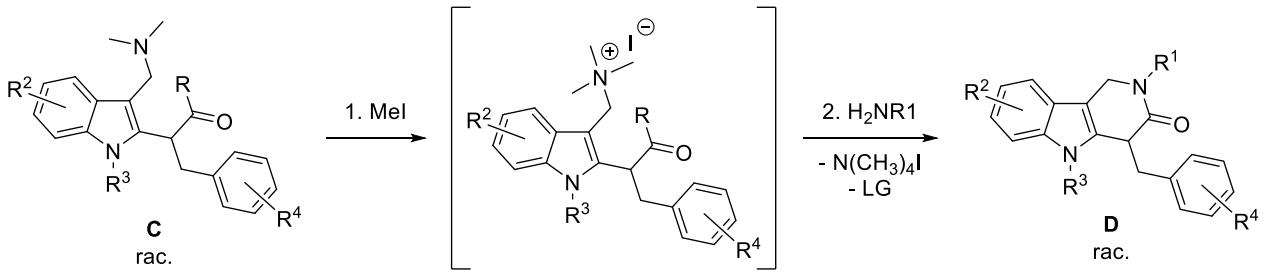
Scheme 18 shows the original plan to synthesise the type **C** acrylamides. One option was to react indole amines of the type **B** with an activated version of acrylic acid in the presence of an auxiliary base. Alternatively, one could, with the help of any coupling reagent, convert acrylic acid and a primary or secondary amine of type **B** to gain a type **C** intermediate. Due to the fact that, apart from gramine, no indoles with 3-methylene amine groups are available for sale, the obvious conclusion therefore was to start the synthesis originating from indole-3-carbaldehydes of type **A** (the model synthesis had been planned with the moieties R^2 = 4 x H and R^3 = H for **A** in Scheme 18), for which a variety of analogues are purchasable, too. A reductive amination reaction could then easily convert such aldehydes to any desired primary or secondary amine of the type **B**. This path was originally the preferred one, because if one wants to vary the substituents of the benzyl residue on the 4-position of the dihydropyridone **F** or the pyridone **G** (see Scheme 16), the most economic and thereby preferred strategy would be to introduce the residues that are planned to vary in the final structures, as late as possible. At that time and through all the syntheses planning of this chapter it had not been possible to foresee if a protective group would be needed for the indole nitrogen. Therefore, in all the figures in this chapter, for the residue R^3 one option is for it to be a protective group (labelled as PG) of some sort. Of course, if one should have been used at any point, the molecule would have to be deprotected at some point later in the synthesis, or rather as the last synthesis step. This is not imaged in any of the figures or elaborated in the chapter, since using protective groups, to anticipate that, did not lead to the solution of the problems that came up during this approach.

3.1.2 Approach 2 - building up the A-ring originating from the 2-position of gramine analogues of type B



Scheme 19: Retrosynthesis for approach 2. R = alkoxy or any other LG; R^1, R^3 = H, Alk; R^2 = any; R^4 = *o*-Cl, *m*-Cl, *p*-Cl, *p*-OCH_3.

Parallelly, a second idea to build up the 3-oxo-γ-carboline of type **E** (see Scheme 19) had been thought through in case there would be no satisfactory results from the first approach. In general, it was also possible to build up the dihydropyridone ring starting with an, this time, intermolecular radical substitution on gramine analogues of type **B**, again by using the method of Destarac et al.[49] with dilauroyl peroxide (DLP) as radical initiator and a xanthate of the type **A**. The resulting **C**-type derivative that carried now the desired substituted benzyl residue with the for this project planned R^4 variations (R^4 = *o*-Cl, *m*-Cl, *p*-Cl, *p*-OCH_3), needed to have an activated form of carboxylic acid (R = alkoxy or any other LG), too. With an ester group for example, it would later be possible to perform an intramolecular ring closure condensation reaction, reported for this molecule class by Bracher and co-workers[21] a few years ago.



Scheme 20: Type **D** dihydropyridone formation according to the synthesis method of Wollein et al.[21]. R = alkoxy or any other LG; R^1, R^3 = H, Alk; R^2 = any; R^4 = *o*-Cl, *m*-Cl, *p*-Cl, *p*-OCH.

Using this method[21], the *N*,*N*-dimetylaminomethylene residue in the 3-indole position of **C** would be transposed to a tetraalkylammonium ion by adding iodomethane, consequently generating a leaving group from the tertiary amine (see reaction step 1. in Scheme 20). Through an in-situ addition of an alkylamine or ammonia solution, while excluding trimethylamine and R (= alkoxy or

any other LG), a dihydropyridone of the type **D** should form holding the according residue R^1 as alkyl or H (see reaction step 2. in Scheme 20). For the model reaction it was planned to use gramine itself (R^2 = 4 x H, R^3 = H for **B** in Scheme 19) that can be purchased. Essentially, one had to start the synthesis development with the xanthate building blocks of the type **A** and by that determine the residue that would later become the 4-position residue on the **E**-type pyridones and the **D**-type dihydropyridones (see Scheme 19) from synthesis step one. As mentioned in the previous chapter, this circumstance made the approach less favourable. In the beginning one had to think through the essential characteristics of the **A**-type building blocks and how to gain them.

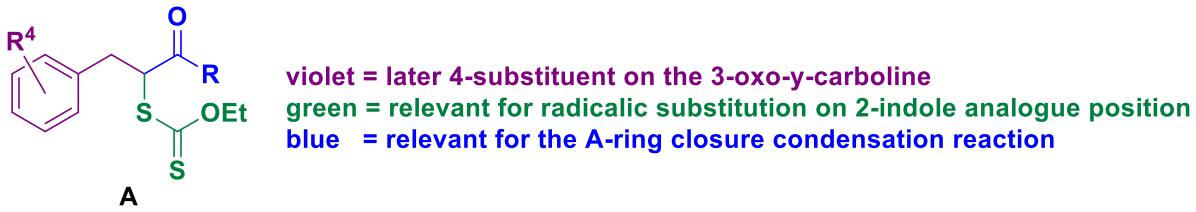
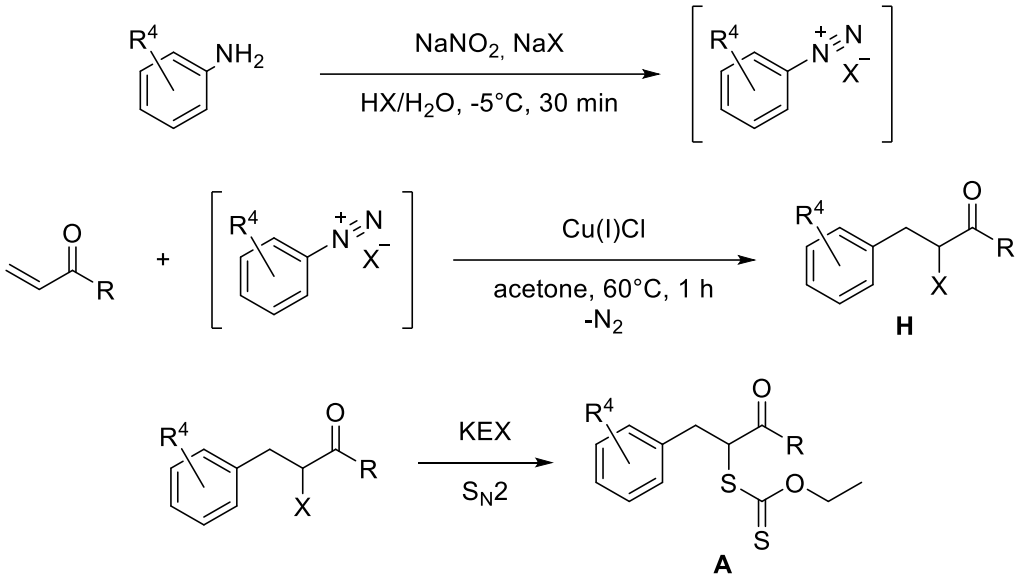


Figure 10: Essential type-**A** building block characteristics. R = alkoxy or any other LG (for this approach); R^4 = *o*-Cl, *m*-Cl, *p*-Cl, *p*-OCH_3.

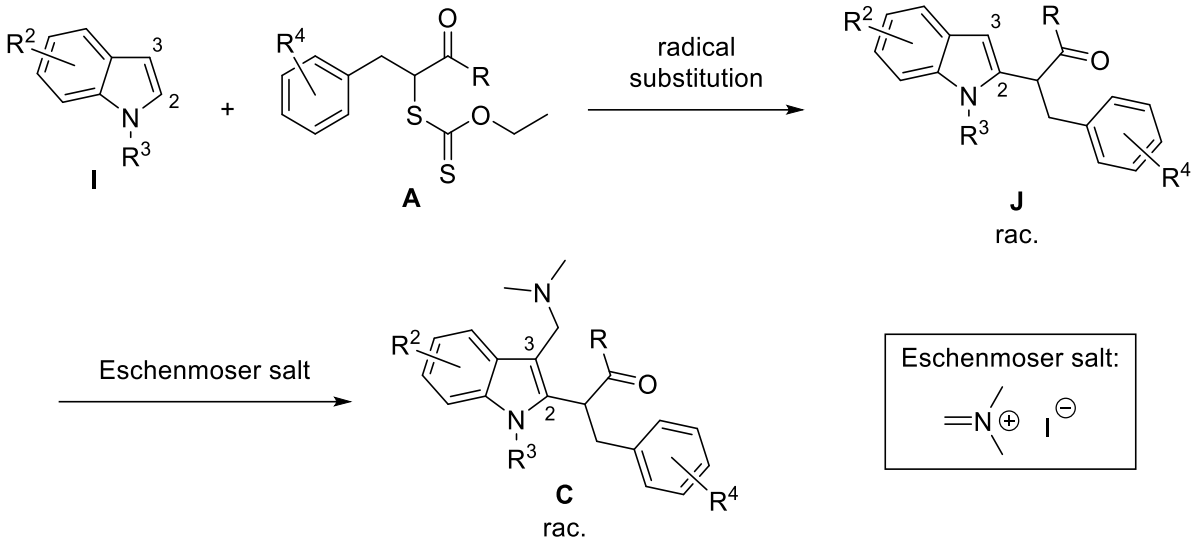
The first essential feature they would need to have was an activated form of a carboxylic acid, indicated **blue** in Figure 10, which would be relevant for the ring closure condensation reaction of the dihydropyridones of the type **D** and from which it would be possible to generate 3-oxo-γ-carbolines of the type **E** (again see Scheme 19) from. The second essential feature, coloured **green** in Figure 10, was the *O*-ethyl dithiocarbonato residue. It would be the key structure element to performing an intermolecular radical substitution on the 2-positon of any gramine analogue **B** (from Scheme 19) and should be easily accessible *via* a S_N2 reaction from an α-halogen carboxylic acid ester. Apart from the functional groups that would be necessary for building up the A-ring of the final compounds, the third indispensable structure element (**violet** in Figure 10) on the molecule would be the substituted benzyl residue one wished to have at the 4-position of the 3-oxo-γ-carbolines **E** / dihypyridones **D** in the end (see Scheme 19). The Meerwein arylation, for which the mechanism is displayed in the first two lines of Scheme 21, is the reaction of choice that includes the introduction of all key functional groups – the activated carboxylic acid group, the α-halogen group and the functionalised benzyl residue – at the same time. The Meerwein arylation products are classically synthesised from anilines. Considering having a broad spectrum of cheap and purchasable anilines to choose from commercial sources, this molecule class seemed to be a good choice for a starting material. In addition, this choice of educt enables the introduction of any desired benzyl ring substituents, if that was intended. Even if the desired aniline was not available, one still would have the option to chemically vary anilines functionally. As can be seen in Scheme 21, at temperatures below 0°C and under acidic conditions, a diazonium salt can in theory be generated from the aniline of one's choosing. It is then in-situ reacted with an

α,β-unsaturated carbonyl compound, using Cu(I)Cl as catalyst. Having isolated the halide product of type **H**, it is further reacted in a nucleophilic substitution reaction with potassium-*O*-ethyl dithiocarbonate (KEX) to yield the **A**-type xanthate product. Since the Meerwein arylation has been known for more than 80 years now with a lot of examples in literature and besides, the reaction was reported to tolerate a variety of functional groups as phenyl substituents including H, alkyl, aryl, *O*-alkyl, Cl, Br, I, CO_2-alkyl, CONH-alkyl, $CONH_2$, SO_2, NO_2, and CF_3[56], this synthesis step was assumed not to be an obstacle in this approach.



Scheme 21: Planned Meerwein arylation and subsequent xanthates **A** syntheses. X = Cl, Br; R = OH, OEt, NH_2, NHMe; R^4 = *o*-Cl, *m*-Cl, *p*-Cl, *p*-OCH_3.

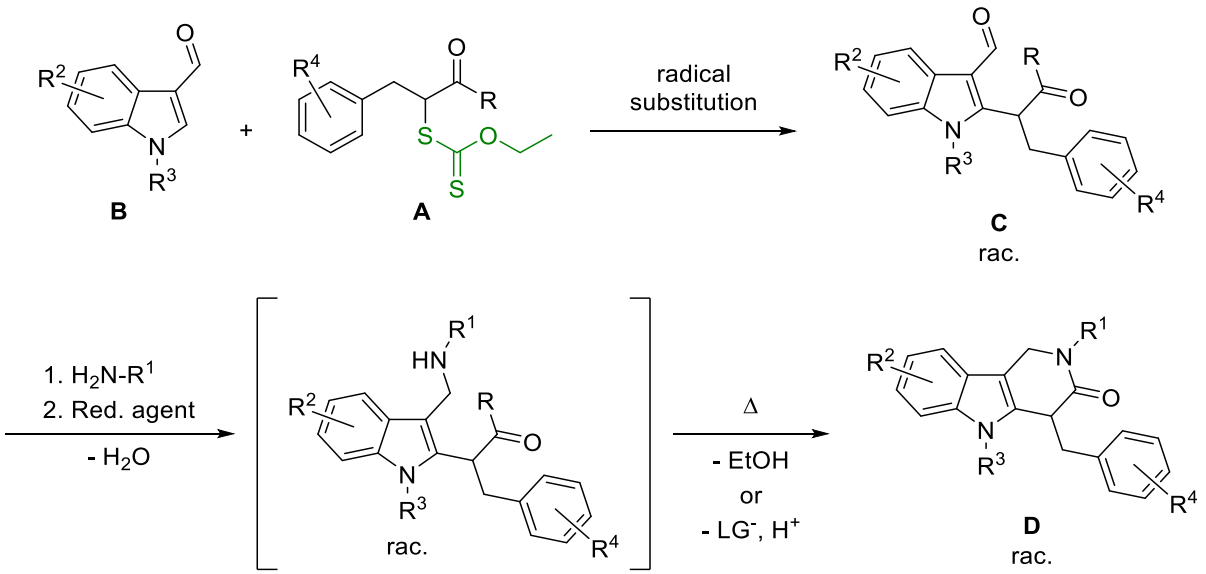
Out of scientific interest and, to anticipate that, because we wanted to try different ring closure reactions later, the Meerwein arylation had been planned to perform with different alkenes (R = OH, OEt, NH_2, NHAlk) rather than only with one alkyl acrylate (R = alkoxy) (see the caption of Scheme 21). The residue R = OEt has exemplary been chosen for the route development as representative of all potential alkyl acrylates (R = alkoxy) and R = NHMe has been chosen as representative of all potential R = NHAlk residues. One last potential variation is to mention considering the order of the synthesis steps which is imaged in Scheme 22. If the radical substitution reaction (see Scheme 19) on gramine analogues **B** would not lead to the desired 2-substituted gramine derivative **C**, one could also try to reverse the order of the reaction steps. For example, as can be seen in Scheme 22, one could try to perform the radical substitution reaction beforehand with an **A**-type xanthate on a 2,3-unsubstituted indole analogue in the style of **I** and then later substitute at the 3-position of **I** to obtain the resulting indole analogue of the type **J**, using the method Wollein et. al.[21] had used, to generate the gramine derivative **C**. The *N*,*N*-dimethyl-methyleneiminium chloride, also called Eschenmoser's salt, (see Scheme 22) would then aminomethylate the 3-position of **J** in a mild way, not using strong acids or bases.



Scheme 22: Reverse synthetic approach to 2,3-substituted indole analogues, involving the radical substitution at C-2 and subsequent aminomethylation at C-3 in the style of Wollein et. al.[21]. = alkoxy or any LG; R^1, R^3 = H, alkyl ; R^2 = any; R^4 = *o*-Cl, *m*-Cl, *p*-Cl, *p*-OCH_3.

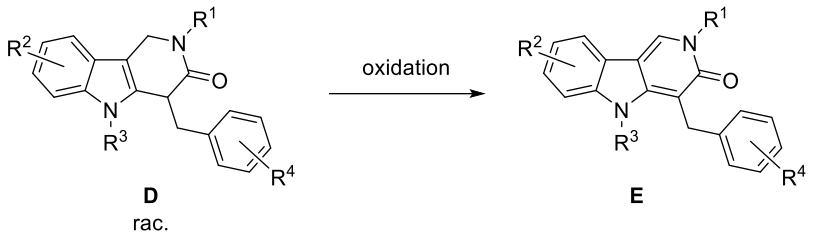
3.1.3 Approach 3 - building up the A-ring originating from the 2-position of indole-3-carboxaldehydes

Again, for this approach the Meerwein arylation was chosen as variable access to the building blocks **A** (see Scheme 21 in the previous chapter) that might be introduced into the molecule structure to become the later substituted benzyl residues at the 4-position of the 3-oxo-γ-carbolines of type **E** and the reduced **D**-type dihydropyridones (see Scheme 19) respectively. The planned synthesis of the building blocks **A** has been elaborated in the previous chapter and is not going to be explained in detail here. As coupling partner for the radical substitution at C-2, it had been planned in this modified approach to use (benzene ring substituted) indole-3-carbaldhydes of the type **B**, as imaged in Scheme 23. Any 2,3-unsubstituted indole analogue **I** from Scheme 22 could easily be transposed into a 3-carboxaldehyde derivative **B** (in Scheme 23), performing a Vilsmeier-Haack formylation reaction for example. The exact same strategy had been pursued by Canché Chay at al.[57], who formylated (with a Vilsmeier-Haack formylation) a group of 2,3-unsubstituted indoles at the 3-position and then carried out a successive radical 2-position substitution, using the same radical chemistry with xanthates and DLP as radical initiator[57] we had planned for this approach and which was already mentioned in the last two chapters. Again, as shown in Scheme 23, the already in the last chapter mentioned radical initiator DLP should induce a homolytical division of xanthate type **A** into a •SCSOEt and the corresponding •alkyl radical, which reacts further with the 2-position of the type-**B** educt, to yield a product of the type **C**. When looking at the resulting 2-substituted idole-3-carbaldeyhde derivative **C**, there are two options from here.



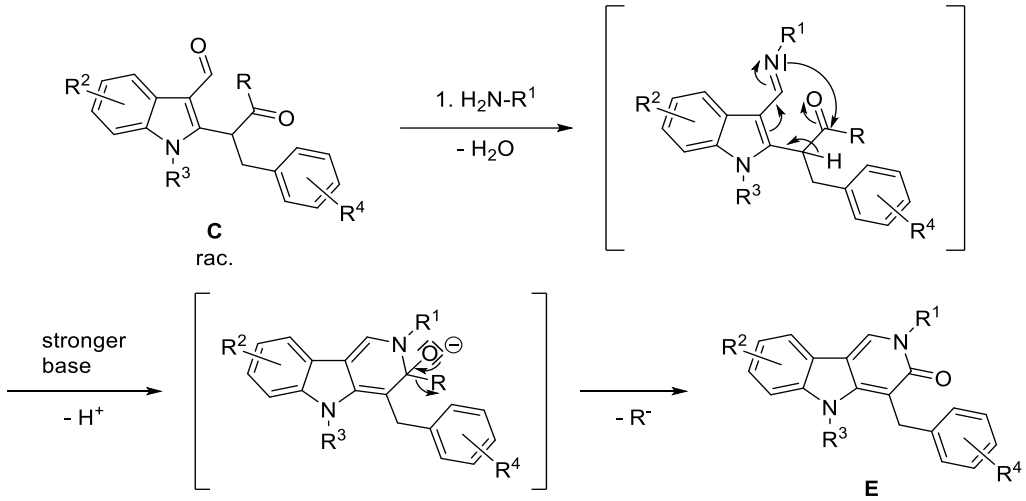
Scheme 23: Reductive amination of the aldehyde **C** and subsequent cyclisation to achieve a **D**-type dihydropyridone (R = alkoxy or any LG; R^1, R^3 = H, alkyl; R^2 = any; R^4 = *o*-Cl, *m*-Cl, *p*-Cl, *p*-OCH_3).

As can still be observed in Scheme 23, the first option was to add stochiometric amounts of ammonia or a primary amine $H_2N\text{-}R^1$, then the resulting imine could be further transformed by a reduction agent to an amine. If the flask was then exposed to an increased temperature, the heat treatment would hopefully induce a nucleophilic addition of the amine to the carbonyl group in proximity and while the alcohol or respectively the leaving group and a proton was/were eliminated, a dihydropyridone of the type **D** would form. From the dihydropyridine **D** again one could try to oxidise it to obtain the desired pyridone **E** (see Scheme 24).



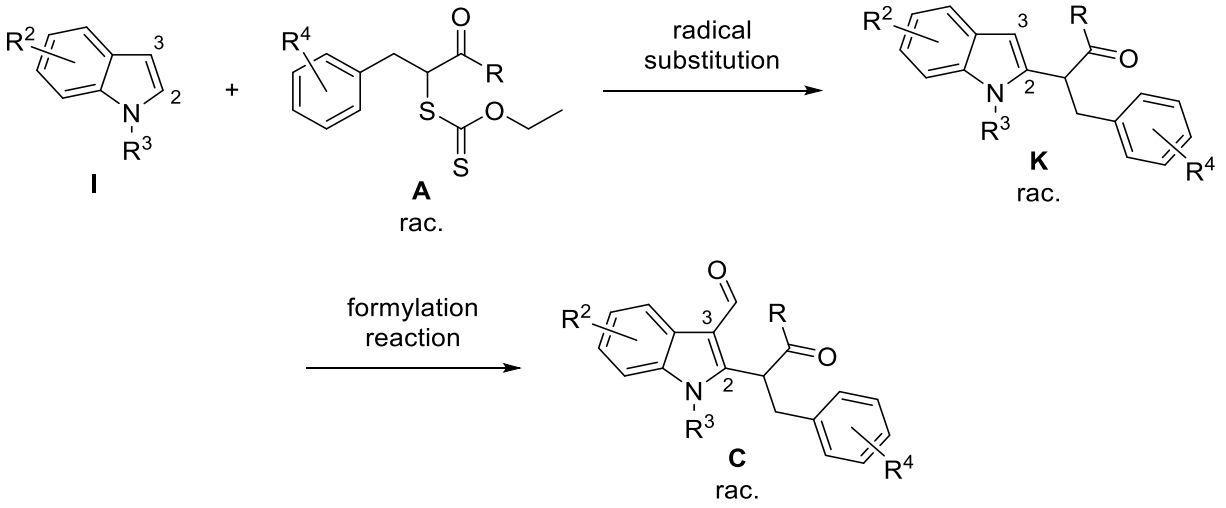
Scheme 24: Oxidation of dihydropyridone of the type **D** to the pyridine of the type **E**. R^1, R^3 = H, alkyl; R^2 = any; R^4 = *o*-Cl, *m*-Cl, *p*-Cl, *p*-OCH_3.

Zhang et al.[58] have published a method using NBS and pyridine to oxidise dihydropyridones to pyridones[58], however since NBS is also used for aromatic bromination reactions, this might not be the best idea after all, which brings us to the second potential option to prepare the 3-oxo-γ-carbolines of the type **E** starting from aldehydes of the type **C**. In this scenario and as imaged in Scheme 25, the amine with the preferred residue R^1 would be added stoichiometrically to an aldehyde **C**. After letting the aldehyde group condensate with the amine, while excluding water, the imine would build. A stronger base could be added afterwards. The acidic proton at the carbon, α-positioned to the carbonyl group, is estimated to be easily eliminated under these conditions.



Scheme 25: Imine condensation and subsequent nucleophilic addition-elimination reaction to form the **E**-type E 3-oxo-γ-carbolines. R = alkoxy or any LG; R^1, R^3 = H, alkyl, aryl; R^2 = any; R^4 = *o*-Cl, *m*-Cl, *p*-Cl, *p*-OCH_3.

Finally, the electrocyclic reaction of the formed enolate leads to a 3-oxo-γ-carboline in the style of **E**. In analogy to the last potential variation of approach 2 in Chapter 3.1.2, there is one last potential variation for this approach, as shown in Scheme 26. Again, it would be another option to firstly substitute on the 2,3-unsubstituted indole analogue of the type **I**, then formylate on the 3-position of **K** subsequently to obtain the type **C** aldehyde.

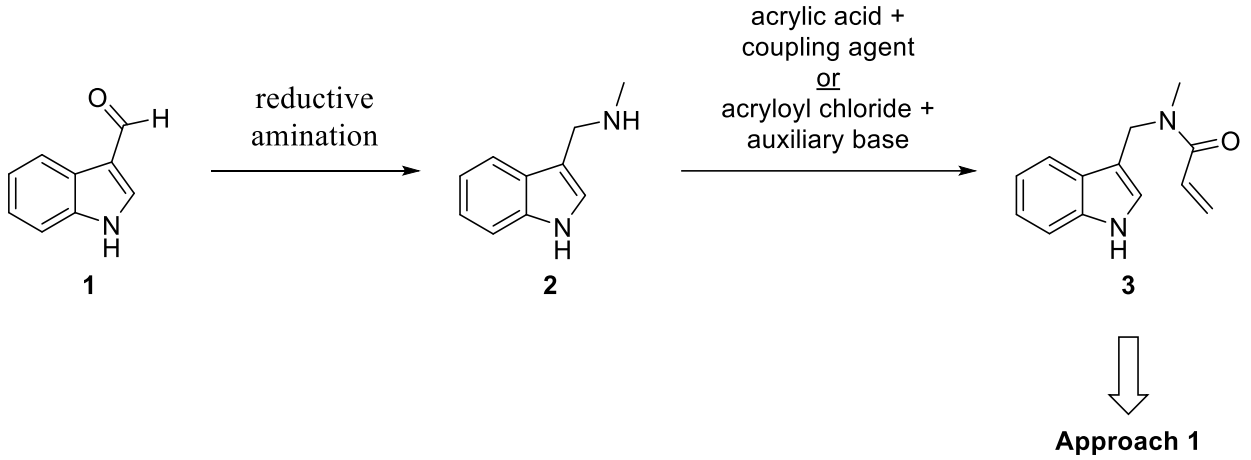


Scheme 26: Synthesis of the type **C** 2- and 3-substituted indole analogue. R = OEt or any LG; R^1, R^3 = H, alkyl; R^2 = any; R^4 = *o*-Cl, *m*-Cl, *p*-Cl, *p*-OCH_3.

Though Canche Chay et al.[57], as mentioned already earlier in this chapter, first performed the formylation (using the Vilsmeier-Haack reaction) and hereinafter the radical substitution reaction using the same xanthate chemistry[57] we wanted to use for this project, it did not mean, that the reaction step would not work if in a reversed order. Since however Osornio et al.[59] had claimed that they have successfully carried out a C-2 substitution on a 2,3-unsubstituted indole before[59], we appropriately kept this alternative order (as shown in Scheme 26) of reaction steps in mind as another way to generate 2-substituted indole-3-carbaldehydes of the type **C**.

3.1.4 Intended model reactions for method verification and approach choosing to synthesise highly substituted 3-oxo-γ-carbolines

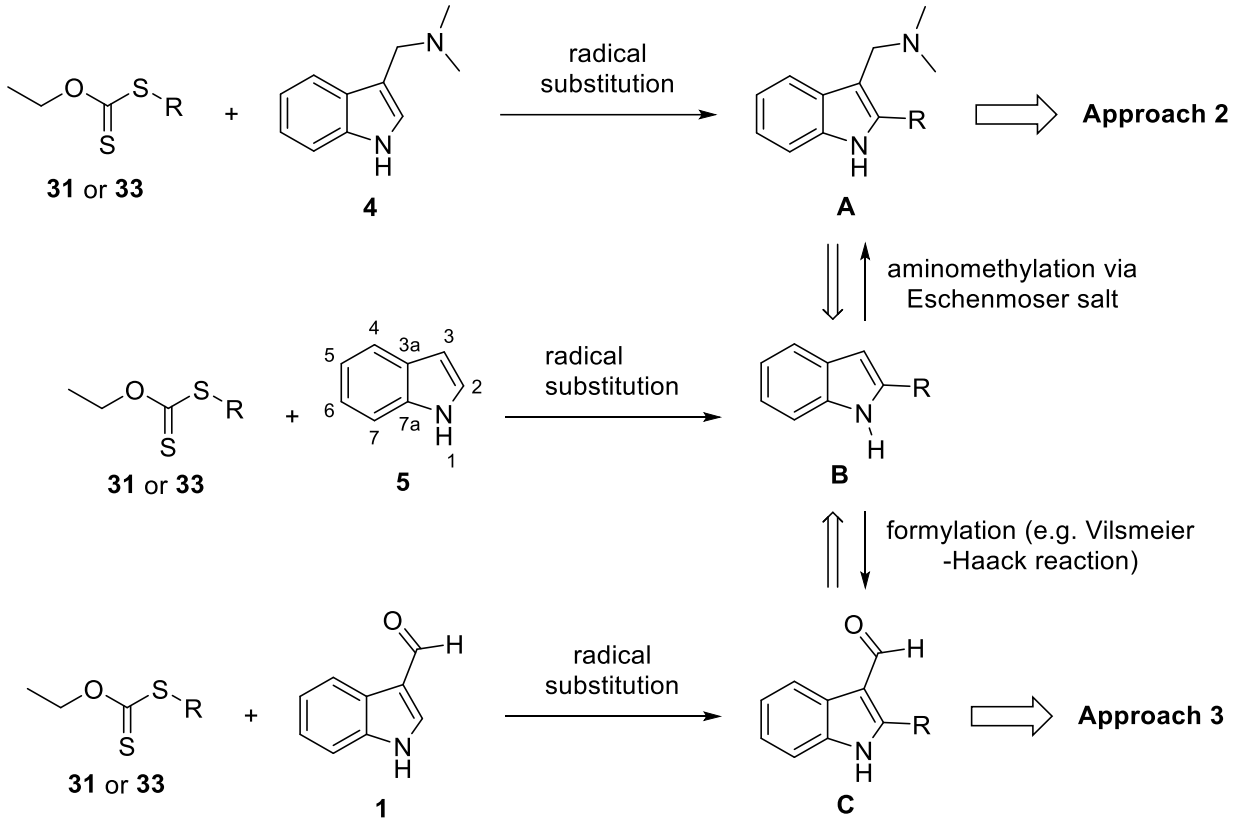
Since the preferred way to prepare the 1,4-disubstituted 3-oxo-γ-carbolines of the type **G** (see Scheme 16) was approach 1, elaborated in Chapter 3.1.1, it was essential to synthesise the acrylamide **3** as a model reaction, whereat **3** would have the desired *N*-indol-3-ylmethyl acrylamide residue. The model synthesis should be carried out starting from indole-3-carboxaldehyde (**1**).



Scheme 27: Exemplary reactions for the validation of approach 1. A reductive amination as a first step, followed by the arylamide synthesis.

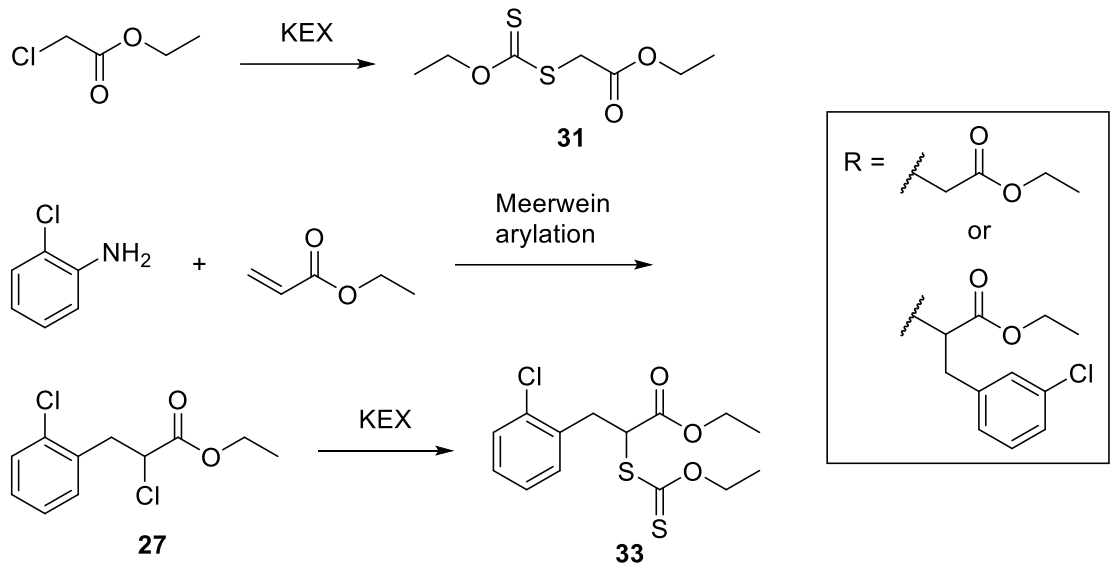
As shown in Scheme 27, a reductive amination of the aldehyde **1** should yield an amine **2**, that furthermore should be transposed to the acrylamide **3**. The amide synthesis would either be carried out using acrylic acid and a coupling agent, e.g., or a carbodiimide or HATU. Alternatively, one could perform the coupling reaction with acryloyl chloride and an auxiliary base. If the acrylamide **3** could not be generated and above all could not be generated in sufficient quantities, it would lead to the dismissal of approach 1. For determining if approaches 2 or 3, elaborated in the Chapters 3.1.2 and 3.1.3, could be taken into consideration, a few model radical substitution reactions had been planned in parallel. According to Zard and co-workers[53], intramolecular radical substitutions at the 2-position were possible for 2- and 3-unsubstituted indoles as for 3-Boc protected indoles.[53] Osornio et al.[59] performed a radical substitution at the 2-position of a unsubstituted indole and on a indole-3-carbaldehyde analogue.[59] Although this chemistry seems to tolerate a diversity of functional groups (as nitriles, esters, carbamates, amides, ketones *etc*.)[60], this chemistry involves the necessity to use protective functional groups for primary aliphatic amines[60-61], whereas the indole nitrogen has not been reported to be a disturbing factor, when unprotected[50, 57, 59]. It was consequently fundamental to confirm the accuracy of the claimed 2-indole substitutions former described in literature[53, 57, 59-60]. Also, it was essential to examine for which 3-position functionalised indoles it is generally possible to perform the attempted radical

substitution reactions and of course – the objective of the strategy – to help with the decision which approach to follow.



Scheme 28: Model reactions to verify applicability of approaches 2 and 3 and to confirm the applicability of claimed literature syntheses. R = see Scheme 29.

As can be seen in Scheme 28, three radical substitutions had been planned to undertake in the beginning. The first intended experiment, shown in the first line, was a radical substitution with gramine (**4**) as educt. If successful and if the product of type **A** could be sufficiently generated, it would be profitable to pursue approach 2. The last line in scheme 28 shows the second planned experiment, this time using indole-3-carboxaldehyde (**1**) as educt. If this substitution reaction yielded the 2-substituted derivative of the type **C** in adequate amounts, approach 3 would be a promising option. Needless to say, if there was an interest to introduce further residues into the primary indole structure, which is to say the 4- to 7-position of the indole (**5**), one could synthesise 2- and 3-unsubstituted indole analogues and then transpose them to gramine derivatives by means of Eschenmoser salt, or to indole-3-carboxaldehyde derivatives by means of formylation, all prior to the radical substitution. Accordingly, one last experiment had been planned, which is seen in line two of Scheme 28. The substitution reaction was planned to try on indole (**5**) directly which would in theory yield **B**-type products. Therefore, for the model reactions, an appropriately substituted xanthate had to be synthesised first.



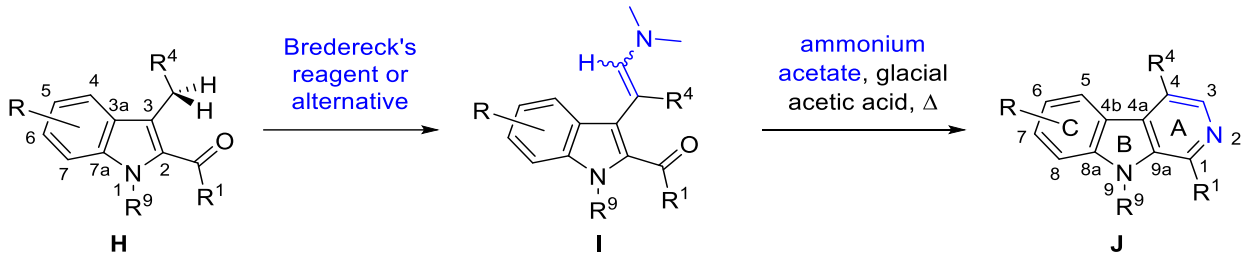
Scheme 29: Planned xanthates syntheses for the model reactions.

A simple xanthate **31** (see Scheme 29), that would be prepared with the method of Reyes-Gutierrez et al.[51], had been chosen to be used for the first model reactions. As seen in the first line of Scheme 29, ethyl chloroacetate should be reacted with potassium ethyl xanthogenate (KEX), to undergo a S_N reaction to yield xanthate **31**. Parallelly and also shown in Scheme 29, it was worked already on the synthesis of the Meerwein arylation product **27**, and its xanthate successor **33**, which was also intended to prepare with the method of Reyes-Gutierrez et al.[51]. Since the reaction would be relevant for both potential approaches 2 and 3, an easy and essential synthesis method needed to be found. This xanthate product **33**, to anticipate that, was also used later in the model reactions for the substitution reaction on indole-3-carboxaldehyde (**1**). Depending on which model reactions proved that one of the approaches 1-3 would be the best synthetic pathway, it was essential to pursue the most promising one to the end, which is to say until one exemplary 3-oxo-γ-carboline could be obtained. Pursuing the total synthesis to the end had for this reason to be part of the model syntheses. Although, the successful radical substitution would be the determining key step for the feasibility of the synthesis route, there might be other synthetic problems at the end of the synthesis route, that could not have been foreseen while planning the syntheses of the approaches 1-3.

3.2 Synthesis planning for the project – highly substituted β-carbolines

3.2.1 1,4-Disubstituted β-carbolines

For this work, as was already mentioned in Chapter 2.2, we concentrated on introducing particular functional groups on the 1- and 4-positions, or rather said on A-ring variations of the β-carbolines. In the following, to say it up front, we did not plan to do any N^9-alkylation reactions on the synthesised β-carbolines. *N*-Alkylation reactions of **J** could still be performed, if needed, in the future. As outlined in Scheme 30, the plan to get to the **J**-type 1,4-substituted β-carbolines was to generate them from 2-and 3-substituted indoles of the type **H**.

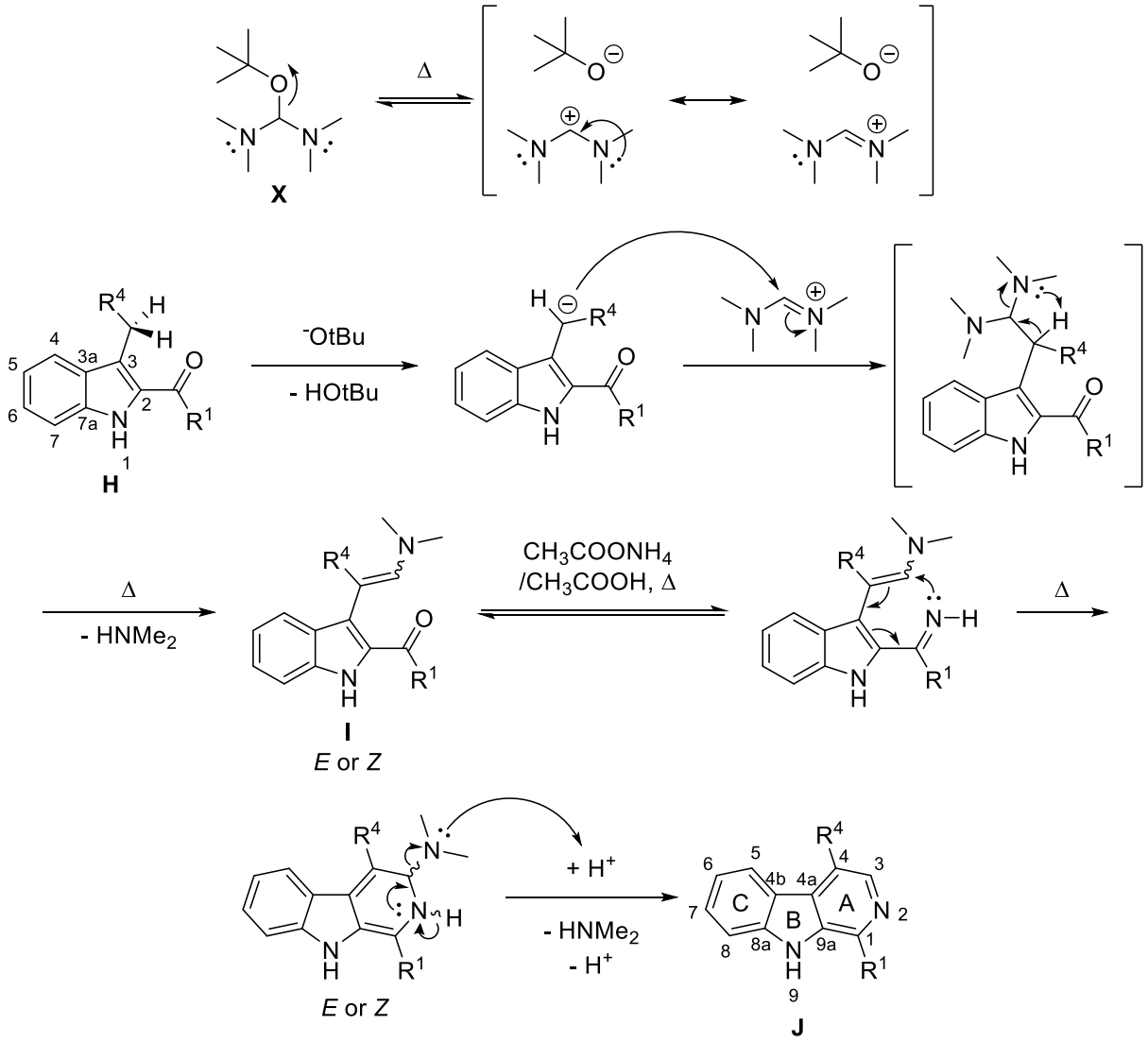


Scheme 30: Synthesis from type **H** 2-, 3 substituted indole analogues to 1,4-disubstituted β-carbolines of the type **J** *via* Bredereck's reagent and subsequent A-ring formation reaction. Planned residues for this work: R = 4-, 5-, 6-, 7-H or R = 4-, 5-H and 6-, 7-Cl (for the indole intermediate); R^1 = Alk, Ph; R^4 = $CONMe_2$, $CONH_2$, COOEt, CN, $COCH_3$, COPh.

It had been planned to build up the A-ring of the β-carbolines by using the Bredereck's or an alternative reagent to generate a *N*,*N*-dimethyl enamine group from the to the residue R^4 α-positioned methylene group, attached to the **H**-type indole's 3-position. R^4 therefore needs to be an electron withdrawing group, to render the methylene group with an acidic proton (coloured blue in Scheme 30), which is essential for the activation of the functional group. Starting the last reaction with the enamine substituted indole intermediate **I**, the addition of ammonium acetate and glacial acetic acid in combination with applying heat to the reaction solution would then lead to the A-ring formation of the **J**-type 1,4-substituted β-carbolines. This type of condensation-elimination reaction, was already successfully performed for the construction of fused pyridine rings by Bracher[62] and Kamlah et al.[33], whereby they had a different leaving group (ethoxy)[33] than I had planned to use in this work. Also as mentioned in Chapter 2.2, Untergehrer used the same method for generating the 1,4-disubstituted β-carbolines.[40-41] A mechanism proposal, in the form of an E_1 elimination mechanism, is displayed in the following Scheme 31. The reaction is always started with the addition of the Bredereck's reagent (tert-butoxybis(dimethylamino)methane (**X**)), which decays with the addition of heat to $^-$OtBu and a carbocation species, which stabilizes through alternating between the resonance structures of the carbocation and an iminium form. The secreted $^-$OtBu deprotonates the indole intermediate at the most acidic position, which in this scenario must be the methylene group, that is directly connected to the indole's C-3. The

generated carbanion couples with the iminium species and while $HNMe_2$ is eliminated, the enamine species forms in the expectation, that a mix of both *Z* and *E* isomers emerge. Addition an excess of an ammonium salt and glacial acetic acid, the resulting imine undergoes a pericyclic reaction in which the A-ring is created consequently. Finally, in an effort to restabilise energetically, acid and thermically catalysed, the $HNMe_2$ departs while the A-ring of the product aromatises.

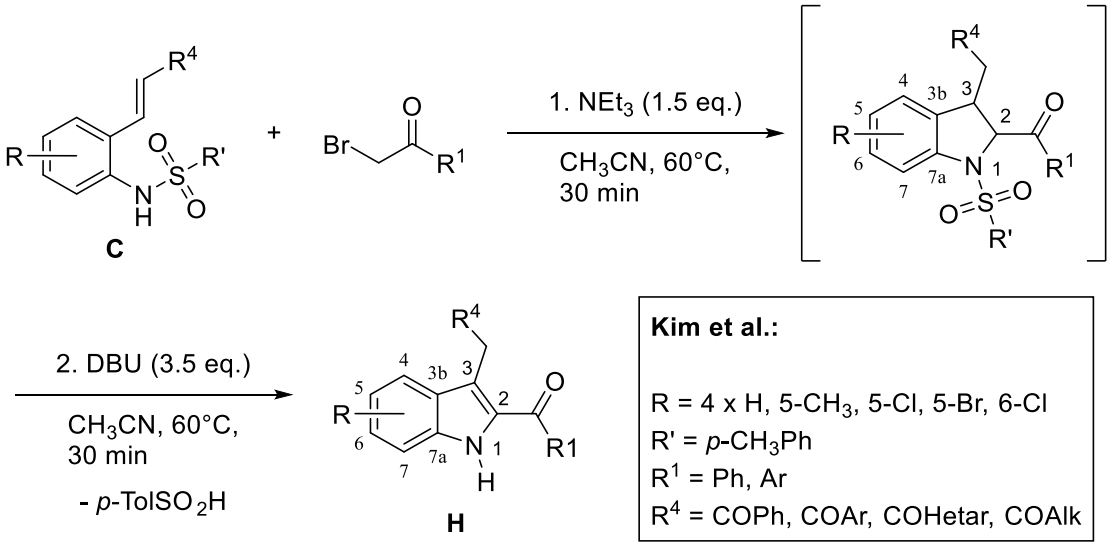
Mechanism proposal (R^4 = EWG):



Scheme 31: A mechanism proposal, for the condensation-elimination reaction, induced through the thermic activation of the Bredereck's reagent.[41] R^4 has to be an electron withdrawing group (EWG).

While thinking the synthesis route reversely we had to think about what claim we had on the chemical features of the 2- and 3-residues of the type-**H** indole precursors (in Scheme 30) and how we could easily introduce those onto the molecular structure. The functional groups on the 2- and 3-position of the indole analogue needed to have already the residues R^1 and R^4, that would finally make out the substituents on the 1- and 4-position of the β-carboline (see Scheme 30) and in addition to that have a methylene group between the indole's 3-position and R^4, which could

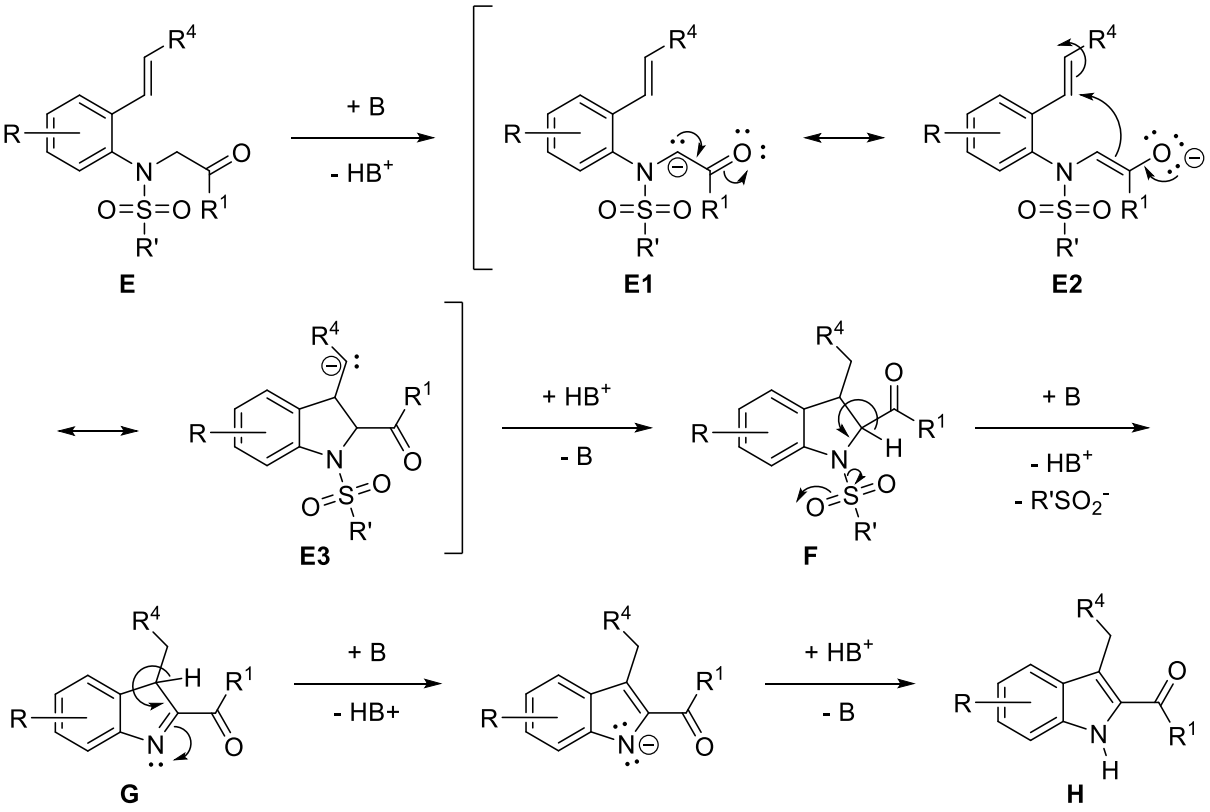
further be functionalized into the enamine group, that is finally needed for the ring closure reaction to the **J**-type 1,4-disubstituted β-carboline. How would we now synthesise an indole in the style of **H** in an elegant, cheap, efficient, short and also possibly easy way, in a manner that would allow us to introduce any desired residue for R, R^1 and R^4? We have found an interesting method to build up 2,3-disubstituted indoles, published by Kim et al.[48] in 2016, which we wanted to use up to a certain point and which would allow us to build up the indole from *ortho*-alkene functionalised, *N*-disubstituted anilines. As shown in Scheme 32, they reacted these **C**-type multi-substituted anilines with 2-bromoacetophenone or an aryl analogue of that and transposed them to 2,3-disubstituted *N*-tosylated indolines intermediate using the base triethylamine. In the second synthesis step they added the strong base DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) in situ. The indoline intermediate then further reacted to the **H**-type indole, while formally a sulfinic acid departed.[48]



Scheme 32: In situ synthesis of the 2,3-substituted indole intermediate of the type **H**.[48]

Starting from *N*-disubstituted anilines in the style of **E**, their proposed mechanism is displayed in Scheme 33. To go through the shown mechanism briefly, the, to the ketone's α-positioned methylene group of the educt **E**, is deprotonated by a strong base. The deprotonated intermediate **E1**, in an effort to restabilize, switches between the resonance structures **E1** and **E2** and the free electron pair of **E2** finally attacks the Michael system in proximity, which needs to have an electron withdrawing group (EWG) for the residue R^4. In Kim's work though, as already mentioned, they chose only ketones for the residues R^4.[48] The resulting third resonance structure **E3** is reprotonated in the α-position of R^4 and the multi-substituted indoline intermediate **F** forms. Again, the acidic (now) methine group, α-positioned to the acyl residue (COR^1), is deprotonated by DBU and the electron pair rearranges while formally the sulfinate is eliminated to give the intermediate **G**. In the last two steps, the molecule tautomerizes base catalysed to the desired multi-substituted indole **H**. 1,8-Diazabicyclo[5.4.0]undec-7-ene, or

more commonly DBU, has also been proved to function efficiently for this reaction by Bracher and co-workers[40-41] later, whereby the effectiveness of the method was attested. The plan to use the synthetic protocol of Kim et al.[48] lead to the necessity to find an efficient synthetic approach to these multi-substituted anilines of the type **E** in Scheme 33, while the reactions would need to allow the introduction of a variety of residues for R, R^1 and R^4.



Scheme 33: Kim et al.'s proposed mechanism of the 2,3-substituted indole **H** formation with (B = DBU).[48] The residues R, R', R^1 and R^4 can be extracted from Scheme 32.

What would now be the best method to introduce the necessary residues on the aniline? The following Figure 11 gives a brief overview, which essential groups and by which chemistry they should be introduced in this work. Basically, the **E**-type multi-substituted anilines need to have four different structure elements, coloured green, red, purple and blue. According to Kim et al.[48], what is needed as aniline **E**'s substituents is firstly a to the aniline H_2N-group *ortho*-positioned, unsaturated residue with the desired group R^4 at the other end[48], displayed in green. R^4, using this approach, needed to be an electron withdrawing group (EWG) again, which of course needed to be compatible with the Michael reaction, which would be the key step for the generation of the indoline intermediate of the **F**-type (see Scheme 33 again). R^4 needed further to be compatible with the Heck reaction, by means of which the olefinic group (green in Figure 11) should be introduced in this work. In consequence, the exemplary residues for R^4 were selected according to needs and compatibility[56] with both the Michael and the Heck reaction. Of course, since the vinyl group should be introduced through a Heck CC-coupling it would be necessary to start the

synthesis with an aniline (or a phenyl ring substituted aniline), which equates the blue residue in Figure 11.

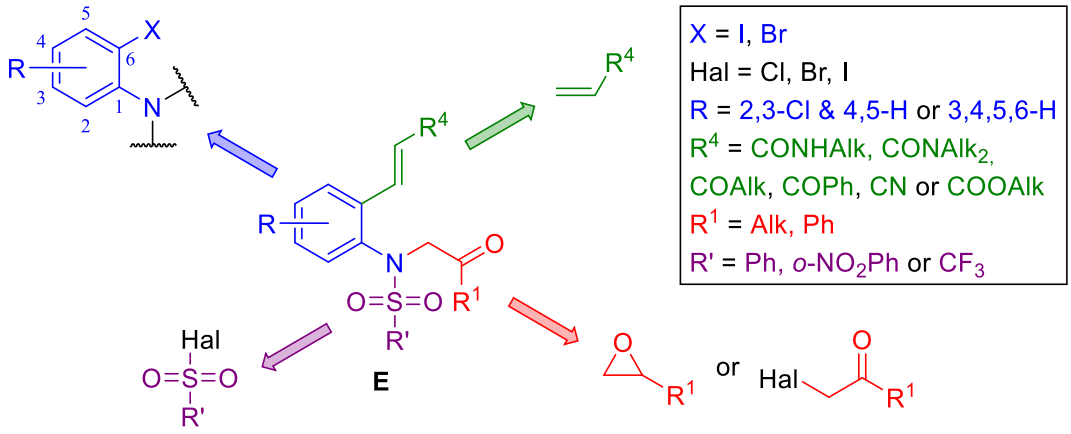
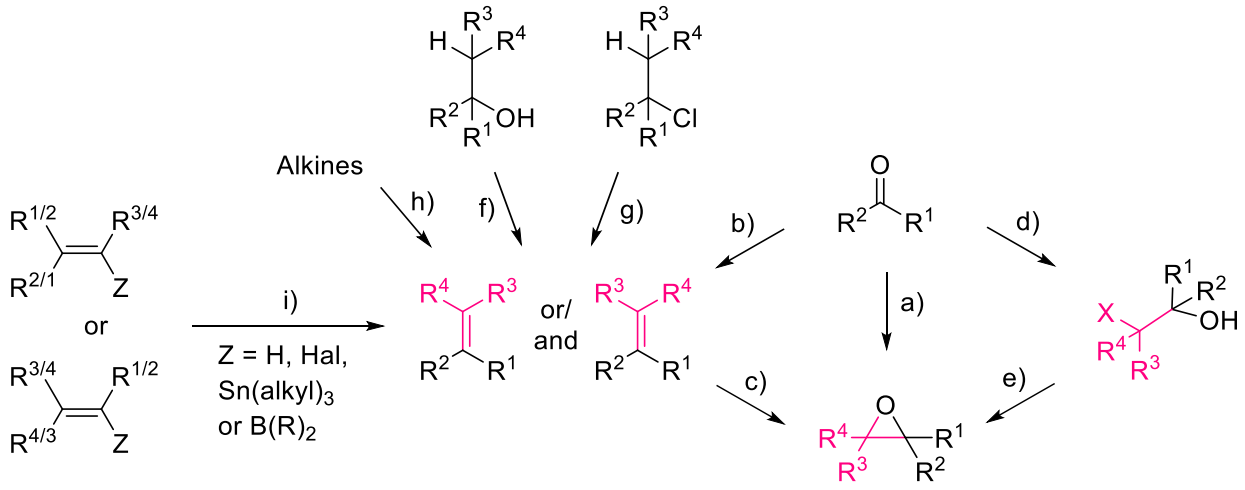


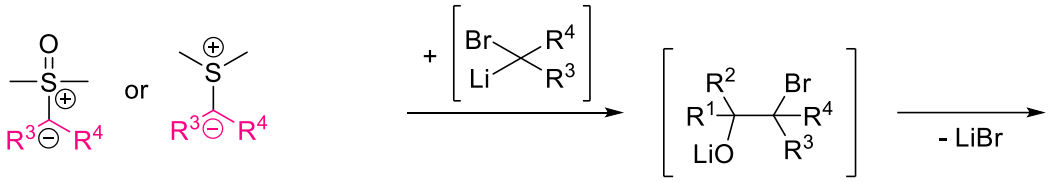
Figure 11: Essential structure elements of **E** and the envisioned ideas to introduce the for this work desired residues R,R^1 and R^4.

Essential for the later Heck reaction the aniline needed to have an iodide or bromide in the ortho position to the NH_2-group. When looking at the molecule structure of **AnnH-71** (Figure 8 in Chapter 2.2), the easiest way to introduce functional groups at the β-carboline's C-ring, or rather said the chloro substituents at the 7- and 8-position, is to start building up the molecule starting from 2,3-dichloroaniline. Again, anilines seemed like the perfect starting material to build up the desired 2,3-disubstituted indoles. However, o*rtho*-brominated or iodinated aniline analogues cannot be commercially purchased in a great variety; therefore, it was essential to find a halogenation method for anilines, that would meet our claims to halogenate in the *ortho*-position of the NH_2-group of the aniline. The third essential functional group for the indole ring closure reaction, imaged in detail in Scheme 33, is displayed in purple in Figure 11. The -O_2S-R' group, as mentioned before, that has the function of leaving group and is essential for the transformation from the indoline **F** to the indole **H**. The last residue that would be necessary to perform an indole synthesis is redly imaged in Figure 11. The, to the carbonyl α-positioned methylene group plays an essential part at the indole pyridine-ring closing. The methylene group is being deprotonated by a strong base and the resulting Michael donor attacks the Michael acceptor system, which is vinylogous connected to the EWG group and that equates R^4. Therefore, the methylene group α-positioned to the carbonyl group, contributes to the 2-position of the indoline intermediate/indole product, while the remaining part COR^1 of the red residue becomes the substituent on the indole's C-2. The first obvious method to introduce the red residue is, like already performed by Kim et al.[48] and also in the work of Untergehrer[40-41], to perform a nucleophilic substitution reaction with an α-halogen substituted ketone. However, these kinds of substances are known to be not nice to work with, due the fact that they were /have been broadly applied as chemical warfare agents (in the past).[63-64] Two, which have been used in the works of Untergehrer[40-41] and Kim et al.[48], are

chloroacetone and bromoacetophenone. Chloroacetophenone, which only differs from bromoacetone slightly and presumably undergoes the same reaction mechanisms as its chloro analogue, is a known to be a very toxic lacrimator that can cause epithelial damage and chemosis, or if inhaled in higher doses, might even result in death due to pulmonary injury and/or asphyxia[64]. It is however still used as riot control agent today[63] but due to it is high toxicity and severe injuries, which have resulted from earlier exposure, less toxic tear gases (for example pepper spray) are now more commonly used.[63] Furthermore, chloroacetone was used as active agent in tear gasses during World War I, and is now only used in industrial synthetic production processes.[63] Since the work with these substances war rather dangerous, thereby affording special safety measures and furthermore, 1-substituted 2-halo ethan-1-one cannot be bought with a wide range of functional groups from commercial sources, we decided to pursue a safer and more flexible approach *via* epoxide chemistry. Using epoxides as reaction partners would yield secondary alcohols as a result, which though could later be oxidised to the redly displayed acyl residues from Figure 11. The detailed plan to generate those is elaborated subsequently in this chapter. As can be seen in Scheme 34, there are several options to generate an epoxide, for example directly from a ketone using sulfur-ylides under Cory-Chaykovski conditions a).[65-66] They could further be generated from alkenes (see c)), which previously could have been prepared from aldehydes or ketones, using Wittig[56, 67], Tebbe or HWE (Horner-Wadsworth-Emmons) conditions (b))[56], only to name a few. Of course, there are much more options to generate alkenes in general. Most common methods include the application of CC-cross coupling reactions (see conditions i)), for example the Stille, Suzuki or Heck coupling reaction, that would not be under the restriction to originate from ketones necessarily.[56] Carrying on with the resulting multi-substituted alkenes, they could be transposed subsequently to epoxides by applying Prilezhaev/ Jacobsen-Katsuki/ Sharpless/ Shi (c)) or similar conditions which involve the usage of organic peroxides like *m*-chloroperoxybenzoic acid, TBHP (*tert*-butyl hydroperoxide) or inorganic peroxides like potassium peroxy-sulfate (Oxone) as oxidizing agents.[56] A last important way to gain an epoxide from a ketone is to mention. It would be also be possible to generate an α-halo alcohol (see reaction conditions d)) from the ketone, for example through a turbo Grignard reaction.[68-70] The resulting α-halo alcohol product could be further transposed to an epoxide in an intramolecular Williamson ether synthesis (e)).[56]



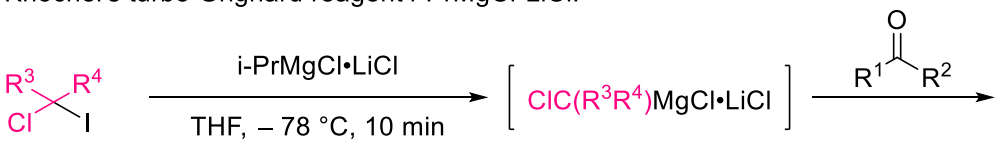
a) **Corey-Chaykovski** ($R^{3/4}$ = H): **Cainelli et al.:**



b) **Wittig reaction** ($R^{1,2}$ = H, alkyl, alkynyl, aryl; $R^{3/4}$ = H, alkyl, alkenyl, allyl, aryl, benzyl, -CO_2R, -SO_2R, -CN, -COR): **Tebbe** (for $R^{3/4}$ = H): or **HWE** (R = alkyl, R^3 = H or alkyl, R^4 = EWG):

c) **Prilezhaev** (not enantioselective), **Jacobsen**/ **Sharpless**/**Shi** (enantioselective) epoxidation

d) Clososki et al. ($R^{1,3,4}$ = H, R^2 = alkyl, alkenyl, aryl, hetar., Ph) - "**Turbo Grignard**" conditions using Knochel's turbo Grignard reagent *i*-PrMgCl•LiCl:



e) **Williamson-ether synthesis** (intramolecular)

f) dehydrogenation through base

g) dehydrohalogenation through base

h) **Birch reduction** (NH_3 + Li) or H_2 + Lindlar cat.

i) CC-couplings, for example: **Suzuki**, **Stille**, **Heck**, ...

Scheme 34: Various ways to generate epoxides.[56, 65-66, 68-74]

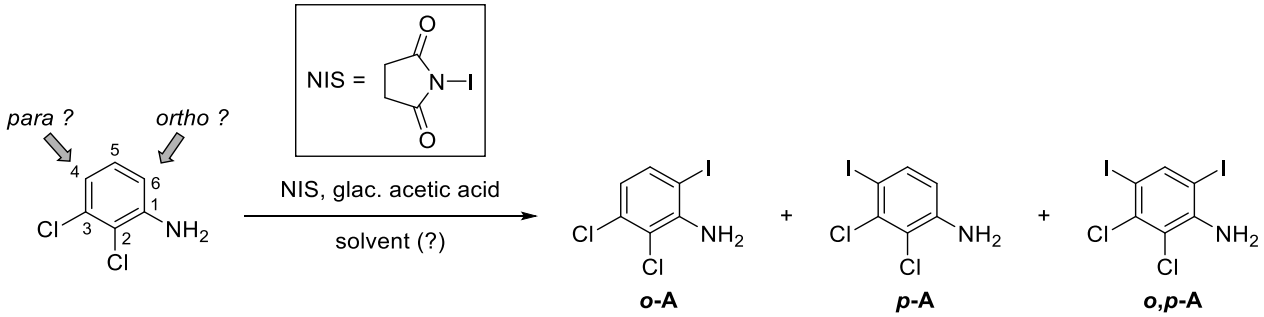
Alternatively, desired alkene could be prepared from an alkyne through either of the conditions h)[71-73] or of course, they could also be obtained from an alcohol (f)) by an α,β-dehydrogenation or from a halo-compound by performing an α,β-dehydrohalogenation reaction. Having elaborated all the obvious advantages of using epoxides over α-halo ketones, which have been used in the works of Kim et al.[48] and Untergehrer et al.[40-41] to introduce the red residue (see Figure 11), at that point of the project planning, it was essential to determine in which order the differently coloured residues from Figure 11 should be introduced. Furthermore, it was essential to determine if this epoxide chemistry was even compatible with this approach to building up the indole intermediates. If yes, it was essential to work out the most efficient preparation way - concerning mainly the order of the reactions by which all the coloured residues from Figure 11 should be introduced, but also regarding the yields, financial spending, practicability, compatibility of all functional groups with the used chemistry and finally, the stability of the generated intermediates - to prepare indoles of the type **H** (from Scheme 30 to Scheme 33). As already mentioned earlier in this chapter, from the beginning it was meant to find a synthetic approach to efficiently prepare **AnnH71** analogues, which needed to have 7- and 8-position halogen substituents. However, for the sake of finding a general synthesis route for all C- and A-ring substituted β-carbolines we had planned and did the synthesis route developing process with 2-iodoaniline as starting material, which and to forestall that, yielded 5- to 8-unsubstituted β-carbolines later. The route development should start with a few model reactions, with the interest to find out the best order of consecutively carried out reactions. The first thing, which was important to find out, was if there was a way to halogenate multi-substituted anilines more or less selectively in the *ortho*-position. This reaction ideally needed to have high yields and *ortho*-position regioselectivity, because as a first synthesis step should be unproblematic and result in a productive yield, since we wanted to use the Heck reaction to substitute the iodo-substituent later. Usually certain substituents, depending on the mesomeric effects “M” and the inductive effects “I” of all the substituents, conduct substitutions either in the *ortho*- and *para*-position, whereas other groups conduct substitutions in in the *meta*-position.[75-76] Apart from the directing effect of each group, the substituents either have an activating or a deactivating effect on the reactivity of the educt.[75-76]

ortho-/*para*-directing (activating or deactivating) groups: [33, 34]

+I/+M (e. g. -O^-) – very strongly act. > -I/+M (e. g. -NH_2, -NR_2, -aryl) – strongly activating > +I (e. g. -alkyl) – moderately act. > -H (reference standard), > -I/+M (e. g. -F) – very poor activating > -I/+M (e. g. -Cl, -Br, -I, -CH=CH-COOH) – weakly deactivating

meta-directing (deactivating) groups: [33, 34]

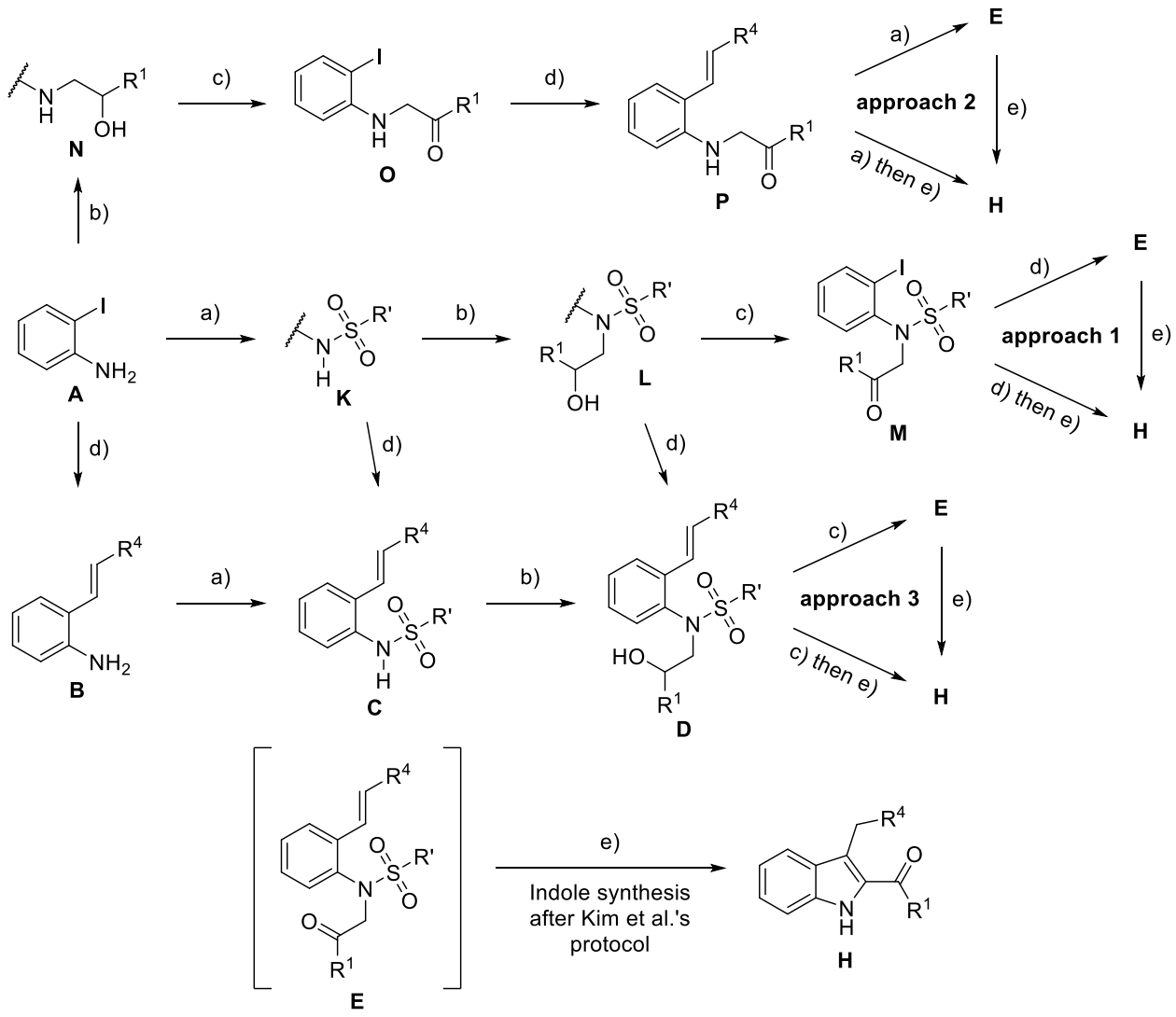
-I/-M (e. g. -COOR, -COOH, -CHO, -COR, -CN, -NO_2, -SO_3H, -$^+NH_3$, -$^+NR_3$) – strongly deactivating > -I (e. g. -SR_2, -CF_3) – strongly deactivating



Scheme 35: Planned model reaction to generate *ortho*-iodinated 2,3-dichloro aniline regioselectively.[75-76]

The educt, 2,3-dichloro aniline in Scheme 35, would be the starting aniline from which we would hopefully be able to build up the β-carboline. When one looks at the listing of functional groups in Scheme 35, that would influence aromatic substitutions, one can see that both the 2- and 3-chloro substituents and the H_2N-group tends to conduct the substitution reaction in theory, all inducing *ortho*-/*para*-substitutions. The aniline's H_2N-group is the primary directing group, since it is strongly activating the substitution, while the chloro substituents only weakly activate the reaction. The 3-position chloro substituent probably also contributes to the directing effect slightly, while the other 2-position chloro substituent is inferior towards the summed up directing effects of the other groups. We therefore can expect that the substitution takes place preferably at the 4- or/and the 6-position. So, if one should estimate, there would be an about 1:1 ***o*-A** to ***p*-A** outcome, if the iodination agent would be added slowly and in portions. In theory, the side-product C could form as well of course. We found an interesting paper, published in 2011 by Shen et al.[77] in which was reported, that the ratio of ***o*-A**:***p*-A**:***o*,*p*-A** could be directly influenced by the solvent in which was worked. As had been claimed by them and according to several different sources, the *para*-substitution would always dominate in the competition and therefore structure B always forms predominantly. In the aforementioned paper, they did some model experiments, intending to increase the yields of ***o*-A**, by just adjusting some of reaction conditions. Firstly, they started with altering the solvent and tested for all common synthesis solvents, whereby ***o*-A** was always obtained in poor yields from 2-23% and only methylene chloride (40%) and benzene (42%)

obtained higher yields. For all different solvents, only in one case they isolated the substance ***o*,*p*-A** in a 1% yield. In a second attempt to increase the yields of ***o*-A**, they varied the equivalents of the added acid and tried the reaction with the solvents that brought the best yields from the solvent trial but only for the experiments with benzene, they managed to increase the yields for ***o*-A** to 89%.[77] Resulting from these findings for this project, I had planned to perform the synthesis with benzene and alternatively methylene chloride as solvents. Since benzene is known to be quite cancerogenic, I hoped that for methylene chloride as solvent I could also obtain sufficient yields. It this reaction did not yield sufficient amounts of product ***o*-A**, there would be no point establishing a route with the Heck reaction as one of the key reactions. Assuming that the *ortho*-iodination would work without difficulties, the other essential task was to find the right order of reactions, therefore some model reactions had been planned (see the next Scheme 36), that would determine the best order. In the knowledge that the Heck reaction, out of all these singular reactions, would be the most expensive one, since it involved handling quite expensive palladium catalysts, it was decided to try that step in the end. The approach 1 – involving the sulfonamide **K** synthesis (a)), followed by the alcohol **L** synthesis (b)), the Swern oxidation (c)) to **M**, the Heck reaction (d)) to **E** and finally (in situ) the indole **H** erection (e)) – was therefore the most favoured one. Of course, if any of the single steps should not work because of groups incompatibilities, there would always be the option to try the Heck reaction from any of the intermediates obtained through the syntheses of approach 1. One could then just proceed with approach 3. Since we found a few papers in which sulfonamides could be transposed successfully in a Heck reaction[78-79], we knew, that was a potential alternative. If approach 1 could not yield satisfactory results, it would also be possible to firstly prepare one indole of the type **H** according to approach 2. The alcohol **N** would in this case be prepared from the aniline **A** (see conditions b)), then the alcohol **N** would be oxidated (d)) to **O**. The Heck reaction (d)) should yield **P**. Having obtained the ketone **P**, it would finally be reacted by applying the conditions a) to get **E** and under (in situ) conditions e), **E** would react the desired indole intermediate **H**. The least favourable synthesis route to generate the indole intermediate **H** was approach 3, as the Heck reaction (d)) to **B** was to be performed first in large quantities, rendering the approach the most expensive. Successive to the Heck reaction, the sulfonamide **C** should be synthesised through conditions a). Starting from the sulfonamide **C**, the reaction sequence b), c) and then (in situ) e) would then hopefully result in the indole of the type **H**. All three approaches 1-3 have one potential advantage in common. The penultimate reaction step – d) for approach 1, a) for approach 2 and c) for approach 3 – all would be conducted under basic conditions. Since each reaction d), a) and c) as the penultimate step afforded bases anyway one could for all three approaches, if we got so far with any of the approaches, try to shorten the preparation time and saving resources by preparing the **H**-type indole in situ, by adding DBU (see conditions e)) successively to the reaction solution, which then just needed to be heated up so that the indole intermediate **H** would form.



a) Cl-SO_2-R', pyridine, CH_2Cl_2 (or neat), 0°C-rt

b) +  + base/acid/LA or/and Δ catalised

c) Swern oxidation: $(CO)_2Cl_2$, $SO(CH_3)_2$, TEA or other base (?)

d) Heck CC-coupling:

+  + palladium catalyst (cat.), $P(Ph)_3$ (cat.),

TBAB (?), K_2CO_3/NEt_3 or other base (min. 1 eq.)

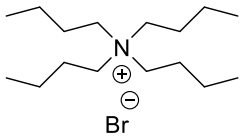
e) DBU, Δ

residues for the model reactions:

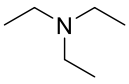
R^4 = $CONMe_2$; R_1 = CH_3 and Ph

R' = Ph, *ortho*-NO_2-Ph or CF_3

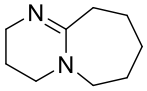
TBAB =



TEA =



DBU = 1,8-Diazabicyclo[5.4.0]undec-7-en

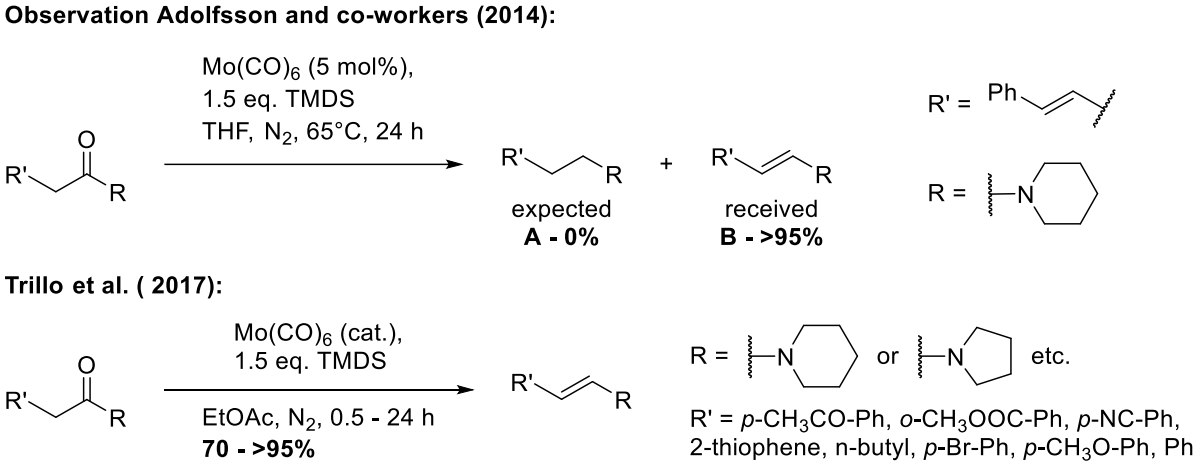


Scheme 36: Planed model reactions to indoles of the type **H** for approach verification.

The essential precondition for that naturally, would be that the former reaction d)/a)/c) was already completed. The reaction progress, having added all the components of the reactions d), a) or c), would of course be monitored by TLC control. I therefore kept this potential alteration in mind. For the model reactions I chose quite inert residues. R^4 for all the model reactions should be $-CON(CH_3)_2$. Therefore, all Heck reactions, which have been performed in the model reactions for this project, have been performed with *N*,*N*-dimethylacrylamide. For R^1 it was decided to perform all reactions with two different residues, one the one hand the phenyl group and on the other an alkyl residue, for which as representative the methyl group was chosen exemplary. In the previous works, which handled from the search to create new ways to prepare these 2,3-disubstituted indole intermediates, for R' always a phenyl or toluyl residue was used[48]. In this project, additional to working with the phenyl residue for R', I also performed some experiments with R' = $-CF_3$ and 2-nitrophenyl, in the interest of validating if the phenyl/toluyl sulfinate is the best possible leaving group, or if any of the others provided better results as a leaving group. In case that in the one of the approaches 1-3 lead to one successfully prepared 1,4-disubstituted β-carboline in the style of **J** (from Scheme 30), the route had been planned to be repeated in the same way, with the same residues R^1 and R^4, but instead of the residue R' being phenyl, the whole synthesis route should be performed to the end one time with $-CF_3$ and one time with 2-nitrophenyl.

3.2.2 Side project - 1-substituted and 1,3-disubstituted β-carbolines

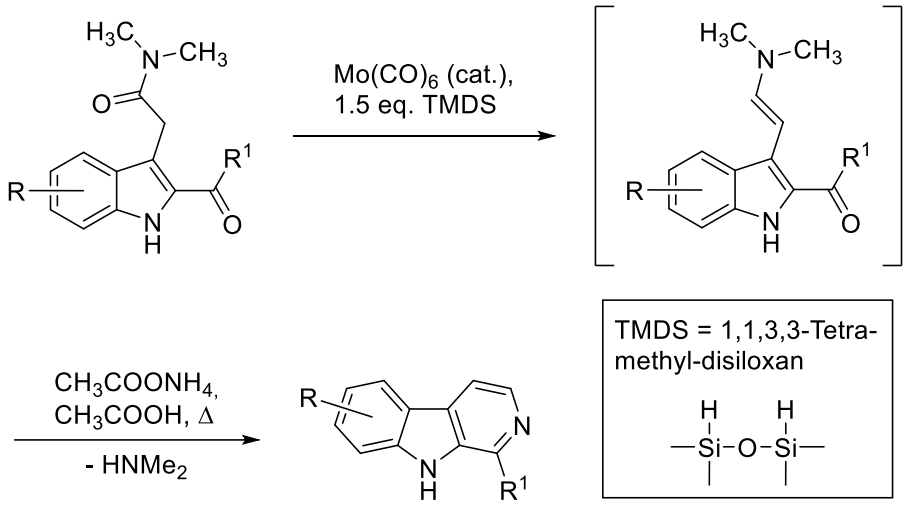
As also mentioned in Chapter 2.2 already, we moreover wanted to show that 1-substituted and 1,3-disubstituted β-carbolines could also be introduced by this approach, starting from the same 2,3-disubstituted indole intermediates of the type **H** of Chapter 3.2.1. To mention that in advance, only one exemplary 1- and one exemplary 1,3-disubstituted β-carboline were prepared from one coincidentally chosen indole intermediate. The idea behind that was to just to indicate, that β-carbolines with certain residues at C-1 or C-1 and C-3 can in theory also be prepared from them. Since however Kamlah et al.[33] and Untergehrer[41] have already found effective approaches to generate 1-substituted, 1,3-disubstituted (and even 1,3,4-trisubstituted) β-carbolines with certain substituents, for which the preparation methods are in detail represented in their PhD theses[38, 41] and their published literature[31, 33, 40], the investigations for synthetically preparing 1- and 1,3-disubstituted β-carbolines were therefore only superficially carried out in this work.



Scheme 37: New ways for selective reduction of amide carbonyls in the presence of more reactive carbonyl functional groups.[80-81]

For the preparation of one exemplary 1-susbstituted β-carboline we wanted use a method, which can be seen in Scheme 37 and to our best knowledge, has firstly been discovered and was published by Adolfsson and co-workers in 2014.[81] In their paper, they reported a method to mildly reduce carbonyl functional groups of *N*,*N*-disubstituted amides chemoselectively to alkylamines, using catalytic amounts of molybdenum hexacarbonyl, or shortly written $[Mo(CO)_6]^0$, and the mild reduction agent 1,1,3,3-tetramethyldisiloxane (TMDS).[81] The general idea behind that, was to find a milder reduction agent than aluminium hydride reductants, e. g. LAH (lithium aluminium hydride) as most common representative, which are known to not only reduce the carbonyls of amides, but also - very readily and typically even preferred - aldehydes, ketones, acid chlorides, nitriles and aromatic nitro compound[82]. However, when they tried the in Scheme 37 imaged reaction (from 2014) with an educt, which had an α-positioned methylene group next to amide's carbonyl, instead of the expected ethane amine **A**, they surprisingly isolated an enamine **B** instead, even in a

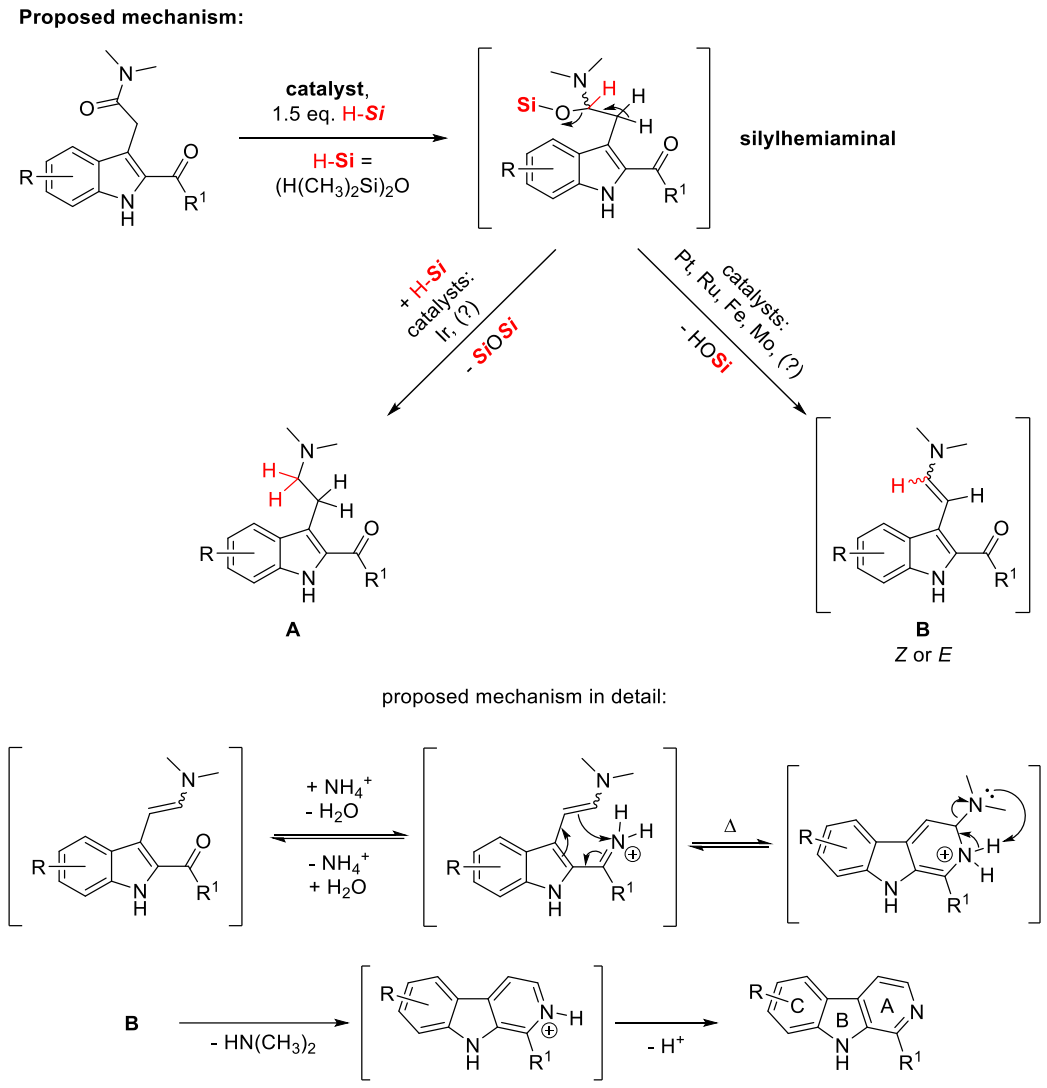
quantitative yield.[81] In 2017, Adolfsson and co-workers[80] published an optimised protocol for this reaction and proved through their analytic data, that this enamine preparation method tolerates a series of functional groups (see Scheme 37 again).[80] In an third paper from 2017, they reported an in-situ variant of the same reaction protocol in which triazolines were in-situ prepared from the previously generated enamines.[83] The authors claimed for this reaction, that the in-situ preparations furnished higher yields compared to the yields they obtained from a two-step reaction.[83] It was proposed that this phenomenon resulted from the high reactivity of enamines.[83] Knowing all these details, the following reaction (see Scheme 38) for one later to be incidentally chosen indole intermediate should be performed:



Scheme 38: Planned exemplary synthesis of one 1-substituted carboline and the proposed mechanism from a **H**-type indole with R^4 = $CONMe_2$.

In this case R^4 would need to be an amine of course, since we needed an amine functional group to provide a leaving group. I had chosen to perform the reaction with the tertiary amide residue -$CONMe_2$. In-situ, as was already advised, it was planned to perform the ring closure condensation reaction, already performed by Kamlah et. al.[33], who simply used a mixture of ammonium acetate, glacial acetic acid and treated the solution with heat whereby in their case, the leaving group was ethanolate instead. Mechanistically, as can be seen in Scheme 39, the mechanism for the enamine building has already been proposed a few times in literature. According to Tahara et al.[84], a silylhemiaminal formation is induced from the original methylene *N*,*N*-dimethyl carboxamide.[84] After the formation, two things could happen theoretically. Depending on the catalyst, either the amine **A**, or the enamine **B** forms, whereby Tahara et al.[84] have only used platinum, ruthenium, iron and iridium catalysts in their research.[84] Using Volkov et. al.[81]'s protocol, using $Mo(CO)_6$ as a catalyst and TMDS as reduction agent, would hopefully though yield the enamine **B**.[81] Starting with the enamine **B**, the in-situ addition of ammonium acetate and glacial acetic acid, using the method of Kamlah et al.[33] would lead to an electrocyclic

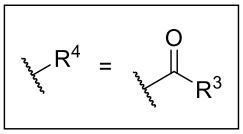
reaction. Following the elimination of a dimethylamine, the β-carboline would be created as can be seen in the proposed mechanism in Scheme 39.



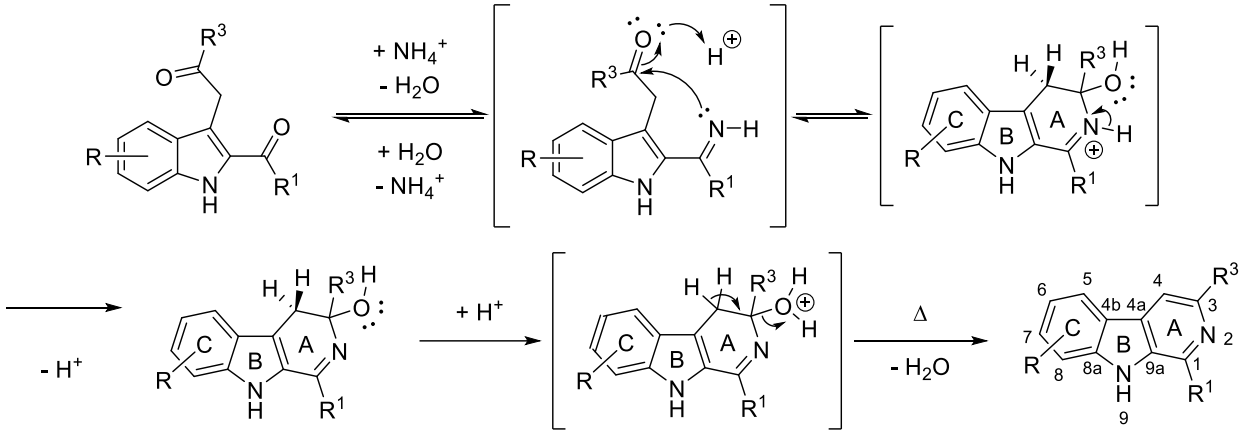
Scheme 39: Mechanism proposal for the formation of C-1 substituted β-carbolines.[84]

The 1,3-disubstituted β-carboline on the other hand should be generated just by performing a condensation reaction of a diketone intermediate, again starting from the same indole intermediates for which a preparation method had been planned in the last Chapter 3.2.1. The product should be prepared using the synthetic protocol of Kamlah et al.[33] again, using CH_3COONH_4, glacial acetic acid and heat treatment to generate 1,3-substituted β-carboline. For the proposed mechanism, two potential mechanisms are in theory possible again (see Scheme 40), this time rather depending on the chemical features of the residues R^1 and R^3 in the diketone (R^4 = -COR^3), which means - if the first or the second mechanism option is pursued would depend on, which of the two carbonyl groups was more nucleophilic. Again, one exemplary synthesis should be performed from a randomly chosen **H**-type indole precursor again, for which the

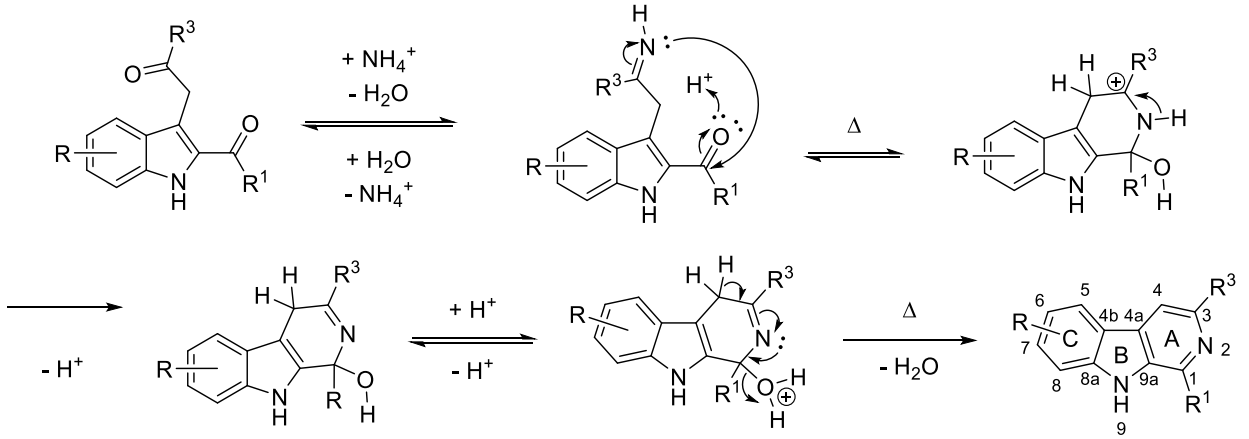
residues R^1 and R^4 would be chosen later and incidentally. As only restriction though, R^4 would needed to be a ketone or aldehyde in the style of COR^3.



Mechanism proposal - option 1:



Mechanism proposal - option 2:



Scheme 40: Potential mechanism for the formation of 1,3-disubstituted 1,3-substituted β-carbolines.

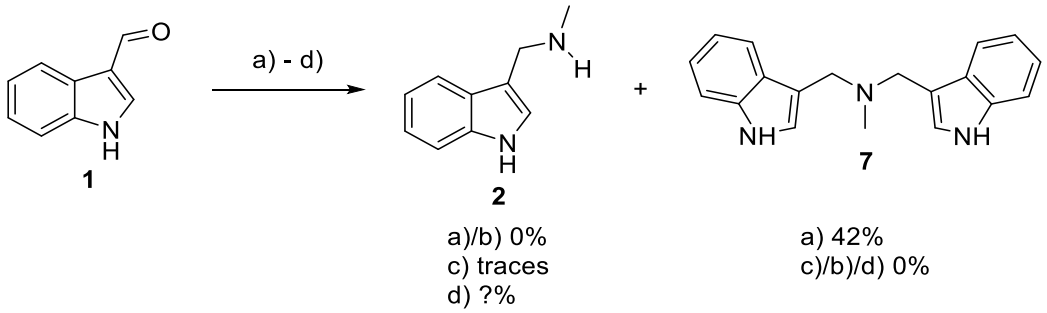
4 Results and discussion

4.1 Project 3-oxo-γ-carbolines and their dihydro analogues

For deciding which of the approaches 1 to 3, all elaborated in subchapters of Chapter 3.1, to choose from, the model reactions (see Chapter 3.1.4) were carried through.

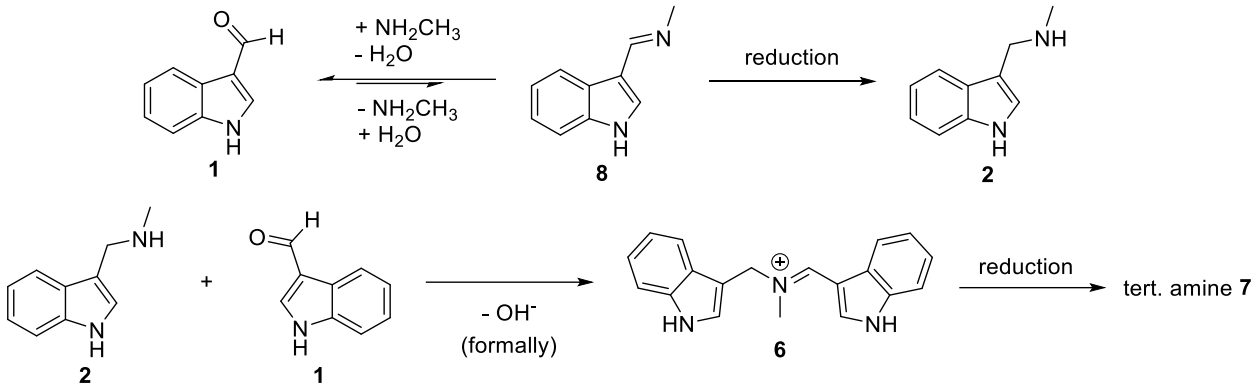
4.1.1 Model reactions for method selection

The first step for the validation of approach 1, elaborated in subchapter 3.1.1, was a reductive amination reaction for which indole-3-carboxaldehyde (**1**) was chosen as educt. Sodium cyanoborohydride was used as reduction agent in the beginning. Compared to sodium borohydride, which would have been the first obvious choice, the Borch reduction has the advantage of being incredibly selective concerning the target functional group and in addition to that the preferred target functional group varies at different pH values.[85] At pH 3-4 it reduces aldehydes and ketones selectively.[85-86] If the pH was between 6 and 8, on the one hand the reaction would become very slow but on the other hand the more basic imines are preferentially protonated and get therefore reduced much faster or rather more selectively than aldehydes or ketones.[85-86]



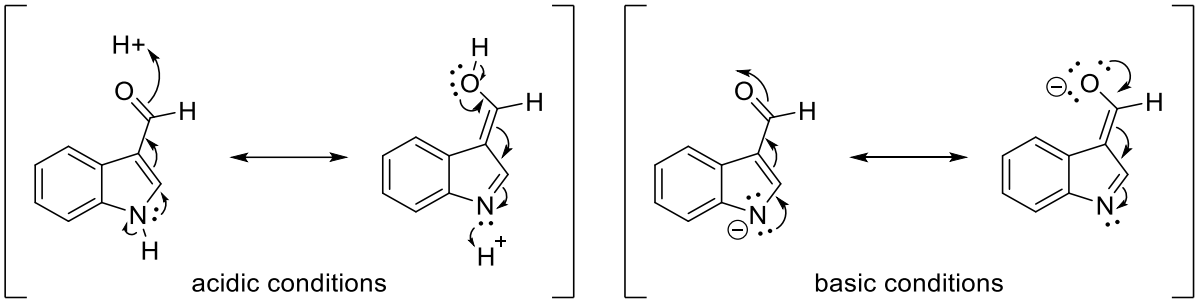
Scheme 41: Reductive amination for valuating approach 1 in subchapter 3.1.1. a) 1. 2.5 eq. NH_2CH_3, rt, 2 h, MeOH; 2. CH_3COOH (pH 6), 1 eq. $NaCNBH_3$, rt, 36 h. b) 5 eq. NH_2CH_3, rt, 4 h, MeOH; 2. 1 eq. $NaCNBH_3$, rt, 36c) 2 eq. $Ti(iPrO)_4$, 2 eq. NH_2CH_3, 18 $NaCNBH_3$, rt, 5 d. d) 1. 20 eq. NH_2CH_3, rt, 24 h, MeOH; 2. 1 eq. $NaBH_4$, rt, 1 h.

The first reductive amination a), as imaged in Scheme 41, was performed in the style of Borch et al.[87]. Although, the reaction description was followed minutely, no product **2** could be isolated through the reaction workup. Instead, merely the tertiary amine **7** was isolated in 42% yield. One theoretical explanation of the outcome, was that (imaged in Scheme 42) the equilibrium between the aldehyde **1** and the built imine **8** is shifted in favour of the aldehyde **1** side, although the small amounts of built imine **8** would be instantly reduced to an amine **2** under these conditions. Compared to methylamine as primary amine, the newly built secondary amine **2** is more nucleophilic, thus it preferably attacks the formyl group of **1** and the iminium species **6** forms which is further reduced to the tertiary amine **7**.



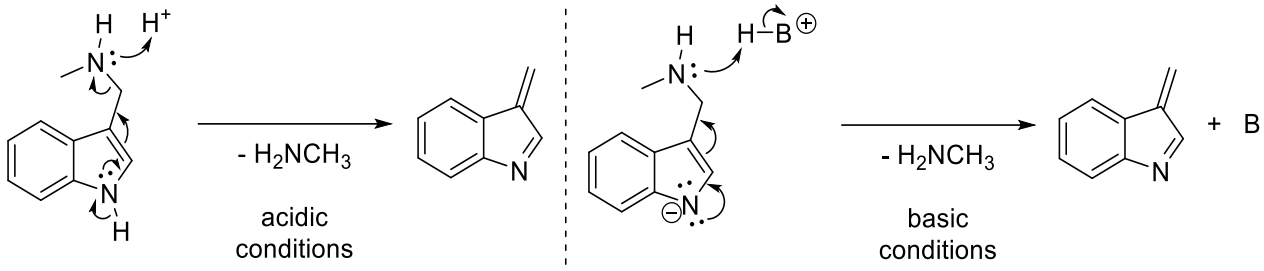
Scheme 42: Suggested mechanism for the preferred dimer formation at conditions a) in Scheme 41: Reductive amination for valuating approach 1 in subchapter 3.1.1.Scheme 41.

The second experiment b) (see the Legend of Scheme 41) was performed according to the same synthesis descriptions by Borch et al.[87], however for this experiment the equivalents of methylamine were increased and the addition of the glacial acetic acid was omitted. Regrettably, after the addition of the reduction agent, no amine **2** could be found again. The third experiment was performed using a variated method of the Borch reduction, this time using the Lewis acid $Ti(iOPr)_4$ instead of the Broensted acid, published by Mattson et. al.[88] in 2002. Deplorably, no product could be isolated from this reaction either. With these results from the Borch reaction, it was decided, that sodium cyanoborohydride might not be a fitting reduction agent after all. One last reaction d) (see scheme 41) was carried out using the method of Ferrarini et al.[89], using sodium borohydride instead, which can be worked with under basic conditions as well. Knowing this time, that the equilibrium between the aldehyde **1** and the built imine **8** shifts in favour of the aldehyde **1**'s side, the methylamine equivalents were increased severely and it was stirred for a longer time, before the reducing agent was added. After the working up processes the crude, dried impure solid was analysed by MS and NMR analysis. It could be detected in the spectra, that approximately half of the solid was the desired product, but when the product was purified by column chromatography though, no product could be received through that. When looking at the indole-3-carbaldehyde (**1**) under acidic conditions for example, it is incredible curious, that the formyl group would be so inert under those conditions used in the reactions a)-d) (see Scheme 41), because usually aldehydes are incredible reactive functional groups. This might be explained by a theory, which is imaged in Scheme 43. The formyl group of **1** is vinylogous connected to the indole nitrogen. In acidic or basic conditions, the molecule stabilized itself by switching between both resonance structures, whereby it becomes presumably very stable and more unreactive.



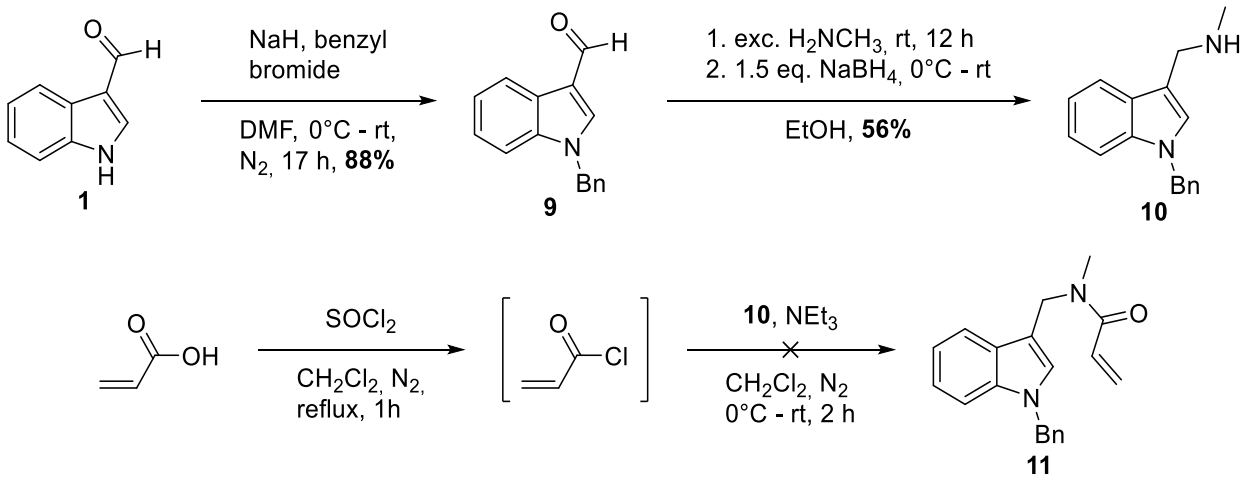
Scheme 43: Resonance structure stabilised indole-3-carbaldehyde **1** in acidic and basic conditions.

In principle, the same incidence might cause the observed instabilities of indole-3-methanamine (**2**), as is schematically illustrated for acidic and basic conditions in Scheme 44.



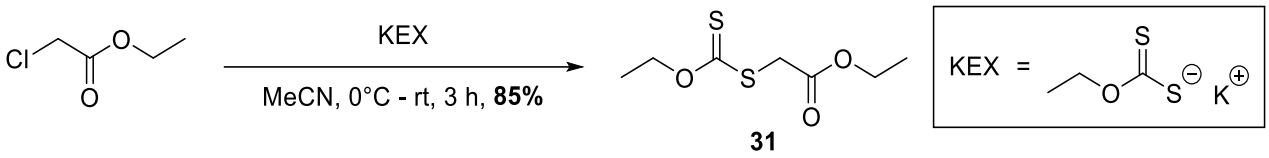
Scheme 44: Suggested mechanisms for the indole-3-methanamine **2** instabilities caused by acidic or basic conditions, whereby B = base.

On these grounds, it was decided to try one last reductive amination on an *N*-protected indole-3-carbaldehyde. When the indole nitrogen was substituted with a protective group for example, the molecule would be unable to form resonance structures which then would lead to a welcome lower stability, or rather higher reactivity, of the aldehyde educt and a higher stability in the desired amine product. As protection group, a benzyl residue was chosen for the model reaction. The benzyl protection of the indole-3-carbaldehyde (**1**) was performed according to the synthesis instructions of Xu et at.[90]. The reaction and purification processes proceeded without complications and product **9** could be obtained in very good yield (see Scheme 45). The gained aldehyde **9** was further chemically converted in a reductive amination, again using the method of Ferrarini et al.[89]. As imaged in Scheme 45, the desired *N*-methylamine **10** could this time be isolated in a 56% yield.



Scheme 45: Successful reductive amination of the benzyl protected idole-3-carboxadehyde and subsequent reaction with acryloyl chloride.

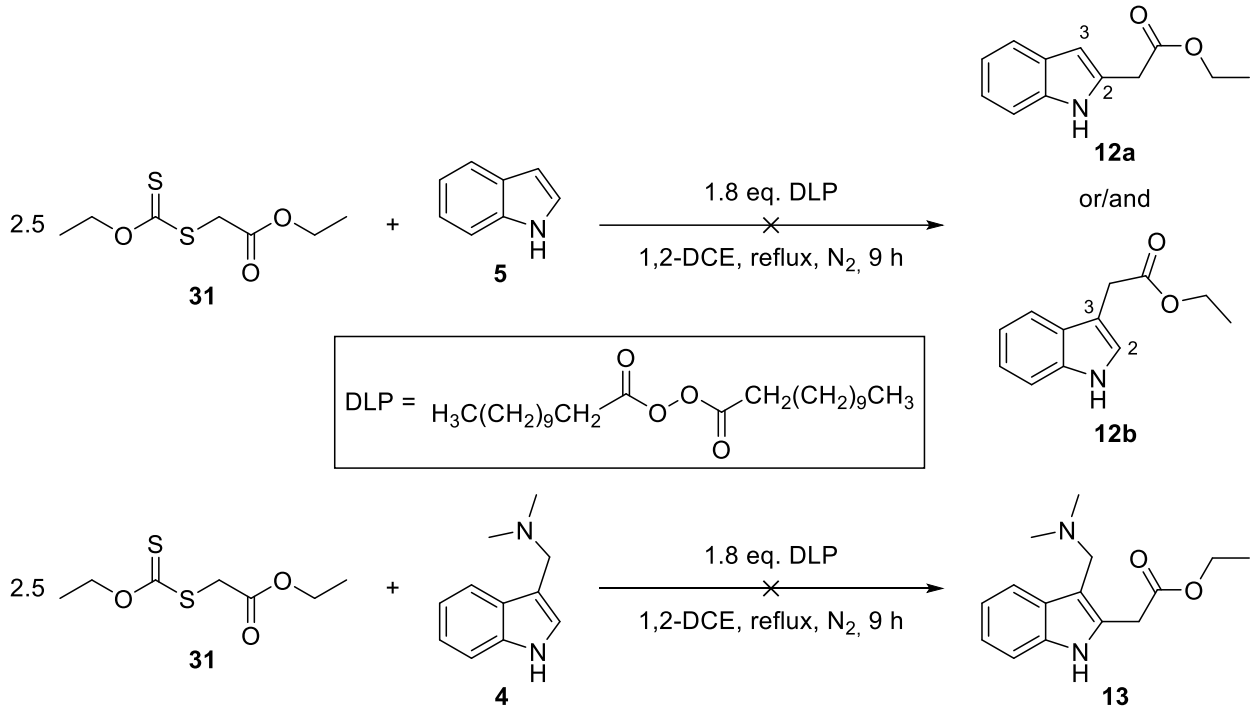
Further, acrylic acid was reacted with thionyl chloride to afford acryloyl chloride. The excess thionyl chloride was then removed in high vacuum, the crude acid chloride was redissolved in dry methylene chloride and under protective gas, triethylamine and the amine **10** were added. After having removed the solvent, the NMR and MS analysis of the crude resulting solid showed regrettably no traces of the desired acrylamide product **11**. Part of the educt **10** could be obtained back, while most of it seemed to have decomposed during the reaction. Although, there are some reported successful methods[91-92] for the preparation of indole-3-methanamines, at that point it was decided to not pursue the approach 1 further. The instability of indole-3-methanamines that was not only observed in my experiments, but also had been reported in literature earlier[91] , was a problem that could not even been overcome by using a benzyl protective group. As sole consequence, approach 1 was discarded, in the hope that the approaches 2 or 3 would lead to more promising results.



Scheme 46: First xanthate **31** model reaction.

The first reaction tried out using the preparation method of Reyes-Gutiérrez et al.[51], to test the accessibility of the remaining synthesis plans, was the xanthate synthesis. As pictured in Scheme 46, ethyl 2-chloroacetate and potassium *O*-ethyl dithiocarbonate, furthermore described abbreviated as KEX, could be converted to the corresponding xanthate **31** in a very good yield. For the approach 2, the radical substitution on the 2-position of indole (**5**) had to be carried through. Apart from that it had to be tested, if the reaction would be also applicable with gramine (**4**). The reaction conditions for both reactions, that can be seen in Scheme 47, were imitated as described

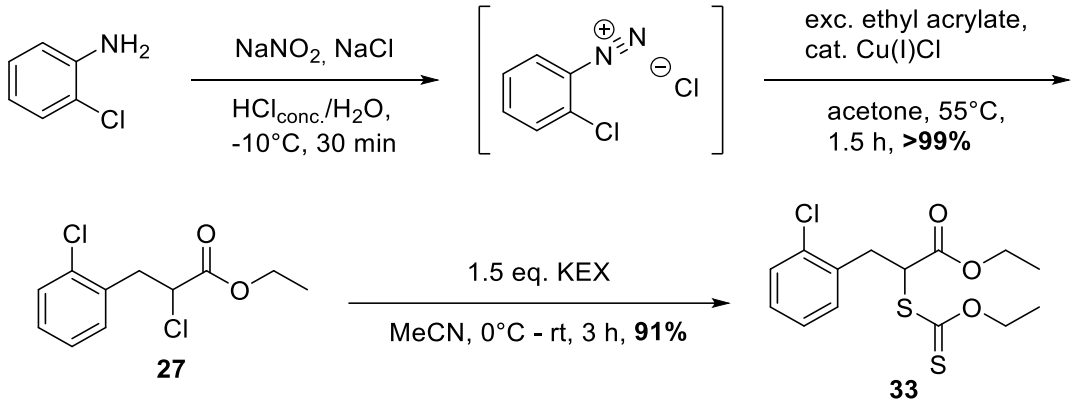
by Reyes-Gutiérrez et al.[51] again. 2.5 equivalents of the xanthate **31** and 1 equivalent of **4** or **5** were submitted to a flask and the added solvent was degassed with nitrogen for 15 min. The first portion of the radical initiator dilauroyl peroxide (see scheme 47), furthermore abbreviated as DLP, was added and the solution was refluxed to start the reaction. The entire mass of DLP was not added in one portion at the beginning of the reaction but was rather added in equal portions at the beginning of each hour. Every time the flask was opened for the addition, the reaction solution was degassed with nitrogen again.



Scheme 47: Model reactions for approach 2 in chapter 3.1.2.

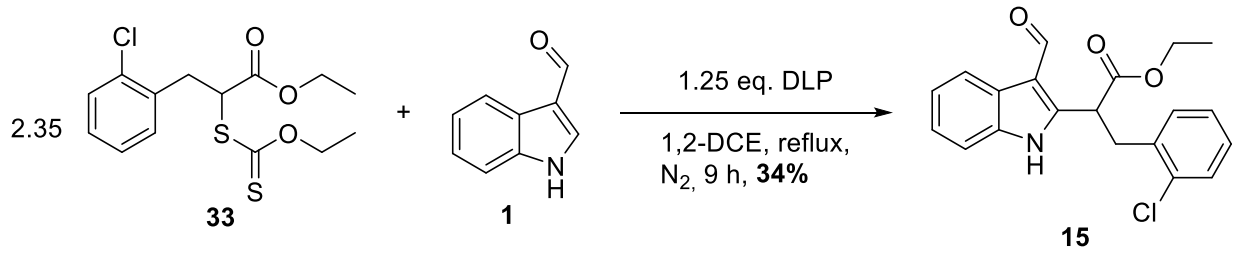
The model reaction on the unsubstituted indole (**5**) had already been described as successfully performed by Osornio et al.[59], however when the reaction was imitated with the same xanthate **31** they did it with[59], as can be seen in Scheme 47, only traces of the product could be found in the reaction mixture. It is unknown if the reaction was regioselective to gain the 2-position substituted product **12a** or the 3-position substituted product **12b**, since no sufficient amount of either could be isolated to obtain any analytic data from the substance, apart from an MS spectrum of course. It is to mention, that most of the used educt **5** could be recovered through the purification process. It if further to mention, that there was one significant difference between the reaction Osornio et al.[59] claimed to having performed and the one done for this work. The reaction for this work was carried out in five times the scale as they did it.[59] As can be seen in the second line of Scheme 47 also, the model reaction on gramine (**4**) yielded no product either. In this case, instead of not reacting, the educt seemed to have decayed during the reaction, therefore none of the educt could be obtained back. As consequence of the unsuccessful model reactions for the

approach 2, it had to be discarded in the hope that the model reactions for approach 3 would provide better prospects. In parallel to the model reactions for approach 2, it was essential to address the task of finding an efficient way to synthesise the building blocks of the type **A** (from Figure 10 in Chapter 3.1.2), which would be needed for approach 3. The reaction steps, as already elaborated in the Chapters 3.1.2 and 3.1.4, would be a Meerwein arylation, followed by a S_N reaction to substitute the halogen to give an *O*-ethyl dithiocarbonato residue. The first reaction step in Scheme 48 was performed in the style of Komoschinski et al.[93]. However, Cu(I)Cl instead of $Cu(II)Cl_2$ was used as a catalyst, since it made more sense when one considers the mechanism of the Meerwein arylation and in addition to that, Matiichuk et al.[94] have already reported in 2003, that Cu(I)Cl has worked just as well in their reactions.



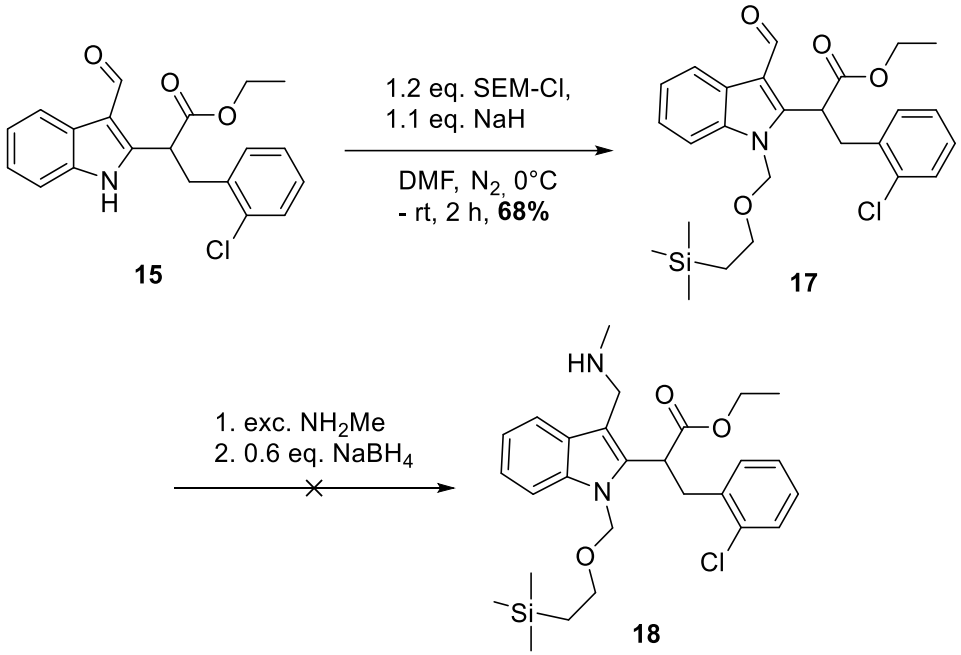
Scheme 48: Model synthesis of the first xanthate building block example **33**.

Starting with 2-chloroaniline as educt (in Scheme 48), the diazonium chloride salt was generated, which was further reacted in situ with an excess of ethyl acrylate in the presence of a catalytic amount of Cu(I)Cl. The resulting halide **27** could be isolated through the purification process in a quantitative yield. Using 1.5 equivalents of KEX, **27** was then converted in an excellent yield to the xanthate **33**, again following the preparation instructions of Reyes-Gutiérrez et al.[51]. Only the synthetic approach 3, described in detail in Chapter 3.1.3, was left at that point. If the radical substitution on the indole-3-carbaldehyde (**1**) failed, the Zard chemistry would be rendered inapplicable for the purposes of this project. When it was time to perform the model reaction on the indole-3-carbaldehyde (**1**), the xanthate **33** (in Scheme 48) had been already successfully generated. Since substance 33 contained already the *o*-chlorobenzyl residue, we actually wanted to substitute the C-2 of the indole-3-carbaldehyde (**1**) with, the radical substitution model reaction was performed with the xanthate **33** directly. Originally though, the intention was to use the xanthate **31** (see Scheme 46).



Scheme 49: Model reaction for the approach 3 (see chapter 4.1.1).

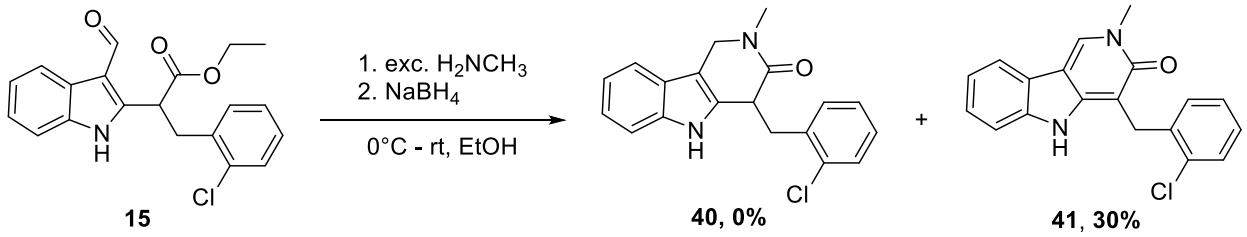
The reaction in Scheme 49, was performed according to the protocol of Reyes-Gutiérrez et al.[51] again, but with slightly decreased equivalents of the xanthate **33** and the radical initiator DLP. As can be seen, to our delight the desired product **15** could be obtained in a 34% yield. Deriving from product **15**, the reductive amination reaction wanted to be tried again. Since we have gathered the experience, that protecting the indole nitrogen would increase the stability of the built product, it was decided to protect the indole nitrogen of **15** with 2-(trimethylsilyl)-ethoxymethyl chloride (SEM-Cl) before the reductive amination was carried through. As can be observed in Scheme 50, the protection reaction according to the method of Muchowski et al.[95] worked with a fair yield of 68%. However, when the reductive amination reaction to **18** was performed again following the synthesis instructions of Ferrarini et al.[89], the reaction control indicated that instead of reacting, the educt **17** had just decomposed.



Scheme 50: SEM-protection of the indole **15** and attempted subsequent reductive amination to substance **18**.

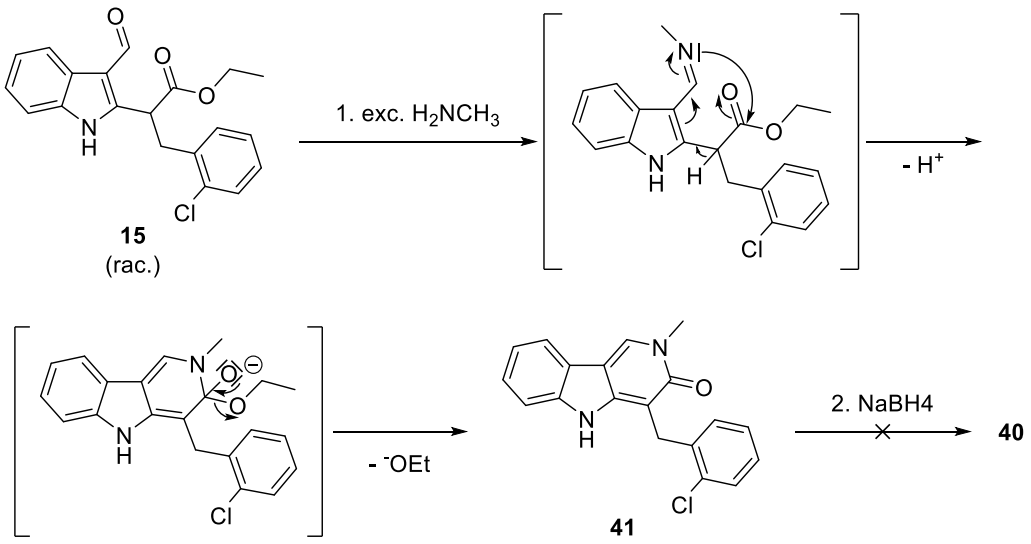
After having performed an NMR analysis of **17**, a small share of the substance of was laid aside, with the intention to analyse the substance by mass spectrometry and IR later. Though when dealing with the substance a few days later it was discovered that the substance had completely

decayed. For this reason, only the NMR analysis is displayed in the experimental part (see Chapter 7.3.3) for the compound **17**. Presumably this intrinsic instability of **17** lead to the failed reductive amination reaction. Having this unexpected result, there was just one other option left to try, which was performing the reductive amination without a protective group on the indole nitrogen. As can be seen in Scheme 51 the reductive amination, following the synthesis instructions of Ferrarini et al.[89], yielded the pyridone **41** in a 30% yield, rather than the open-chain amino ester or the expected dihydropyridone **40**. Interestingly, no remaining educt or any derivative from it could be isolated from the purification processes, concluding that most of the educt or any derivative of that must have decomposed during the reaction.



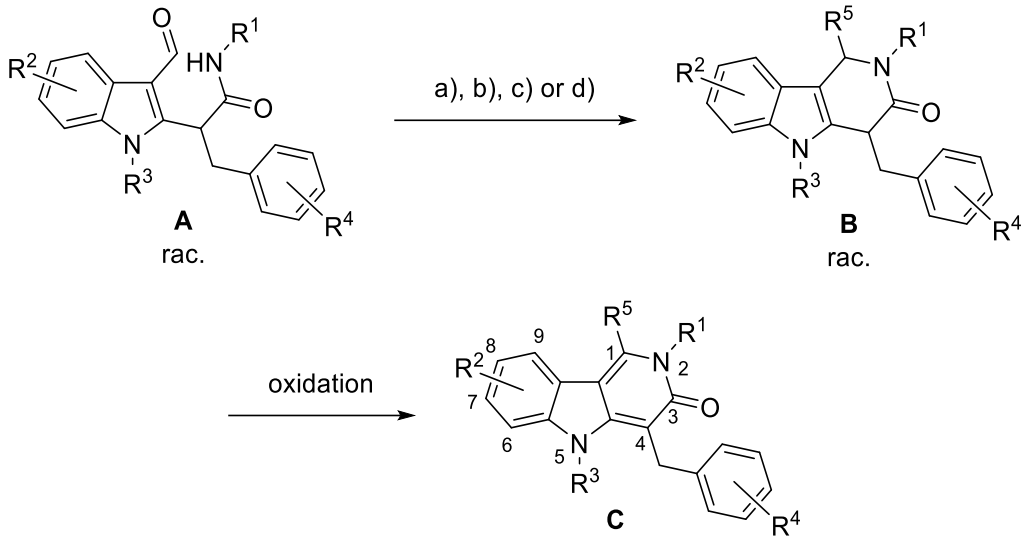
Scheme 51: Last step - the reductive amination reaction, with the 2-substituted indole-3-carbaldehyde **15**, leading directly to the 3-oxo-γ-carboline **41**.

When one looks at the reaction outcome shown in Scheme 51, there is only one logical explanation for this result. Scheme 52 shows the proposed mechanism of the last synthesis step. The built imine, descending from the aldehyde **15**, instantly attacked the ester's carbonyl group in proximity while at the same time, the to the carbonyl α-positioned proton was eliminated through the added methylamine base. After that reaction step, ethanolate was eliminated to create the pyridone's A-ring of the resulting 3-oxo-γ-carboline **41**.



Scheme 52: Reaction outcome of the first exemplary reductive amination reaction.

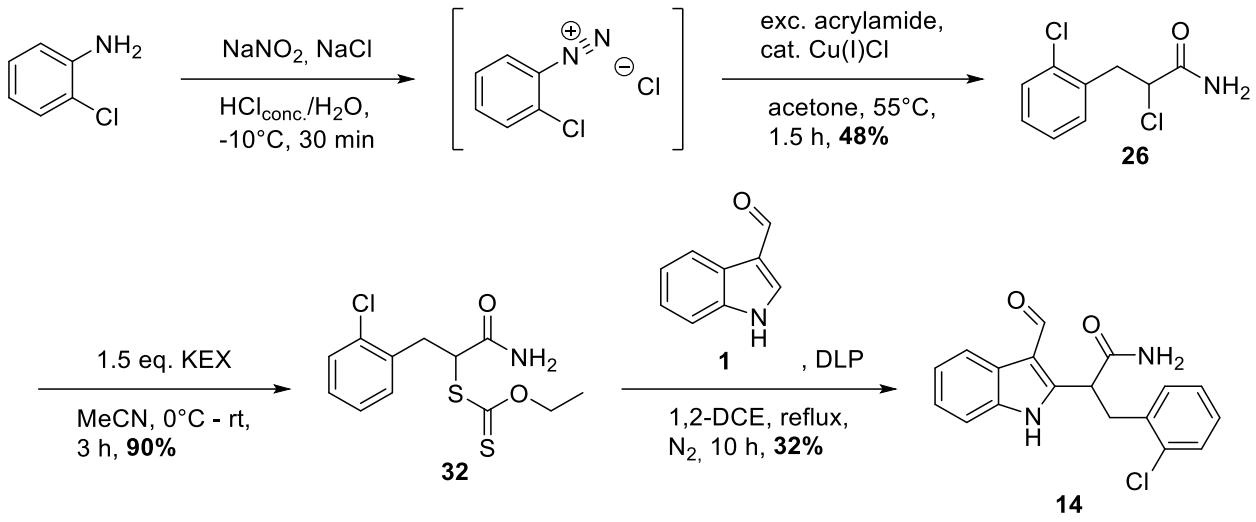
That did all happen before the reducing agent could be added to the solution. This claimed mechanism was of course later double checked with a control experiment. To anticipate it, later during the exemplary syntheses of the 3-oxo-γ-carbolines**,** the exact same method was used to generate them from their aldehyde educts. Since the preparation of the 3-oxo-γ-carboline **41** was performed successfully only by the addition of an amine, while the reduction agent addition was omitted, therefore the proposed mechanism can, with a probability bordering on certainty, equated with the one in Scheme 52. When looking at the structure of **15** in Scheme 52, the α-positioned methine group is on the one hand influenced by the electron withdrawing effect of the ester's carbonyl group and on the other hand connected by vinylogy to the electron withdrawing effect of the formyl (or imine) group, rendering the methine group quite acidic. The ethoxy group elimination though is essential for the dihydropyridone **40**/ pyridone **41** formation. Alcoholates are known to be quite strong bases and also because having a slight excess of also basic methylamine, the acidic methine group eliminates the proton readily. This side reaction consequentially arising from the basic conditions, in which it was worked, could be foreseen although we did expect that it happened rather under an energy-enriched condition, for example by applying heat to the reaction solution. Using stochiometric amounts of methylamine and performing the reaction under cooler conditions, would probably not solve the problem. The A-ring formation requires the ethanolate elimination, which is a too strong base apparently that would always deprotonate the acidic methine group consequently leading to the pyridone **41** formation again. Trying the Borch reduction again was considered, but the former bad experiences with the reaction for indole-3-aldehydes, mentioned at the beginning of this chapter, brought us to the conclusion, that there was maybe a better functional group than the ester group originating from which we could construct the dihydropyridone's A-ring and that in addition would give us more control over the last reaction step or rather over the acidic proton. If one had an amide group instead of the ester group, there were a few other options to perform the ring closure reaction, this time inducing an intramolecular reaction between the formyl and the amide group of an **A**-type substance, using reductive and other conditions - the suggestions a)-d) for an alternative ring closure reaction can be seen in labelling of Scheme 53.



Scheme 53: Potential intramolecular ring closure reaction between an amide and the formyl group of **A**. a)[96] TFA, Et_3SiH, CH_2Cl_2, H_3CCN or toluene, rt, 2-4h; b)[97] 1. Ti(*i*OPr)$_4$, 18 h, THF, rt; 2. RMgX or $NaBH_4$, THF, 1 h, 60°C (R = Alk, (Het)Ar; X = Cl, Br); c)[98] (Het)Ar, cat. Bi(OTf)$_3$, DCM, DCE or $MeNO_2$; d)[99] Pd/C/Na_2SO_4, H_2, 40 bar, EtOAc, 100°C (Eschweiler-Clarke conditions).

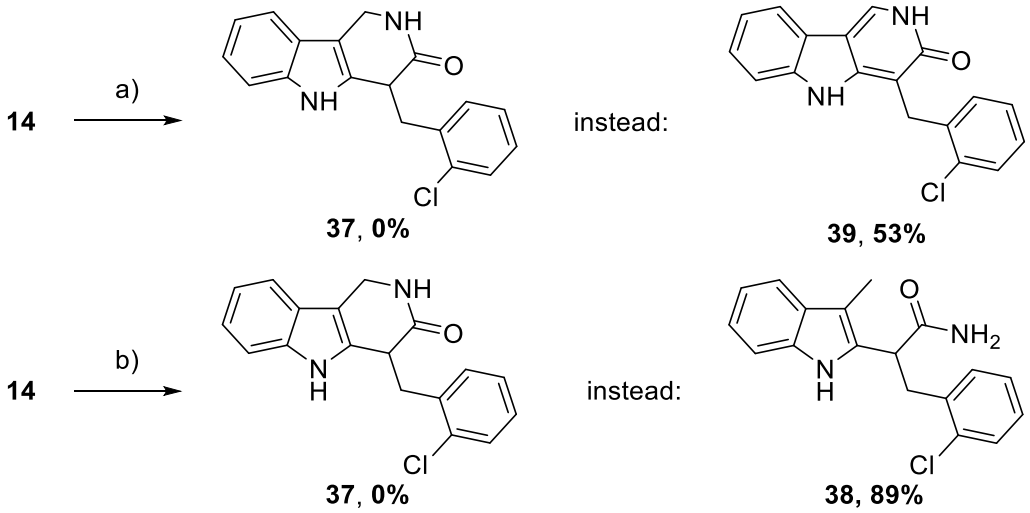
Dubé et al.[96] for example have published a method in 1999, synthesising an amide (for R^5 = H in Scheme 53) from an aldehyde and another amide using the reduction agent triethylsilane (Et_3SiH) under strongly acidic conditions[96]. Dai et al.[97] have published an interesting way (see method b) in Scheme 53) using a Lewis acid (Ti(*i*OPr)$_4$) to induce a condensation reaction between the amide and aldehyde group to an imine[97]. After that reaction step was completed, they used a Grignard reagent to introduce an alkyl residue into the structure[97], that if we copied that style, in our scenario would allow us to introduce an alkyl residue R^5 on the 1-position of the 3-oxo-γ-carboline of the type **C**. This potential made this synthetic approach particularly interesting. They also reported, that if they used $NaBH_4$ instead of the Grignard reagent, they had obtained a hydrogen on the to the nitrogen α-positioned residue[97], that would, if we applied the same method again, analogously be our residue R^5. Reaction conditions c) were published by Schneider et al.[98]. They reported a three-component reaction between amides, aldehydes and arenes[98]. In this case an imine condensation between an aldehyde and an amide functional group was induced by the Lewis acid Bi(OTf)$_3$.[98] The created imine, again induced by Bi(OTf)$_3$, was in this case nucleophilicly attacked by the arene's electrons, creating finally an amide with an to the amide nitrogen α-positioned methylene group that was on the other side connected to the arene group.[98] The last synthetic variant labelled as conditions d) in the legend of Scheme 53, was published in 1994 by Fache et al.[99]. They reported an *N*-alkylation of amides using Eschweiler-Clarke conditions.[79] For this last method d), for our educt, we would only get a proton as residue R^5. Since there are so many synthetic options not only for potentially getting the reduced version **B** of our **C**-type 3-oxo-γ-carboline, but also because it could allow the potential structural variation of introducing an alkyl

residue for R^5 which would finally become the residue at the 1-position of **B** and **C** in Scheme 53, we had to try synthesising the amide **14** in Scheme 54.



Scheme 54: Synthesis of the amide **14**.

Generating the Meerwein arylation product **26** in Scheme 54, using the synthetic instructions of Komoschinski et al.[93] again, now using acrylamide as the Michael system, went with fair yields. The xanthate **32** could be obtained in an excellent yield, whereby the radical substitution reaction at C-2 of indole-3-carbaldehyde (**1**) provided only a 32% conversion to **14**. Both reactions were performed according to the method of Reyes-Gutierrez et al.[51] again. From **14** as educt, using conditions a)[96] and b)[97] (detailed conditions can be found in the legend of Scheme 55), it was tried to prepare the dihydropyridone **37**.



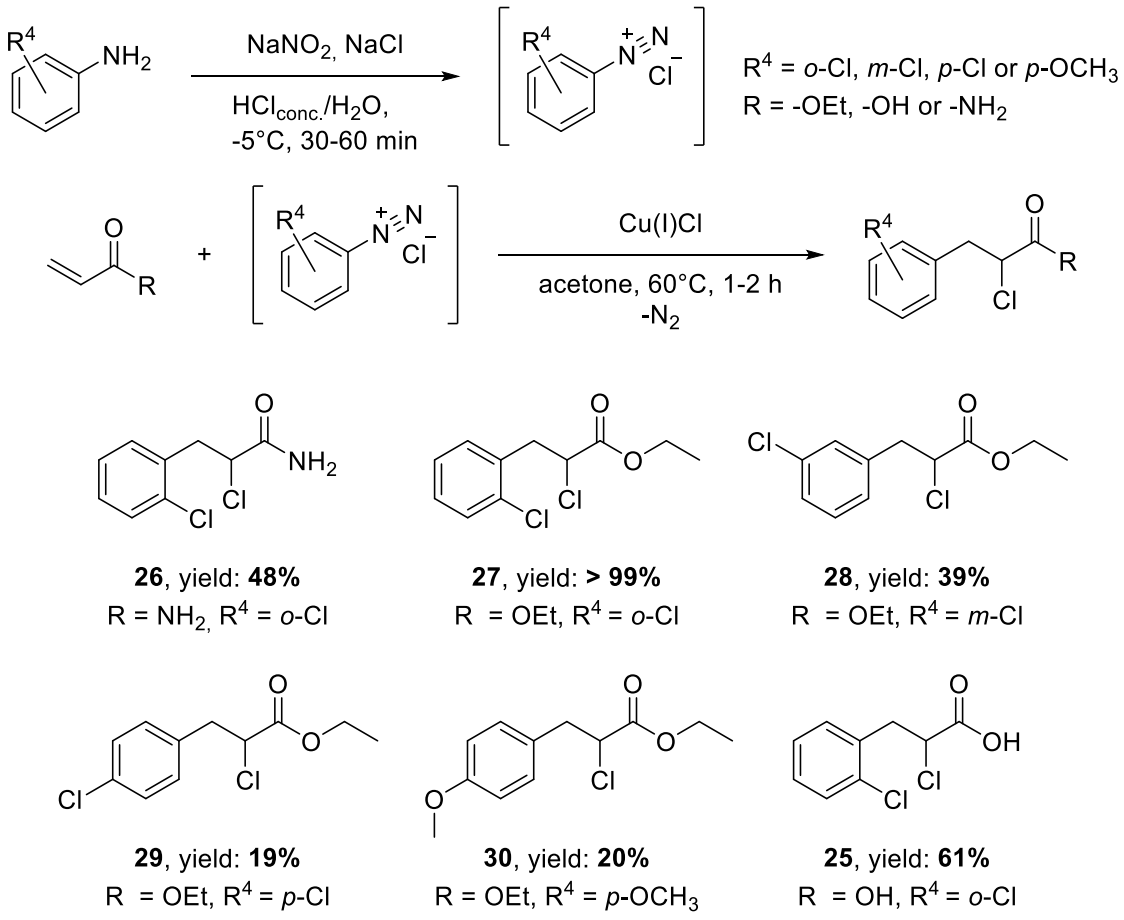
Scheme 55: Failed syntheses of **37**. a)[96] TFA, Et_3SiH, H_3CCN, 24 h, 50°C b)[97] 1. Ti(*i*OPr)$_4$, 1 h, THF, 0°C - rt; 2. $NaBH_4$, THF, 2.5 h, rt.

With the reductive conditions a), we surprisingly did obtain the pyridone **39** instead. That outcome showed, that even under quite acidic and reductive conditions, the pyridone **39** formation was

unexpectedly preferred. The conditions b) also did not yield the expected product, but instead the 3-methylated indole analogue **38** was isolated. This result suggested that the aldehyde just was reduced not only to an alcohol, but the results suggest, that the alcohol was then further reduced to the C-2 substituted 3-methyl-1*H*-indole **38**. Alternatively, the built dihydropyridone **37** was not stable under these conditions. Either way the product **37** could not be obtained through these conditions. The synthesis of the educt **14** (in Scheme 54) did not yield high amounts of product, and therefore there were problems to accumulate enough substance amounts. Because of this reason and because there was another time-consuming project that required attention, a break was taken at that point from searching for a synthetic way to prepare the dihydropyridones. The amide **14** might still be a potential precursor for the dihydropyridone **37**, but the research for a synthetic pathway to generate dihydropyridones was regrettably not resumed during the time frame of this work. To anticipate it, the accumulation problems for the products, that came up during the radical substitution reactions, are in detail described in Chapter 4.1.2. Concluding the results from all the model reactions performed for the planned approaches 1-3 (elaborated in the subchapters of Chapter 3.1), only approach 3 led to one successful total synthesis of one exemplary 3-oxo-γ-carboline, which was **41** (in Scheme 52). Although this pathway potentially might provide a good method to prepare 3-oxo-γ-carbolines in only a few steps, the model reactions showed that it will most likely not provide a good solution for the generation of their reduced analogues.

4.1.2 3-Oxo-γ-carbolines syntheses

Since in the last chapter one 3-oxo-γ-carboline total synthesis has been successfully performed following the synthetic approach 3 (elaborated in subchapter 3.1.3), we wanted to show on a few exemplary syntheses, that this synthetic approach can be performed for a variety of substituted anilines. The lead structure **uwIND086** (see Figure 7 in Chapter 2.1) has an *ortho*-chloro benzyl residue on the 4-position, it was started with slight structural variations of the 4-benzyl residue or rather said with the syntheses of the building blocks. The Meerwein arylation products as shown in Scheme 56, were all synthesised according to the method of J. Komoschinski et al.[93], again with the one variation of using Cu(I)Cl instead of Cu(II)Cl_2 since we learned from Matiichuk et al.[94], that the reactions would also be feasible with a copper(I) salt[94].

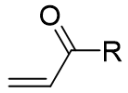


Scheme 56: Results for the Meerwein arylations, performed for the building blocks syntheses.

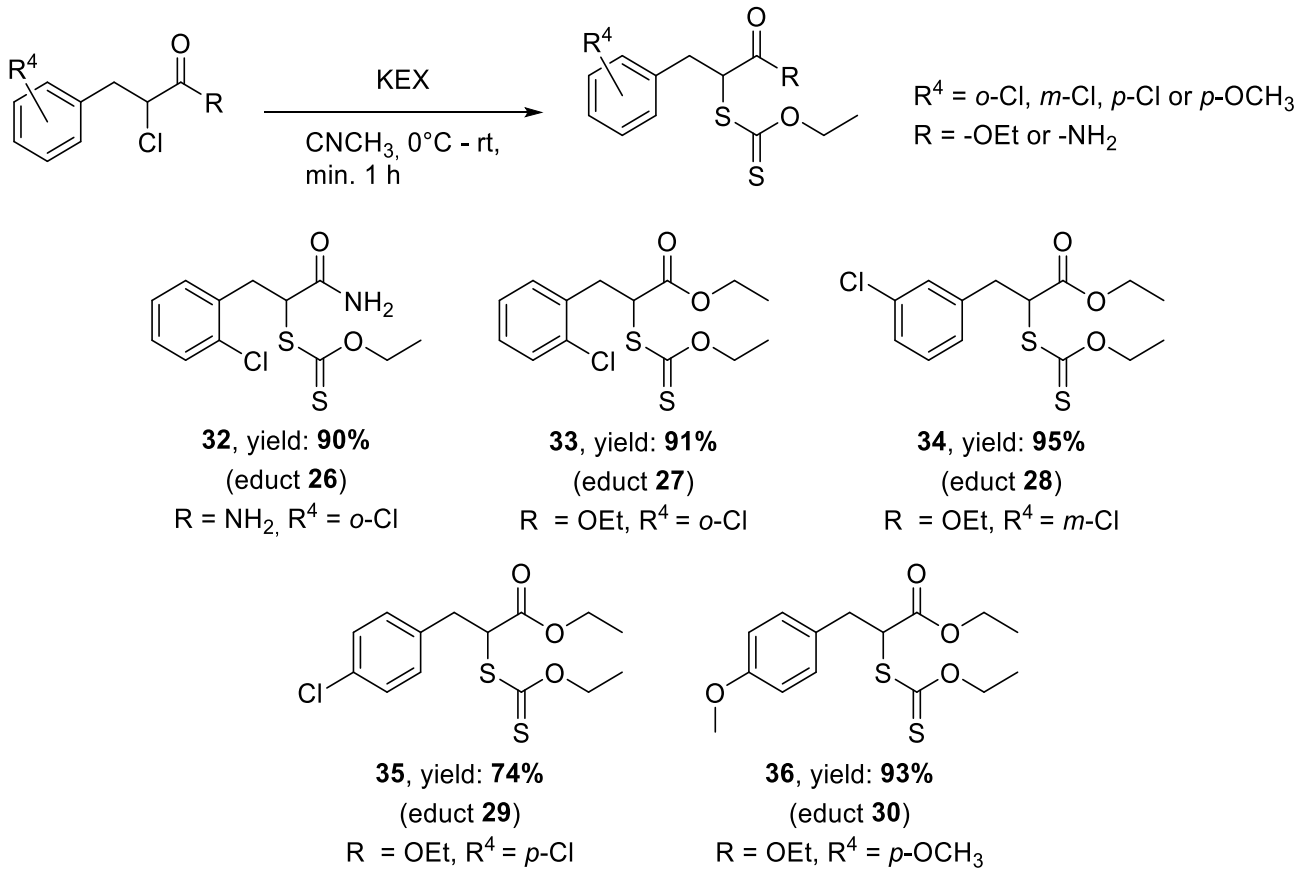
With the original ulterior motive to further pursue the route establishment for the dihydropyridones, also the carboxylic acid **25** was generated, which should hereinafter be used as a starting material to generate a variety of *N*-alkylated amides from it. Compound **25** was incidentally not converted to a xanthate, because there was a high chance that the carboxylic acid group was not compatible with the Zard chemistry. This statement is based on an observation of Zard and co-workers[100] that was reported in 2018. They found out that a carboxyl group and the *O*-ethyl dithiocarbonate

residue can exist next to each other in one molecule[100], but if one tried the radical substitution reaction, after the reaction had taken place, the carboxyl group of the substituted residue would decompose into carbon dioxide while leaving the corresponding alkyl residue behind[100]. It therefore made no sense for this project to convert the carboxylic acid **25** into a xanthate. As can be observed when looking at Scheme 56, the Meerwein arylation yields for the different products **25**-**30** went from poor to quantitative, including the results from the model reactions in the last chapter. These specific outcomes had nothing to do with the different reactivities of the functional groups as was learned later. Intending to accumulate a larger quantity of halide **29** (see Scheme 56), the reaction was repeated, coincidentally using different aniline educt scales, while the other reagents were increased or decreased proportionally. Interestingly, when scaling up the reaction, the yields turned out to be higher. When decreased educt amounts were used accordingly, the yields would decrease. The same phenomenon could be observed for three different products (**27**, **28** and **29** from Scheme 56), that had been exemplary synthesised in differently scaled reactions. The specific educt amounts and the resulting yields are all displayed in Table 1.

Table 1: Scaling experiments for the Meerwein arylation products **27**-**29**.

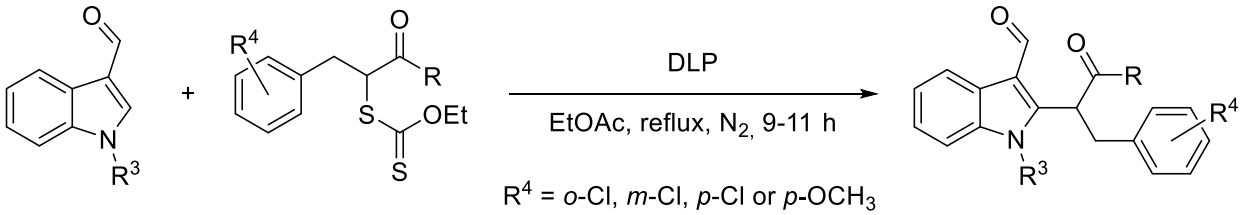
product		**aniline educt R^4**	**n (aniline educt)**	**yield**
27	R = OEt	*o*-Cl	19,6 mmol	**20%**
			39,2 mmol	**>99%**
28	R = OEt	*m*-Cl	157 mmol	**35%**
			236 mmol	**39%**
29	R = OEt	*p*-Cl	9,76 mmol	**1%**
			38,6 mmol	**3%**
			115 mmol	**14%**
			230 mmol	**19%**

For the first reaction step of the synthesis route, that phenomenon would actually be an advantage when one considers potential industrial production later. For some of the products in Scheme 56 we just accepted the poor yields instead of wasting time further optimizing the reaction, because simply there were already enough of the product amounts to go on with. The next synthesis step for generating the building blocks was the substitution reactions with potassium *O*-ethyl dithiocarbonate (KEX) to generate the xanthates for the subsequent radical substitution reactions. As shown in Scheme 57, the syntheses for the xanthates **32**-**36** all went with good to excellent yields. Again, the results from the model reactions in Chapter 4.1.1, which yielded **32** and **33** are displayed with the other synthesised xanthates **34**-**36**.

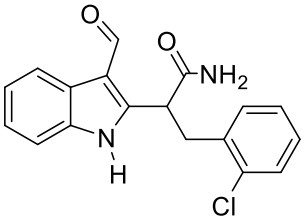


Scheme 57: Performed xanthates **32**-**36** syntheses to generate the building blocks from the halide educts **25**-**30** from Scheme 56.

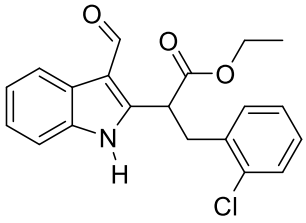
The radical substitution reactions (see Scheme 58) were again performed following to the preparation protocol of Reyes-Gutierrez et al.[51] Either indole-3-carbaldehyde (**1**) or alternatively the *N*-methylated derivative **123** were used as educts. The xanthate products **32**-**36** were used as coupling partners and were utilized normally as a 2.5 equivalents excess, with regard to the one equivalent of (*N*-methyl) indole-3-carbaldehyde educt (**1**) or (**123**). The elaborated reaction conditions can be extracted from the Chapters 7.2 and 7.3.4. When looking at Scheme 58, the results were similar to the two model reactions from the last chapter. Including the results from the model reactions, the yields were all between 15% and 49%. Since the isolated product yields were so poor, in an attempt to accumulate enough of each substance, the syntheses were repeated again using coincidental (*N*-methyl) indole-3-carbaldehyde (**1**) or (**123**) educt amounts, while the other reagents were increased proportionally. This time, when the reactions were scaled up though, it seemed as if the product yields decreased unproportionally.



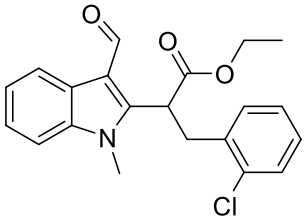
R^4 = *o*-Cl, *m*-Cl, *p*-Cl or *p*-OCH_3
R^3 = H or CH_3; R = -OEt or -NH_2



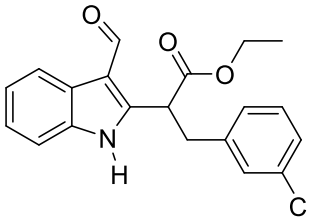
14, yield: **32%**
(xantate educt **32**)
R = NH_2, R^3 = H, R^4 = *o*-Cl



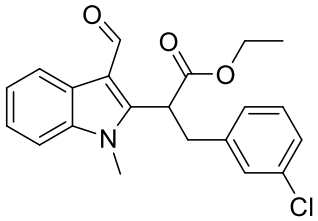
15, yield: **34%**
(xantate educt **33**)
R = OEt, R^3 = H, R^4 = *o*-Cl



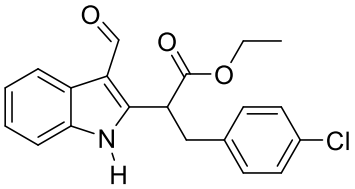
16, yield: **21%**
(xantate educt **33**)
R = OEt, R^3 = CH_3, R^4 = *o*-Cl



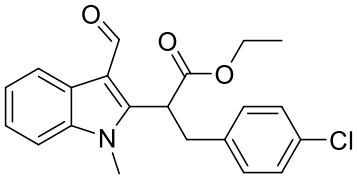
19, yield: **43%**
(xantate educt **34**)
R = OEt, R^3 = H, R^4 = *m*-Cl



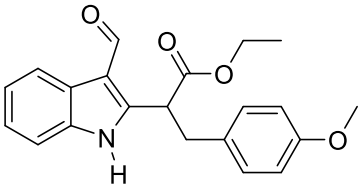
20, yield: **39%**
(xantate educt **34**)
R = OEt, R^3 = CH_3, R^4 = *m*-Cl



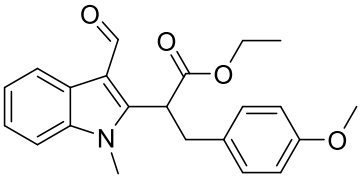
21, yield: **24%**
(xantate educt **35**)
R = OEt, R^3 = H, R^4 = *p*-Cl



22, yield: **33%**
(xantate educt **35**)
R = OEt, R^3 = CH_3, R^4 = *p*-Cl



23, yield: **49%**
(xantate educt **36**)
R = OEt, R^3 = H, R^4 = *p*-OCH_3



24, yield: **15%**
(xantate educt **36**)
R = OEt, R^3 = CH_3, R^4 = *p*-OCH_3

Scheme 58: Results for the radical substitution products **14**-**16** and **19**-**24**. The corresponding xanthate educts **32**-**36** can be extracted from Scheme 57.

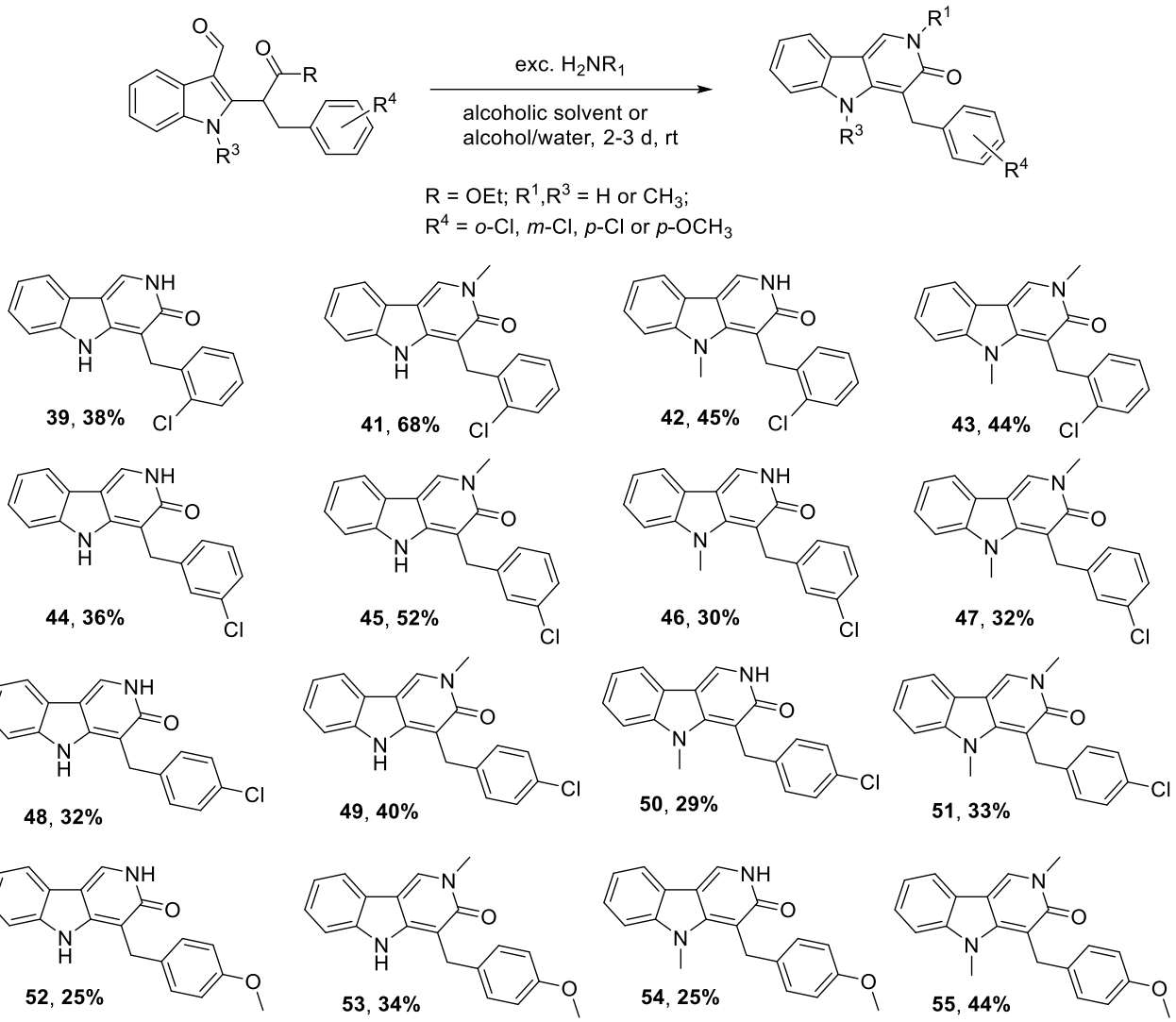
The yields of the differently scaled reaction, this time for the products **14**-**16** are exemplary illustrated in Table 2, proving that scaling up the radical substitution reactions leads to decreased yields. When looking at these results, it might be justified to critically question the outcomes of the model radical substitution reactions with gramine (**4**) and the 2,3-unsubstituted indole (**5**) in Chapter 4.1.1, which had been performed in rather larger scales. It is possible, that the model radical reactions did not yield any product, exactly out that reason that they were scaled too high. It is unclear however, if that is a for this project specific problem, or if this phenomenon is a common problem of this chemistry.

Table 2: Scaling experiments for the radical substitution reaction. Educts **32**-**34** can be gathered from Scheme 57, whereas the products **14**-**16** can be from Scheme 58.

product	xanthate educt	xanthate amount	n (indole educt)	yield
14	**32**	1.5 eq.	1.07 mmol	**32%**
		1.5 eq.	2.42 mmol	**22%**
16	**33**	1.2 eq.	923 µmol	**21%**
		1.2 eq.	1.72 mmol	**17%**
15	**34**	1.2 eq.	1.38 mmol	**34%**
		1.2 eq.	8.62 mmol	**22%**

The poor yields and the further yield decimation when scaling up the reactions caused significant problems during my syntheses. Most of the reactions to give the products **14**-**16** and **19**-**24** had to be performed several times to accumulate enough of the substances to perform the final two reactions that had been planned for each educt **14**-**16** and **19**-**24**. Another problem appeared during the syntheses. When observing the reaction TLC controls, they always showed that lots of side reactions had happened apart from the wanted reaction, rendering the crude products very hard to purify. The products could only be purified by column chromatography, whereby it is to mention that all the products required several purification attempts and in some cases could not even be purified to our satisfaction. The products also showed instability in even slightly acidic conditions, which as consequence came with a necessity to distillate the column chromatography solvents over K_2CO_3 before using them. These problems hindered the project a lot concerning the invested time juxtaposed to the generated results. Finally having enough of each substance **14**-**16** and **19**-**24,** the 3-oxo-γ-carboline syntheses could be performed following our own synthetic protocol from Chapter 4.1.1., in which the failed synthesis of the dihydropyridines yielded the 3-oxo-γ-carbolines instead. This time of course, no reduction agent was added. All the detailed reaction conditions, as can be seen in Scheme 59, the 3-oxo-γ-carbolines went from fair to rather poor yields. The products **41**, **42**, **46** and **48** could be gained through crystallisation or precipitated spontaneously during the reaction while the rest of the products needed to be purified by column

chromatography. The TLC reaction controls showed in most of the cases that all the educts had reacted, but either a lot of side reactions had happened or some of the products had probably decayed after the formation, which proportionally caused the poor yields. Another problem appeared during the purification processes. As was realized for the first synthesised substance **41**, during the column chromatography purification, a significant amount of product was lost due either product instability or poor solubility, which was curious.



Scheme 59: Performed 3-oxo-γ-carbolines syntheses.

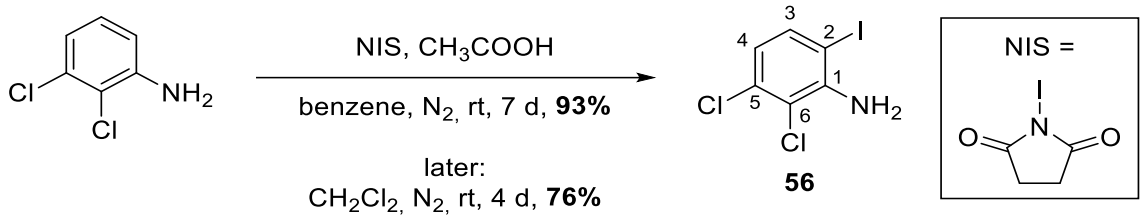
After the column purification, the excess of solvent had to be removed. When too much heat was applied through the rotary evaporator bath though, the solution visibly changed colour. When the concentrated solution was then examined by TLC control, it seemed like more substance components had appeared. The whole substance classes stability seemed to be prone to heat induced degradation when being in solution, therefore it was tried later with the other products not to apply too much heat during the solvent evaporations. These problems were unexpectedly a challenge for this substance class, because most of the substances were hardly soluble but still

had to be purified by means of column chromatography. It is esteemed that the product yields were much higher than the ones actually isolated, but some of the product amounts went regrettably irrecoverably lost through the purification processes.

4.2 Project β-carbolines

4.2.1 Ortho-selective iodinated anilines as essential precursors

The first synthesis that needed to be performed, was the *ortho*-iodination of 2,3-dichloroaniline. We found two remarkable papers, published by Shen et al. in 2011 and 2012, in which they claimed, having found a – and to quote them – "convenient, regioswitchable method"[77] to iodinate 2,3-dichloroaniline in an overwhelming regioselectivity either the *ortho*- or *para*-position of the aniline's -NH_2 group.[77, 101] According to them, and as already mentioned in Chapter 3.2.1, the *para*-product formation tends to form much more willingly in general, but according to their results the *ortho*- or *para*-product ratio could simply be manipulated, depending simply on the used solvent.[77, 101] Since these authors had reported before that methylene chloride or even better benzene brought the highest yields for the regioselective *ortho*-iodination, whereby it is to mention that in the case of methylene chloride, they've reported yields around poor to fair and very good ones for benzene.[77] They further reported much higher yields, when only one equivalent of acid was used rather than an excess.[77] Based on these results, I decided to perform the first try with statically dried benzene, knowing that if the yields were high enough I might later switch to the much less harmful methylene chloride, in the hope, that this variation would also bring sufficient yields. The protocol of Shen et al.[77] was used with two slight variations – in my case only dried solvents were used and the reactions were performed under nitrogen atmosphere.



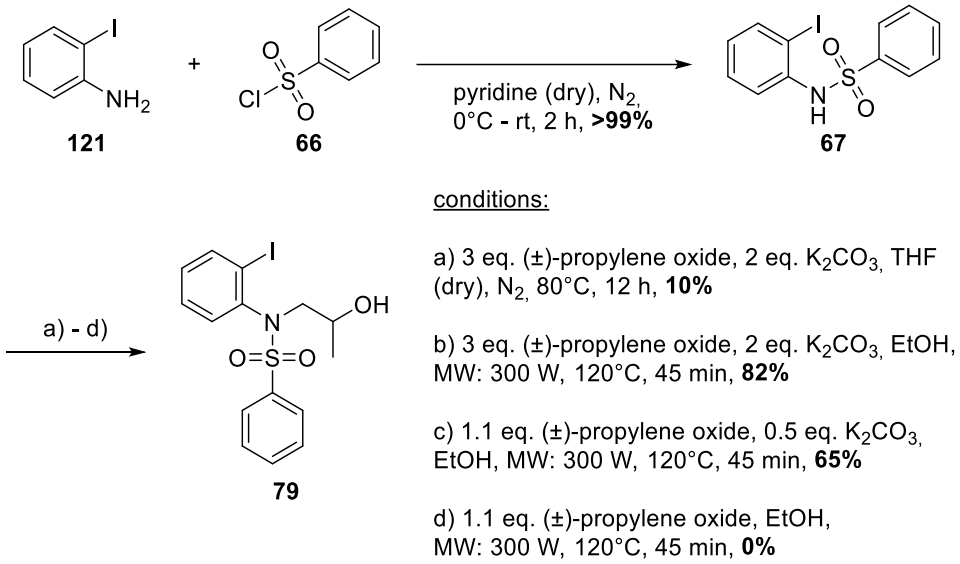
Scheme 60: First experiments to regioselectively *ortho*-iodinate 2,3-dichloroaniline.

The reaction (see Scheme 60) was performed the with 1.09 equivalents of NIS, 1.19 equivalents of glacial acetic acid and benzene as a solvent. The first experiment, the reaction brought a stunning 93% yield for the regioselective *ortho*-product **56**. Later, the same reaction was performed with methylene chloride as a solvent and yielded 76% of **56**, which was still an adequate amount of substance to go on with and should actually been preferred, if anyone has to repeat this specific synthesis later. In both cases, the reaction progress was monitored by TLC control and both reactions were only aborted when no educt was visible on the TLC control any more. After having satisfactory results for this reaction, the next aim was to find the best way to prepare the 2,3-substituted indoles, knowing that based on having a good way to prepare 2-iodo-5,6-dichloroaniline the Heck approach would be the most interesting method to introduce the unsaturated residue at the 6-C of the aniline. Actually, only one synthetic example has been tried

for this project, since it was the only *ortho*-iodinated aniline that was needed. If anyone was interested in preparing further *ortho*-iodinated anilines, holding other functional groups, the findings of this work or rather the findings of Shen et al.[77, 101], are an ideal basis to start with.

4.2.2 2,3-Disubstituted indole intermediates - model syntheses for approach 1

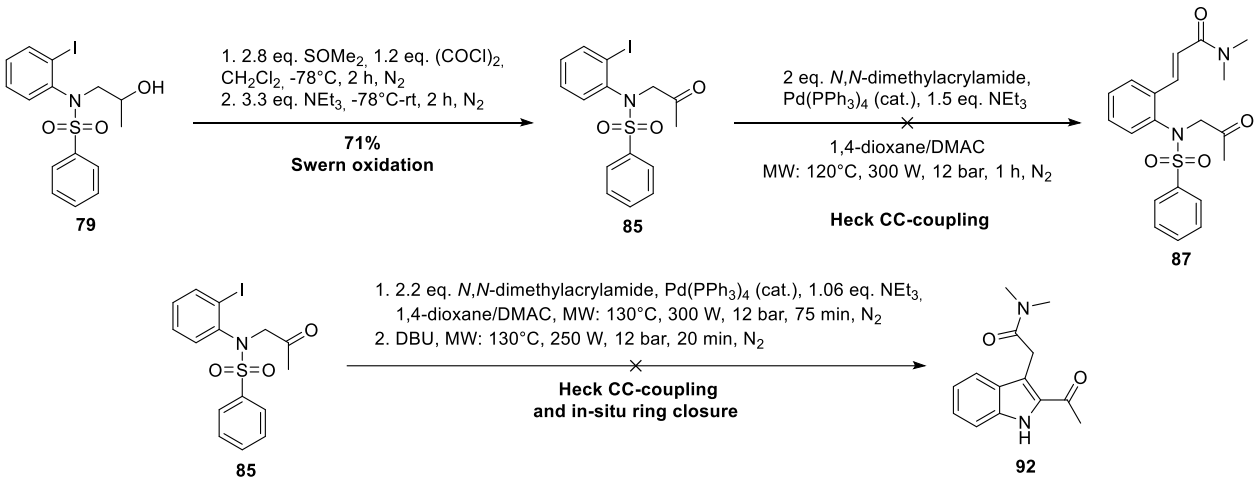
From here, as expressed beforehand, the route development was conducted with 2-iodoaniline instead of 2-iodo-5,6-dichloroaniline, since it was the cheaper starting material and as again mentioned earlier, previous investigations showed, that these chloro-substituents might become an interference factor during the route development, which might decrease the yields. As already outlined in Chapter 3.2.1, I tried the approach 1 (see Scheme 61) first, in which the sulfonamide **67** should be generated as a first step.



Scheme 61: Method finding – The first test reactions for approach 1.

Imaged in Scheme 61, are the first test reactions for the first approach. Using the preparation protocol of Yin et al.[102], starting from 2-iodoaniline (**121**) and benzenesulfonyl chloride (**66**) whereby no additional solvent was used next to the dry pyridine, yielded the sulfonamide **67** very satisfyingly in a quantitative yield and the product could easily be purified by column chromatography. The next reaction should be a nucleophilic ring opening reaction of propylene oxide to obtain the alcohol **79**. According to literature, sulfonamide groups easily perform nucleophilic ring opening with epoxides (and K_2CO_3 as auxiliary base).[103] When searching for the best preparation method, I found, there was a moderate variety of synthetic options, to induce this type of reaction between epoxides and sulfonamides. Most of the publicised methods included bases, acids, Lewis acids or some sort of Lewis acid-base combination or were simply performed using no auxiliary reagents to induce the reaction. I decided to just perform a few test reactions in the beginning with Broensted bases, starting with a protocol published by Cleator et al.[104] (see conditions a) in Scheme 61), who used heat treatment as activation method for inducing the nucleophilic ring opening of the epoxide using K_2CO_3. Having stirred at 80°C for 12 h, I could disappointingly just isolate 10% yield for product **79**, while most of the educt was obtained back. The second reaction (conditions b) which was tried, again using K_2CO_3 in a microwave assisted

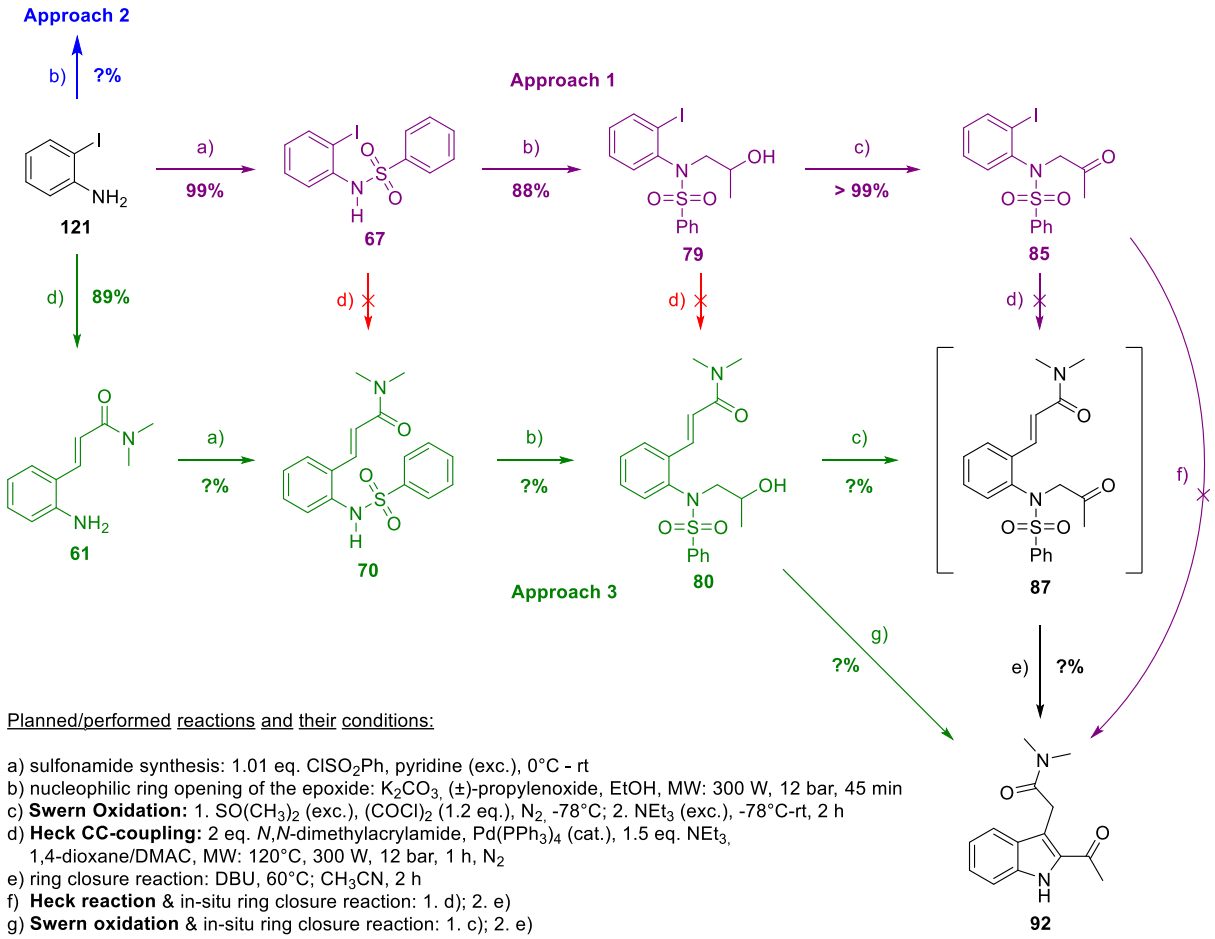
approach by Yang et al.[105] with 120°C of temperature, yielded a surprising and also satisfying 82% yield of the desired product **79** on the first approach. However, a few side reactions had taken place back then, which was visible on the TLC control, but the evolved side-products were not examined further. Out of interest to improve this synthesis step further, I performed the same reaction with lower amounts of auxiliary base and only 1.1 equivalent of (±)-propylene oxide (see condition c)), but having isolated the product, the yield seemed to have decreased with lower educt and base amounts. It was consequently decided to perform all future reactions with a slight excess of both the epoxide educt and the base equivalents. One last reaction, see conditions d) was performed in the interest to find out if the auxiliary base was even needed, or if the microwave irradiation, plus the increased temperature alone would induce the reaction, but not using any auxiliary base did not lead to a formation of the product. Although at this point of the route development I had decided to pursue the alcohol syntheses with Broensted auxiliary bases, later in this chapter, to pre-empt that, Lewis acid-based alcohol syntheses will still play a role later in the chapter after the next one and for the final synthesis route, therefore Lewis acids chemistry has been elaborated quite thoroughly earlier in this chapter. Having found a satisfactory method to synthesise the alcohol, the Swern oxidation was the next step. The third and fourth step, the Heck reaction and subsequent DBU treatment, would hopefully lead to our desired indole intermediate. From this intermediate, we then would be able to prepare the 1,4-disubstituted β-carboline.



Scheme 62: Approach 1 model reactions – first Swern oxidation and the Heck reactions.

Scheme 62, shows the according next few synthesis steps and their results. The ketone **85** could be synthesised from the alcohol **79** according to the original Swern oxidation synthesis description of Omura et al.[106] and yielded satisfying 71% of yield on the first try. The following first Heck reaction, to obtain the acrylamide derivative **87**, was performed using an improved method[107], which was developed a few years ago by a former colleague of mine, Dr. Nghia Ong. For his project[107] he had developed a microwave supported variation of the Heck reaction, for which the

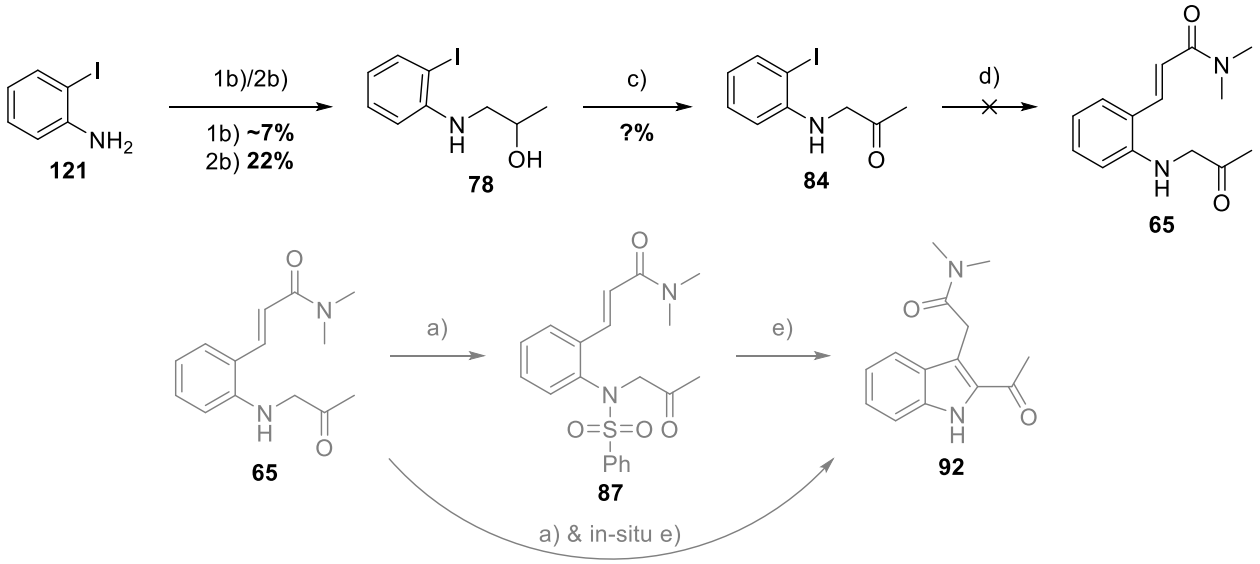
original protocol he had found in a reference book named the “Organikum”[108]. Following his synthesis instructions, the Heck product could regrettably not be generated. According to literature, the sulfonamide group should not be a disturbing factor, since we found a paper[78] in which the authors had performed a Heck reaction with an excellent yield, under slightly different conditions though, but indeed with a sulfonamide holding an iodo-substituent in the *ortho*-position and further they had performed the reaction in even higher temperatures, around 140°C.[78] Instead of the expected reaction progress, TLC reaction control showed, that a huge variety of substances had formed while the educt could not be found. This result led to the conclusion, that the educt **85** had indeed reacted, but then one of the intermediates or even the formed product **87** had presumably decayed. Since it was not known at that time, how instable the Heck product **87** really was, I decided to try an in-situ version of the reaction - to aim for the indole intermediate **92** directly. This second reaction was performed, in the hope, that the maybe the instable Heck product **87** would not needed to be isolated. I accordingly undertook the same Heck reaction with an immediate successive addition of DBU to induce a subsequent ring closure reaction hopefully, still working under microwave conditions. Regrettably again, this variation did not provide the desired indole derivative **92**.



Scheme 63: Attempts to find a solution to the problems with the Heck reaction. All reactions, equipped with a question mark for a yield, had not been performed at this stage of the route development.

At that point, in the middle of approach 1, as can be seen in Scheme 63, I tried to find a way around the problem, by performing a few test reactions (red) with the former intermediates **67** and **79** from approach 1 (purple), in an effort to evade to approach 3 (coloured green), and with the 2-iodoaniline (**121**) too, which was the original educt. Neither the intermediate **67**, nor **79** yielded any product regrettably, although again the reaction instruction, again using Dr. Ong's protocol[107], were followed minutely in each case. When however, the same Heck reaction protocol was used on 2-iodoaniline (**121**) itself – which would be the first step for the reaction order, if we pursued the approach 3 – the reaction yielded 89% of the expected product **61** on the first try. At that stage of the research, it became clear, that we would not get to the desired indole intermediate **92**, through pursuing the approach 1. Even though the first synthesis step of approach 3 had already been successfully performed, as already mentioned in Chapter 3.2.1, the approach 3 was originally the least attractive one, for this reason the model reactions for testing the approaches 2 and 3 were in reality performed parallelly, but are in the next two chapters elucidated separately.

4.2.3 2,3-Disubstituted indole intermediates - model syntheses for approach 2



Planned/performed reactions and their conditions:

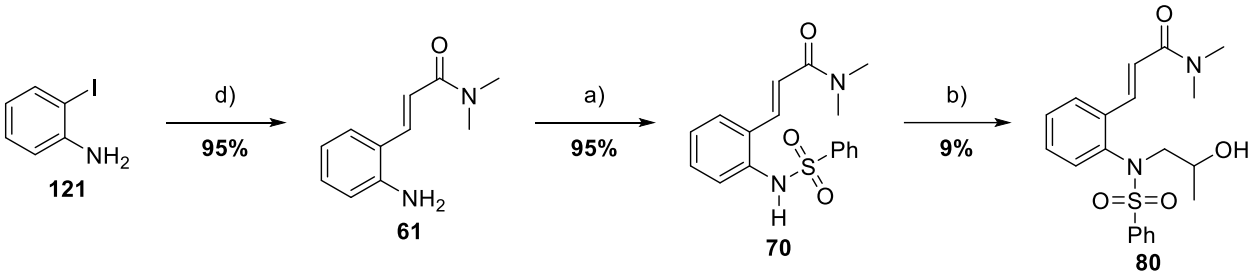
a) sulfonamide synthesis: 1.01 eq. $ClSO_2Ph$, pyridine (exc.), 0°C - rt
nucleophilic ring opening of the epoxide:
1b) 2 eq. K_2CO_3, 1.1 eq. (±)-propylenoxide, EtOH, MW: 100 W, 12 bar, 130°C, 2 h
2b) LiCl (cat.), 1.1 eq. (±)-propylenoxide, MeOH (dry), N_2
c) **Swern Oxidation:** 1. $SO(CH_3)_2$ (exc.), $(COCl)_2$ (1.2 eq.), N_2, -78°C; 2. NEt_3 (exc.), -78°C-rt, 2 h
d) **Heck CC-coupling:** 2 eq. *N*,*N*-dimethylacrylamide, $Pd(PPh_3)_4$ (cat.), 1.5 eq. NEt_3, 1,4-dioxane/DMAC, MW: 120°C, 300 W, 12 bar, 2 h, N_2
e) ring closure reaction: DBU, 60°C; CH_3CN, 2h

Scheme 64: Model reactions for the approach 2.

As can be seen instantly in Scheme 64, there had been problems with the approach 2 already at the first reaction step. Starting with 2-iodoaniline (**121**), it was tried to perform the reaction according to the method of Yang et al.[105] again, although in hindsight the K_2CO_3 did most likely not take part in this reaction, since it is a weaker base than the aniline. Surprisingly, this time, when it was looked at the reaction control, a lot of different substance spots were visible on the TLC plate, indicating, that either a whole lot of different reactions had taken place, apart from the desired one or that the product was simply not stable. The product could though be isolated through column chromatography in an about 7% yield for **78**, using the reaction conditions 1b). Having obtained such a low percentage of yield using this particular protocol, I decided to try one alternative, using a Lewis acid instead. Since there were many options to choose from, I just decided to just pick one Lewis acid randomly and ended up with performing the first test reaction with LiBr, using the synthetic protocol of Chakraborti et al.[109], who in their reactions had claimed to have added the LiBr in a catalytic scale. Using the conditions 2b) and after having stirred at room temperature and under exclusion of light, the reaction control (TLC) still showed an educt spot, but seeing only the product spot apart from the educt spot, showed no side products so far, telling me, that this time the reaction proceeded with more controlled concerning the outcome. Fife

days later, the reaction control still showed the presence of educt, however the reaction was aborted due to poor efficiency of time, but the product was still isolated through column chromatography, which furnished the product **78** in a 22% yield. At that point, it was decided to just go on to the next synthesis step. If there would not appear any further problems during the route development for this approach, it would still be an option to later search for a better method for the nucleophilic ring opening reaction. For the next preparation step (the Swern oxidation) to substance **84**, again the protocol of Omura et al.[106] was followed minutely. Having used DMSO, oxalyl chloride and triethylamine under protective gas and water free conditions, it was visible on the TLC reaction control that the reaction to the ketone **84** had taken place. However, there were some side products visible on the reaction control, too. Purification by column chromatography could not lead to a satisfactory purification of the product **84**, therefore the following Heck reaction to the compound **65** was performed with the crude educt, again using the method of Dr. Ong's protocol[107]. The subsequent Heck reaction though did not yield any of the product **65**, regrettably. Of course, one could try the Heck reaction again, after the sulfonamide had in theory been synthesised beforehand, but the experiences with the model reactions for approach 1 had already shown that the Heck reaction would probably not work with the $PhSO_2$- group present, hence it was decided against trying this. In the meanwhile, there had been much better result results generated for the approach 3 anyway. So having these overall results for the approach 2, it was decided to abort this pathway.

4.2.4 2,3-Disubstituted indole intermediates - model syntheses for approach 3

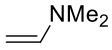


conditions:

a) $ClSO_2Ph$, pyridine, CH_2Cl_2 (or neat), 0°C-rt

b) +  + 3 eq. K_2CO_3, MW: 100 W, 130°C, 4.5 h, EtOH

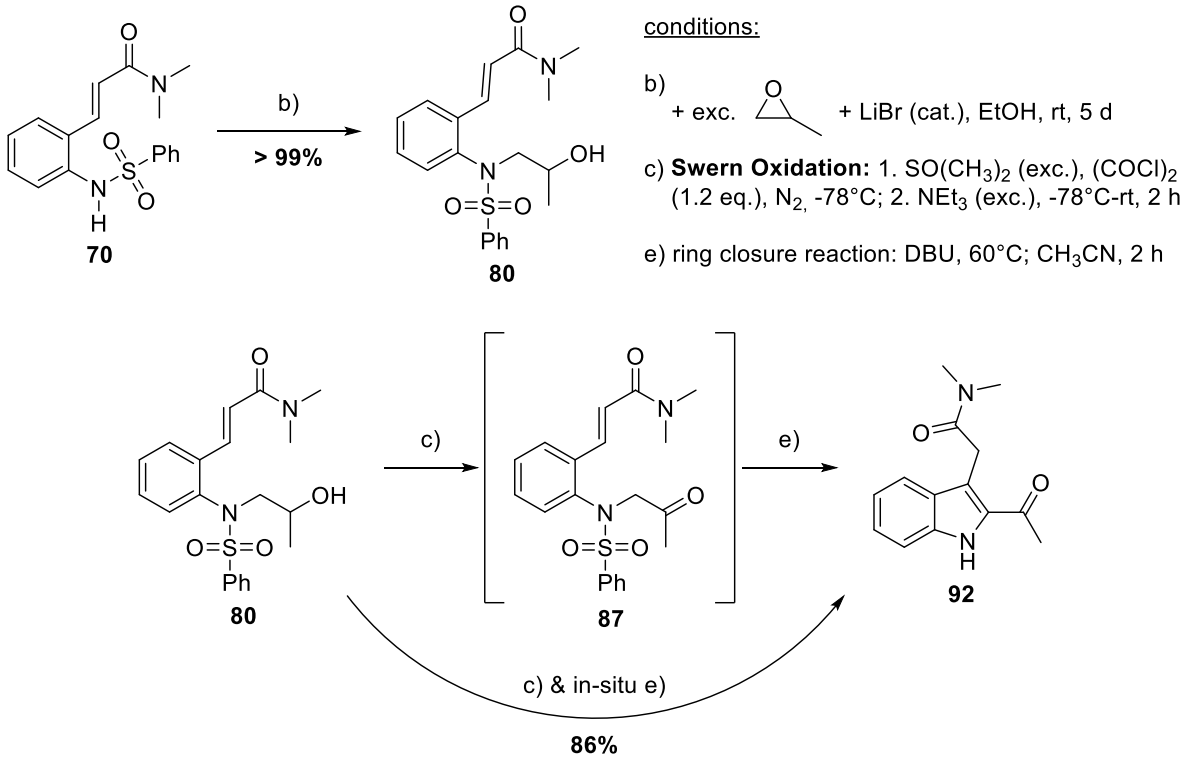
d) Heck CC-coupling:

+  + $Pd(II)(CH_3COO)_2$ (cat.), $P(Ph)_3$ (cat.), TBAB, K_2CO_3 (1 eq.)

Scheme 65: First model reactions for the approach 3.

Before the model reactions for approach 3 started, it was searched for an alternative Heck reaction protocol, since the former used protocol[107] by Dr. Ong only allowed limited amounts of the used substances, because the largest synthesis microwave vials only allowed preparations with the maximum working volume amounts of 35 mL, which limited the 2-iodoaniline (**121**) mass amounts for each synthesis to an about 500 mg - 1.00 g (total mass) amount scale – just to give an example. So, for the first synthesis step a) in Scheme 65, I tried to find a new preparation protocol. It was decided to perform the reaction according to the protocol of Sharif et al.[110], using palladium(II) acetate and PPh_3 instead of $Pd(PPh_3)_4$, K_2CO_3 instead of NEt_3 and additionally the phase transfer reagent TBAB (tetrabutylammonium bromide). The new protocol provided very pleasing 95% of yield for the compound **61** on the first try. In this case, the product **61** did not even needed to be purified by column chromatography, but could rather be isolated in a sufficient purity by extracting the product several times with acidified water, while the organic layer was discarded. The combined aqueous extracts, containing the protonated substituted aniline **61**, were then basified to pH 9-10 in an open container using solid K_2CO_3, then the mixture was extracted several times with an organic solvent. After the solvent had been evaporated, the NMR analytics of the crude product **61** showed, that it had been obtained in a sufficient purity already. The sulfonamide **70** could be prepared in a 95% yield as well, again following the protocol of Yin et al.[102]. When it was tried though to prepare the alcohol **80** with the earlier applied protocol[105], using K_2CO_3 to initiate the nucleophilic ring opening reaction, the expected product **80** was built, but only in bad yields (9%). It was decided to try another synthesis method.

The only other auxiliary reagent to induce the nucleophilic ring opening of the epoxide (alternatively to conditions b)), which had been tried before in this work and which furnished promising results so far was the Lewis acid LiBr, so I decided to try this reaction again using the synthesis protocol of Chakraborti et al.[109]. Expecting, based on the earlier experiences (see Chapter 4.2.3), that the reaction progress would proceed rather slowly I added a larger excess of the epoxide and it was stirred for several days until the reaction control showed the complete depletion of the educt. The solvent was removed and the crude substance was redissolved in methylene chloride and washed several times with water to remove the excess of epoxide. After the solvent was removed completely, NMR analysis showed that the product **80** had formed in a gratifyingly quantitative yield with an already sufficient purity (see Scheme 66).

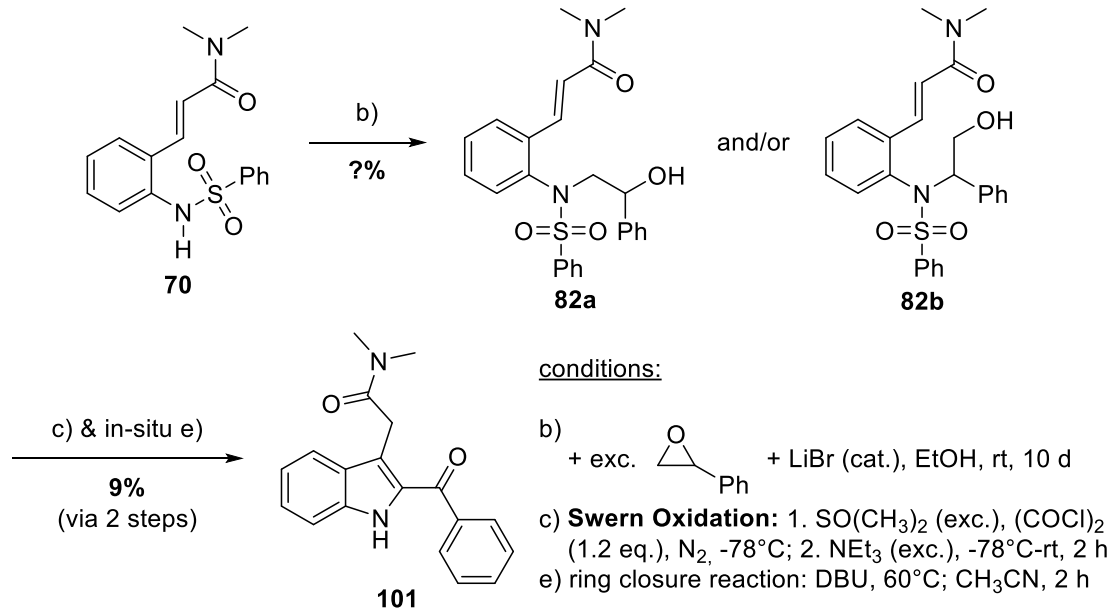


Scheme 66: Successful alcohol synthesis according to Chakraborti et al.[109]'s method and the subsequent reactions and their outcome.

One specific phenomenon appeared, when the alcohol **80** was analysed by NMR analysis, that has to be mentioned at that point. When a sample of **80** was tried to be characterised through the NMR analysis, although TLC control had shown only one substance, the spectrum showed, that the alcohol tend to appear in the spectra in the form of rotamers, which not only appeared as a minimum of two separate signal set (which would usually suggest the presence of two different substances), but also the multiplicity of all separate peaks was severely altered from the expected ones, which lead to huge problems during the data evaluation, since the identification of certain functional groups was impossible. A clear and evaluable NMR spectrum could finally only be obtained at high temperature measurements around 100°C.

For the following two reactions c) and e) in Scheme 66 it was decided to try the in-situ version at first. Starting from substance **80**, again the original protocol of Omura et al.[106] was used and as expected the (TLC) reaction control indicated the familiar good result. After the oxidation had been stopped by the addition of NEt_3 and after allowing the reaction solution to warm up to room temperature, DBU and acetonitrile (as solvent) were added to the reaction solution and, working with an open flask, the mixture was stirred for another 2 h at 60°C (equating to Kim et al.'s protocol[48]). Having purified it through column chromatography, the desired indole intermediate **92** could finally be isolated in a very good yield of 86% (determined over two steps). The alternative method, separating the reaction steps c) and e) and isolating the ketone **87** after the reaction step c), was not tried any more since subjectively looked at, the in-situ method to **92** had already provided a sufficiently good result – even over two steps.

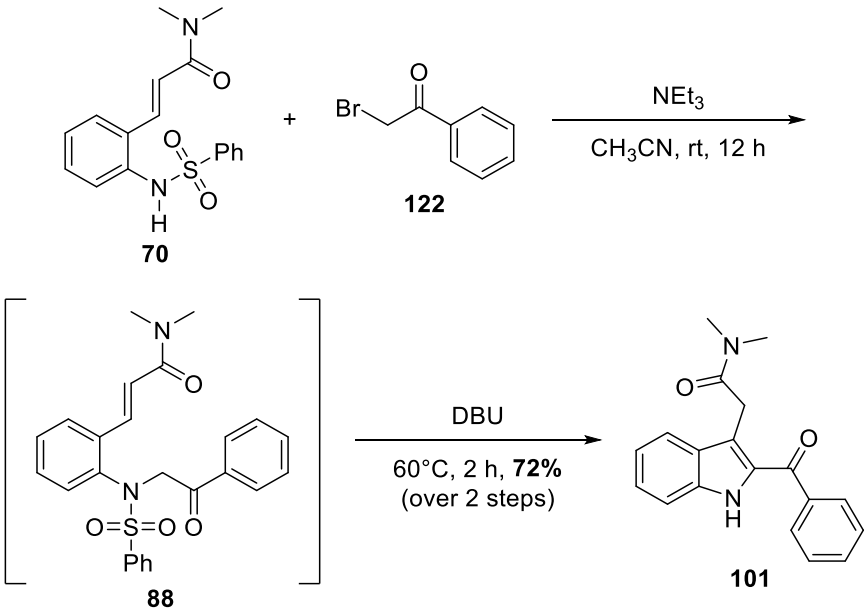
Since we were successful with an aliphatic epoxide (propylene oxide), I wanted to check, if the developed method could also be applied to aromatic epoxides. According to Chakraborti et al.[109]'s findings, the aniline's free electron pair tends to regioselectively attack the aliphatic epoxide's unsubstituted methylene group nucleophilicly, inducing a lithium Lewis acid catalysed S_N2 mechanism, which they performed all in quantitative yields.[109]



Scheme 67: Preparation attempt to obtain the indole intermediate **101** through the new synthetic pathway.

However, when they tried the same reaction with styrene oxide and aniline, they found that aromatic amines react predominantly at the benzylic carbon atom, than at the terminal carbon atom.[109] A few years later though, Pujala et al.[111] reported the same observation although they had used $LiBF_4$ as Lewis acid.[111] To confirm these findings, one experiment was performed using styrene oxide (as epoxide) and LiCl as Lewis acid. As shown in Scheme 67, the earlier obtained sulfonamide **70** was reacted under conditions b). When analysing the TLC reaction control, the

mass could be found for (either) product **82a** or/and **82b**. It is to mention at that point, that compared to the reaction with an aliphatic epoxide propylene oxide the reaction with the aromatic epoxide took more than double the time. Since a lot of side-product formation could be observed on the reaction control, the reaction was aborted prematurely when educt was still present in solution. One disadvantage of using epoxide chemistry became clear at the point, when we got to the purification processes. In the earlier synthesis, using (±)-propylene oxide as epoxide, the product could easily be separated from the excess epoxide, through extracting the excess epoxide with water. This method worked so efficiently because (±)-propylene oxide dissolves better in water than in organic solvents in comparison to the product, which tended to remain in the methylene chloride phase. However, having worked with styrene oxide instead, being a more nonpolar epoxide, it could not be removed through the extraction process. It was attempted to separate it from the product(s) by column chromatography, but although some of the epoxide could be separated from the products, most of the whole amount was eluted with the products fractions. Since it was impossible to isolate the product(s) and because of that, not possible to determine the yield percentage, I proceeded to the next two reaction steps working with the crude product. Having followed the protocols minutely, after the reaction steps c) and in-situ e) the column chromatography purification yielded only about 9% yield for the product **101**, determined over 2 steps. Having this result and not enough substance to go on with for the final syntheses of the corresponding 1,4-disubstituted β-carboline, it was decided to use Kim's[48] method to prepare the desired indole intermediate **101**, since this preparation way was one synthesis step shorter anyway, but less flexible of course considering the possibilities to introduce a wide range of residues onto the C-2 of the indole analogue.

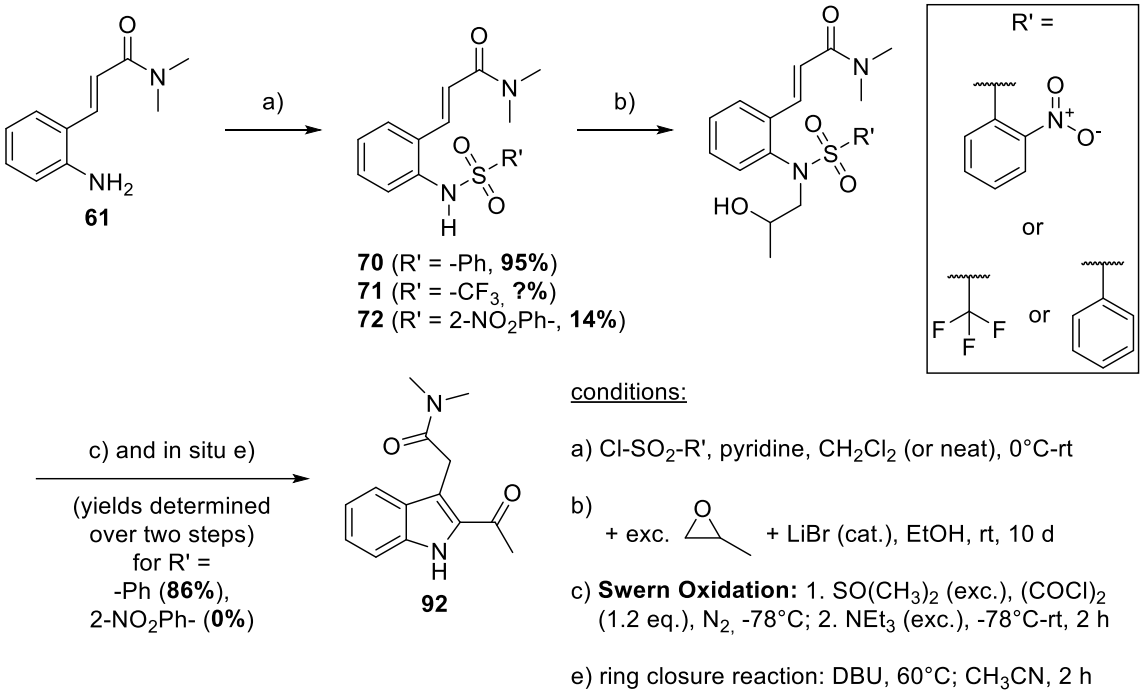


Scheme 68: Preparation of indole **101** using Kim et al.[48]'s method.

As illustrated in Scheme 68, the preparation of **101** using 2-bromoacetophenone (**122**) triethylamine and the subsequent in-situ addition of DBU, furnished the product **101** in a gratifying 72% yield on the first try. Since the preparation of 2-aroyl substituted indoles seemed to be more reliable and sufficient when performed as is shown in Scheme 68, in the following chapters to pre-empt that, these were synthesised according to this this method.

4.2.5 1,4-Disubstituted β-carbolines - model reactions for finding the best leaving group and experiments with aromatic epoxides

Having finally an efficient method to produce (certain) 2,3-disubstituted indoles, it was essential to investigate two things, as follows: Firstly, it was important to find out if the phenyl sulfonyl (-SO_2Ph) residue provided the best leaving group. In attempt to increase the yield for the above-described indole synthesis or any of the previous steps, another two leaving groups were supposed to be tested in comparison – for this experiment, instead of reacting the earlier produced Heck reaction product **70** with R' = $ClSO_2Ph$ (phenylsulfonyl chloride), triflyl chloride ($ClSO_2CF_3$) for **71** and 2-nitrobenzenesulfonyl chloride for **72** were used as coupling partner, respectively (see reaction a) in Scheme 69). The results for the reactions with the residue R' = phenyl are in the following scheme also repetitively given to enable the reader a clear overview of the differences between the results for different sulfonamides **70**-**72**.



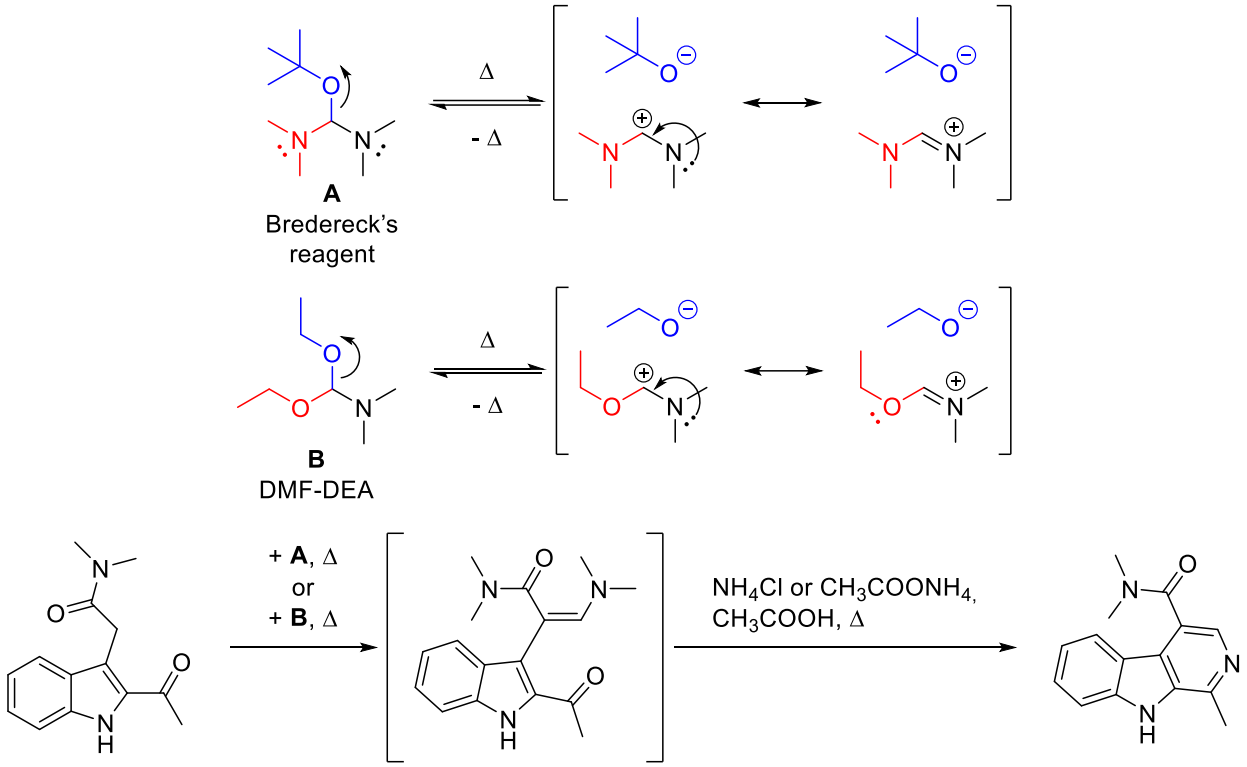
Scheme 69: Performed reactions to find a potentially better leaving group.

As imaged in Scheme 69, for the first synthesis step a) the sulfonamides **71** and **72** were again prepared according to the protocol of Yin et al.[102]. However, when attempting to purify **71** by column chromatography, the product isolation could not be achieved. The combined column fractions, which contained product according to TLC-MS analysis of the reaction control, had been combined and the eluent had been removed using the rotary evaporator and high vacuum. Since the remaining solid, which indeed contained product but impure one, that only made out less than 15 yield-% of the expected ~100% product yield, it was decided to abort the experiments with the triflyl group at that point due to timely inefficiency. For R' = 2-nitrophenyl, the experiments went better in the beginning. Although the first synthesis step only yielded 14% of the product **72**, it

could be easily isolated through column chromatography. It was not really clear, why only such a low percentage of educt had reacted with the sulfonyl chloride and most of the educt **61** was obtained back through column chromatography, since the protocol had been followed minutely. Although compared to the excellent yield for the former performed sulfonamide **70** (R' = phenyl), the reaction had not shown the same outcome, it was decided to go on with the intended route. The following alcohol synthesis did not provide any obstacles. After five days of stirring the educt **72** under conditions b) the reaction control didn't show any remaining educt, while only one other spot seemed to have appeared, which was most probably product (confirmed by TLC-MS analysis). After having removed the solvent, methylene chloride was added and the epoxide and remaining LiCl were again removed through the established extraction process with water. The remaining organic layer was dried in high vacuum, after the solvent had been removed. The crude product was converted in the following Swern oxidation and in situ indole formation, using the formerly used protocols of Omura et al.[106] and Kim et al.[48] (conditions c) and in situ e) in Scheme 69). Unexpectedly, no formation of product **92** had been detectable on the reaction control. It seemed that either the educt **72**, one of the intermediates, or the product **92** itself had decomposed during one of the two synthesis steps. These results led to the conclusion, that the originally chosen leaving group, which held phenyl for the residue R', already provided the best leaving group for the developed synthesis route.

4.2.6 1,4-Disubstituted β-carbolines syntheses – model reactions

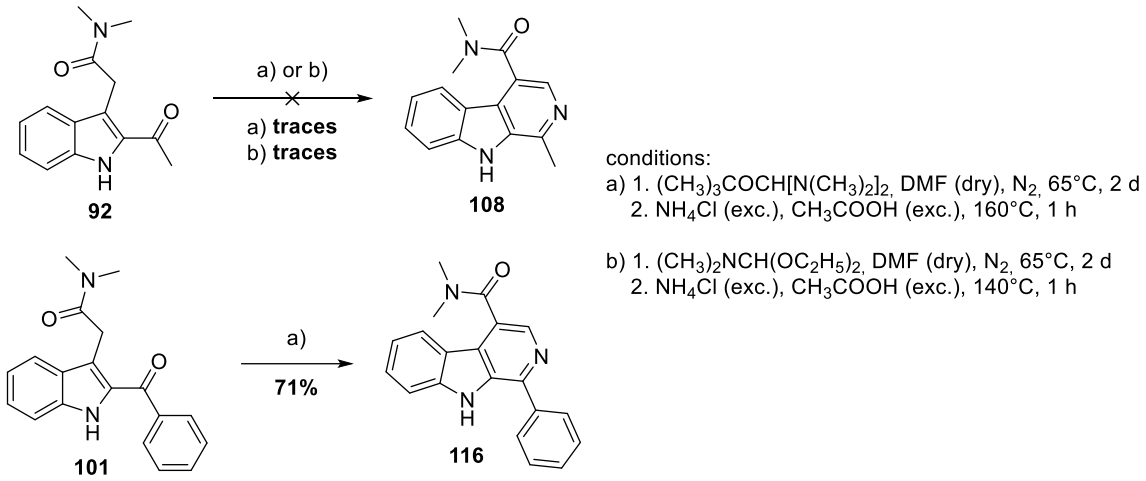
Since we now had the desired indole intermediates **92** and **101** in hands, for which the preparations had been elucidated in the chapter before the last, the most important thing was to try the last preparation step – or differently phrased, the two last in-situ steps – for generating the two corresponding 1,4-disubstituted β-carbolines. As can be seen in Scheme 70, starting from the indole **92**, to react it to the enamine intermediate derivative, the educt could either be treated with Bredereck's reagent (also known as *tert*-butoxy bis(dimethylamino)methane; see reagent **A**), or subjected to a dimethylformamide dialkyl acetal, for example *N*,*N*-dimethylformamide diethyl acetal (also called DMF-DEA; see reagent **B**).



Scheme 70: The chemistry of amide acetals: pKa (HOtBu) = 19[112]; pKa (HOEt) = 16[112]; pKa ($HN(CH_3)_2$) = 10.71. First leaving group is shown in blue, the second leaving group is shown in red.

When looking at the leaving groups, the reactants both release alcoholates (coloured blue) as the first leaving groups upon heating. In case of **A**, it would be *tert*-butanolate, which is a stronger base than the ethanolate[112], that is released by the reactant **B**. It is however to mention, that given the pK_a values of both of their conjugated acids (*tert*-butanol (for **A**) and ethanol (for **B**)), both bases are to be regarded as very strong bases. One significant difference though between both is that, compared to ethanolate (EtO^-), *tert*-butanolate (*tert*-BuO^-) is a non-nucleophilic base - due to the steric hinderance caused by the $-C(CH_3)_3$ group. In the further reaction progress, the second part, later to become the second leaving group, is coloured red in Scheme 70. In case of **A**, the leaving group it is dimethylamine ($HN(CH_3)_2$) while for **B** ethanol (EtOH) departs. Compared to the

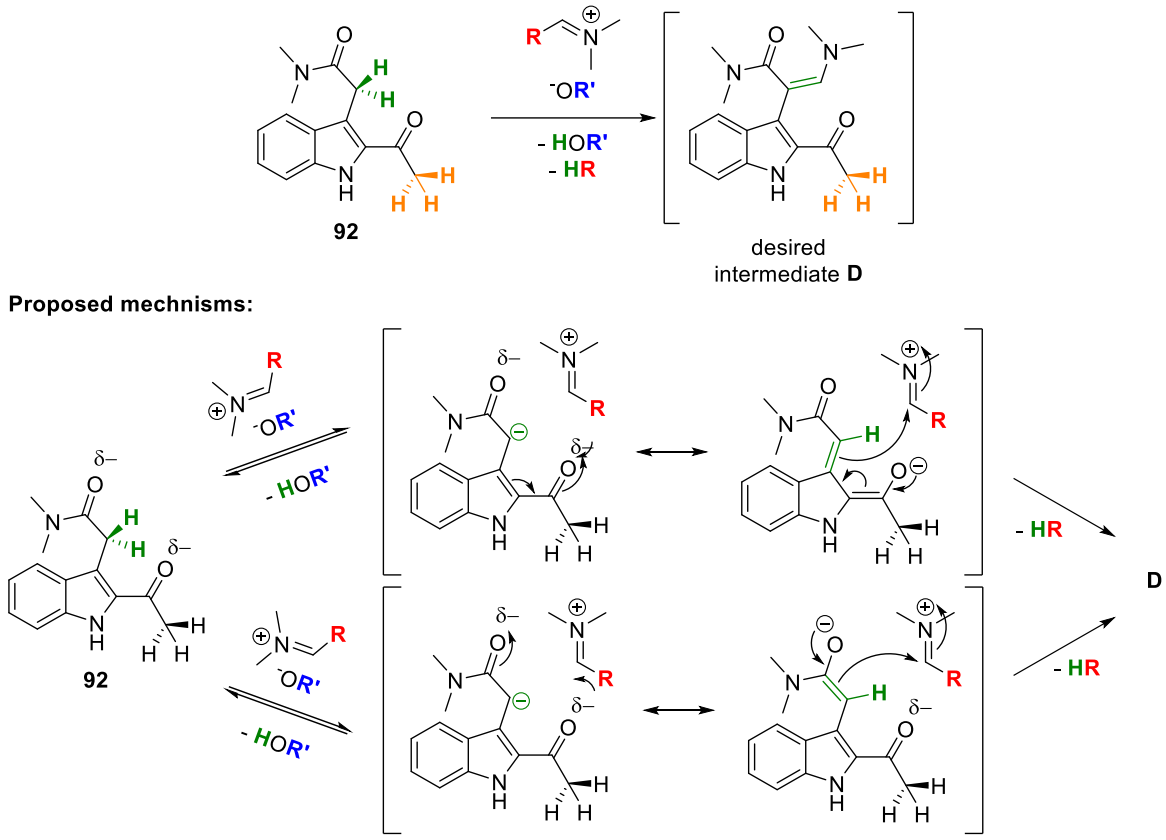
departed ethanol, dimethylamine is a base and, in addition to that, a nucleophilic one. Having to choose from two options, in the assumption that **A** (compared to **B**) would expose the indole educt **92** to harsher reaction conditions, I decided to try both conditions in the intention to compare the outcome. Scheme 71 shows the first two reactions, starting with the educts **92** and **101** from the chapter before the last.



Scheme 71: First β-carboline test reactions.

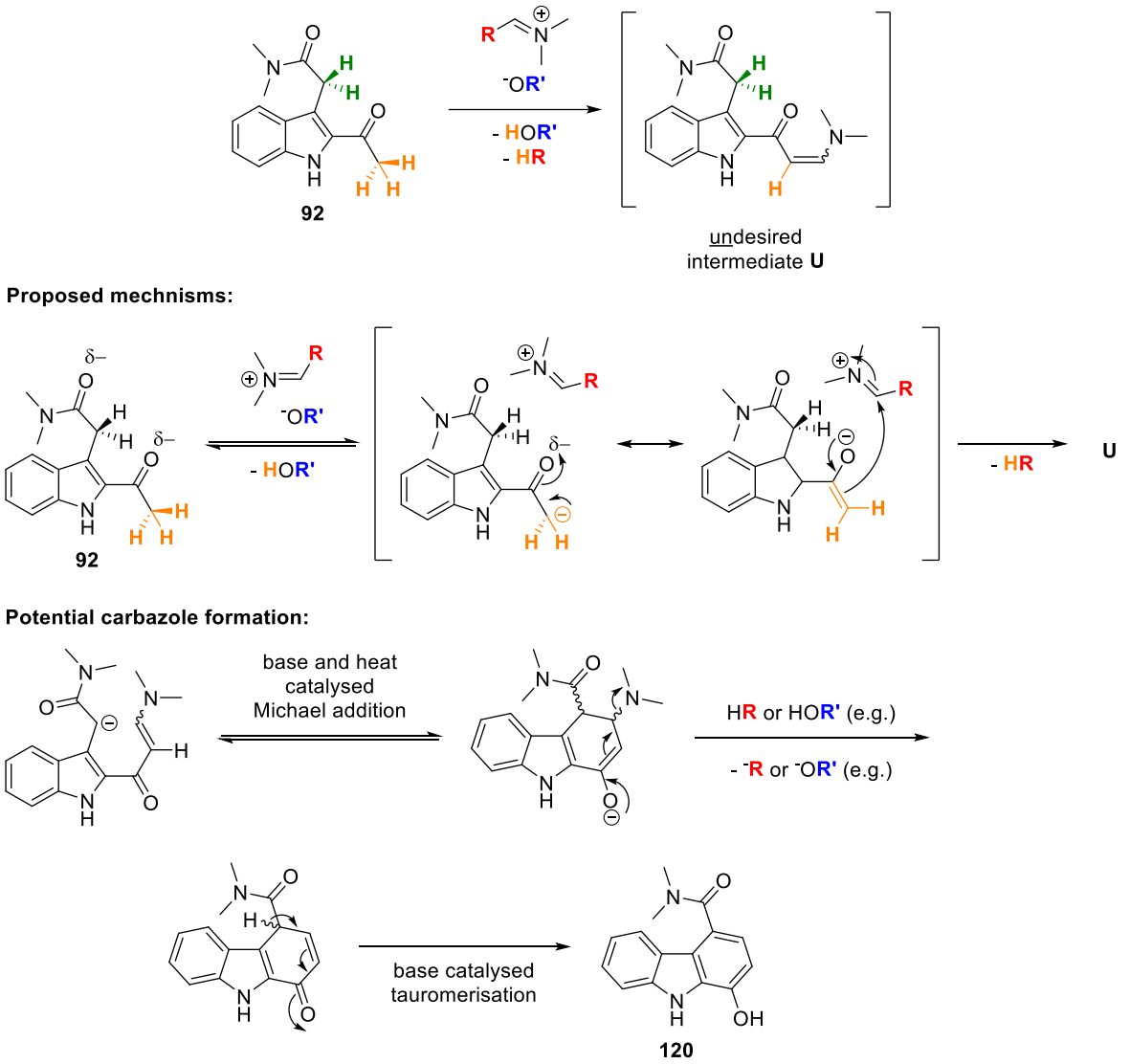
As can be seen and starting from educt **92**, both the Bredereck's reagent and the DMF-DEA yielded product or any constitutional isomer thereof (determined by TLC-MS), though when in both cases, it was tried to purify the product **108** in both cases by column chromatography, whereat only traces of the product **108**/structural isomer could be found in the combined column fractions seeming to hold product. Having tried the reaction conditions a) and b), in both cases a lot of spots had appeared on the TLC control during the reactions, hinting that a lot of undesired side reactions must had taken place, which not only rendered the following column chromatography purifications difficult and time consuming but also lead to no sufficient substance amount isolation to actually receiving data/spectra to be able to confirm the product formation. When however, the same reaction conditions a) were applied to educt **101**, the 1-phenyl substituted β-carboline **116** could be isolated, through having performed column chromatography, in a pleasing 71% yield on the first try. Since the only difference between the two educts **92** and **101** as were the residues next to the carbonyl groups on the C-2 of the indoles - methyl for **92** and phenyl for **101**. For **92**, the methyl residue had resultingly to be the disturbing factor. In case of educt **92**, having two alkyl residues we wondered in the beginning of the project, which of the two aliphatic groups would be the more acidic one, because in theory, two different things might happen when the Bredereck reagent, or alternatively the DMF-DMA is added. When one looks at the educt **92**, there are two potentially reacting groups, coloured orange and green in Scheme 72. The to the carbamide's carbonyl α-positioned methylene group (green) is not only exposed to the electron withdrawing effect of the amide's carbonyl, but are also in vinylogy exposed to the electron withdrawing effect

of the keto group at C-2. From what we expected, the combination of both withdrawing effects in combination should render the methylene group more acidic than the methyl group (orange), which is only exposed to the electron withdrawing effect of the ketone. It is to mention though, that amides tend to have a very low willingness to react with nucleophiles - not to say this functional group is inert - so in consequence the effect of the amide's withdrawing effect should be significantly lower compared to the effect, the ketone exerts. So, if the methylene group is in fact more acidic than the methyl group, then the proposed mechanism for the formation of the desired intermediate **D** is imaged in Scheme 72.



Scheme 72: The desired reaction and the expected mechanism for educt **92**. **R** = -N(CH$_3$)$_2$ or -OEt, **R'** = -tBu or -OEt.

So, if the methylene group is not more acidic than the methyl group, then the proposed mechanism for the formation of the resulting undesired intermediate **U** is imaged in the next Scheme 73. Of course, **U** could undergo further side reactions, like the formation of carbazoles. The formation of carbazoles under basic conditions, has already been observed by Dr. Untergehrer in our group in his works[40-41], therefore we knew this was a potential disruptive factor for my works. So, if the methylene group is not more acidic than the methyl group, then the proposed mechanism for the formation of the resulting undesired intermediate **U** is imaged in Scheme 73.



Scheme 73: Undesired side reactions and one potential outcome. **R** = -N(CH$_3$)$_2$ or -OEt, **R'** = -tBu or -OEt.

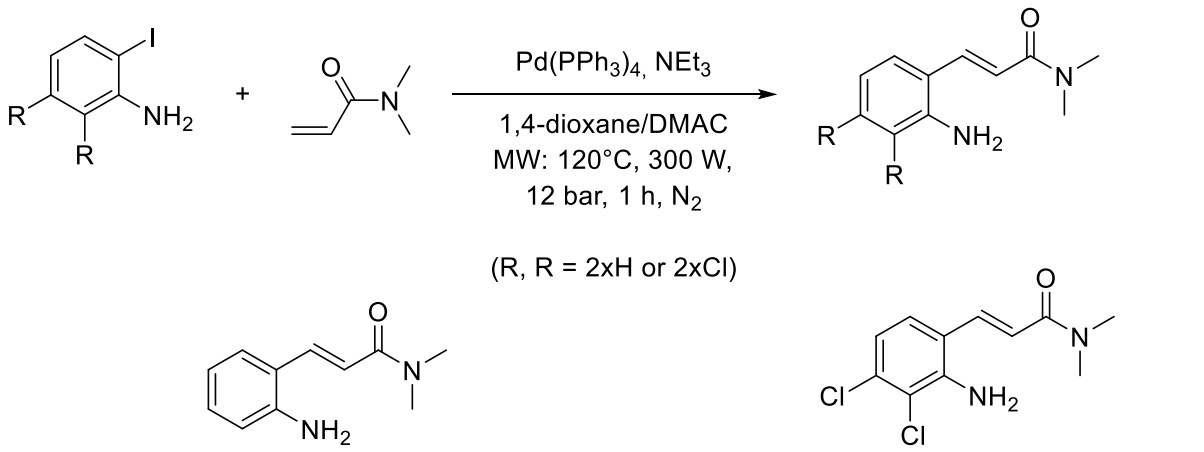
In spite of the β-carboline synthesis for the 2-alkyloyl indole **92** (Scheme 71) had not worked, one still could claim that we had now established a preparation method for 1,4-disubstituted β-carbolines in general, since the preparation for the 2-benzoyl indole **101** (again Scheme 71) had worked perfectly through this method. Considering that the acidity of the competing alkyl groups might change in favour of the (indole's) C-3 attached methylene (orange in the last two Schemes), if we exchanged the amide group for another functional group, we just decided to just try a selection of alternative functional groups exemplary in the later studies and which are enumerated in Chapter 4.2.7.

4.2.7 Synthesis of 1,4-disubstituted β-carbolines – holding carboxamides, nitriles, esters, alkyl or phenyl ketones in the 4 position

Some of the single reactions/reaction results, which have already been mentioned in earlier chapters where the model reactions are elucidated, are mentioned with their results in this chapter again, to give any reader the chance to compare the results, to allow them to keep track of similar reactions and to enable them to compare the overall results.

Different variations of the Heck C,C-coupling and their outcome

Having now established a method for the preparation of 1,4-disubstituted β-carbolines in principle, a few exemplary syntheses should be performed, with certain chosen residues. All syntheses were started from the purchasable 2-iodoaniline (**121**) or 2,3-dichloro-6-iodoaniline (**56**), for which the synthesis results have been described in the earlier Chapter 4.2.1.. Following the earlier successfully used approach 3, which is elaborated in Chapter 4.2.4, the Heck reaction was the first reaction to be performed. As already mentioned, in the beginning a microwave assisted method was used to prepare the first two Heck products **61** and **57**, for which the conditions and the results can be found in Scheme 74.



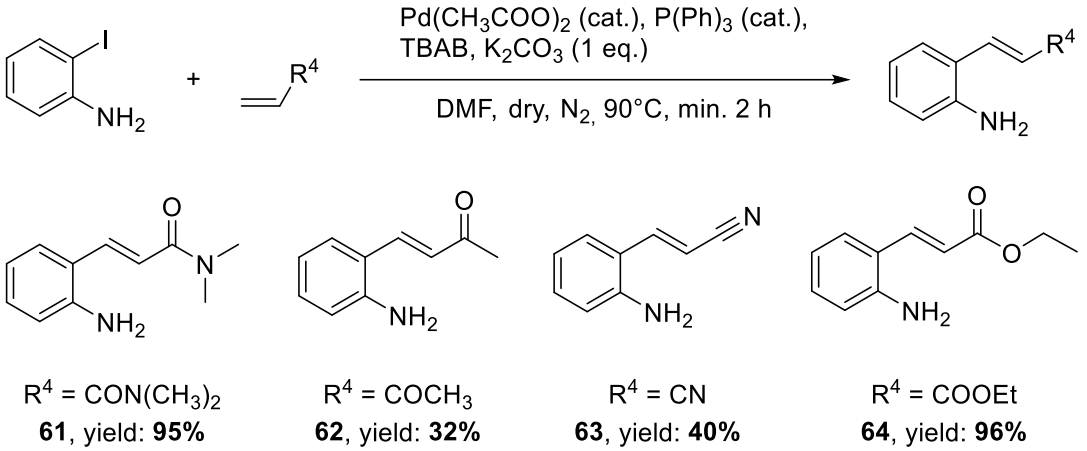
61, yield: **89%**
(educt: 2-iodoaniline (**121**))
R = H; R^4 = $CON(CH_3)_2$

57, yield: **89%**
(educt: 2,3-dichloro-6-iodoaniline (**56**))
R = Cl ; R^4 = $CON(CH_3)_2$

Scheme 74: Original Heck reaction under microwave conditions according to the protocol of Dr. Ong[107], based on the original protocol, published in the book "Organikum"[108].

Later, due to restrictions when it came to the upscaling of the reaction, as mentioned in one of the earlier chapters, I decided to switch the preparation method, und tested the new method in the beginning for efficiency first, by preparing the substance **61** again with the new method. As can be seen in Scheme 75, with the new method by Sharif et al.[110], it was not only possible to upscale the reaction, but also it was managed to increase the yield of **61** slightly from very good to excellent. A selection of functional groups for R^4 should be tested in the Heck reaction, to confirm

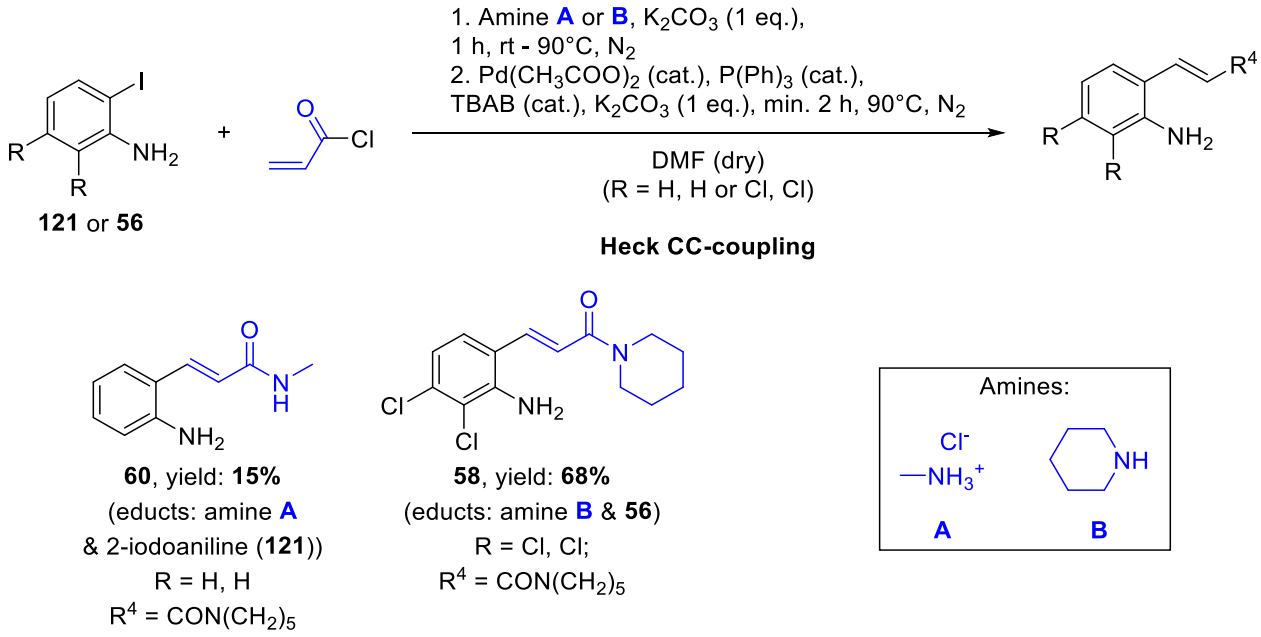
that the reaction would tolerate a variety of functional groups. As has been claimed earlier in literature, according to theory, the Heck reaction should tolerate a diversity of groups for R^4 – like aldehyde[113], alkyl[56, 113], aryl[56, 113], *N*,*N*-disubstituted carbamide[114], ester[110, 113-115], ether[113], heteroaryl[76, 113], hydroxy[113, 115], ketone[114-115] or nitrile[113, 115, 114] residues – which all, of course, had to be compatible with the later to be performed Michael reaction, too. We accordingly decided to perform the Heck reaction with 2-iodoaniline and a selection of acryls, holding the residue R^4 = $CON(CH_3)_2$, COOEt and $COCH_3$ or CN, as an unsaturated coupling partners.



Scheme 75: Performed Heck reactions in a closed flask and the outcomes for the method (by Sharif et al.[110]).

The results in Scheme 75 determined that for all of these residues, the Heck reaction could be performed in yields from excellent to poor. I tried to increase the substance amount of the generated nitrile **63** by repeating the reaction several times, but compared to the firstly received yield of 40%, the repeated reactions all had a yield below 10%. For the generated ketone **62**, I expected a worse result than for the others Heck reactions, because I anticipated the generated compound **62** to be prone to intermolecular condensation with itself. Nevertheless, in an attempt to save time, I tried the Heck reaction without having protected the aniline's $-NH_2$ prior to the C,C-coupling. Since there was enough substance amount of **62** to go on with, I did not repeat this reaction – neither with, nor without protecting the aniline's $-NH_2$ group beforehand – but it is very possible that the yield would increase, if a protective group was introduced earlier, however this is speculation of course. There was another issue at that point which appeared to be a drawback in the beginning. The Heck reaction, in the beginning appeared like it could only be performed with pre-existing and purchasable acrylamides or the molecule had to be modified later, for example starting from the ester **64** or any of its successors later. If one wants to prepare amides for example, they can typically either be generated under basic conditions from acrylic acid chlorides and amines or alternatively through amide coupling reagents, starting with a carboxylic acid and an amine. Since the Heck C,C-coupling required a base anyway, I wondered if there was an in-situ method, combining both reactions, the amide synthesis and the Heck reaction, in one. The

research for the in-situ method lead me to a paper, published by Priebbenow et al.[115] in 2011, in which the Heck reaction was performed in-situ, right after the acrylamide was generated under basic conditions from acrylic acid chloride and an amine. Out of interest, I decided to perform two test reactions, with the amines **A** and **B**, which are both shown in Scheme 76. I wanted to have the substance *N*-monomethyl acrylamide for the next reaction steps, however I had realized earlier, that the required educt had an exorbitant price and could only be purchased in large quantities. I therefore decided to try to prepare **60** with the in-situ variant of the reaction. As amine for this reaction, I needed to use methylamine (H_2N-CH_3) – but methylamine is a gas, which is not easily and only purchasable in strongly diluted solutions and apart from these facts, it had to be purchased and later used in a dry solvent – compatible with the Heck reaction – and under protective gas. So, I wondered if I could use the hydrochloride salt **A** instead, because it is very cheap, a solid and therefore much more practical to utilise in a reaction. Because of the mentioned advantages, I just decided to perform a test reaction with the •HCl salt **A** instead, using the shown reaction conditions in Scheme 76. The reaction yielded **60** only in a 15% yield. Considering that all the alternative preparation ways to gain **60** would involve the usage of much more expensive chemicals, subjectively looked at, justifies the preference for this preparation way nevertheless.

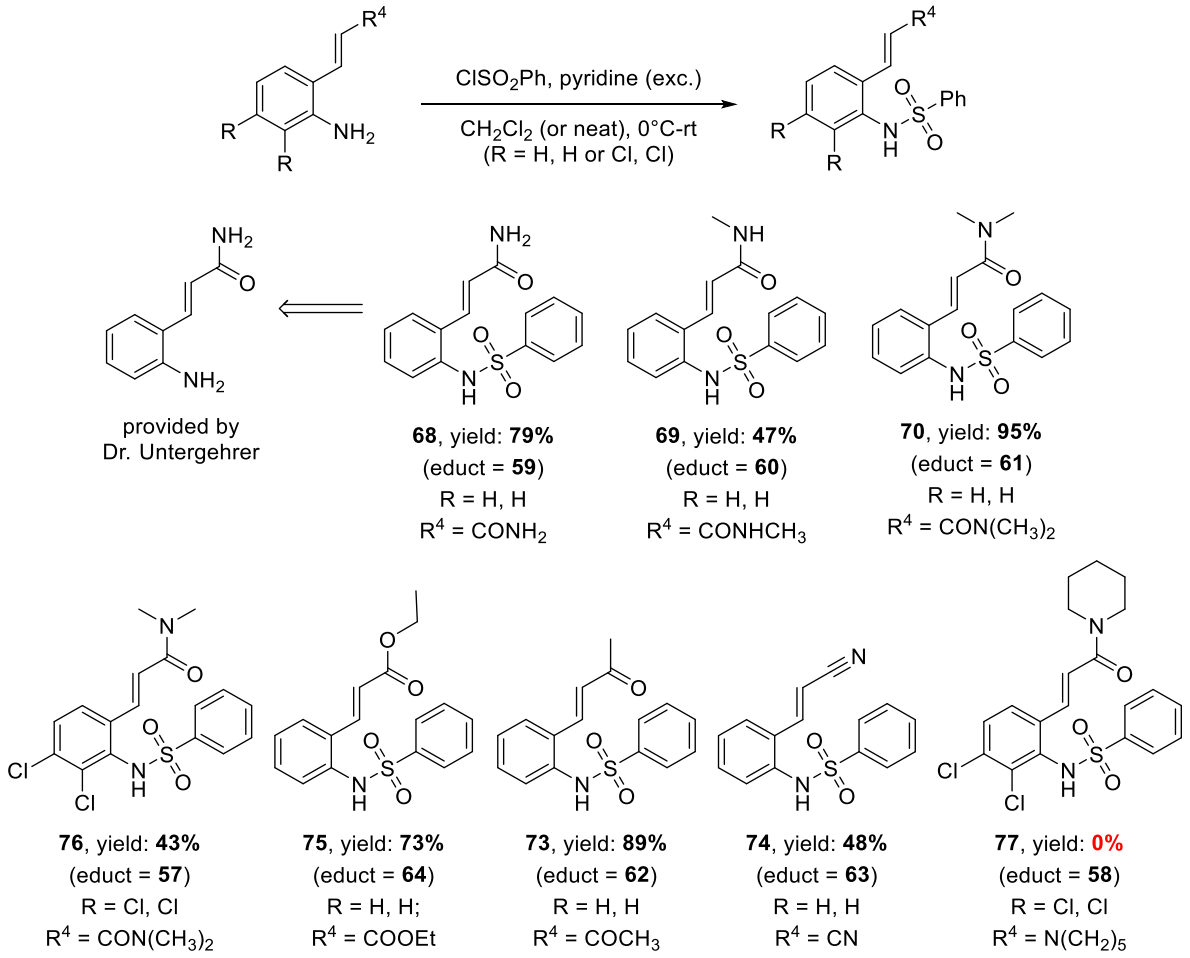


Scheme 76: Performed in-situ Heck reactions and their outcome.

Out of scientific interest, another example was tried, this time using the amine **B** (piperidine) instead of any hydrochloride derivative of **B**, whereat the amine **B** itself was chosen at random. Also, another aniline was used, in particular the reaction was performed with 2,3-dichloro-6-iodoaniline (**56**), which had earlier been prepared. This time the result was better, since the product **58** could be isolated through column chromatography in a good yield of 68%.

Performed phenylsulfonamide syntheses

Since we now had all desired Heck reaction products in hands, the next reaction step to perform was the sulfonamide syntheses. The reaction were all performed using the already earlier used protocol published by Yin et al.[102], which is in detail described in Chapter 7.2. As shown in Scheme 77, the sulfonamide syntheses nearly all yielded product, however the yields differed immensely from poor to excellent. The educt numbers and structures can be all extracted from the Scheme 74, Scheme 75 and Scheme 76 - apart from the primary amide educt on the upper left of Scheme 77, which was generously provided by Dr. Untergehrer. In one case, the product could not be generated at all (see substance **77**).



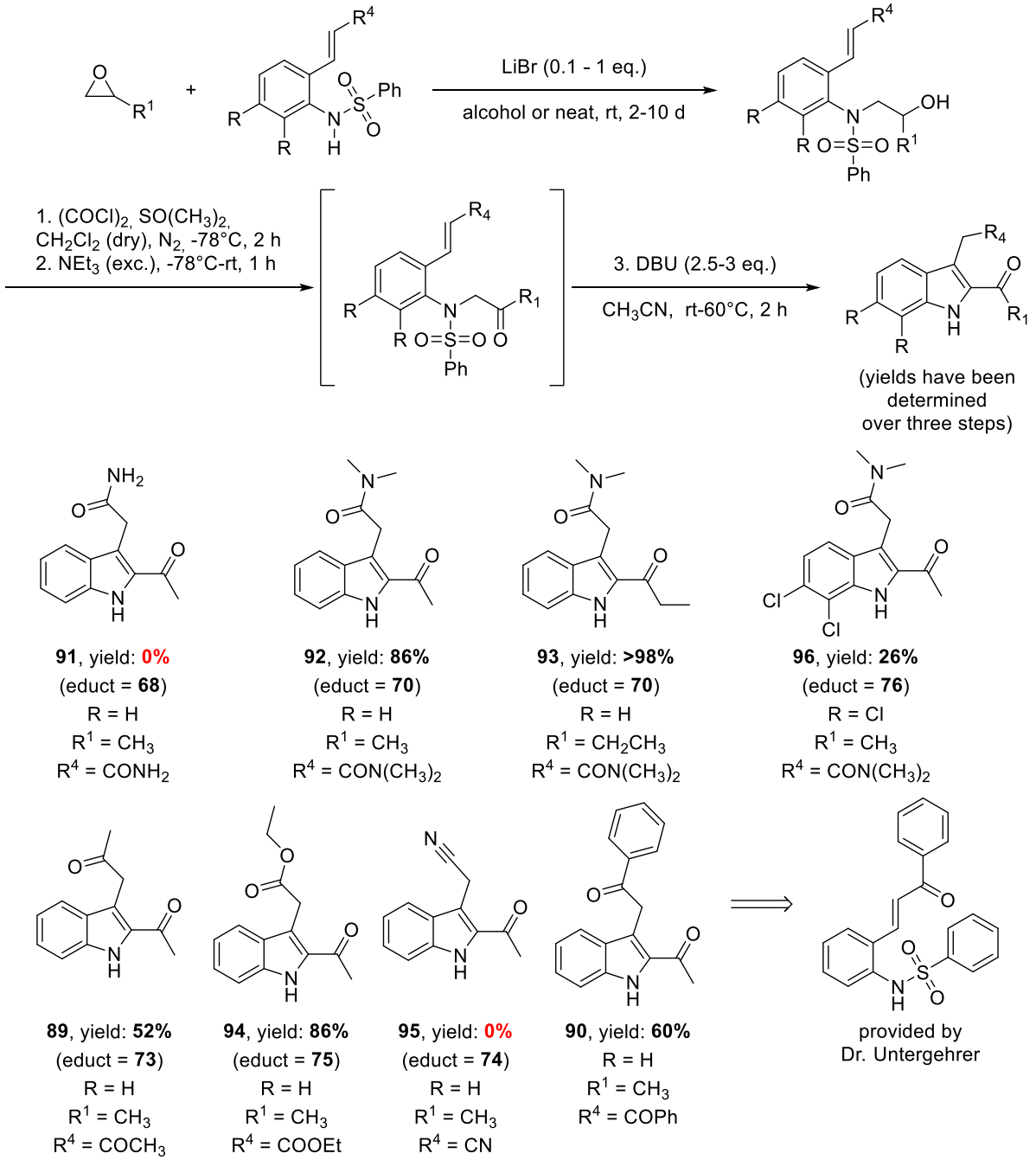
Scheme 77: Performed sulfonamide syntheses and their outcome. The educt nubers and structures can be extracted from Scheme 74, Scheme 75 and Scheme 76.

When looking at the first three substances **68**, **69** and **70**, considering the functional groups are really similar, apart from the differences in the steric claim of the $-NH_2$, the $-NHCH_3$ and the $-N(CH_3)$ group. Out of these three groups the steric claim of these groups should decrease in the following order: $-N(CH_3) > -NHCH_3 > -NH_2$. However, if the steric hinderance influenced the results, the yield should have decreases with the growing steric hinderance – which was not the case here.

Observing the results from these three sulfonamides, one might argue, that with the switching *N*-substituents, the amides carbonyl's quality as a nucleophile might change slightly. Since the carbonyl in each case is vinylogue connected to the aniline's phenyl and thereby might influence the acidity of the aniline's -NH_2 group (of the educts) or the -NH-SO_2Ph group (of the products). Considering this potential phenomenon, unsatisfactory, there could not been detected a trend in the results either. In case of the substance **77**, the reaction was repeated several times, while the conditions and/or equivalents had been varied each time slightly. No matter which conditions, instead of the product **77**, only the disubstituted side-product (and remaining educt) could be isolated in each case, hinting that the formed mono-substituted product was much more reactive than the educt itself. The formed product therefore did not linger in solution, but continued to react on, while the educt remained. A proposal to solve this problem will be mentioned in another chapter of this work (Chapter 6.2), since the attempts to solve this problem could not be performed during the timeframe of this work. Nonetheless, we now had a selection of sulfonamides to perform the nucleophilic ring opening and the following reactions with.

2-Alkyloyl substituted indoles: preparation *via* alcohol intermediates

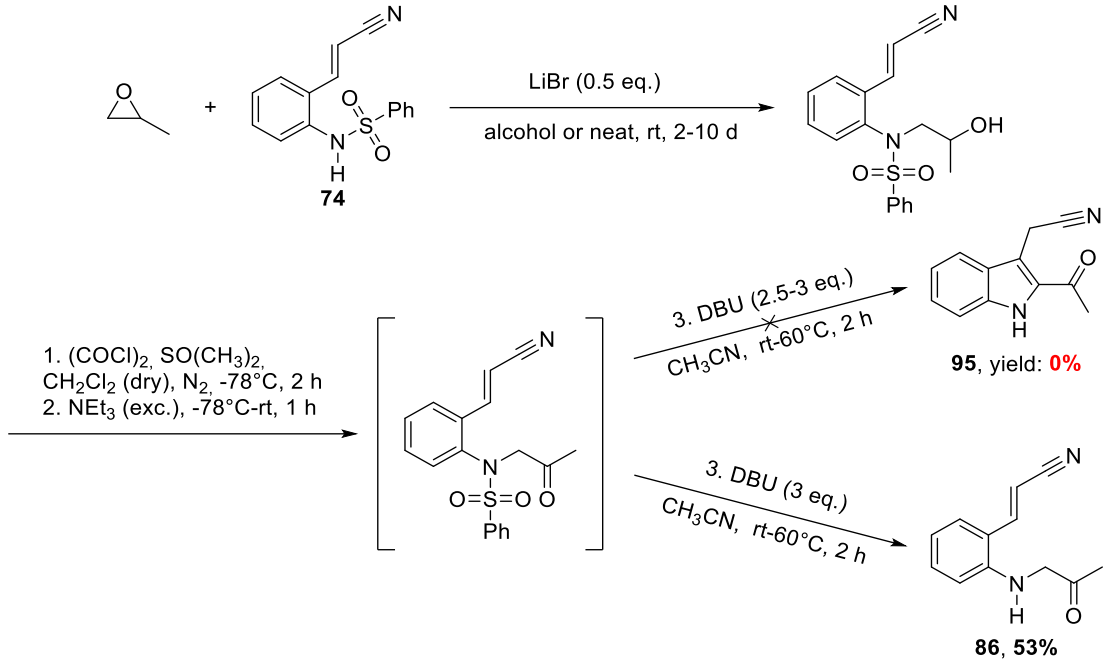
The next step, starting from the sulfonamides **68**-**70** and **73**-**76**, the indole intermediates should be synthesised from them. From the model reactions we already knew that the nucleophilic ring opening of the epoxides to generate the secondary alcohol intermediates from them was performed best with the Lewis acid LiBr as activating agent, using the preparation protocol of Chakraborti et al.[109]. The reactions were always monitored by TLC control and the reaction was only aborted when the educt was consumed. In the knowledge that the product analyses would be very difficult, based on the tendencies of the alcohols to appear as rotamers in any NMR spectra, it was decided to perform all the reactions to the stage where the substituted indoles would form - and then determine the yields over three synthesis steps. From the model reactions in Chapter 4.2.4 with propylene oxide it was already known that the excess of propylene oxide could predominantly be removed trough dissolving the crude product with methylene chloride and then extracting the excess of epoxide with water. The resulting purity of the product had been sufficient for the next reaction step. Correspondingly, the in Scheme 78 shown alcohol syntheses, which were either performed neatly or with an alcoholic solvent (methanol, ethanol or propanol), the neat reactions were either quenched with methylene chloride and then washed with water or the alcoholic solvent was removed by means of vacuum, then the crude substance was then redissolved with methylene chloride and washed with water. The extraction process of the excess of epoxide, to state that clearly, was the sole purification step for this reaction step – for every substance. The solvent was removed afterwards, the substances were dried in high vacuum and then, with no further analysis, used in the next two synthesis steps – the Swern oxidation, followed by the Michael addition-elimination reaction.



Scheme 78: Performed 2-alkyloyl indole intermediates syntheses and their outcomes. The educt numbers and structures can be extracted from Scheme 77 (R = 2 x H or 2 x Cl).

As can be seen in Scheme 78, the yields for the indole intermediates, which were isolated through column chromatography in each case, ranged from poor to quantitative. When looking at the results in one can clearly see a trend when one compares the results for the amides. It seemed as if the reaction had gone better, the higher *N*-substituted the amide group was. In case of the primary amide **91**, the product could not be isolated at all. When looking closer, the problem seemed to have already appeared at the alcohol synthesis stage. A few days after the epoxide had been added to the sulfonamide **68**, a white nearly insoluble (neither in water nor in any common organic solvent) solid had precipitated after a few days. TLC control showed, that educt

had reacted but product had not formed at all. Since the precipitate could not be dissolved in a low volume of any organic solvent (for an NMR analysis) and because the molar mass could also not be assigned to any expected side product, the reaction could not be investigated for potential side reactions that had been taken place. Consequently, the interference factor could not be eliminated for this reaction product **91**. It is though possible that the reaction could have worked with (a) protective group(s), in replacement of the amide's hydrogens, since one can see clearly on the results for the tertiary amides **92**, **93** and **96**, that the reaction tolerates a tertiary amide group. Regrettably, during the time frame of this work, no reaction could be performed with the sulfonamide **69** (see Scheme 77) for comparison, due to a lack of a sufficient educt amounts. The results, in comparison with the primary and tertiary amide, would have been very interesting. Maybe the usage of (a) protective group(s) could have solved the problem with the primary amide **91**, though any further investigations in that direction could not been carried out during the timeframe of this work.

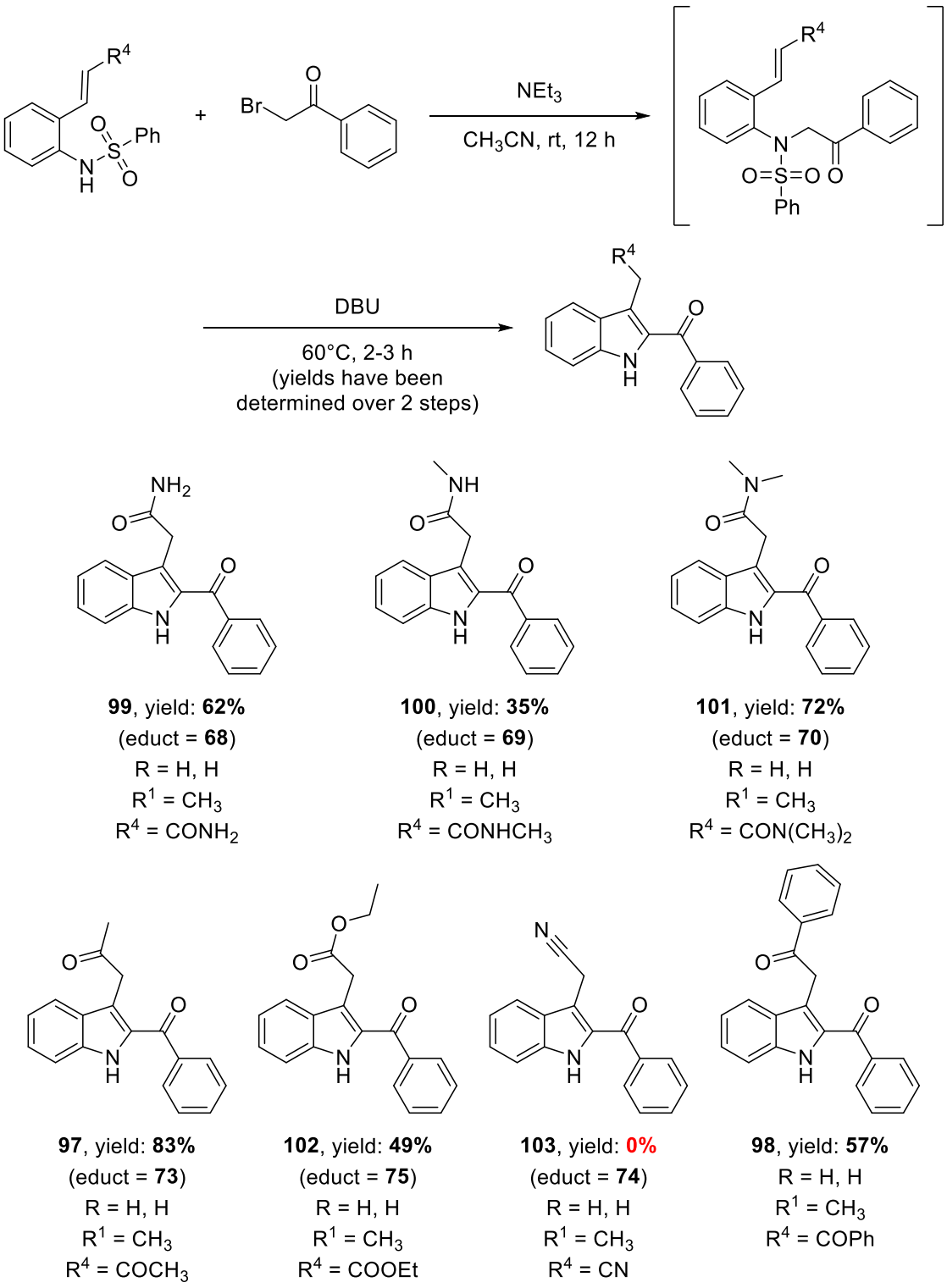


Scheme 79: Failed attempt to generate the 2-acyl indole-3-acetonitrile **95**.

As more detailed imaged in Scheme 79, in case of the substance **95** (holding R^4 = CN), it was visible, that starting from sulfonamide **74** the first two preparation steps did (according to TLC-MS control) proceed successfully, however after the ketone intermediate was treated with DBU, instead of the expected indole **95**, only degradation products could be isolated through the purification processes. The most prominent of those was the substance **86**. Having achieved this result on the other hand indicated, that the electron withdrawing effect of the nitrile group was not strong enough to induce the, for the indole **95** formation, crucial Michael addition.

2-Benzoyl substituted indoles

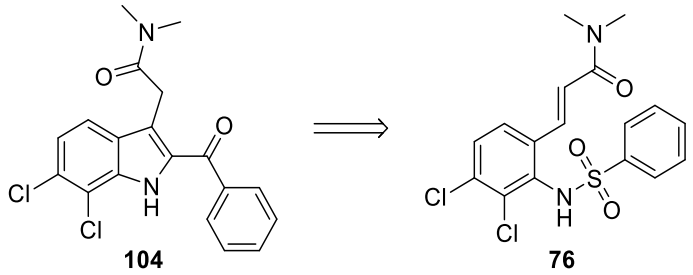
From the model syntheses (in Chapter 4.2.4), that the formerly used epoxide chemistry had not worked as well as with ethylene oxides holding a phenyl residue in the 2-position, but we still wanted to establish a method to generate 1,4-disubstituted β-carbolines with aromatic substituents in the 1-position. It was therefore decided to prepare the 2-benzoyl substituted indole intermediates according to the method of Kim et al.[48], which certainly was an already established method. The primary focus for synthesising those was however to generate a certain number of 2-benzoyl substituted indole intermediates efficiently and rapidly, so that these could then serve as educt examples to prepare a certain selection of 1,4-disubstituted β-carbolines from them. The produced sulfonamides, as imaged in Scheme 77, should again therefore serve as precursors for this reaction. As can been seen in Scheme 80, the syntheses results went mostly from poor to very well. Despite the result for the nitrile **103** was expected, because there still was some leftover educt **74** (see Scheme 77), the reaction was performed anyway. The 0% yield, which was obtained for substance **103** confirmed the assumption that the nitrile group does in fact not provide a strong enough electron withdrawing group to induce the crucial Michael addition – for this class of molecules at least. This result led to the dismissal of all attempts to generate any indoles holding acetonitrile at the C-3 through this method. It was to deduce from the overall results so far, that compared to the method with which the earlier 2-alkyloyl substituted indoles had been produced, apart from it taking less time to proceed the whole synthesis, this method showed no significant advantage over the other. If one had to argue sides however, the advantage was rather on the epoxide chemistry's side, due to the fact, that this chemistry allows an introduction of a much wider range of aliphatic groups, than the other method does.



Scheme 80: Performed 2-phenyl acyl indole intermediates **97**-**103** syntheses. The educt numbers and structures are extractable from Scheme 77. The educt for substance 98 was again provided by Dr. Untergehrer (see educt from Scheme 78).

One substance could regrettably not being prepared at all. As shown in Scheme 81, it had originally been the plan all along to prepare the substance **104** from the educt **76**, but regrettably there was not enough educt **76** (see Scheme 77) substance amounts left to do that. After having finished the synthesis route establishment, it had been planned to produce a larger selection of

indoles holding 6-,7-dichloro substituents anyway. So, for the time being, the preparation of those was put on hold, in the intention to proceed with them after the route was established. Deplorably, during the timeframe of this work, I did not proceed with the preparation of those, because the route establishment had been prioritised and that took too much of my time to have any left to proceed with the 6-,7-dichloro substituted indoles.

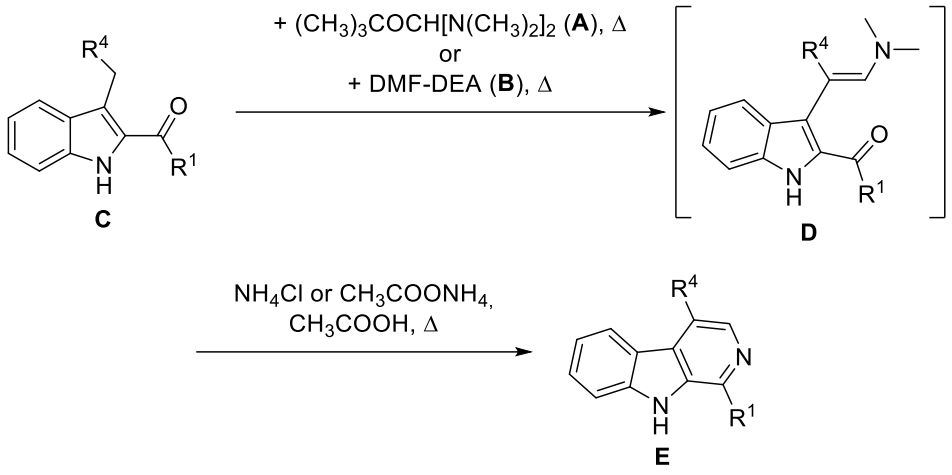


Scheme 81: Regrettably not performed synthesis of this 6-, 7-dichloro substituted indole **104**.

Of course, if there were requirements later to produce a selection of 6-,7-dichloro substituted indoles, they could be generated easily, taking the findings of this work into account.

Synthesis of 1,4-disubstituted β-carbolines

We now had a selection of indoles to prepare 1,4-disubstitued β-carbolines from. As had been already earlier elucidated in Chapter 4.2.6, there were in general (minimum) two choices of reagent to introduce the enamine group, one being the Bredereck's reagent (**A**), the other DMF-DMA (**B**) (see Scheme 82). The general procedure of the reaction for the **C**-type indoles to the **E**-type 1,4-disubstituted β-carbolines can be seen in Scheme 82.



Scheme 82: General reaction procedure for the performed 1,4-disubstitued β-carboline syntheses.

It was started with the earlier prepared indoles, holding alkyl residues for R^1 for which the results can been seen in the following Figure 12.

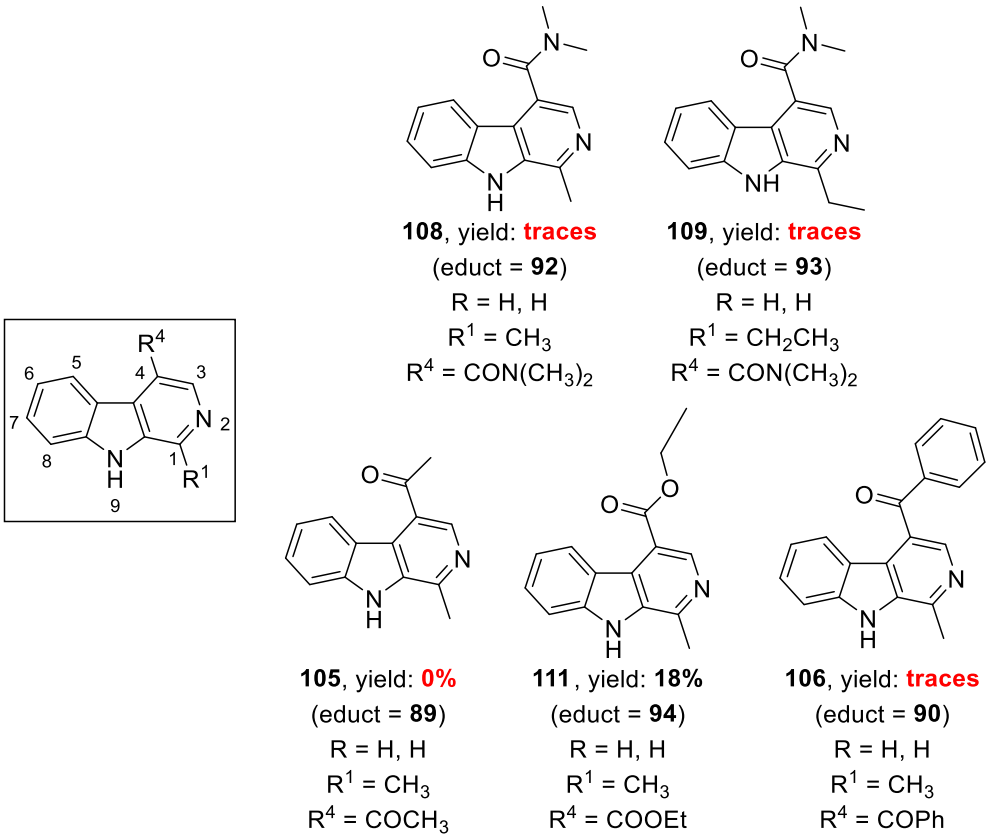


Figure 12: Performed 1,4-disubstitued β-carboline syntheses for $R^1 = CH_3$ or CH_2CH_3. The educt structures and numbers can be extracted from the earlier Scheme 78.

After the first (test) reaction with educt **92** had be performed using the Brederick's reagent **A** (see Scheme 82) for the enamination reaction to the intermediates in the style of **D**, although the TLC reaction control had shown that some of the educts or maybe even the enamine derivatives of the type **D**, apart from the expected reactions also underwent some side reactions. After the second reaction step had been performed, the product **108** (see Figure 12 again) could be found on the TLC reaction control and product could be found *via* TLC-MS analysis. However, when the product was tried to purify by column chromatography, only traces of product could be found in the dried substance, which could be obtained from the combined column fractions. It was assumed, that the Bredereck's reagent might expose the educt **92** or the corresponding enamine derivative to too harsh reaction conditions, therefore the reaction was repeated, this time using the reagent **B** (DMF-DEA from Scheme 82). The desired enamine and later the β-carboline product **108** were both detected on the TLC reaction control, again by TLC-MS, but regrettably after having performed the column chromatography again only traces of the desired β-carboline product **108** could isolated through the purification process. It is not necessary to mention, since in both cases no appreciable substance amount could be isolated, that the isolated product traces might also have been some sort of structure isomer of the desired product – since no NMR analysis could be performed due to the lack of substance amount. Since we already had a selection of indoles with alkyl residues for R^1, the other educts have all been reacted with DMF-DEA

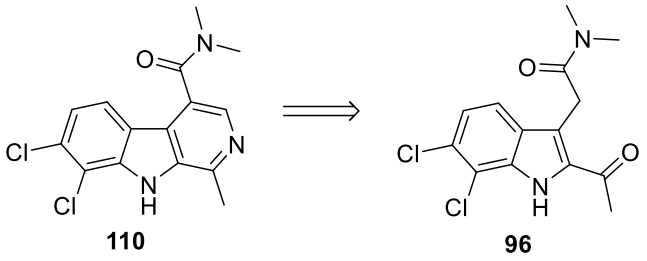
(*N*,*N*-dimethylformamide diethyl acetal) in the same manner. The results for the performed 1,4-disubstitued β-carboline syntheses for $R^1 = CH_3$ or CH_2CH_3 can all be seen in Figure 12.

In nearly in all of the cases, it was visible through the TLC reaction control, that a lot of side reactions had taken place during both reaction steps. The product, or any structure isomer of that, had been detectable by TLC-MS for all the reactions, apart from one, for which no product (substance **105**) spot could be detectable through TLC-MS. Only in case and with an 18% yield, enough substance amount of the ester **111** could be isolated through column chromatography to perform the necessary analytics.

Table 3: Listed results and syntheses conditions for the 1-alkyl substituted β-carbolines syntheses (Bredereck's reagent (**A**) and DMF-DMA (**B**)).

β-carboline	educt	R^1	R^4	step 1. reagent (A or B)	reaction step 1. temperature, time	reaction step 2. temperature, time	yield
108	**92**	CH_3	$CON(CH_3)_2$	**A** **B**	90°C, 2 h	160°C, 1 h	**traces** **traces**
109	**93**	CH_2CH_3	$CON(CH_3)_2$	**B**	90°C, 45 min	150°C, 1 h	**traces**
111	**94**	CH_3	COOEt	**A** **B**	120°C, 2 h	140°C, 2 h	**18%** **10%**
105	**89**	CH_3	$COCH_3$	**A** **B**	120°C, 2 h	140°C, 1.5 h	**0%** **0%**
106	**90**	CH_3	COPh	**B**	100 °C, 45 min	160°C, 1 h	**traces**

After the failed attempts to prepare theses β-carbolines, I made a few experiments with Bredereck's reagent (**A**) or DMF-DMA (**B**). All the used conditions for the β-carboline syntheses are listed in Table 3. Regrettably, neither reagent **A** nor **B** showed any advantage over the other.



110 **96**

Scheme 83: Intended reaction to generate one exemplary 7,8-dichloro 1,4-disubstituted β-carboline **110**.

Of course, as shown in Scheme 83, it had been the plan all along to prepare the more interesting 7,8-dichloro 1,4-disubstituted β-carboline **110** from educt **96**, but after this indole intermediate synthesis had been performed, there was deplorably not enough of the educt **96** to go on with the

next preparation step. The repreparation of the indole intermediate **96** though could not be fulfilled during the timeframe of this work.

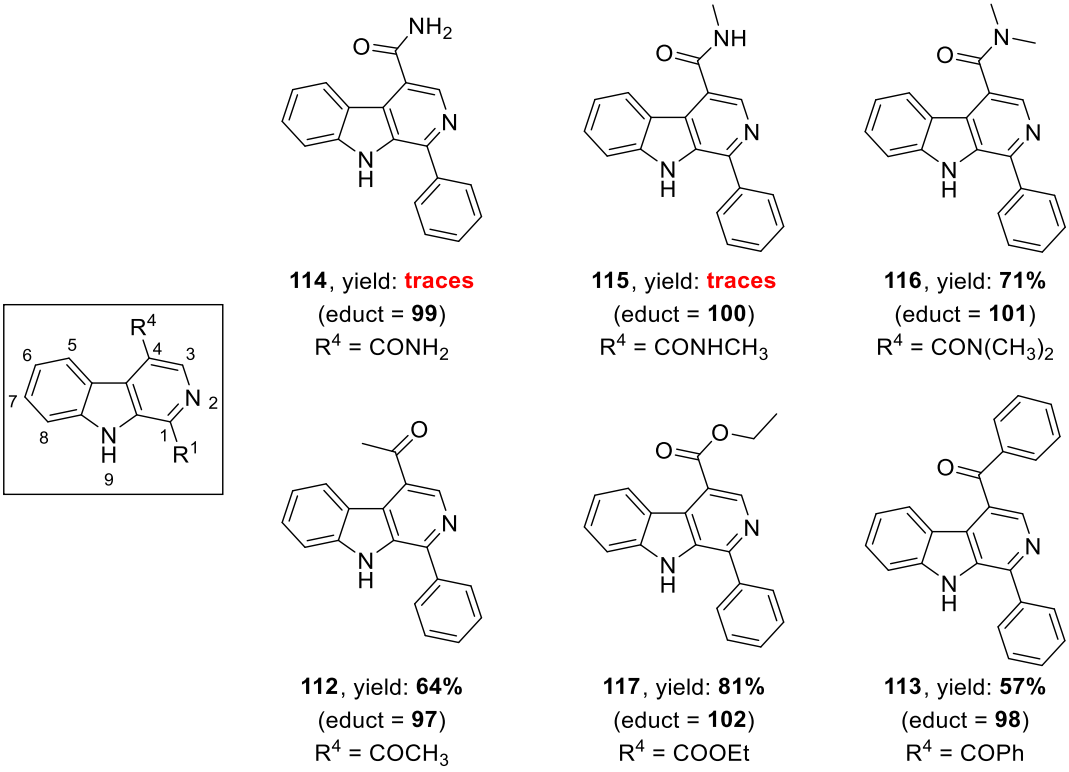
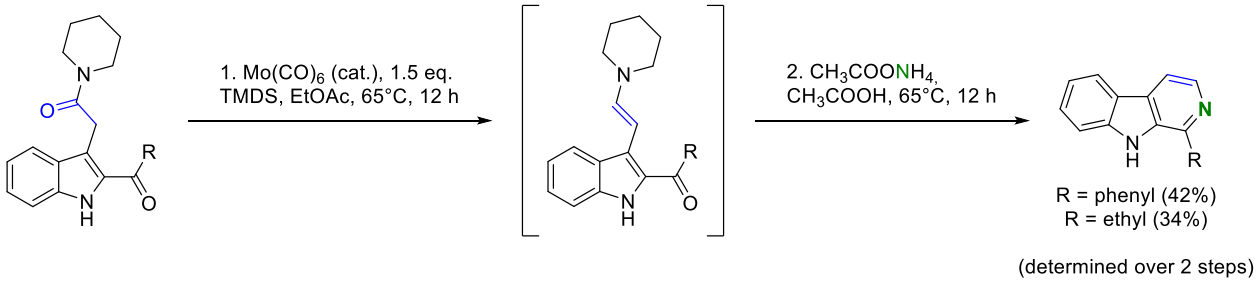


Figure 13: Performed 1,4-disubstitued β-carboline syntheses for R^1 = phenyl. The educt numbers and structures are extractable from Scheme 80.

As we had such devastating results for the 1-alkyl substituted β-carbolines, we wanted to know if we would have the same problems with the 1-phenyl substituted β-carbolines. But when the formerly prepared substituted indole intermediates, displayed in Scheme 80, were subjected to the same reaction conditions, the results proved to be much better in comparison. As imaged in Figure 13, the reactions in which the indole intermediate had an ester or a ketone on the C-4, the results went from fair to very well. When it came to the primary and secondary amides **114** and **115**, only traces of the products, or of a structure isomer of that, could be detected on the reaction control. Again, when the products were tried to purify by column chromatography, in both cases, no sufficient amounts could regrettably be isolated to perform the required set of analyses to determine, if they were even the product. Surprisingly, for the tertiary amide **116** preparation provided an unexpected yield of 71%. One theory for the primary and secondary amine reactions not to work in comparison to the tertiary one, might be the fact, that the primary and secondary amides can be potentially NH-deprotonated. In this case, the NH acidity was probably stronger than the acidity of the, to the amide's carbonyl's α-positioned, methylene group. In retrospect and also with regard to the results (see Figure 12) which we have gotten for the 1,4-disubstitued β-carboline syntheses, holding alkyl groups at the C-1, a potential NH-deprotonation might also have provided a disturbance factor in the earlier syntheses.

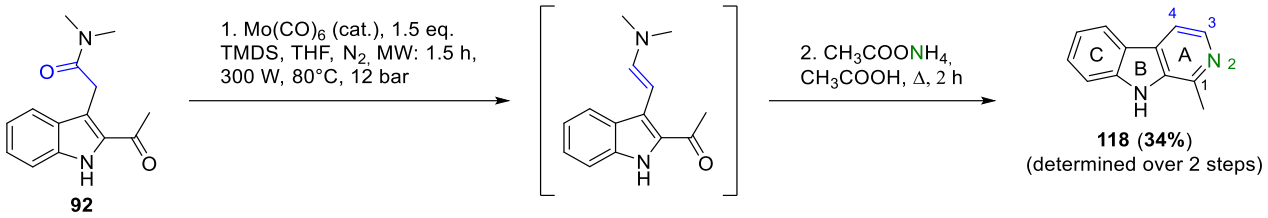
4.2.8 Exemplary syntheses of one 1-substituted and one 1,3-disubstituted β-carboline

The synthesis (see Scheme 85) of the C-1 methyl substituted β-carboline harmane **118** was performed from the formerly prepared intermediate **92** from last chapter. It is to note, that in this scenario and as shown bluely in Scheme 85, the amide's carbonyl-C of the indole **92** with this type of reaction becomes part of the harmane (**118**)'s basic structure rather than be a part of the C-4 substituent - to specify, it becomes the C-3 of the harmane (**118**)'s pyridine (A-ring). The chemoselective amide reduction, next to a more reactive keto group, was performed according to a method of Trillo et al.[116] (published 2017), which was an faster variant in comparison to the method, Untergehrer has utilised for his work[41]. Untergehrer back then used the same amounts of $Mo(CO)_6$ and TMDS but, in comparison to my used method, he performed the reaction with EtOAc as solvent and in a normal stirring flask.[41] The resulting enamine intermediates he though did not isolate, but transposed them further under an CH_3COONH_4/glacial acetic acid atmosphere to the resulting C-1 R-substituted β-carbolines and determined the yield over two steps (R = phenyl (42%) and R = ethyl (34%)). The two exemplary syntheses which had been performed by him, can be observed with his results in the following Scheme 84 and were extracted from his dissertation.[41]



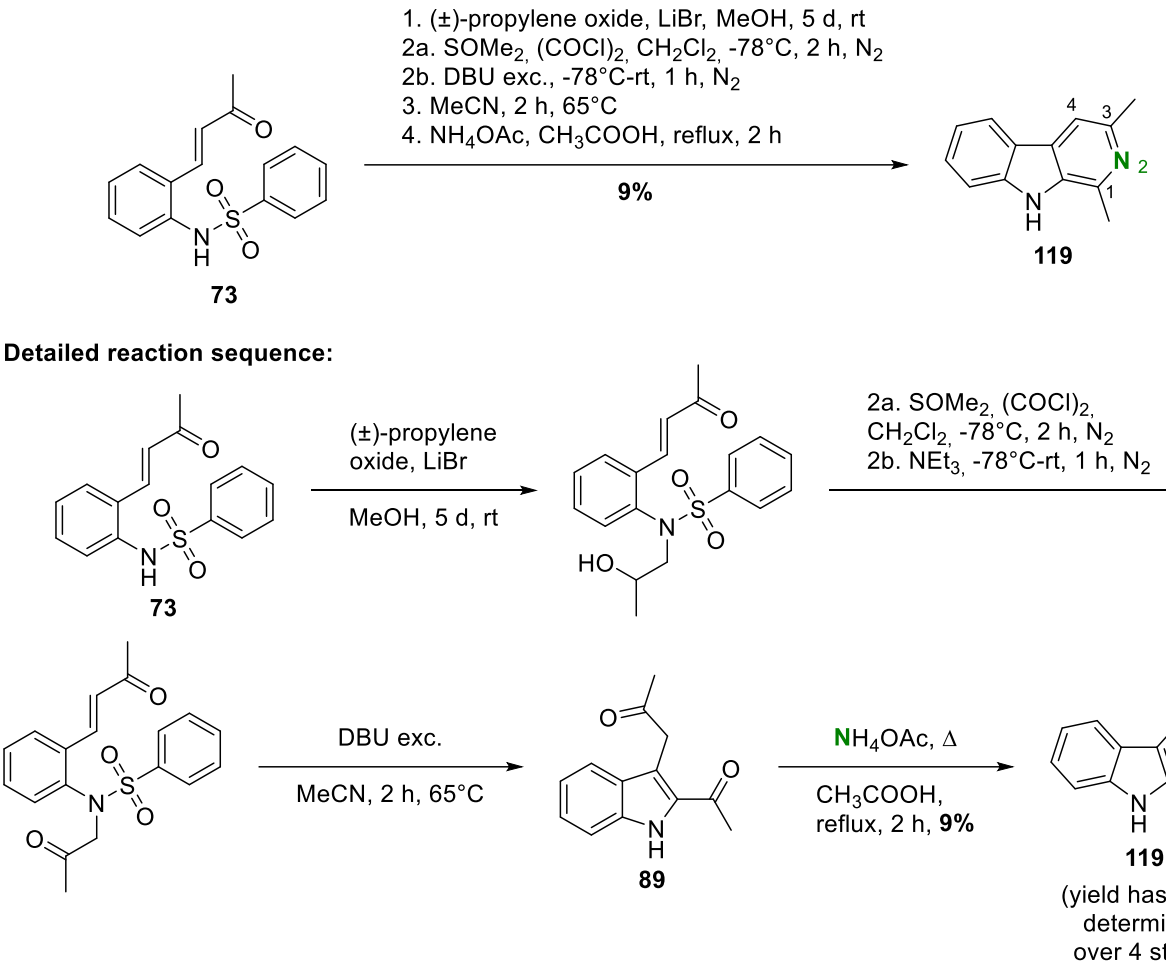
Scheme 84: The two exemplary syntheses Untergehrer had performed for his dissertation.[41]

To utilise the method Trillo et al.[116], my reaction was to be performed in a microwave synthesis reactor instead. $Mo(CO)_6$, in this special chemoselective reaction, functions as an amide group selective reduction catalyst, while TMDS (1,1,3,3-tetramethyldisiloxan) functions as the reducing agent. As far as is known to us, the detailed mechanism of this reaction is unknown, although the results suggest, that the catalyst $Mo(CO)_6$ takes part by activating the amide functional group selectively, which then in an activated state undergoes the reduction with the reduction agent TMDS. From there, the suggested mechanism can be observed in Chapter 3.2.2, Scheme 39 and is not going to be repeated here. The subsequent and in-situ condensation reaction, induced by the addition of CH_3COONH_4/CH_3COOH and the continuous heating of the reaction solution, again following Kamlah et al.'s protocol[31], yielded the desired product **118** in a 34% yield. The CH_3COONH_4's nitrogen again became the 2-N of the harmane (**118**) – see Scheme 85.



Scheme 85: My exemplary synthesis of one 1-substituted β-carboline **118**.

The exemplary synthesis of one 1,3-disubstituted β-carboline was performed starting with the sulfonamide **73** and is shown, even in detail, in the following Scheme 86. The reaction was performed in 4 steps, using the same protocols that had been used for the previous syntheses. The nucleophilic ring opening reaction using LiBr as Lewis acid and (±)-propylene oxide as coupling partner (reaction step 1. – according to Chakraborti et al.[109]'s protocol) and the Swern oxidation (reaction step 2a. & 2b. – following Omura et al.[106]'s protocol, conditions: 2a. $SOMe_2$, $(COCl)_2$, CH_2Cl_2, -78°C, 2 h, N_2; 2b. DBU exc., -78°C-rt, 1 h, N_2) were performed successively, as has been done like this in most of the previous ketone syntheses. The protocol of Kim et al.[48] was again used to synthesise the indole intermediate **89**, however when the indole intermediate **89**, this batch at least, was tried to purify by column chromatography, the product could not be obtained in a sufficient purity therefore no yield was determined at that stage. The next reaction, ,using Kamlah et al.'s protocol[31] again, was therefore performed with the crude indole intermediate **89** and the yield was correspondingly determined over 4 steps in the end. The indole **89**, being a diketone, reacted with **N**H_4OAc/glacial acetic acid again and the pyridine ring of product **119** was built again including the nitrogen of **N**H_4OAc to become the 2-N of the 1,3-disubstituted β-carboline **119**. During the last reaction step a noteworthy lot of side reaction products could be found on the TLC control, which might have explained the quite poor overall yield of 9% for the product **119**, which was determined after the product **119** could be finally successfully purified through column chromatography. All in all, it is to conclude, that the developed route for the preparation of certain 2,3-disubstituted indole intermediates is not only perfectly suitable for the fabrication of 1,4-disubstituted β-carbolines, but also provides a quick method for the preparation of specific 1-substituted and 1,3-disubstituted β-carbolines. It is thought to emphasise, that this is only true for indole holding certain functional groups in the C-3 position.



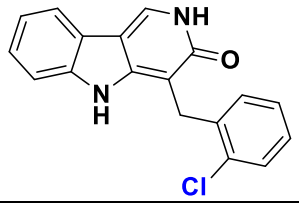
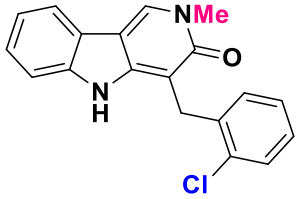
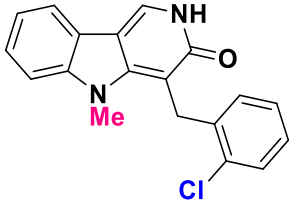
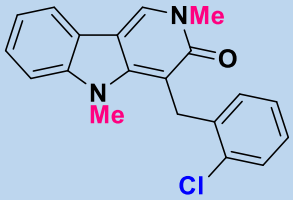
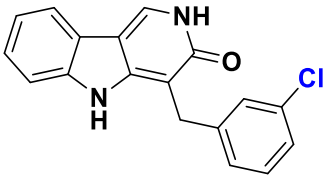
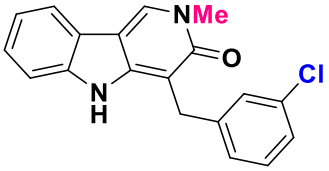
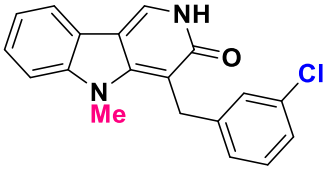
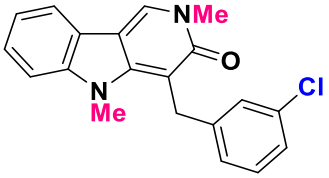
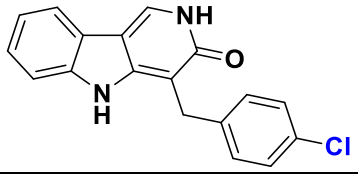
Scheme 86: Exemplary synthesis of one the 1,3-disubstituted β-carboline 119.

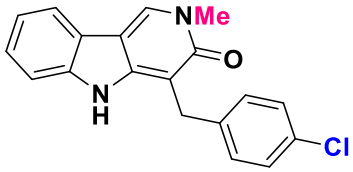
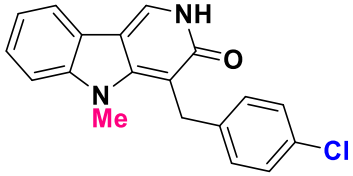
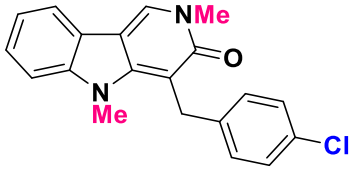
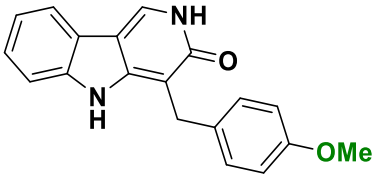
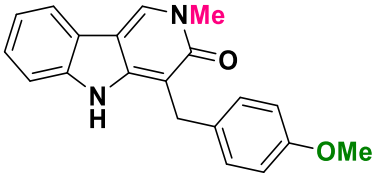
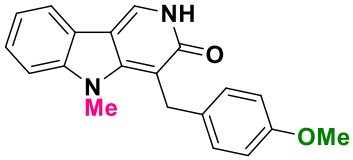
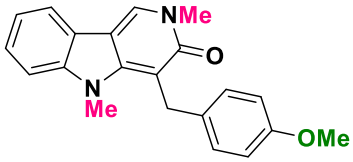
4.2.9 MTT ((3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay

For preparing the MTT viability assay, HL60 cells had been transferred to a 96-well plate (100µL/well) at a density of $9x10^5$ cells/mL and the well plate had been incubated overnight at 37 °C, with 90 % air humidity and under a 5 % CO_2 air concentration. A stock solution of all substances of 10 mM in DMSO was prepared for each substance to be tested and a dilution series (with the factors 0^1/10^0.85/10^0.70/10^0.65/…) was prepared from each stock solution using DMSO again as diluent. For each 96-well plate row, a rising and known concentration of substance was added in contrast to a last reference well, only containing cells, medium and DMSO (with a final concentration of 1 µg/mL) that should act as control. All substances were treated in this way and all measured conditions were further prepared in triplicates to receive three measurement values for each substance and concentration. Having treated the cells, each well with a specific concentration and substance, the 96-well plate was then incubated for 24 h at 3°C, with 90% air humidity and under a 5% CO_2 air concentration. After that step, 10 µL of the MTT stock solution (5 mg/ 1 mL of phosphate buffered saline (PBS), pH 7.4) was added to each well and the cells were incubated another 2 h under the same conditions. To dissolve the formed Formazan crystals, 190 µL of pure DMSO was added to each sample and the plates were set on a microplate shaker for 1 h until the Formazan had dissolved, then the optical measurement was performed promptly. For determining the cell viability, the absorbance was measured promptly at λ = 570 nm (reference wavelength λ = 630 nm) in an ELISA well plate reader MRX microplate reader (DYNEX Technologies, Chentilly, USA). The graphical representation of all measured absorption values y = viability [%] plotted against x = log(concentration [µM]) gave the IC50 at the infection point of the generated sigmoid function, generated by Prism 5.0 (GraphPad, USA).

To calculate the IC_{50} value, the average absorption for the cells treated with pure DMSO (representing ideal growth and proliferation conditions) equals 100% viability. The resulting IC_{50} values can be extracted from the following Table 4. Having a look at the results from the MTT tests, it is clear, that none of the tested substances outstrip the results obtained from substance **43**, which is structurally the same compound as **uwIND086** (see Chapter 2.1). Noticeable however is the fact, having methyl substituents both at the 2- and 5-position increase the inhibitory activity of the compounds severely, when observing the differences in the IC_{50} between for example the first four substances of Table 4 (substance numbers **39**, **41**, **42** and **43**).

Table 4: MTT test results for the 3-oxo-γ-carbolines.

Substance Nr.	Molecular structure	M [g/mol]	HPCL purity [%]	IC_{50} [µM]
39		308,765	>99	**> 50.0**
41		322,792	100	**130**
42		322,792	- (not well soluble)	**> 50.0**
43 **(uwIND086)**		336.819	100	**3.80**
44		308,765	99	**> 50,0**
45		322,792	98	**30,8**
46		322,792	94*	**> 50,0**
47		336.819	95*	**56,6**
48		308,765	>99	**> 50,0**

49		322,792	99	**33,9**
50		322,792	99	**> 50,0**
51		336,819	100	**29,1**
52		304,349	100	**165**
53		318,376	99	**> 50,0**
54		318,376	- (not well soluble)	**> 50.0**
55		332,403	97	**18,0**

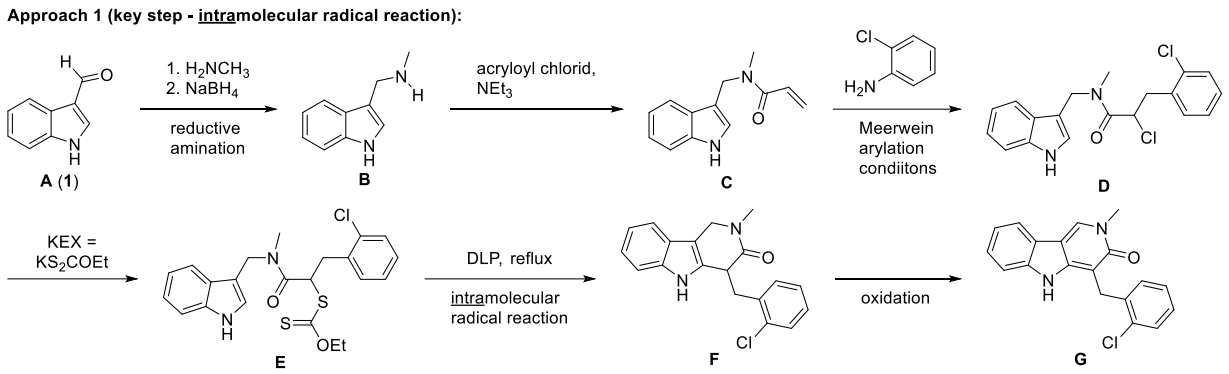
* Due to substance amount shortage, it was refrained from further purification attempts in order to have enough substance to perform biological tests.

In two cases, the substance **49** (2-NMe, 5-NH) over **50** (2-NH, 5-NMe) and the substance **45** (2-NMe, 5-NH) over **46** (2-NH, 5-NMe), the 2-NH and 5-NMe substituted substances in comparison to the 2-NMe and 5-NH seemed to have lower IC_{50} concentrations. This fact suggests that an alkyl substituent in the 5-position is more crucially influencing the cell viability for this substance class. However, a larger variety of substances within this substance class would have to be prepared and tested to confirm this hypothesis.

5 Summary

5.1 3-Oxo-γ-carbolines and their dihydro analogues project

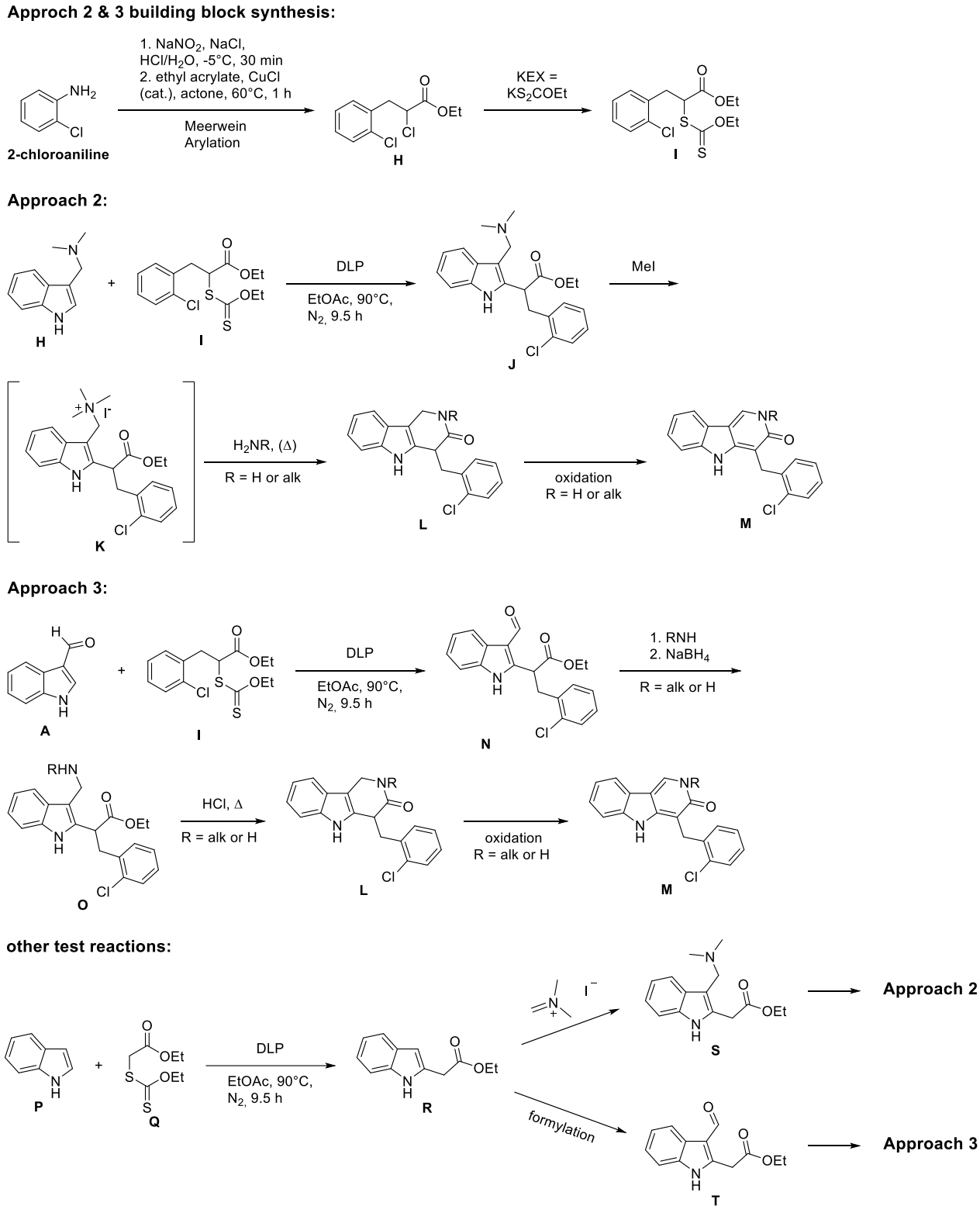
The preparative approach for the synthesis of multiple substituted 3-oxo-γ-carbolines was determined by implementing certain model reactions, all outlined in detail in the Chapters 3.1.1 to 3.1.3. The following Scheme 87 images the approach 1, which shows the first plan for the preparation of 3-oxo-γ-carbolines of the type **G** and their reduced type **F** precursors. The approach 1 is in detail explained in Chapter 3.1.1.



Scheme 87: Synthesis approach 1 to final products **F** and **G**.

approach 1 had been planned to start from 1*H*-indole-3-carbaldehyde **A** (**1**) as it was called in this thesis. A reductive amination to **B** and a coupling with acryloyl chloride should yield the unsaturated substance **C**. The Meerwein arylation using **C** to gain **D** and the following transformation of **D** using KEX (KS_2COEt) salt should have yielded the xanthate **E**. The key step, the intramolecular radical reaction, would then generate **F** from **E** which further could be oxidised to the 3-oxo-γ-carboline **G**.

The two alternative approaches 2 and 3, elaborated in the Chapters 3.1.2 and 3.1.3 and as shown in Scheme 88, required a way to synthesise certain building blocks, for which a representative (**I**) should have been prepared from 2-chloroaniline in two steps. The xanthate **I** should in a first step be generated from a halide **H** with KEX (potassium-*O*-ethyl dithiocarbonate), which had been previously prepared from 2-chloroaniline in a Meerwein arylation. Having achieved that, the xanthate **I** should further be used as reaction partner for the approach 2, this time, intermolecular key step reaction – the radical substitution reactions with gramine (**H**). The 2,3-disubstituted indole **J** had been planned to convert to a dihydropyridone of the type **L** through a successive reaction with MeI and an amine of one's choosing (for example NH_3 or NH_2Alk). Oxidation of **L** would then yield the pyridone in the style of **M**. The approach 3, starting from indole-3-carbaldehyde (**A**), had been planned to react with the xanthate **I** in the again intermolecular radical substitution reaction - to receive 2,3-disubstituted indole **N**.

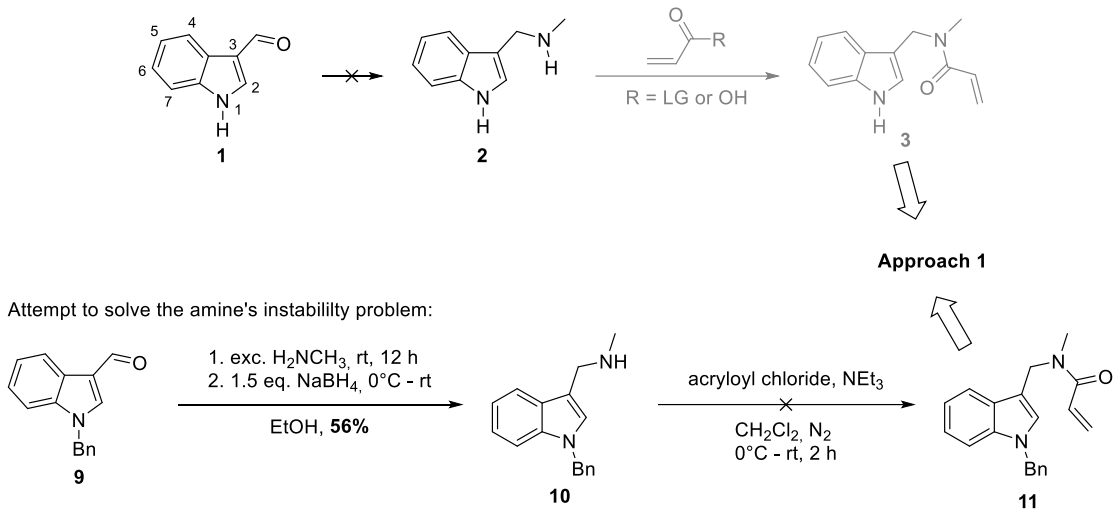


Scheme 88: Planned approaches 2 & 3, synthesis of the building block representative **I** and other test reactions.

Starting from **N**, a reductive amination with H_2NR (R = H or alkyl) and successive addition of $NaBH_4$ should have yielded the amine **O**. Exposing **O** to an (acid and) heat treatment, had been planned then to lead to the formation of the **L**-type dihydropyridone. Substance **L** again would be oxidisable to the **M**-type pyridone. Finally, and in the intent to determine if the unsubstituted

indole (**P**) would undergo the substitution at the indole's C-2 as well, it had been the plan to treat indole (**P**) with DLP in the presence of the xanthate **Q**. The, hopefully generated, C-3 unsubstituted indole **R** could maybe be transformed to a 2-substituted gramine (**S**) using the Eschenmoser's salt and approach 2 might be pursued from there. Alternatively, from **R**, one might formylate at the C-3 of the indole **R** and the hopefully built aldehyde **T** might again be used to pursue the approach 3 from there.

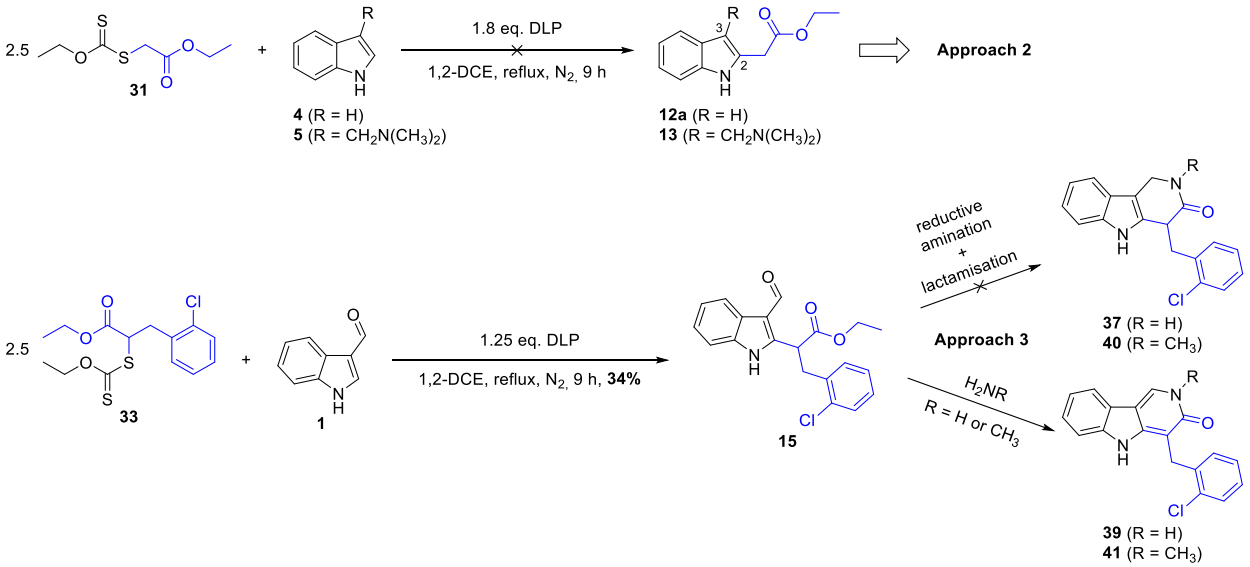
The model reactions for route establishment of approach 1, which is elaborated in subchapter 3.1.1, failed early. Originally (see Scheme 89), it had been the plan to build up the 3-oxo-γ-carboline, starting from 3-position formylated indoles. However, the first reaction step, which was the reductive amination of indole-3-carbaldehyde (**1**), failed due to product **2** instability. The following reaction, greyly shown in Scheme 89, could therefore not be performed. The introduction of a protective group prior to the reductive amination did not solve this problem and consequently the approach 1 was aborted then.



Scheme 89: Results for the model reaction of approach 1 (X = Cl, Br, I).

As imaged in Scheme 90, the model reactions that were carried out to help with the decision which approach (2 or 3) to follow. To determine, if maybe the approaches 2 or 3 would provide an access to the preparation of 3-oxo-γ-carbolines, some model reactions were performed with the xanthates **31** and **33**. As imaged in Scheme 90, both model reactions for the approach 2, did not yield any substitution products. Combined with the xanthate **31**, neither the unsubstituted indole (**5**), nor gramine (**4**) underwent the radical substitution reaction, that should have been induced through the radical initiator dilauroyl peroxide (DLP). Having achieved these results, they lead unavoidably to the dismissal of the approach 2. However, the indole-3-carbaldehyde derivative **15** could be generated with a 34% yield through the same radical reaction, using DLP as radical initiator from indole-3-carbaldehyde (**1**) and the xanthate coupling partner **33**. Several

attempts to generate the dihydropyridines **37** and **40** through a reductive amination and successive pyridone formation failed regrettably.

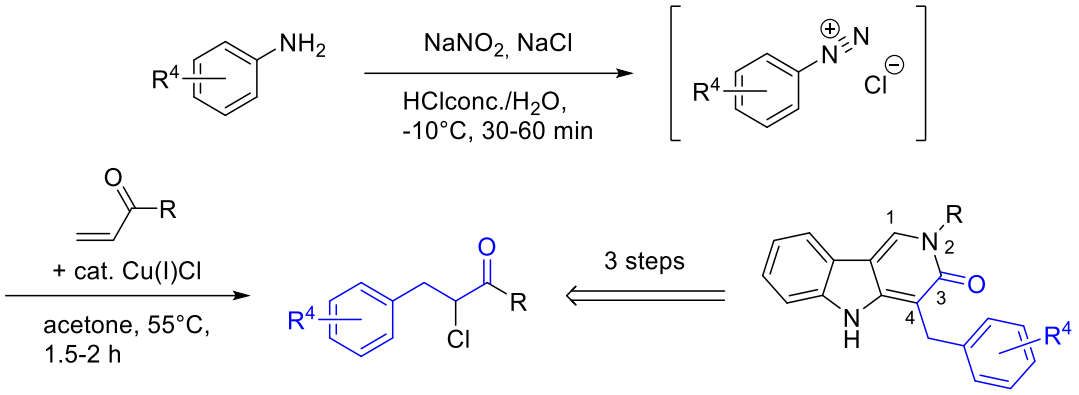


Scheme 90: Summed up results for the results for the approach 2 and 3 model reactions.

In this regard, all synthetic attempts are in detail described the Chapter 4.1.1. The 3-oxo-γ-carbolines **39** and **41** could be received as unexpected products in the last synthesis step instead of the desired dihydropyridone products **37** and **40**. These results finally offered the possibility to pursue the attempt to synthetically prepare multi-substituted 3-oxo-γ-carbolines through the approach 3, although we this synthetic approach did not provide a good method for the preparation of the also desired reduced variant of the 3-oxo-γ-carbolines, the dihydropyridone.

The first step of approach 3 were the building blocks, that would be accessible through the Meerwein arylation. The reaction was performed with several functional groups, for the residues R^1 and R^4, which are given with the yields for each reaction in Table 5.

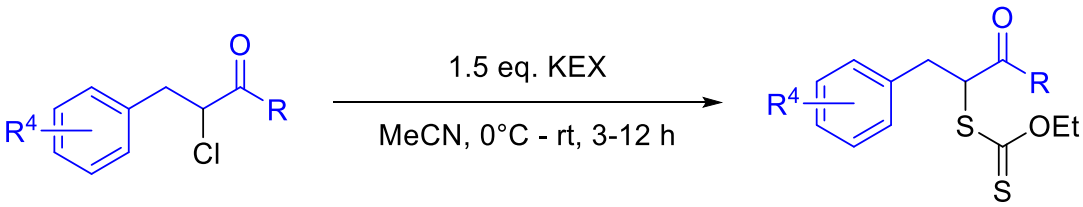
Table 5: Summary of the results for the Meerwein arylation products.



Substance	yield	R	R^4
26	**48%**	NH_2	*o*-Cl
27	**quant.**	OEt	*o*-Cl
28	**39%**	OEt	*m*-Cl
29	**19%**	OEt	*p*-Cl
30	**20%**	OEt	*p*-OCH_3
25	**61%**	OH	*o*-Cl

Table 6 shows the results for the next reaction step, the preparation of the xanthates. As can be observed, the yields all went from good to excellent/quantitative. Only the carboxylic acid **25** (see Table 5 was not reacted to the next stage, because it was learned in the meanwhile, that carboxylic acids are badly to not at all compatible with this kind of chemistry.

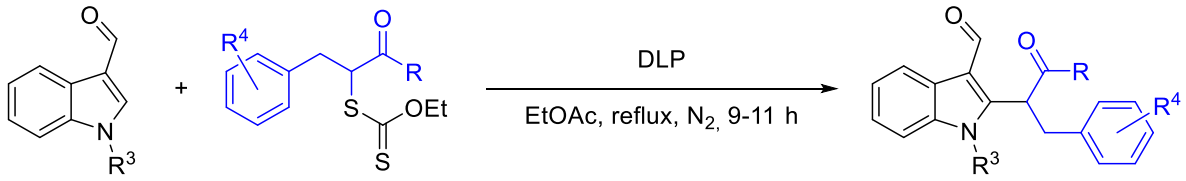
Table 6: Results for the xanthate syntheses. The corresponding educts can be extracted from Table 5.



Educt	Substance	yield	R	R^4
26	**32**	**90%**	NH_2	*o*-Cl
27	**33**	**91%**	OEt	*o*-Cl
28	**34**	**95%**	OEt	*m*-Cl
29	**35**	**74%**	OEt	*p*-Cl
30	**36**	**93%**	OEt	*p*-OCH_3

Following approach 3 (outlined in subchapter 3.1.3), radical substitutions at C-2 of the indole 3-carbaldehyde intermediates went smoothly, although the yields were all just poor to fair (see Table 7).

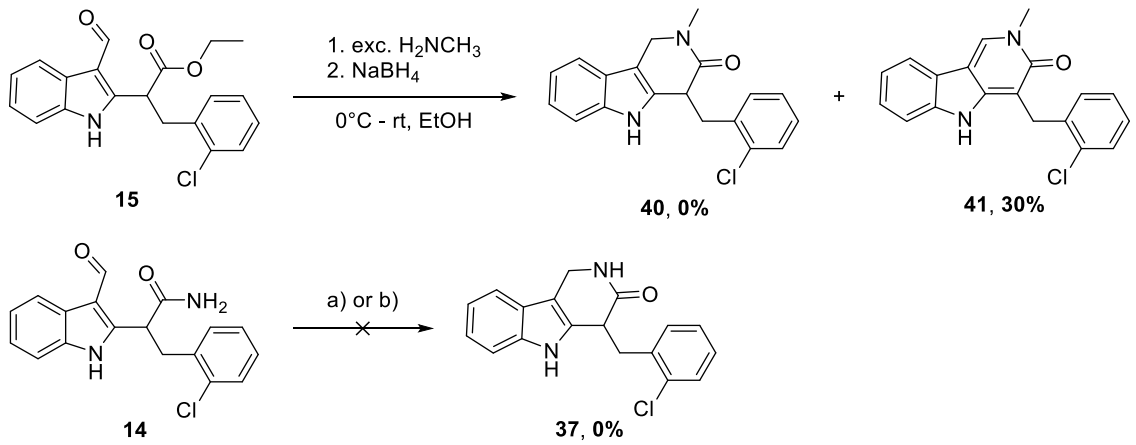
Table 7: Results for the radical substitution reactions. The corresponding educts can be extracted from Table 6.



Educt	Substance	yield	R	R^3	R^4
32	**14**	**32%**	NH_2	H	*o*-Cl
33	**15**	**34%**	OEt	H	*o*-Cl
33	**16**	**21%**	OEt	CH_3	*o*-Cl
34	**19**	**43%**	OEt	H	*m*-Cl
34	**20**	**39%**	OEt	CH_3	*m*-Cl
35	**21**	**24%**	OEt	H	*p*-Cl
35	**22**	**33%**	OEt	CH_3	*p*-Cl
36	**23**	**49%**	OEt	H	*p*-OCH_3
36	**24**	**15%**	OEt	CH_3	*p*-OCH_3

At this point a significant restriction came up concerning the upscaling of the experiments. An intentional scale variation (see the scaling experiments in Chapter 4.1.2) of these this radical substitution reaction showed that, the higher the used quantities, the lower the yields of the substitution products.

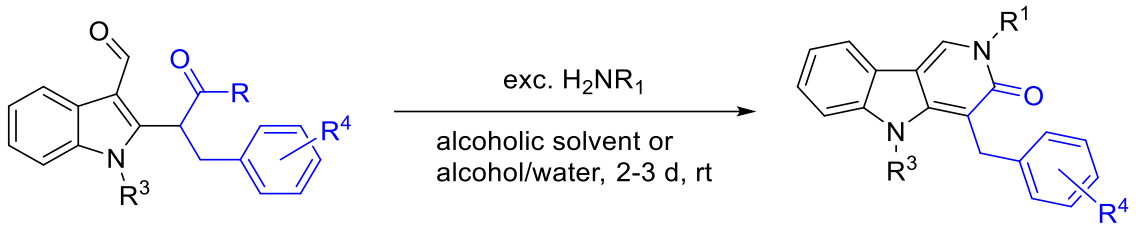
For the next reaction step, as extensively investigated and elaborated in Chapter 4.1.1 and as shown in Scheme 91, all selected reductive amination reactions following a lactamisation reaction and starting from indoles **14** or **15,** failed. Neither $NaBH_4$, $HSiEt_3$ nor $NaBH_4$ in combination with the Lewis acid $Ti(iOPr)_4$ did lead to a successful formation dihydropyridine **37** or **40**. However, the addition of an amine of choice seemed to have been enough as inducing reagent to generate the pyridone **41** instead.



Scheme 91: Test reactions to find an approach to gain the dihydropyridones **40** and **37** and the first synthesis of one exemplary 2,4-disubstituted 3-oxo-γ-carboline 41. Conditions: a)[96] TFA, Et_3SiH, H_3CCN, 24 h, 50°C b) 1. $Ti(iOPr)_4$, 1 h, THF, 0°C - rt; 2. $NaBH_4$, THF, 2.5 h, rt.

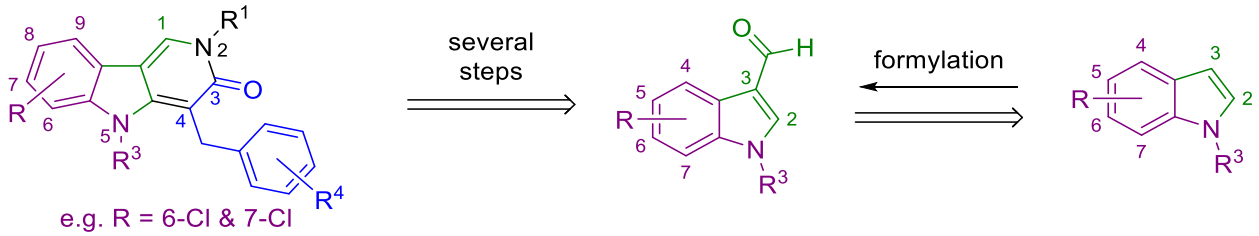
Finally having a way to synthesise 3-oxo-γ-carbolines, 16 exemplary compounds (see Table 8) could successfully be prepared using this synthesis route.

Table 8: Results from the final 3-oxo-γ-carbolines syntheses. The educts can be extracted from Table 7.



Educts	Substance	yield	R	R^1	R^3	R^4
15	**41**	**68%**	OEt	CH_3	H	*o*-Cl
15	**39**	**38%**	OEt	H	H	*o*-Cl
16	**43**	**44%**	OEt	CH_3	CH_3	*o*-Cl
16	**42**	**45%**	OEt	H	CH_3	*o*-Cl
19	**45**	**52%**	OEt	CH_3	H	*m*-Cl
19	**44**	**36%**	OEt	H	H	*m*-Cl
20	**47**	**32%**	OEt	CH_3	CH_3	*m*-Cl
20	**46**	**30%**	OEt	H	CH_3	*m*-Cl
21	**49**	**40%**	OEt	CH_3	H	*p*-Cl
21	**48**	**32%**	OEt	H	H	*p*-Cl
22	**51**	**33%**	OEt	CH_3	CH_3	*p*-Cl
22	**50**	**29%**	OEt	H	CH_3	*p*-Cl
23	**53**	**34%**	OEt	CH_3	H	*p*-OCH_3
23	**52**	**25%**	OEt	H	H	*p*-OCH_3
24	**55**	**44%**	OEt	CH_3	CH_3	*p*-OCH_3
24	**54**	**25%**	OEt	H	CH_3	*p*-OCH_3

To sum it up - I successfully managed to create a cheap and short (only four steps) synthesis route for the preparation of 4-benzyl substituted 3-oxo-γ-carbolines, which is very flexible, when it comes to variations of the 2-, 4- and 5-residues, whereat it is to mention, that we aimed for specific residues in the 4-position as shown in Scheme 92.



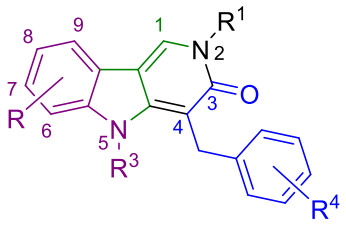
Scheme 92: Next step – creating further (C6-C9) substituted 3-oxo-γ-carbolines, which could derive from (multi)substituted indoles or 3-formylated indoles. R^1, R^3 = alkyl or H.

This route will probably allow also flexible and multiple variations in the positions 6 to 9 of the 3-oxo-γ-carbolines, however this is left to be proven and could be pursued in a potential future

project. If there was an interest to produce a series of for example 6-, and 7-position or other 6-9 (multi)substituted compounds, one would have to build up the corresponding 4-7 (multi)substituted indole-3-carbaldehydes or 2,3-unsubstitited indoles, for which a variety of synthesis approaches already exist.

To mention the MTT results at last, the results showed that compound **43**, which equals **uwIND086** that was our original hit, performed the best in the cell viability assay. Methyl substituents at the 2- (R^1) and 5-positions (R^3) increased the inhibitory activity, particularly when both positions are methylated. However, exceptions are noted, suggesting that the presence of alkyl substituents at the 5-position may be more influential. The need for further testing to confirm these findings is acknowledged. For the complete MTT results, see Table 9.

Table 9: MTT Test results for the 3-oxo-γ-carbolines (R = 4 x H for all substances).



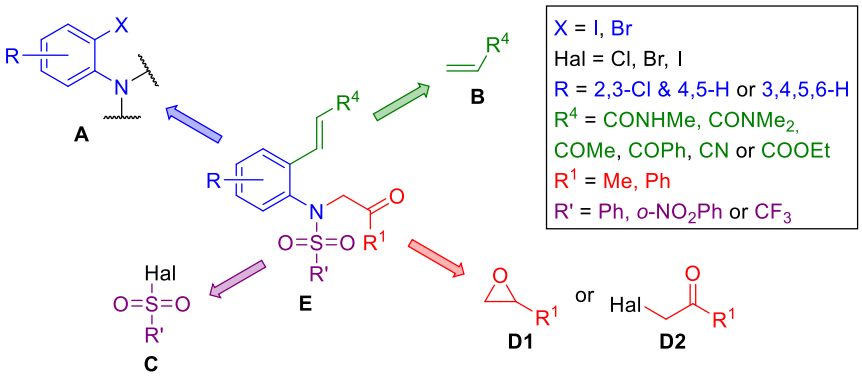
substance Nr.	R^1	R^3	R^4	HPCL purity [%]	IC_{50} [µM]
39	H	H	*ortho*-Cl	>99	**> 50.0**
41	CH_3	H	*ortho*-Cl	100	**130**
42	H	CH_3	*ortho*-Cl	- *	**> 50.0**
43 (= uwIND086)	CH_3	CH_3	*ortho*-Cl	100	**3.80**
44	H	H	*meta*-Cl	99	**> 50.0**
45	CH_3	H	*meta*-Cl	98	**30.8**
46	H	CH_3	*meta*-Cl	94**	**> 50.0**
47	CH_3	CH_3	*meta*-Cl	95**	**56.6**
48	H	H	*para*-Cl	>99	**> 50.0**
49	CH_3	H	*para*-Cl	99	**33.9**
50	H	CH_3	*para*-Cl	99	**> 50.0**
51	CH_3	CH_3	*para*-Cl	100	**29.1**
52	H	H	*para*-OCH_3	100	**165**
53	CH_3	H	*para*-OCH_3	99	**> 50.0**
54	H	CH_3	*para*-OCH_3	- *	**> 50.0**
55	CH_3	CH_3	*para*-OCH_3	97	**18.0**

* Compound was not well soluble, therefore no HPLC purity could be determined.

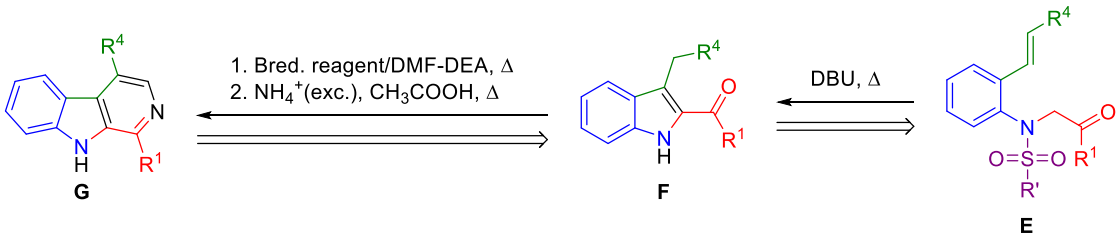
** Due to substance amount shortage, it was refrained from further purification processes, to have enough substance for the biological tests.

5.2 Project β-carbolines

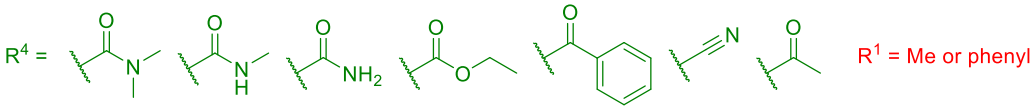
For this project and as imaged in Scheme 93, an approach to 1,4-disubstituted β-carbolines of the type **G** was to be developed. The essential intermediate to prepare for this to achieve was an intermediate of the type **E**. The route should be developed starting from a 2-iodo aniline as representative for a 2-halo aniline in the style of **A**, which later could be exchanges for variably substituted 2-halo anilines. The greenly coloured residue was to be introduced *via* the Heck CC-coupling with an unsaturated coupling partner **B**. The violet residue on the intermediate **E**, which should later function as leaving group, should be introduced *via* a reaction with the aniline's (**A**) unsubstituted H_2N-group **and** a R'-SO_2-Hal (**C**) and a base. The redly coloured residue at last, should be introduced through an **D1**-type epoxide, carrying the residue R^1. If not possible, we could have fallen back on introducing the red residue *via* alpha-haloketones in the style of **D2**, holding a residue R^1 of choice.



Planned transformation from the key intermediate **E** over the indole **F** to the muli-substituted ß-carbolines of the type **G:**



The planned residues R^1 and R^4, for which examples of ß-carbolines of the type **G** should be generated, to test for tolerance towards specific functional groups and to substantiate the variability of the synthetic route:

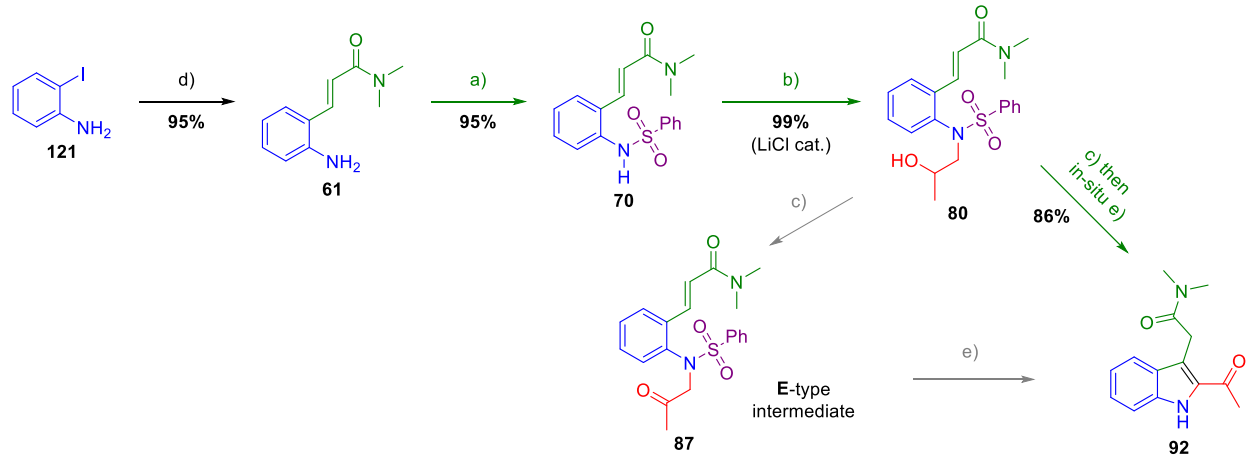


Scheme 93: The general idea of the synthetic approach over the key intermediate **E** and the **F**-type indole to multi-substituted β-carbolines in the style of **G** - with the planned residues R^1 and R^4.

Having found an access to prepare the **E**-type intermediates, treating them with a strong base (DBU) would hopefully deliver the desired 2,3-disubstituted indoles (**F**), which again could be transformed to the desired 1,4-disubstituted β-carbolines in the style of **G**, using the Bredereck's

reagent/DMF-DEA (*N,N*-dimethylformamide diethyl acetal) and a successive ammonium and acid treatment. The planned residues R^1 and R^4 are shown in the bottom of Scheme 93. It is to mention, that for the synthesis step with the Bredereck's reagent to work, R^4 must be an electron withdrawing group, therefore.

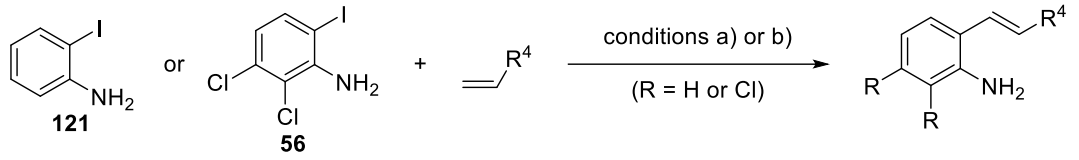
Having planned the synthesis approaches 1-3 in advance, all elaborated in Chapter 3.2.1, the approach 3 showed promising results in the end. As shown in Scheme 94 and starting from the 2-iodoaniline (**121**), the Heck reaction (conditions d)) led to the formation of the amide **61** with a 95% yield. The following sulfonamide **70** synthesis (under conditions a)) brought product in a 70% yield again using phenylsulfonyl chloride and pyridine as an auxiliary base. The nucleophilic ring opening reaction with LiCl as Lewis acid and propylene chloride as coupling partner delivered the alcohol **80** in quantitative yields, which could finally be oxidised under Swern conditions and successive heating with DBU (in-situ conditions) to our desired 2,3-disubstituted indole intermediate **92**. The key intermediate of the type **E** from Scheme 93, which in our approach 3 (from Scheme 94) would have been the intermediate **87**, was never isolated since the reactions c) and e) from the alcohol **80** to the indole intermediate **92** could be performed in-situ.



Scheme 94: Successful approach 3 - conditions: a) Cl-SO_2-R', pyridine, CH_2Cl_2 (or neat), 0°C-rt; b) (±)-propylene oxide, K_2CO_3 or LiCl, rt, neat or alcoholic solvent; c) 1. $(CO)_2Cl_2$, $SO(CH_3)_2$, -78°C 2. NEt_3, -78°C-rt, 1-2 h; d) *N,N*-dimethyl acrylamide, $Pd(CH_3COO)_2$ (cat.), $P(Ph)_3$ (cat.), TBAB (cat.), 1. eq. K_2CO_3; e) DBU, CH_3CN, 1 h, 60°C. (The failed reactions arrows are shown in red, the green and black reactions arrows shall display the reactions, which went successfully. The grey ones show the reactions, which were never performed, but outline the originally planned preparation method.)

Having finally a preparation pathway, given through the successfully performed model reaction, this pathway was to tried with several residues R^1 and R^4 (see Scheme 93), the following Heck reactions were performed using the three different synthetic protocols a)[107-108], b)[110] and c)[115] (see the following Table 10) out of different reasons.

Table 10: Heck-CC coupling results and conditions.

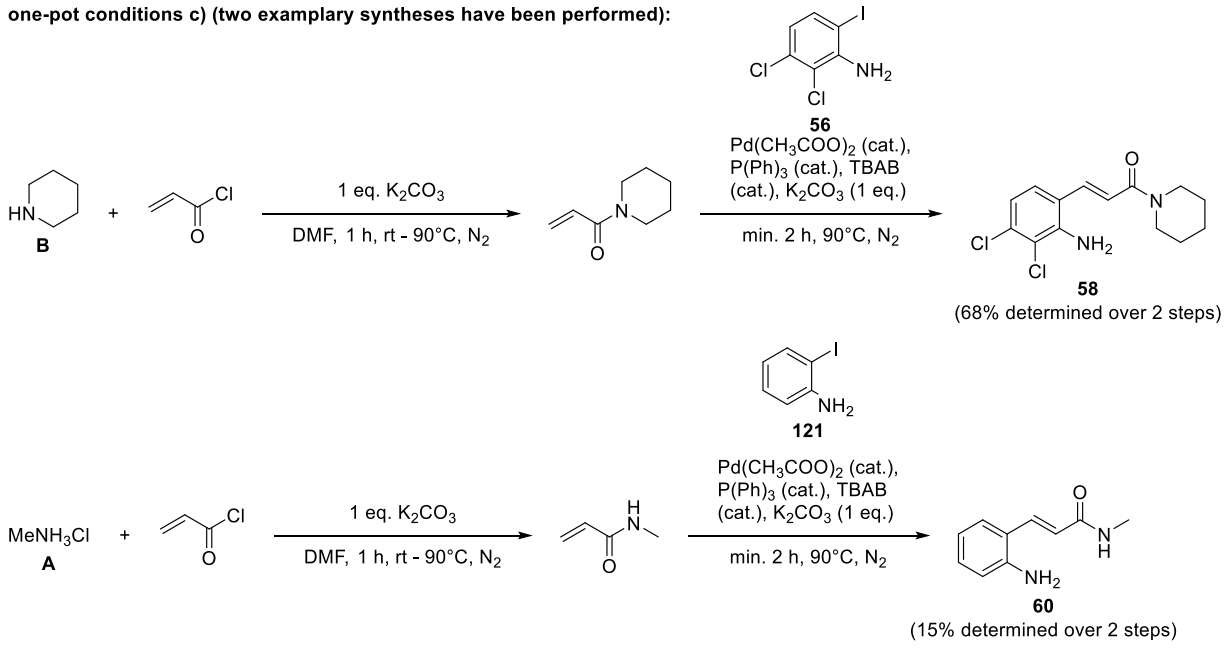


product	educt	R	R^4	yield	protocol
61	**121**	H	$CON(CH_3)_2$	**89%** **95%**	a) b)
57	**56**	Cl	$CON(CH_3)_2$	**89%**	a)
63	**121**	H	CN	**40%**	b)
64	**121**	H	COOEt	**96%**	b)
62	**121**	H	$COCH_3$	**32%**	b)

a) $Pd(PPh_3)_4$, NEt_3, 1,4-dioxane/DMAC, MW: 120°C, 300 W, 12 bar, 1 h, N_2
b) $Pd(CH_3COO)_2$ (cat.), $P(Ph)_3$ (cat.), TBAB, K_2CO_3 (1 eq.), DMF, dry, N_2, 90°C, min. 2 h

The Heck reactions were originally started to be performed with conditions a)[107-108] with $Pd(PPh_3)_4$, NEt_3 under synthesis microwave conditions. However, due to the volume restrictions of the synthesiser microwave vessels, for upsizing reasons it was switched to Sharif et al.'s protocol b)[110] nevertheless, this time using $Pd(CH_3COO)_2$ (cat.), $P(Ph)_3$ (cat.), TBAB, K_2CO_3 in a synthesis flask and under protective gas.

Due to a lack of purchasable precursors it was switched later to the one-pot acrylamide synthesis and subsequent Heck protocol c)[115] this time, which could allowed us to prepare all sorts of amides (see Scheme 95). In the first step of the synthesis to the acrylamide **58**, piperidine (**B**) was firstly transposed to the acrylamide through the addition of K_2CO_3.

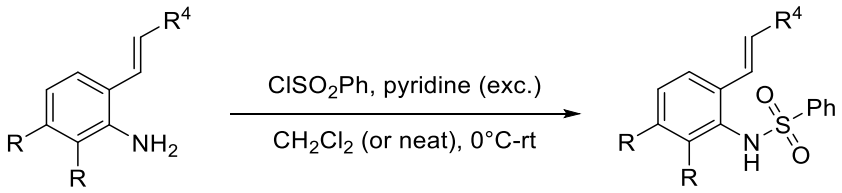


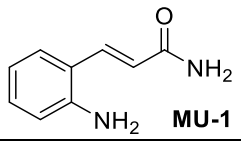
Scheme 95: Detailed schematic illustration of the syntheses of substance **60**.

The intermediate was not isolated, but the aniline **56** was added in a one-pot manner with the remaining for the Heck CC-coupling required reagents, after which the product **58** could be isolated. The acrylamide **60** could be prepared in the same way, but methylammonium chloride (**A**) was taken instead of the piperidine (**B**) and 2-iodoaniline (**121**) had been taken instead of the aniline **56.** To sum up all the Heck CC-coupling reaction results, the outcomes for the yields for the nitrile **63**, the ketone **62** (both in Table 10) and the secondary amide **60** (see the upper Scheme 95 again) proved to be surprisingly low. Since it was expected from literature claims[56] that nitriles are tolerated within Heck-conditions, it was surprising for us to find out that they cause problems in our setup. The ketone **62** synthesis did not go as satisfactory as the other syntheses and additional to that there were problems with the purification processes. The results for the secondary amide **60** can regrettably not be explained rationally. Finally, to say for this reaction step, the results were satisfying altogether.

The generated Heck-products, listed up in Table 10, were used as educts to prepare the sulfonamides in the next step, for which the yields are listed up in Table 11. All sulfonamides could be synthesised successfully, apart from the substance **77**.

Table 11: Summed up results of the sulfonamide syntheses. The educt **MU-1** was provided by Dr. Untergehrer.

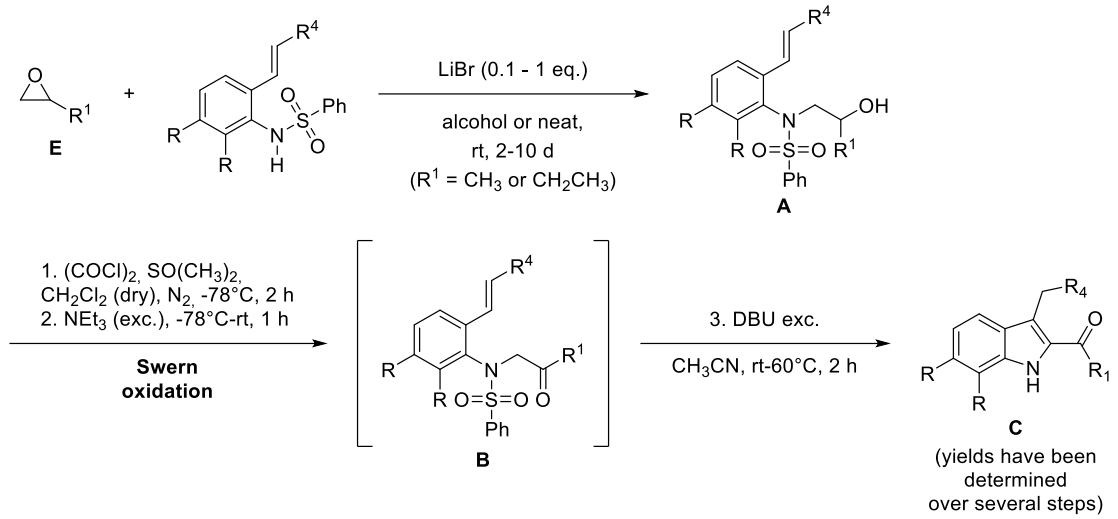


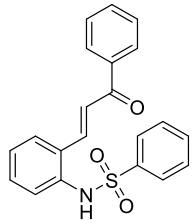
Sulfonamides Nr.	educt Nr.	R	R^4	yield
68	 **MU-1**	H	$CONH_2$	**79%**
69	**60**	H	$CONHCH_3$	**47%**
70	**61**	H	$CON(CH_3)_2$	**95%**
76	**57**	Cl	$CON(CH_3)_2$	**43%**
75	**64**	H	COOEt	**73%**
73	**62**	H	$COCH_3$	**89%**
74	**63**	H	CN	**48%**
77	**58**	Cl	$CON(CH_2)_5$	**0%**

Using the sulfonamides as educts in the next reaction, the 2-alkyloyl indoles were synthesised using the same subsequent synthetic pathway (approach 3), which was established with the model reactions from Scheme 94. In this next synthesis step (see Table 12), each sulfonamide was chemically transformed to an **A**-type alcohol, using an epoxide in the form of **E** (holding a specific residue R^1) and catalytic amounts of the Lewis acid LiBr. The **A**-type alcohol intermediates

were not purified at that stage, but were first extracted, dried and the crudely used in the next reaction step, which was the Swern oxidation. The yields have accordingly been determined over two steps.

Table 12: 2-Alkyloyl indole syntheses and the results. Compound **MU-2** was provided by Dr. Untergehrer.

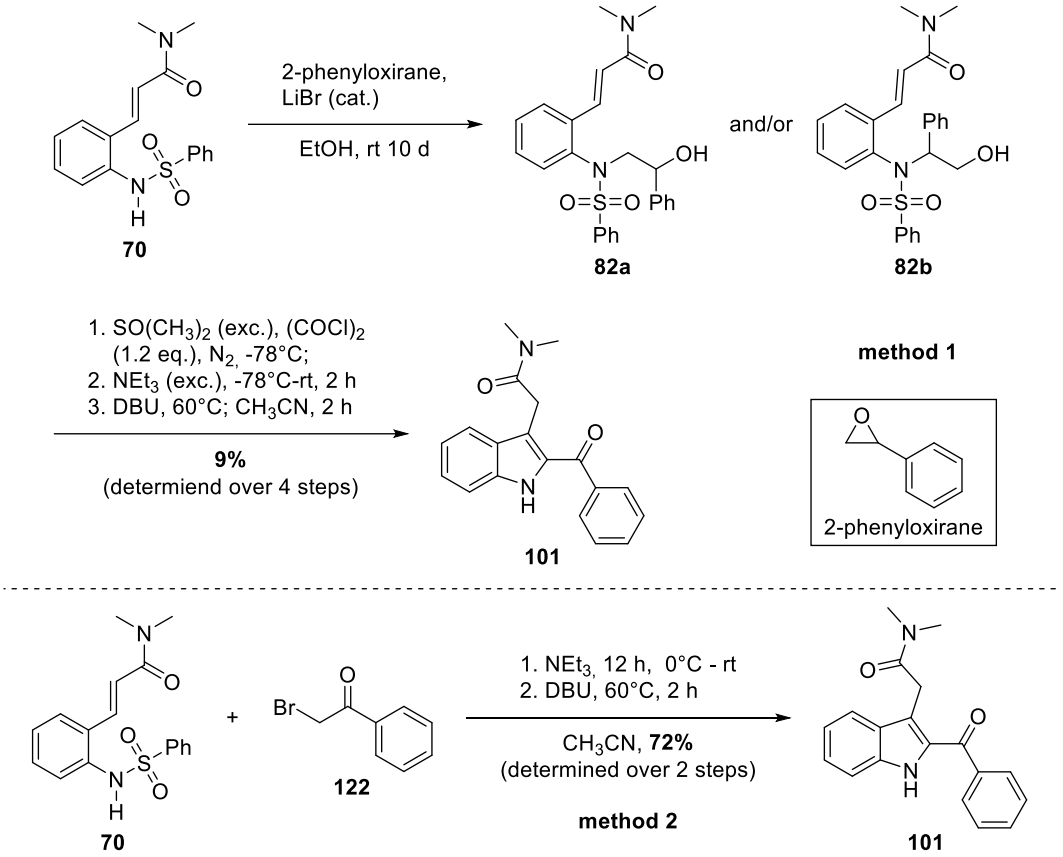


indole product	sulfonamide educt	R	R^1 (alkyl)	R^4	yield
91	**68**	H	CH_3	$CONH_2$	**0%**
92	**70**	H	CH_3	$CON(CH_3)_2$	**86%**
93	**70**	H	CH_2CH_3	$CON(CH_3)_2$	**>98%**
96	**76**	Cl	CH_3	$CON(CH_3)_2$	**26%**
94	**75**	H	CH_3	COOEt	**86%**
89	**73**	H	CH_3	$COCH_3$	**52%**
95	**74**	H	CH_3	CN	**0%**
90	 **MU-2**	H	CH_3	COPh	**60%**

As can be observed in Table 12, the results for the 2-alkyloyl indole syntheses went from poor to quantitative, apart from the primary amide **91** and the nitrile **95**, which did apparently not form at all. If one wishes to exploit this method further, more research must be done concerning functional groups tolerances (for R^1) in the future.

The same approach 3 from Scheme 94, using epoxide chemistry, was also tried in the hope to generate one exemplary 2-benzoyl substituted indole compound **101** (see Scheme 96 now) using

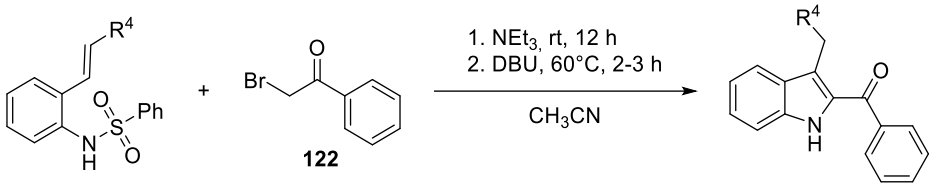
the same strategy and 2-phenyloxirane (styrene oxide) as coupling partner, however the method 1 in Scheme 96) did though not show the same promising results for this model reaction.



Scheme 96: The problem with the incompatibility of epoxides holding aromatic residues with the method.

Based on my results in Scheme 96, the desired 2-benzoyl substituted indole **101** was instead synthesised according to the, formerly by Kim et al.[48]'s, established method 2 imaged in Scheme 96, using triethylamine as auxiliary base, 2-bromoacetophenone **122** as coupling partner and DBU in the second reaction step, to induce the Michael reaction-desulfinilation-tautomerisation cascade. Having much better results from this method 2 (Scheme 96), the 2-benzoyl substituted indoles have all been synthesised according to this protocol[48]. As shown in Table 13, the results for the 2-benzoyl substituted indoles syntheses went predominantly from poor to very well, apart from the nitrile **103** again, which could not be obtained at all. This result again confirmed the former observation that the nitrile group does not provide a suitable electron withdrawing group for our situation.

Table 13: Results for the 2-benzoyl substituted indoles syntheses according to Kim et al.'s protocol. The structure of **MU-2**, provided by Dr. Untergehrer, is shown in Table 12.

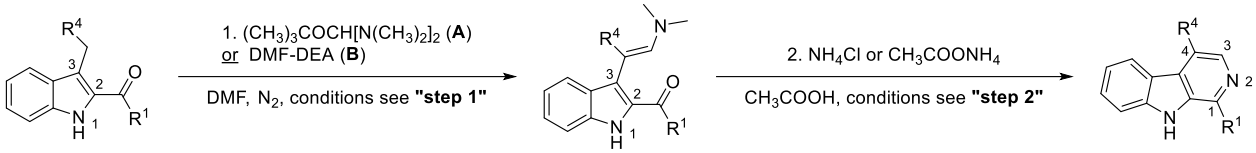


indole product	sulfonamide educt	R^4	yield
99	**68**	$CONH_2$	**62%**
100	**69**	$CONH(CH_3)$	**35%**
101	**70**	$CON(CH_3)_2$	**72%**
102	**75**	COOEt	**49%**
97	**73**	$COCH_3$	**83%**
103	**74**	CN	**0%**
98	**MU-2**	COPh	**57%**

In the following, the indoles, which are listed up in Table 12 and Table 13, were reacted with the Bredereck's reagent or DMF-DEA respectively, in the intention to find out which of the residues R^1 and R^4 were compatible with this reaction conditions. Table 14 shows the results for the 1,4-substituted β-carboline syntheses performed in this work, starting from the presented products of Table 12 and Table 13. In the beginning of trying to find the best reaction conditions, two different reagents – the Bredereck's reagent $(CH_3)_3COCH[N(CH_3)_2]_2$ (**A**) and DMF-DEA (**B**) were used for the introduction of the enamine group during reaction step 1. It was expected that reagent **B** would expose the indole educts to slightly less harsh reaction conditions with regard to a volatile group preservation. However, having performed the reaction with three different educts (indoles **89**, **92** & **94**), treated each one time with reagent **A** and one time with reagent **B**, no considerable advantage of **A** and respectively **B** over the other could be finally observed when it came to the obtained yields. Whenever it was assumed, that the indole educt held weak to moderate acidic functional groups, it was decided to perform the reaction with reagent **B** instead of **A**, since **B** was the less aggressive chemical. As is visible in Table 14, for $R^1 = CH_3$ or CH_2CH_3 (alkyl) in most cases only traces or no traces of product at all could be found after the reaction was completed. The only exceptional case was the product **111**, which could be isolated in an 18% yield. This potential outcome had already been considered and assessed in Chapter 4.2.6. Looking in comparison at the results from the indoles **97**, **98**, **101** and **102**, the method seemed very suitable for these educts indeed. Having achieved yields from fair to very good, these results

seem to prove, that this reaction approach works in general, having no competing proton donating groups, which was in fact just the case for R^1 = phenyl.

Table 14: Summary of the results for the 1,4-subtituted β-carboline syntheses of this work. The yields have been determined over two steps.



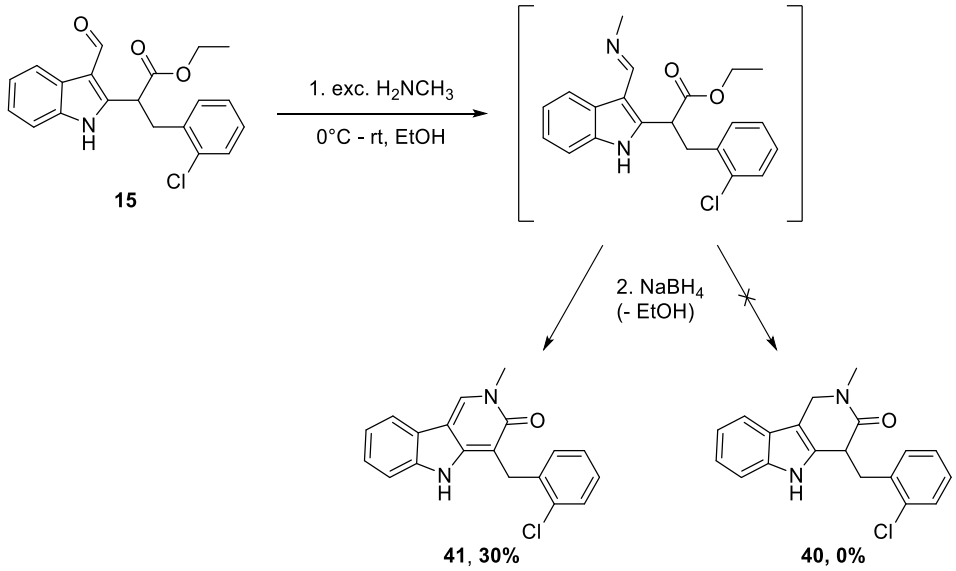
β-carboline	educt	R^1 = alkyl (yellow) or phenyl (green)	R^4	step 1. reagent (A or B)	step 1	step 2	yield
108	**92**	CH_3	$CON(CH_3)_2$	**A** **B**	90°C, 2 h	160°C, 1 h	**traces** **traces**
109	**93**	CH_2CH_3	$CON(CH_3)_2$	**B**	90°C, 45 min	150°C, 1 h	**traces**
111	**94**	CH_3	COOEt	**A** **B**	120°C, 2 h	140°C, 2 h	**18%** **10%**
105	**89**	CH_3	$COCH_3$	**A** **B**	120°C, 2 h	140°C, 1.5 h	**0%** **0%**
106	**90**	CH_3	COPh	**B**	100 °C, 45 min	160°C, 1 h	**traces**
114	**99**	Ph	$CONH_2$	**B**	90°C, 45 min	150°C, 1 h	**0%**
115	**100**	Ph	$CONH(CH_3)$	**B**	90°C, 45 min	150°C, 1 h	**0%**
116	**101**	Ph	$CON(CH_3)_2$	**A**	120°C, 3 h	140°C, 1.5 h	**71%**
117	**102**	Ph	COOEt	**A**	120°C, 2 h	165°C, 2 h	**81%**
112	**97**	Ph	$COCH_3$	**B**	90°C, 45 min	140°C, 2 h	**64%**
113	**98**	Ph	COPh	**A**	120°C, 2 h	140°C, 2 h	**57%**

To sum it up, the epoxide chemistry of this established route was in fact a success, following the approach 3 (in Scheme 94), however this chemistry showed only promising results for the indole syntheses with 2-alkyloyl residues and regrettably not for those with 2-benzoyl residues. The potential to get deprotonated rests accordingly (nearly) solely on the residue R^4 (see R4 in the scheme above Table 14) which for this reaction to work, must be a strong electron withdrawing group indeed. This chemistry could be applied to produce other substituted β-carbolines apart from the ones we focused to prepare within the framework of this work, for example 1-substituted or 1,3-disubstituted β-carbolines. In the Chapters 3.2.2 and 4.2.8 I have shown with two exemplary nonetheless, that other purposes can be found for this type of 2,3-disubstituted indoles and the used chemistry of this work.

6 Outlook

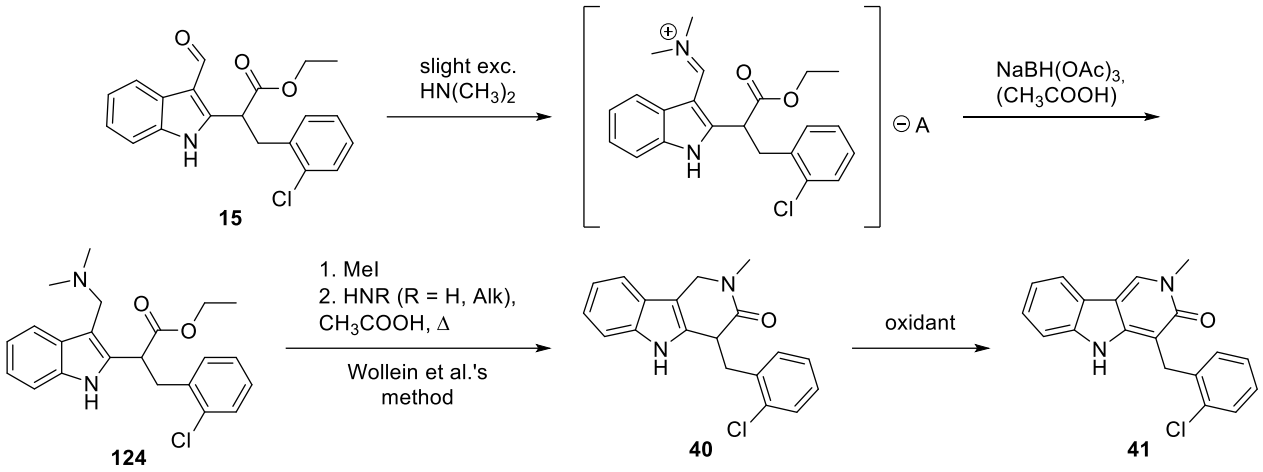
6.1 3-Oxo-γ-carbolines and their dihydro analogues project

In the model reactions of Chapter 4.1.1, it was not succeeded with the used methods to prepare any dihydropyridone (see Scheme 51 / Scheme 97). Scheme 52 shows the proposed mechanism of the last synthesis step. As shown in Scheme 97 now, illustrating the model reaction for the approach finding again, the problem seemed to be in the earlier studies, that after the addition of the ammonia or a primary amine, the from the aldehyde **15** resulting imine intermediate already undergoes an electrocyclic reaction to 3-oxo-γ-carboline **41** and cannot be reduced by $NaBH_4$ beforehand. Substance **40** could therefore not be generated through this synthetic pathway, not even when worked under cooled conditions.



Scheme 97: Failed dihydropyridone **40** synthesis from Chapter 4.1.1.

There is a potential variation of the, in this work established, approach 3 (see Chapter 3.1.3) which could eventually allow us to prepare the reduced variant of 3-oxo-γ-carbolines after all. Imagine instead of using ammonia or a primary amine for the imine synthesis, one would use for example dimethylamine ($HN(CH_3)_2$). We could find several journals, of which only a few representative papers were cited to give a few examples, in which were claimed that the resulting iminium cation could be reduced selectively trough sodium triacetoxyborohydride while tolerating any present ester groups on the reaction partners.[117-121] If we tried this variant of the approach 3 (see Chapter 3.1.3) and as is suggested in Scheme 98, the resulting 2-substituted gramine **124** could then be transformed into the dihydropyridone **40** using Wollein et al.'s method[21] again.



Scheme 98: Potential dihydropyridone **40** synthesis and the subsequent pyridone **41** synthesis in the style of Wollein et al.[21] (A^- = anion).

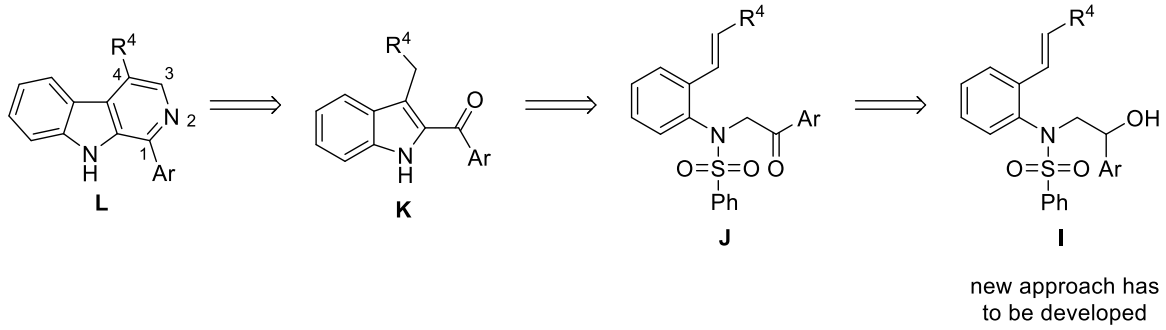
If anyone wished to prepare dihydropyridones in the future – this would be a potential way to approach. From there, in theory, one could obtain the 3-oxo-γ-carboline **41** using an oxidant in the following step.

If one proceeded with this project, in the long run it would be crucial to find a substance which binds to the target enzyme. Having a certain antagonist or agonist adduct could change the potential to crystallise the target enzyme, which would then hopefully allow us to get the crystal structure from an x-ray diffraction experiment. This solution approach would enable us a very precise view on the active side of the enzyme and consequently the drug development could be performed in a much more purposeful way.

6.2 Project β-carbolines

Of course, the for this work prepared β-carbolines could be tested for efficacy on our aimed target enzyme XPD helicase in theory. However, it was decided against testing them for now, since they deviate too much from the original lead structure concerning the functional groups.

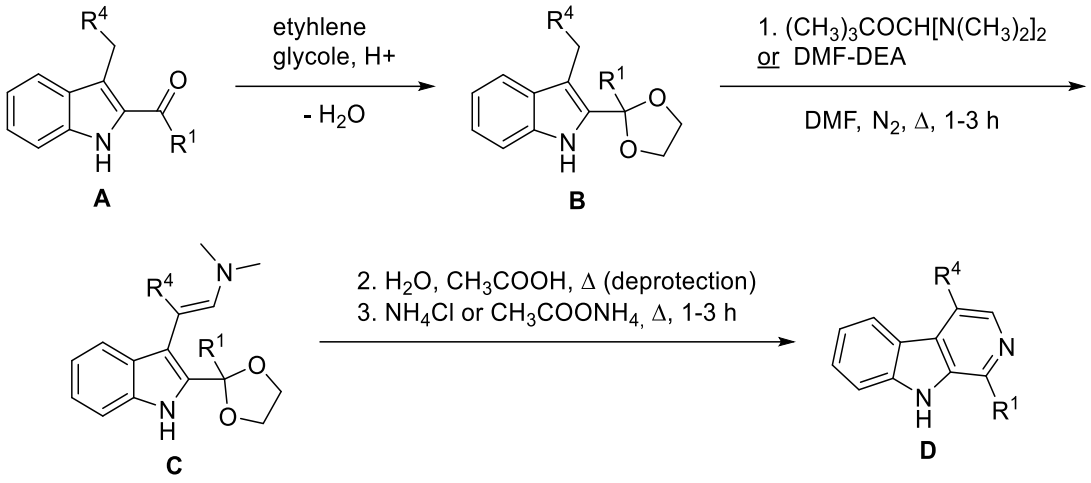
If anyone wanted to proceed with this project in the future, there have been two major problems with this project which should be solved in advance. The first one was the problem with the undesired regioselective preference of the nucleophile, the aniline, for the 2-C of the styrene oxide, as discussed in Chapter 5.2 (Scheme 96) which provided to the undesired regiomer in a huge excess compared to the desired one and therefore it was not possible to utilise this reaction to our needs. Using an alternative Lewis acid won't solve the problem since other researchers have observed the same phenomenon while a variety of different Lewis acids were used in the process.[105, 109, 111, 122-126] Instead, the problem is most likely caused by this specific combination of educts which were tried to be reacted in this work - the aniline and styrene oxide.[109] The cause for the reversal of the regioselectivity for this reaction, using anilines and an epoxide with a singular aromatic residue had, as far as is known to me, primarily been discussed by Chakraborti et al.[109]. So, to solve the problem eventually, I see no other way but to develop a completely different approach to obtain the alcohol intermediates of the type **I** (see Scheme 99).



Scheme 99: New approach has to be developed for the alcohol **I** synthesis, so that finally a way can be found for the synthesis of 1-aryl substituted β-carbolines of the type **L**.

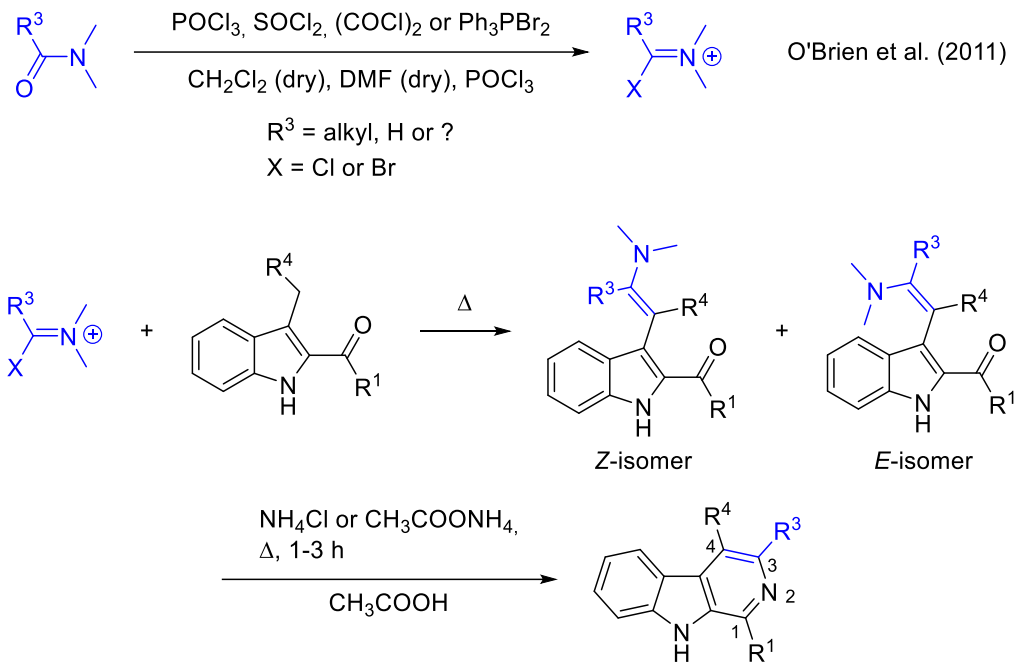
The second major problem of this project was, of course, the last step of this synthesis route that seemed not entirely be suitable for preparing 1-alkyl substituted β-carbolines with the, in this work established method. The problem is clear from the summary Chapter 5.2, or more specifically from the results shown in Table 14. There are even several potential solutions for which in the following are mentioned some potential ideas. One of the first ideas I had was working with carbonyl protection groups (solution 1 in Scheme 100). The ketone group of a **A**-type indole is much more reactive und could probably selectively protected with ethylene glycol to a ketal and then one might just proceed as beforehand. Because of the adjacent ketal of the type **B**, the residue R^1 should have a lower acidity and this fact could make alle the difference in the following reactions. Since

the last step (3. in Scheme 100) is already performed in acetic acid as a solvent, starting in theory from intermediate **C**, one might just add water and acidic acid in the reaction step before. of the reaction and stir for a certain time (under heat) before one proceeds to step 3. to the product **D**.



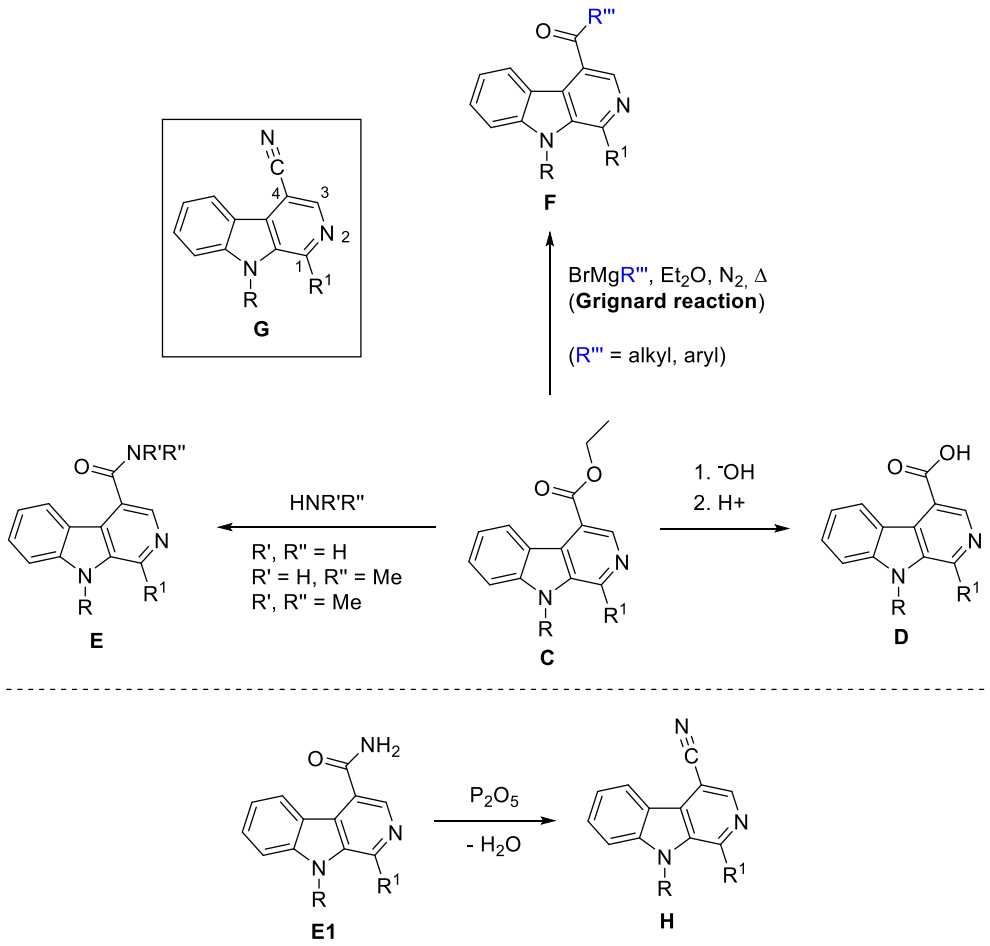
Scheme 100: Ketals as potential problem-solving solution 1. R^4 = EWG and R^1 = alkyl.

This specific synthesis route variation is worth a try because it would only add one additional synthesis step to the whole pathway and further could solve our problem. Further, and to propose a potential solution 2, I found a few interesting papers using the Vilsmeier reagent to prepare enamines under heat and neutral[127-129] or even acidic[130] conditions, whereby it has to be mentioned that this is a rather unusual application of this reagent, which is originally used to introduce formyl groups onto aromatics or heteroaromatics[56]. Although there is a chance of a formylation reaction happening on the aromatic ring instead, this potential variation of the pathway is a particularly interesting one, since it might give us the chance to introduce an additional residue R^3 in the 3-position of the final product! Scheme 101 shows the approach to introduce the enamine group through the Vilsmeier reagent and analogues, which would be a huge benefit of this method. It is to point out specifically, that compared to the conditions I had used in this work which were basic, the new reaction could be performed under neutral or probably even acidic conditions, which essentially could solve the problem with the instabilities of the enamine intermediates (*Z*- and *E*-isomer) I had experienced while performing chemistry with this substance class.



Scheme 101: Potential solution 2 – introducing the enamine residue through the Vilsmeier reagent and its analogues.

A convenient and easy method to prepare the Vilsmeier reagents holding alkyl residues for R^3 has been published by O'Brien et al.[131] in 2011 using amides optional alkyl residue for R^3 (see Scheme 101). If nothing helps one could of course, and to name a third option, further derivatise earlier successfully prepared β-carbolines. As summed up in Chapter 5.2 (in Table 14), the ester synthesis worked in both cases as the only exception, for R^1 = alkyl and phenyl, even though for the phenyl group, the results were much better. Since esters are incredibly versatile when it comes to further derivatising them. From all the other desired products, holding functional groups for R^4 like CN, $CONH_2$, $CONHCH_3$, $CON(CH_3)_2$, $COCH_3$ that had been tried to prepare unsuccessfully in this work while trying to establish the new pathway, all of those can be synthesised originating from the ester group in theory. As shown in Scheme 102, starting from an ester **C** (or actually also starting from any 4-amide), any 4-alkyloyl or 4-aroyl of the type **F** might be accessible through the Grignard reaction, using BrMgR''' (R''' = alkyl or aryl).[56] The use of bases, ^-OH or HNR'R'', would probably lead to a carboxylic acid in the style of **D** (for ^-OH) or to the desired amide in the style of **E** (for HNR'R''), depending on if NH_3, a primary or secondary amide was used in the process. Having obtained the primary amide **E1** then, it's possible to work with a drying/dehydration agent, P_2O_5 for example, to receive a 4-nitrile compound of the type **H**.[76]



Scheme 102: Different means to derivatise the ester to our desired functional groups for R^4, while R = H, alkyl or a protective group.

When the pathway development is optimised in a way, that it is as versatile as possible, one could finally proceed to just preparing a selection of β-carbolines holding the originally desired chloro-substituents on C-7 and C-8 (Figure 14) and then test these for efficacy.

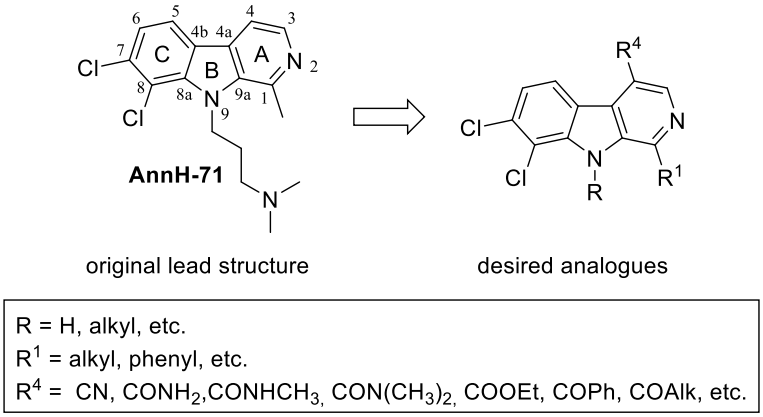


Figure 14: **AnnH-71** and the in the future desired multi-substituted β-carbolines.

7 Experimental part

7.1 Chemicals, gadgets, measurement methods and general conditions

Schleck line techniques

All oxygen or moisture sensitive reaction, mentioned in the following chapters, were performed under protective gas (N_2), using with Schlenk line techniques. All solids or liquids had been placed in the flask before the exchange to the N_2 through a septum, or the solids were added by spatula to the open flask, while degassing the reaction solution. All, in a stock solution, dissolved chemicals that needed to be added later, had been degassed with N_2 before, then added by syringe through the septum. Pure liquid chemicals were added by syringe as well. All used solvents had purchased with inert gas and molecular sieve, were statically dried and stored in a nitrogen atmosphere over molecular sieve or distillated over anhydrous K_2CO_3 and then stored in a nitrogen atmosphere over molecular sieve. They were degassed before and while every withdrawal.

Chemicals and expendable materials

All for the reactions used chemicals and solvents were of p.a. quality and had been purchased from common sources as Tokyo Chemical Industry Co. (Ltd.), Fluka, Merck KGaA, Sigma-Aldrich Chemistry GmbH, Thermo Fisher Scientific incorporation, Alfa Aesar, Acros Organics and Carl Roth GmbH. The pH indicator paper (pH 1-14) and molecular sieves 3 Å and 4 Å used for drying the solvents statically were purchased at the Carl Roth GmbH.

Chromatography

The thin layer chromatography (TLC) plates (brand: POLYGRAM®, phase: SIL G/UV_{254}, surface chemistry: unmodified silica gel (SiOH), backing: polyester, layer thickness: 0.20 mm, particle size: 5-17 µm, plate size: 4x8 cm) used for reaction controls and TLC/CMS analyses, had been purchased by Macherey-Nagel GmbH & Co. KG. Silica gel 60 (0.040-0.063 mm) for column chromatography (230-400 mesh ASTM), purchased from Merck KGaA (Germany), was utilized for all column chromatography purifications.

(MW) Microwave reactor reactions

All microwave assisted syntheses mentioned in this work, were carried out in a microwave synthesizer, model Discover S-Class Plus SP DC-8017 (CEM GmbH). All reactions were undertaken in 10 mL (0.2-7.0 mL of working volume) or 35 mL (2.0-25 mL of working volume) Pyrex® glass pressure vessels with silicone caps, also all purchased from CEM GmbH.

TLC/CMS (TLC-MS) analyses

All TLC/CMS analyses had been performed, using the automated TLC plate reader Plate Express®, coupled with a combined Advion expression® Compact Mass Spectrometer (CMS), both bought from Advion Inc.. The on the TLC plate separated TLC substance spots were ionised in the Advion expression® CMS *via* an ESI- or APCI-ionisation source. ASAP® (Atmospheric Solids Analysis Probe) mass spectrometry allowed direct analysis of samples using the APCI ionisation method. HPLC grade methanol was used as diluent or solvent for the ASAP® measurements.

NMR spectra measurements

All NMR spectra (^{1}H-NMR, ^{13}C-NMR, DEPT, COSY, HMQC, HMBC) were recorded with an Avance III HD 400 MHz Bruker BioSpin (^{1}H-NMR: 400 MHz, ^{13}C-NMR: 101 MHz) or an Avance III HD 500 MHz Bruker BioSpin with CryoProbe™ Prodigy (1H-NMR: 500 MHz, ^{13}C-NMR: 126 MHz) spectrometer (both from Bruker, Billerica, USA). Chemical shifts δ, reported in [ppm], refer to the standardised deuterated solvent peak or the TMS standard signal at δ = 0.00 ppm. Coupling constants J are indicated in Hertz [Hz]. Only deuterated solvents were used for the measurements ($CDCl_3$, CD_2Cl_2, $SO(CD_3)_2$, $CO(CD_3)$ and D_3CCOD). If no specific temperature is given, previous to the NMR shifts in the following chapters, the sample was measured at room temperature.

ESI/EI/CI-MS and HRMS methods[132]

All EI-MS and CI-MS measurements were carried out on a Thermo Q Exactive GC Orbitrap mass spectrometer or a Finnigan MAT 95 sectorfield mass spectrometer. The resolution had been set to approximately 5000 (MAT95) or 50.000 (Q Exactive GC, at *m/z* 200). Depending on the molecular mass of the sample, the measuring range had been set between 40 to 1040 units. EI and CI sample ionisation occurred at 250°C (MAT95) or 300°C (Q Exactive GC) and an electron energy of 70 eV. For CI measurements, isobutane was used as reactant gas. All ESI measurement were performed using a Thermo Finnigan LTQ FT Ultra Fourier Transform Ions Cyclotron resonance mass spectrometer. The resolution had been set to 100.000 at *m/z* 400. Depending on the sample molecular mass value, the measuring range had been set from 50 to 2000 units. The spray capillary voltage of the IonMax ESI-head was set to 4 kV. The heating capillary temperature was 250°C with nitrogen as carrier gas.[132]

IR spectra detection

A Perkin Elmer Spectrum BXII/1000 FT-IR spectrometer with a Smiths ATR polarimeter, Krüss P8000 UV/VIS Varian Cary 50 (with thermostat F33-EH), was used to measure the infrared spectra. The diamond ATR sensor detected the transmissions in [%] against a 650-4400 [1/cm] wavelength range. For all measured IR spectra of the synthesised substances, peak values at that specific wavelength are given with comments in form of alphabetic characters, determining the absorbance intensity (s = strong, sm = medium to strong, m = medium, mw = medium to weak, w = weak).

Melting areas/points

All melting areas/points were measured using a Büchi melting point apparatus, model B-540 (Büchi, Flawill, Switzerland). All melting areas/points have been documented, unaltered as seen and are in the following stated in [°C] units.

Software

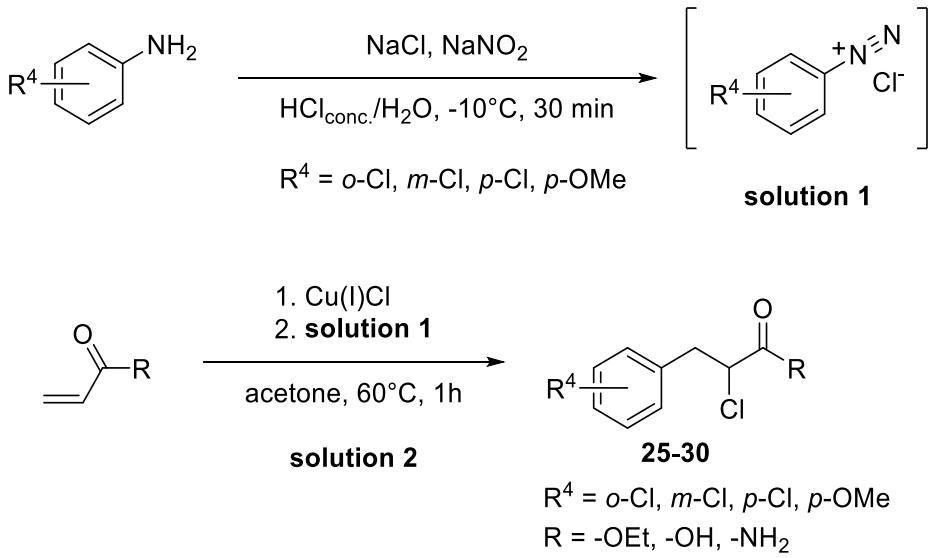
All NMR spectra were edited and evaluated using MestReNova, designed by Mestrelab Research S.L.. ChemDraw 20.0 (PerkinElmer) was used for drawing chemical structures or rection schemes. For the writing and to generate tables, Microsoft Office (Microsoft) was used. Citations were generated, using EndNote, developed by Clarivate Analytics.

7.2 General syntheses protocols and methods

Any deviations from the general protocols as the different solvent mixtures for recrystallizations or column chromatography purifications are mentioned in the following passages where all component amounts are elaborated for each synthesised product accordingly. Therefore, no detailed comments are being made in this chapter about the final purification processes. All reactions, mentioned in this work, were analysed midway and after completion by TLC and the on the TLC plate unravelled substances were analysed subsequently by TLC/CMS to find the desired product. Since, for all conducted reactions, this approach had been the general *modus operandi* and the main method to identify substances on the TLC plates, it is never mentioned in the following chapters.

Syntheses protocol A – Meerwein arylation

The Meerwein arylations were performed with variations according to the synthesis protocol described by Komoschinski et al.[93]. Instead of taking $Cu(II)Cl_2$ though, as described in the patent[93], Cu(I)Cl was chosen as activation reagent, since from what is known about the mechanism of the reaction[56, 133], it made more sense. As general procedure for the syntheses of α-chloro carboxylic acid analogues, two solutions were prepared separately and the reaction was therefore performed in two steps. The procedure is outlined in scheme 103. Firstly, a solution 1 was prepared, stirred for a certain amount of time, and then added to solution 2.



Scheme 103: Synthetic procedure for the generation of the Meerwein arylation products.

As shown in scheme 48, to prepare solution 1 the corresponding aniline and sodium chloride were dissolved in an aqueous 4:1 dilution of a concentrated hydrochloric acid (37%), then the solution was cooled to 0°C. Sodium chloride was added in an aqueous 1:1 dilution of hydrochloric acid.

Sodium nitrite, dissolved in H_2O_d, was then added dropwise to the reaction flask while keeping the temperature below -5°C. Solution 1 was stirred for 30 min at -10°C. Meanwhile, solution 2 was prepared by dissolving acrylic acid or an according analogue in acetone, then heating solution 2 to 60°C. Cu(I)Cl catalyst was added to the solution 2 shortly before the second reaction step. The still chilled solution 1 was added portion by portion with the help of a precooled Pasteur pipette to the 60°C warm solution 2, which followed the evolution of nitrogen gas. After the addition had ended, the mixture was refluxed for another 30 min until the evolution of nitrogen ceased. The cooled to room temperature solution was concentrated *in vacuo* and the remaining watery solution was extracted with three times with 100-300 mL of methylene chloride. The combined organic phases were washed two times with 50-150 mL distilled water then one time with 20-100 mL saturated brine solution and dried over $MgSO_4$. Excess solvent was evaporated by rotary evaporator. Purification could be performed by column chromatography.

Synthesis protocol B – Xanthates syntheses

The xanthates that were used in the radical substitution reactions could easily be prepared following the synthesis description Reyes-Gutierrez et al.[51], published in 2009. The halide precursor was therefore dissolved in a flask with either CH_2Cl_2 or MeCN as solvent and while ice cooling, potassium *O*-ethyl dithiocarbonate (KEX) was added with the help of a spatula in portions over a time period of 15 min. The ice cooling was removed, the solution was allowed to warm up to room temperature and the solution was stirred for 3-12 h until TLC control showed consumption of educt. In case of using acetonitrile as solvent, it was removed by rotary evaporation and the residue suspension was redissolved in CH_2Cl_2. In case of using CH_2Cl_2 as solvent, the solvent removing was skipped and it was directly proceeded to the following steps. The organic layer was washed three times with H_2O_d, one time with saturated brine solution then the CH_2Cl_2 layer was dried over anhydrous $MgSO_4$. The product could be isolated after removing the solvent *via* rotary evaporator and subsequent purification *via* column chromatography, if not stated otherwise.

Synthesis protocol C – Radical substitutions on the 2-indole position

The Zard reaction was always performed in a two- or three-neck flask according to the synthesis instructions of Reyes-Gutierrez et al.[51]. A for 15 min with nitrogen degassed solution of 1,2-dichloroethane or ethyl acetate, containing an indole analogue and an excess of a xanthate, was refluxed for 9-11 h. While degassing each time, solid dilauroyl peroxide (DLP) was added by spatula in equal portions (m_{total}(DLP)/number of reaction hours) at the beginning of each hour. The reaction progress was monitored by TLC control. The reaction was stopped, by allowing the reaction to cool down to room temperature. The excess of solvent was removed by rotary

evaporator and the remaining crude solid was purified by column chromatography, if not mentioned otherwise.

Synthesis protocol D1 – Ring closure reaction of 3-oxo-γ-carbolines

The indole-3-carboxaldehyde or 1-methylindole-3-carboxaldehyde derivative was dissolved in methanol, ethanol, isopropanol or treated neatly if no additional solvent is mentioned in the following sections. A methanolic, THF or ethanolic solution of ammonia or methylamine was added dropwise by syringe. It was stirred at room temperature for minimum 48 h, then organic solvent was removed by means of rotary evaporator and the product was purified *via* column chromatography if nothing else is declared.

Synthesis protocol D2 – Ring closure reaction of 3-oxo-γ-carbolines

The indole-3-carboxaldehyde or 1-methylindole-3-carboxaldehyde derivative was dissolved in methanol, ethanol or isopropanol and a watery NH_3- or CH_3NH_2-solution was added dropwise by syringe. It was stirred at room temperature for minimum 48 h, then excess of organic solvent was removed by rotary evaporator. The remaining watery phase was extracted two times with 20 mL of CH_2Cl_2 and two times with 20 mL of EtOAc. Combined organic phases were washed with two times 10 mL of H_2O_d and one time with 10 mL of saturated brine solution, then dried over anhydrous $MgSO_4$. The excess solvent was evaporated *via* rotary evaporator and the product was purified by column chromatography if not mentioned otherwise.

Synthesis protocol E – Heck reaction

The sulfonamide precursors **66**-**77** were produced using a method, published by Sharif et al.[110] in 2016. For the Heck reaction procedure, all solids were put in a reaction flask with a stirring bar and the air was exchanged to nitrogen, then dry DMF and subsequently all liquid chemicals were added by syringe and the reaction solution was stirred at 100°C for 2 h. Either NEt_3 or K_2CO_3 was used as a base. After allowing the reaction solution to cool down to room temperature, the solution was quenched with 200 mL H_2O_d. If not mentioned otherwise from thereon, the watery layer was extracted three times with 350 mL of EtOAc and the combined organic layers were washed five times with 100 mL of H_2O_d, one time with 30 mL of a 5%-LiCl solution, then one time with 30 mL of saturated brine solution. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. As means of purification, column chromatography was performed, if not mentioned otherwise.

General protocol F – Sulfonamides syntheses

The sulfonamides were prepared, using the synthetic protocol of Yin et al.[102] The halide of choice was either dissolved in dry CH_2Cl_2, then dry pyridine was added, or the educt was treated neatly with dry pyridine, if no additional solvent is mentioned. The arylsulfonyl chloride was added dropwise by syringe after the solution had been cooled down to 0°C. The ice bath was removed and the solution was stirred at room temperature for 12 h. The addition of glacial acetic acid stopped the reaction, then CH_2Cl_2 was added followed by H_2O_d. The layers were separated by separation funnel. The organic layer was washed two times with 20 mL of an acidic watery solution (with an 1% glacial acetic acid additive) then the organic layer was dried over anhydrous $MgSO_4$. Removing the excess solvent by means of rotary evaporator yielded a crude solid. The product was either gained by performing column chromatography or could successfully be isolated through recrystallisation.

General synthesis protocol G – Alcohols syntheses from epoxides

The synthesis instructions of Chakraborti et al.[109] were used, with slight variations, to generate the alcohol intermediates. The sulfonamide and LiBr were submitted to a darkened flask and an alcoholic solvent was added. The epoxide was added by syringe dropwise and it was stirred for 5-7 d at room temperature in the dark. When TLC control showed no remaining educt, solvent was removed by rotary evaporator, then the crude solid was redissolved in CH_2Cl_2 and washed three times with 20 mL of H_2O_d, then one time with 20 mL of saturated brine solution. The CH_2Cl_2 layer was dried over $MgSO_4$ and the solvent was removed by rotary evaporator again. Products were purified by column chromatography.

General synthesis protocol H – 2-Alkyloyl indole analogues syntheses

The nucleophilic ring opening with a subsequent Swern oxidation was performed in 3 steps (see rection schemes for each described substance in the following chapters), according to the method of Chakraborti et al.[109] and Omura et al.[106]. The reaction procedure for the nucleophilic ring opening reaction, described by Chakraborti et al.[109] was imitated minutely, with the one variation of using a solvent instead of reacting the reagents neatly. Therefore, for the first reaction step, a *N*-phenylbenzenesulfonamide analogue, LiBr and an aliphatic epoxide were added to a flask and dissolved in an alcoholic solvent or a mix of CH_2Cl_2/MeOH as solvent mix. It was stirred in the dark for 24 h-7 days. The reaction progress was monitored by TLC control. When no educt was detectible anymore, the solvent was removed by rotary evaporator and the crude solid was redissolved in 100 mL of CH_2Cl_2, then washed three times with 20 mL of H_2O_d and one time with 20 mL of saturated brine solution. The organic layer was dried over anhydrous $MgSO_4$, then dried

by rotary evaporator and further in high vacuum. The crude solid that was yielded from the first step was used with no additional purification methods or analyses in the following step. Step 2. was performed with variations according to the original synthesis protocol, described by Omura et al.[106] (published in 1978). For the Swern oxidation, dry $SOMe_2$ was put in a flask with dry CH_2Cl_2 and cooled down to -75°C. Oxalyl chloride, dissolved in dry CH_2Cl_2, was added dropwise and it was stirred for 20 min at -75°C. The crude solid from the previous part was redissolved in dry CH_2Cl_2, then added slowly to the reaction solution. It was stirred for 2 h at -75°C. The reaction was stopped by the addition of addition an excess of DBU. Step 3. was carried out in-situ again, following a synthesis descriptions of Kim et al.[48]. The reaction was allowed to obtain room temperature, then the flask was opened and MeCN was added. The additional addition of DBU was skipped since there had already been added an excess in the last reaction step. The reaction was stirred at 65°C for 2 h with an open flask, then the residues of solvent were evaporated, the crude residue was redissolved in 100 mL of CH_2Cl_2 and glacial acetic acid was added. The organic layer was washed three times with 20 mL of H_2O_d, one time with 20 mL of saturated brine solution and was then dried over anhydrous $MgSO_4$. Products were purified by column chromatography or gained by recrystallisation.

General protocol I – 2-Benzoyl indole syntheses

Deriving from the *N*-phenylbenzenesulfonamide analogues, the 2-benzoyl indoles could be easily prepared again with the method, published by Kim et al.[48] Accordingly, the sulfonamide and 2-bromoacetophenone were submitted to a flask and the air was exchanged to nitrogen. 20 mL of dry MeCN was added and an excess of NEt_3 was added dropwise by syringe, while ice cooling. The ice bath was removed and the solution was stirred for 12 h at room temperature. When TLC control showed consumption of educts, DBU was added by syringe, the solution was heated up to 65°C and then stirred for 2 h at that temperature. By allowing the solution to retrieve room temperature, then by adding glacial acetic acid, the reaction was stopped. The reaction solution was quenched with H_2O_d and it was stirred for 5 minutes. By using a by separation funnel the organic and watery layer were separated. The organic layer was washed another two times with H_2O_d, then one time with saturated brine solution. After drying the organic layer over anhydrous $MgSO_4$, the excess solvent was removed by rotary evaporator. The resulting crude solids were recrystallized or purified by column chromatography.

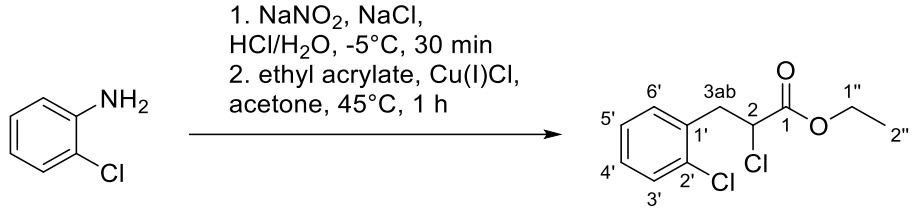
General synthesis protocol J – β-Carbolines syntheses

The β-carbolines syntheses were executed with changes according to the method of F. Bracher[62], published in 1988. The indole analogue was therefore submitted to a one-neck flask and the air was exchanges to N_2, then dry and degassed DMF was added. The solution was heated up to 90°C or 120°C, then *N*,*N*-dimethylformamide diethyl acetal or *tert*-butoxy bis(dimethylamino)-methane was added dropwise. It was stirred at that temperature for 1 h, when TLC control showed no remaining educt. The last step was undertaken again according to the method of Kamlah et al.[31]. After opening the reaction flask, NH_4Cl or CH_3COONH_4 was added in one portion by spatula, followed instantly by glacial acetic acid, which was added by syringe. The temperature was set to 140°C (if no deviation is specifically mentioned for the temperature of reaction step 2.), then it was stirred at that temperature for 1 h. After letting the solution cool down to room temperature, CH_2Cl_2 was added and the solution was washed 5 times with H_2O, one time with watery 5%-LiCl solution and finally with saturated brine solution. The organic layers were dried over $MgSO_4$ then concentrated *in vacuo*. Column chromatography or recrystallization yielded products as solids in yellow to brown colours.

7.3 Data of sythesised compounds – project 3-oxo-γ-carbolines

7.3.1 Meerwein arylation products 25-30

Ethyl 2-chloro-3-(2-chlorophenyl)propanoate (**27**)



27

Chemical Formula: $C_{11}H_{12}Cl_2O_2$ **Molecular Weight:** 247.1150 g/mol

The halide **27** was synthesized according to the general synthesis protocol A (see subchapter 7.2). Solution 1 contained 2-chloroaniline (4.12 mL, 5.00 g, 39.2 mmol) and NaCl (4.01 g, 68.6 mmol). $NaNO_2$ (2.73 g, 39.6 mmol), dissolved in 13 mL of H_2O_d, was added. In total, the 55 mL H_2O_d/HCl solvent of solution 1 contained $HCl_{conc.}$ (12.0 mL, 14.3 g, 145 mmol). For solution 2, Cu(I)Cl (600 mg, 5.88 mmol), ethyl acrylate (15.0 mL, 137 mmol) and 30 mL of acetone were used. Reaction workup was executed as described in the general protocol. Three times 100 mL of CH_2Cl_2, two times 50 mL of H_2O_d and one time 20 mL of saturated brine solution were used. The product **27** could be obtained *via* undertaking column chromatography with an EtOAc:isohexane (1:99) solvent mixture.

Yield and appearance: 9.60 g (38.8 mmol, 99%) as orange viscous oil.

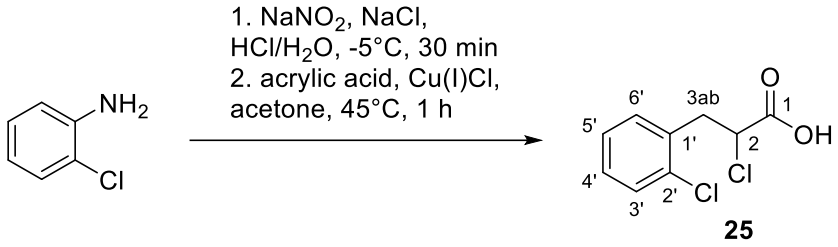
HRMS (EI): m/z = calculated for $[C_{11}H_{11}Cl_2O_2]^{\bullet+}$: 246.02144 ($^{35}Cl$), found: 246.0018 ($^{35}Cl$).

^{1}H NMR (500 MHz, Chloroform-d) δ: 7.45 (dd, J = 6.0, 3.6 Hz, 1H, 4‘-CH), 7.37 (dd, 1H, 5‘-CH), 7.28 (dd, 1H, 3‘-CH), 7.24 – 7.19 (m, 3H, 6‘-CH), 4.60 (dd, J = 8.0, 7.1 Hz, 1H, 2-CH), 4.25 – 4.14 (m, 2H, 1‘‘-CH_2), 3.50 (dd, J = 14.0, 7.1 Hz, 1H, 3a- or 3b-C$\underline{H}_2$), 3.29 (dd, J = 14.0, 8.0 Hz, 1H, 3a- or 3b-C$\underline{H}_2$), 1.24 (t, J = 7.1 Hz, 4H, 2‘‘-CH_3).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 169.27 (1-C_qO), 134.43 (2‘-C_q), 133.80 (1‘-C_q), 132.30 (3‘-CH), 130.67 (8‘-CH), 129.79 (5‘-CH), 127.84 (6‘-CH), 62.26 (1‘‘-CH_2), 55.44 (2-CH), 39.12 (3ab-CH_2), 14.08 (2‘‘-CH_3).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right] =$ 3064 w, 2983 w, 2940 w, 2906 w, 1740 s, 1594 w, 1573 w, 1475 m, 1444 m, 1392 w, 1371 m, 1345 w, 1305 m, 1262 m, 1237 w, 1179 s, 1159 s, 1125 w, 1095 w, 1052 m, 1035 m, 1012 m, 961 w, 927 w, 888 w, 857 w, 802 w, 750 s, 723 m, 702 m, 678 m.

2-Chloro-3-(2-chlorophenyl)propanoic acid (**25**)



25

Chemical Formula: $C_9H_8Cl_2O_2$ **Molecular Weight:** 219.0610 g/mol

The α-chloro carboxylic acid **25** was synthesized according to the general synthesis protocol A (see subchapter 7.2). Solution 1 contained 2-chloroaniline (1.65 mL, 2.00 g, 15.4 mmol) and NaCl (1.57 g, 26.9 mmol). $NaNO_2$ (1.07 g, 15.5 mmol) was dissolved in 2 mL of H_2O_d and added by syringe. In total, the 22 mL H_2O_d/HCl solvent of solution 1 contained $HCl_{conc.}$ (6.00 mL, 7.14 g, 72.5 mmol). For solution 2, Cu(I)Cl (235 mg, 2.30 mmol), acrylic acid (3.70 mL, 3.89 g, 53.9 mmol) and 30 mL of acetone were used. Reaction workup was carried out as described in the general protocol. Three times 100 mL of CH_2Cl_2, two times 50 mL of H_2O_d and one time 20 mL of saturated brine solution were used. Product **25** purification could be achieved through performing column chromatography with an EtOAc:isohexane (1:99) solvent mixture with a 0.2% acetic acid additive.

Yield and appearance: 2.11 g (9.62 mmol, 61%) as whitish orange crystalline solid.

HRMS (ESI): m/z = calculated for $[C_9H_7Cl_2O_2]^-$: 216.98286 (^{35}Cl, ^{35}Cl), 218.97991 (^{35}Cl, ^{37}Cl), 220.97696 (^{37}Cl, ^{37}Cl), found: 216.98282 (^{35}Cl, ^{35}Cl), 218.97990 (^{35}Cl, ^{37}Cl), 220.97700 (^{37}Cl, ^{37}Cl).

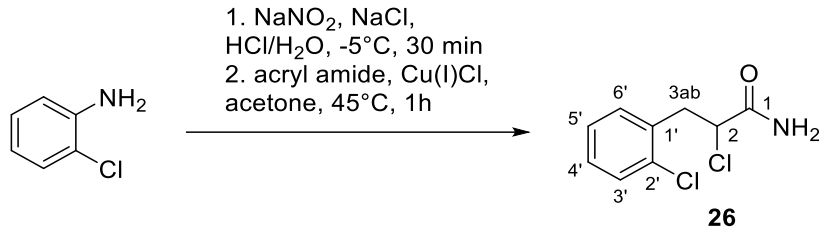
Melting area: 79.7 - 82.3°C

^{1}H NMR (400 MHz, Chloroform-d) δ: 11.10 (s, 1H, -OH), 7.44 – 7.38 (m, 1H, 4‘-CH), 7.35 – 7.30 (m, 1H, 3‘-CH), 7.30 – 7.22 (m, 2H, 5‘- and 6‘-CH), 4.68 (dd, J = 8.4, 6.5 Hz, 1H, 2-CH), 3.59 (dd, J = 14.1, 6.5 Hz, 1H, 3a- or 3b-C$\underline{H}_2$), 3.30 (dd, J = 14.1, 8.4 Hz, 1H, 3a- or 3b-C$\underline{H}_2$).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 174.94 (1-C_qO), 134.41 (2‘-C_q), 133.35 (1‘-C_q), 132.33 (3‘-CH), 129.89 (5‘-CH), 129.26 (4‘-CH), 127.11 (6‘-CH), 55.20 (2-CH), 38.87 (3ab-CH_2).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right]$ = 2923 w, 2555 w, 1713 m, 1594 w, 1573 w, 1475 m, 1443 m, 1417 w, 1344 w, 1310 w, 1297 m, 1285 m, 1274 m, 1258 w, 1222 m, 1211 m, 1166 w, 1125 w, 1050 m, 1034 m, 969 w, 925 m, 870 w, 861 w, 835 w, 803 m, 747 s, 720 w, 689 m, 678 m.

2-Chloro-3-(2-chlorophenyl)propanamide (**26**)



26

Chemical Formula: $C_9H_9Cl_2NO$ **Molecular Weight:** 218.0770 g/mol

Detailed procedure information for the synthesis and the workup of the reaction solution for the resulting α-chloro carboxamide **26** can again be extracted from the general synthesis protocol A (see subchapter 7.2). To solution 1 containing 2-chloroaniline (4.12 mL, 5.00 g, 39.2 mmol) and NaCl (4.01 g, 68.6 mmol), $NaNO_2$ (2.73 g, 39.6 mmol) was added dropwise after being dissolved in 13 mL of H_2O_d. The 37 mL H_2O_d/HCl solvent of solution 1 contained $HCl_{conc.}$ (6.50 mL, 6.82 g, 69.2 mmol). For solution 2, CuCl (600 mg, 5.88 mmol), acryl amide (9.75 g, 137 mmol) and 50 mL of acetone were used. Reaction workup was carried out as described in the general protocol. Three times 200 mL of CH_2Cl_2, two times 50 mL of H_2O_d and one time 50 mL of saturated brine solution were used. Pure product **26** was obtained *via* column chromatography with an EtOAc:isohexane (1:99) solvent mixture.

Yield and appearance: 4.07 g (18.7 mmol, 48%) as white powdery solid**.**

HRMS (ESI): m/z = calculated for $[C_9H_{10}Cl_2NO]^+$: 218.01339 (^{35}Cl, ^{35}Cl), 220.01044 (^{35}Cl, ^{37}Cl), found: 218.01361 (^{35}Cl, ^{35}Cl), 220.01067 (^{35}Cl, ^{37}Cl).

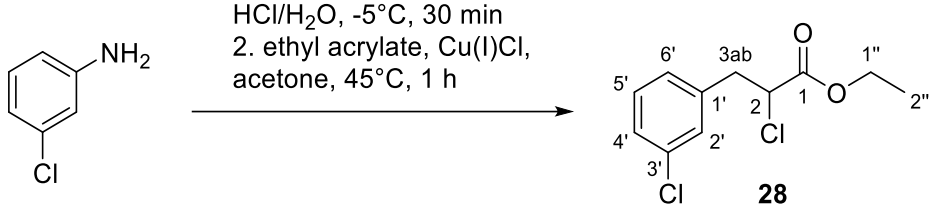
Melting area: 70.6-74.3°C

^{1}H NMR (400 MHz, Chloroform-*d*) δ: 7.42 – 7.35 (m, 1H, 3‘- or 5‘-CH), 7.31 (dd, *J* = 5.7, 3.6 Hz, 1H, 6‘-CH), 7.25 – 7.19 (m, 2H, 4‘- and 3‘- or 5‘-CH), 6.40 (s, 1H, -N$\underline{H}_2$), 5.79 (s, 1H, -N$\underline{H}_2$), 4.64 (dd, *J* = 9.6, 4.7 Hz, 1H, 2-CH), 3.76 (dd, *J* = 14.4, 4.7 Hz, 1H, 3a- or 3b-C$\underline{H}_2$), 3.18 (dd, *J* = 14.4, 9.6 Hz, 1H, 3a- or 3b-C$\underline{H}_2$).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 170.77 (1-C_qO), 134.47 (1‘- or 2‘-C_q), 134.32 (1‘- or 2‘-C_q), 132.26 (6‘-CH), 129.82 (3‘- or 5‘-CH), 128.94 (4‘-CH), 126.96 (3‘- or 5‘-CH), 58.76 (2-CH), 39.31 (3ab-CH_2).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right]$ = 3402 w, 3275 w, 3213 w, 1686 m, 1671 s, 1623 m, 1571 w, 1474 m, 1444 m, 1417 m, 1335 w, 1298 w, 1256 w, 1245 w, 1230 w, 1163 w, 1122 w, 1094 w, 1049 m, 1024 w, 958 w, 950 w, 929 w, 907 m, 860 w, 815 w, 751 s, 734 m, 722 m, 683 m, 670 m.

Ethyl 2-chloro-3-(3-chlorophenyl)propanoate (**28**)



Chemical Formula: $C_{11}H_{12}Cl_2O_2$ **Molecular Weight:** 247.1150 g/mol

The general synthesis protocol A (see subchapter 7.2) was used to generate the α-chloro carboxylate ester **28**. Therefore 3-chloroaniline (25.0 mL, 30.1 g, 236 mmol) and NaCl (25.3 g, 433 mmol) were used for solution 1. $NaNO_2$ (16.4 g, 238 mmol) was added by syringe after being dissolved in 30 mL of H_2O_d. The 300 mL of H_2O_d/HCl solvent that was used contained $HCl_{conc.}$ (77.2 mL, 81.1 g, 823 mmol). For solution 2, Cu(I)Cl (3.49 g, 35.3 mmol), ethyl acrylate (75.0 mL, 68.9 g, 688 mmol) and 150 mL of acetone were used. The reaction workup was performed as described in the general protocol. Three times 300 mL of CH_2Cl_2, two times 150 mL of H_2O_d and one time 100 mL of saturated brine solution were used. Through column chromatography with an EtOAc:isohexane (1:99-4:96) solvent gradient, pure product **28** could be isolated successfully.

Yield and appearance: 22.8 g (92.3 mmol, 39%), orange viscous oil.

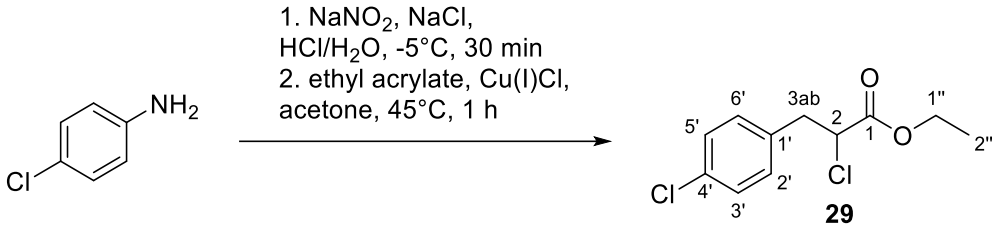
HRMS (EI): m/z = calculated for $[C_{11}H_{12}Cl_2O_2]^{\bullet+}$: 246.02144 ($^{35}Cl$, ^{35}Cl), 250.01553 (^{37}Cl, ^{37}Cl), found: 246.0206 (^{35}Cl, ^{35}Cl), 250.0173 (^{37}Cl, ^{37}Cl).

^{1}H NMR (400 MHz, Methylene Chloride-d_2) δ: 7.29 – 7.26 (m, 2H, 4‘- and 2‘-CH), 7.26 – 7.24 (m, 1H, 6‘-CH), 7.14 (dd, *J* = 5.5, 3.5 Hz, 1H, 5‘-CH), 4.45 (dd, *J* = 7.8, 6.8 Hz, 1H, 2-CH), 4.19 (q, *J* = 7.1 Hz, 2H, 1‘‘-CH_2), 3.34 (dd, *J* = 14.2, 6.8 Hz, 1H, 3a- or 3b-C$\underline{H}_2$), 3.16 (dd, *J* = 14.2, 7.8 Hz, 1H, 3a- or 3b-C$\underline{H}_2$), 1.24 (t, *J* = 7.1 Hz, 3H, 2‘‘-CH_3).

^{13}C NMR (101 MHz, CD_2Cl_2) δ: 169.29 (1-C_q), 138.74 (1‘-C_q), 134.70 (3‘-C_q), 130.43 (2‘-, 4‘- or 6‘-CH), 130.04 (2‘-, 4‘- or 6‘-CH), 128.28 (5‘-CH), 127.98 (2‘-, 4‘- or 6‘-CH), 62.80 (1‘‘-CH_2), 57.86 (2-CH), 41.08 (3ab-CH_2), 14.31 (2‘‘-CH_3).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right]$ = 2982 w, 2939 w, 2251 w, 2168 w, 2009 w, 1993 w, 1738 m, 1599 w, 1574 w, 1477 w, 1431 w, 1391 w, 1371 w, 1345 w, 1300 w, 1261 w, 1236 w, 1178 m, 1158 m, 1095 w, 1080 m, 1017 m, 1000 w, 967 w, 933 w, 886 w, 855 w, 781 m, 711 w, 690 m, 682 m.

Ethyl 2-chloro-3-(4-chlorophenyl)propanoate (**29**)



Chemical Formula: $C_{11}H_{12}Cl_2O_2$ **Molecular Weight:** 247.1150 g/mol

This α-chloro carboxylate ester **29** was synthesised according to the general synthesis protocol A (see subchapter 7.2). Solution 1 contained 4-chloroaniline (3.41 mL, 15.0 g, 115 mmol) and NaCl (12.4 g, 212 mmol). $NaNO_2$ (8.03 g, 116 mmol), dissolved in 30 mL H_2O_d, was added dropwise *via* syringe. The in total 60 mL of H_2O_d/HCl solvent of solution 1 contained $HCl_{conc.}$ (16.2 mL, 17.0 g, 173 mmol). For solution 2, Cu(I)Cl (1.71 g, 17.3 mmol), ethyl acrylate (44.0 mL, 40.4 g, 403 mmol) and 100 mL of acetone were used. Reaction workup was carried out as described in the general protocol. Three times 200 mL of CH_2Cl_2, two times 100 mL of H_2O_d and one time 75 mL of saturated brine solution were used. Product **29** purification could be achieved through performing column chromatography with an EtOAc:isohexane (1:99) solvent mixture.

Yield and appearance: 3.77 g (15.5 mmol, 14%) as brown-orange viscous oil.

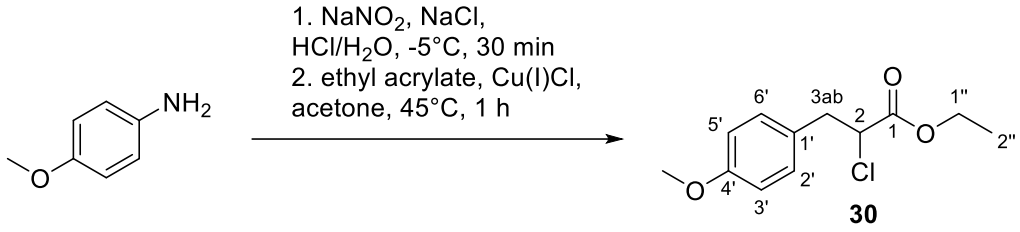
HRMS (EI): m/z = calculated for $[C_{11}H_{12}O_2Cl_2]^{\bullet+}$: 246.02144 ($^{35}Cl$, ^{35}Cl), 248.01848 (^{35}Cl, ^{37}Cl), found: 246.0210 (^{35}Cl, ^{35}Cl), 248.0180 (^{35}Cl, ^{37}Cl).

^{1}H NMR (400 MHz, Methylene Chloride-d2) δ: 7.33 – 7.27 (m, 2H, 2‘- and 6‘-CH), 7.21 – 7.16 (m, 2H, 3‘- and 5‘-CH), 4.44 (dd, J = 7.7, 6.9 Hz, 1H, 2-CH), 4.17 (qd, J = 7.1, 1.8 Hz, 2H, 1‘‘-CH_2), 3.33 (dd, J = 14.1, 6.9 Hz, 1H, 3a- or 3b-C$\underline{H}_2$), 3.15 (dd, J = 14.2, 7.7 Hz, 1H, 3a- or 3b-C$\underline{H}_2$), 1.23 (t, J = 7.1 Hz, 3H, 2‘‘-CH_3).

^{13}C NMR (101 MHz, CD_2Cl_2) δ: 169.33 (1-C_qO), 135.25 (1‘-C_q), 133.62 (4‘-C_q), 131.41 (3’- and 5‘-CH), 129.17 (2’- and 6‘-CH), 62.75 (1‘‘-CH_2), 57.98 (2-CH), 40.80 (3ab-CH_2), 14.32 (2‘‘-CH_3).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right]$ = 2983 w, 2939 w, 2905 w, 1739 s, 1597 w, 1492 s, 1443 w, 1409 w, 1392 w, 1371 m, 1344 w, 1295 m, 1263 m, 1236 m, 1177 s, 1158 s, 1093 s, 1015 s, 962 w, 927 w, 860 w, 809 s, 743 w, 718 m, 698 m, 658 w.

Ethyl 2-chloro-3-(4-methoxyphenyl)propanoate (**30**)



30

Chemical Formula: $C_{12}H_{15}ClO_3$ **Molecular Weight:** 242.6990 g/mol

The synthesis and the workup of the reaction solution for the resulting α-chloro carboxylate ester **30** is to extract in detail from subchapter 7.2 according to the general synthesis protocol A. Solution 1 contained 4-methoxyaniline (3.01 g, 24.4 mmol), NaCl (2.50 g, 42.8 mmol). $NaNO_2$ (1.70 g, 24.7 mmol), dissolved in 5 mL of H_2O_d, was added dropwise. Solution 1, with a total of 37 mL H_2O_d/HCl solvent, contained $HCl_{conc.}$ (10.9 mL, 11.4 g, 116 mmol). CuCl (374 mg, 3.67 mmol), ethyl acrylate (9.5 mL, 8.72 g) 87.1 mmol) and 35 mL of acetone were used to prepare solution 2. Reaction workup was carried out as described in the general protocol. Three times 150 mL of CH_2Cl_2, two times 50 mL of H_2O_d and one time 35 mL of saturated brine solution were used. Column chromatography with an EtOAc:isohexane (0.5:99.5-5:95) solvent gradient yielded pure product **30**.

Yield and appearance: 1.20 g (4.94 mmol, 20%) as yellow viscous oil.

HRMS (EI): m/z = calculated for $[C_{12}H_{15}ClO_3]^{\bullet+}$: 242.07097 ($^{35}Cl$), found: 242.0702 ($^{35}Cl$).

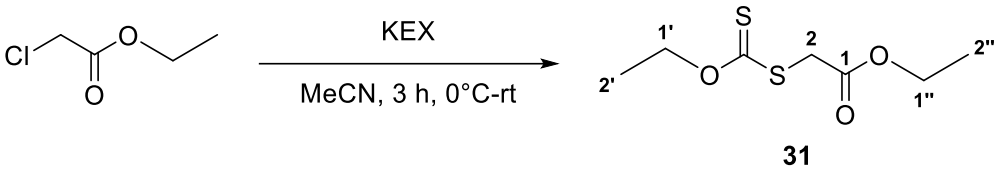
^{1}H NMR (400 MHz, Chloroform-d) δ: 7.17 – 7.11 (m, 2H, 2‘- and 6‘-CH), 6.87 – 6.81 (m, 2H, 3‘- and 5‘-CH), 4.38 (t, J = 7.4 Hz, 1H, 2-CH), 4.18 (qd, J = 7.1, 3.2 Hz, 2H, 1‘‘-CH_2), 3.79 (s, 3H, -OCH_3), 3.30 (dd, J = 14.0, 7.4 Hz, 1H, 3a- or 3b-C$\underline{H}_2$), 3.12 (dd, J = 14.1, 7.4 Hz, 1H, 3a- or 3b-C$\underline{H}_2$), 1.24 (t, J = 7.1 Hz, 3H, 2‘‘-CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 169.42 (1-C_qO), 158.97 (4‘-C_q), 130.54 (2‘- and 6‘-CH), 128.07 (1‘-C_q), 114.10 (3‘- and 5‘-CH), 62.13 (1‘‘-CH_2), 57.79 (2-CH), 55.37 (-OCH_3), 40.44 (3ab-CH_2), 14.11 (2‘‘-CH_3).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right]$ = 2982 w, 2935 w, 2836 w, 2251 w, 2168 w, 2085 w, 2057 w, 1738 m, 1611 w, 1584 w, 1512 m, 1464 w, 1441 w, 1391 w, 1345 w, 1301 m, 1246 s, 1176 m, 1157 m, 1109 m, 1095 w, 1030 m, 963 w, 923 w, 851 w, 821 m, 808 m, 747 w, 697 w.

7.3.2 Xanthates 31-36

Ethyl 2-((ethoxycarbonothioyl)thio)acetate (**31**)



31

Chemical Formula: $C_7H_{12}O_3S_2$ **Molecular Weight:** 208.2900 g/mol

Ethyl chloroacetate (4.35 mL, 5.00 g, 40.8 mmol), KEX (7.85 g, 49.0 mmol) and 75 mL of MeCN were used to synthesise **31** according to the general protocol B (see subchapter 7.2). The solution was stirred for 3 h. 200 mL methylene chloride, three times 75 mL of H_2O_d and 50 mL of saturated brine solution were used for the working up process. Product **31** purification could be achieved by performing column chromatography with an EtOAc:isohexane (5:95) solvent mixture.

Yield and appearance: 7.19 g (34.5 mmol, 85%) as pale-yellow oil.

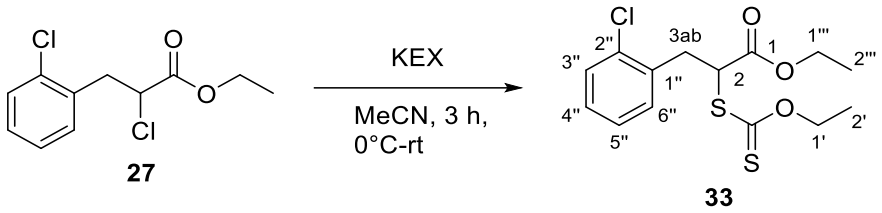
HRMS (EI): m/z = calculated for $[C_7H_{12}O_3S_2]^{\bullet+}$: 208.02279, found: 208.0511.

^{1}H NMR (400 MHz, DMSO) δ: 4.60 (q, *J* = 7.1 Hz, 2H, 1'-CH_2), 4.12 (q, *J* = 7.1 Hz, 2H, 1''-CH_2), 4.04 (s, 2H, 2-CH_2), 1.34 (t, *J* = 7.1 Hz, 3H, 1'-CH_3), 1.20 (t, *J* = 7.1 Hz, 3H, 1''-CH_3).

^{13}C NMR (101 MHz, DMSO) δ: 212.68 (C_qS), 167.58 (1-C_qO), 70.70 (1'-CH_2), 61.28 (1''-CH_2), 37.08 (2-CH_2), 14.02 (1''-CH_3), 13.41 (1'-CH_3).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right]$ = 2982 w, 2938 w, 2903 w, 1734 m, 1463 w, 1443 w, 1388 w, 1365 w, 1294 m, 1216 s, 1148 m, 1109 m, 1043 s, 1025 s, 942 w, 888 w, 863 w, 810 w, 774 w, 689 w.

Ethyl 3-(2-chlorophenyl)-2-((ethoxycarbonothioyl)thio)propanoate (**33**)



Chemical Formula: $C_{14}H_{17}ClO_3S_2$ **Molecular Weight:** 332.8570 g/mol

The general synthesis protocol B (see subchapter 7.2) was used to synthesise the xanthate **33**. KEX (5.21 g, 29.6 mmol), halide educt **27** (4.87 g, 19.7 mmol) and 85 mL of MeCN were used. The suspension was stirred for 3 h. For the working up process, 300 mL of CH_2Cl_2, two times 100 mL of H_2O_d and 50 mL of brine solution were used. Column chromatography with an EtOAc:isohexane (2:98-4:96) solvent gradient provided pure product **33**.

Yield and appearance: 5.95 g (17.9 mmol, 91%) as orange viscous oil.

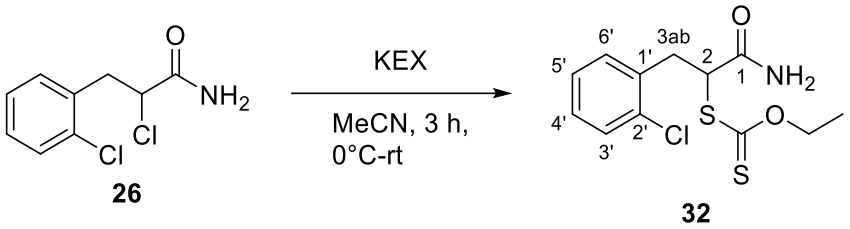
HRMS (EI): m/z = calculated for $[C_{14}H_{17}ClO_3S_2]^{\bullet+}$: 332.0308 ($^{35}Cl$), found: 332.0302 ($^{35}Cl$).

^{1}H NMR (400 MHz, DMSO-d6) δ: 7.47 – 7.43 (m, 1H, 3‘‘-CH), 7.38 – 7.33 (m, 1H, 6‘‘-CH), 7.33 – 7.27 (m, 2H, 4‘‘- or 5‘‘-CH), 4.64 (dd, J = 8.4, 7.6 Hz, 1H, 2-CH), 4.61 – 4.47 (m, 2H, 1‘-CH_2), 4.09 (q, J = 7.1 Hz, 2H, 1‘‘‘-CH_2), 3.37 (dd, J = 14.0, 7.6 Hz, 1H, 3a- or 3b-C$\underline{H}_2$), 3.22 (dd, J = 14.0, 8.5 Hz, 1H, 3a- or 3b-C$\underline{H}_2$), 1.31 (t, J = 7.1 Hz, 3H, 2‘-CH_3), 1.10 (t, J = 7.1 Hz, 3H, 2‘‘‘-CH_3).

^{13}C NMR (101 MHz, DMSO) δ: 210.51 (C_qS), 169.32 (1-C_qO), 134.22 (1‘‘-C_q), 133.39 (2‘‘-C_q), 131.89 (6‘‘-CH), 129.36 (4‘‘- or 5‘‘-CH), 129.11 (3‘‘-CH), 127.25 (4‘‘- or 5‘‘-CH), 70.82 (1‘-CH_2), 61.51 (1‘‘‘-CH_2), 50.98 (2-CH), 33.98 (3ab-CH_2), 13.83 (2‘‘‘-CH_3), 13.32 (2‘-CH_3).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right] =$ 2981 w, 2937 w, 2900 w, 1731 s, 1594 w, 1573 w, 1475 w, 1443 w, 1389 w, 1367 w, 1329 w, 1289 w, 1217 s, 1173 m, 1150 m, 1110 m, 1035 s, 1003 m, 925 w, 856 w, 806 w, 750 s, 723 w, 677 m.

S-(1-amino-3-(2-chlorophenyl)-1-oxopropan-2-yl) *O*-ethyl carbonodithioate (**32**)



26 **32**

Chemical Formula: $C_{12}H_{14}ClNO_2S_2$ **Molecular Weight:** 303.81900 g/mol

The general synthesis protocol B (see subchapter 7.2) was used to synthesise the xanthate **32**. KEX (4.11 g, 23.3 mmol), the halide educt **26** (4.07 g, 18.7 mmol) and 60 mL of MeCN were used. The suspension was stirred for 3 h. 150 mL of CH_2Cl_2, two times 75 mL of H_2O_d and 25 mL of saturated brine solution were used in the working up process. Column chromatography with an EtOAc:isohexane (2:98-4:96) solvent gradient yielded pure product **32**.

Yield and appearance: 5.11 g (16.8 mmol, 90%) as white solid.

HRMS (ESI): m/z = calculated for $[C_{12}H_{15}ClNO_2S_2]^+$: 304.02272 ($^{35}Cl$), 306.01977 ($^{37}Cl$), found: 304.02313 ($^{35}Cl$), 306.02021 ($^{37}Cl$).

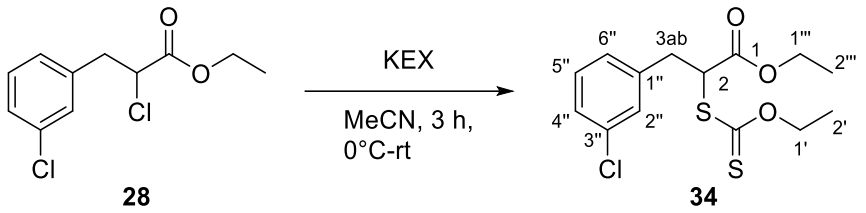
Melting area: 64.7 - 69.7°C

^{1}H NMR (400 MHz, CD_2Cl_2) δ: 7.43 – 7.35 (m, 1H, 3'- or 5'CH), 7.36 – 7.27 (m, 1H, 6'-CH), 7.30 – 7.18 (m, 2H, 4'- and 3'- or 5'CH), 6.07 (s, 1H, -N$\underline{H}_2$), 5.57 (s, 1H, -N$\underline{H}_2$), 4.68 – 4.55 (m, 3H, 2-CH and -CH_2), 3.48 (dd, *J* = 14.2, 7.3 Hz, 1H, 3a- or 3b-C$\underline{H}_2$), 3.18 (dd, *J* = 14.2, 1.7 Hz, 1H, 3a- or 3b-C$\underline{H}_2$), 1.39 (t, *J* = 7.1 Hz, 3H, -CH_3).

^{13}C NMR (101 MHz, CD_2Cl_2) δ: 213.15 (C_qS), 171.85 (1-C_qO), 135.44 (1'-C_q), 134.69 (2'-C_q), 132.35 (6'-CH), 129.93 (3'-CH or 5'-CH), 129.03 (4'-CH), 127.30 (3'-CH or 5'-CH), 71.51 (-CH_2), 52.39 (2-CH), 34.85 (3ab-CH_2), 13.85 (-CH_3).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right]$ = 3380 w, 3175 w, 2978 w, 2939 w, 1672 m, 1656 s, 1622 m, 1572 w, 1551 w, 1474 m, 1443 m, 1412 m, 1359 w, 1332 w, 1306 w, 1267 m, 1236 s, 1205 m, 1145 w, 1112 m, 1046 s, 1000 m, 978 w, 958 w, 949 w, 928 w, 916 w, 860 w, 851 w, 811 m, 794 w, 751 s, 720 m, 706 m, 693 m, 678 m.

Ethyl 3-(3-chlorophenyl)-2-((ethoxycarbonothioyl)thio)propanoate (**34**)



Chemical Formula: $C_{14}H_{17}ClO_3S_2$ **Molecular Weight:** 332.8570 g/mol

Halide **28** (21.9 g, 88.4 mmol), KEX (16.4 g, 92.8 mmol) and 350 mL MeCN were used for the synthesis of xanthate **34**, according to general synthesis protocol B (see subchapter 7.2). After stirring the suspension for 3 h, 400 mL of CH_2Cl_2, two times 200 mL of H_2O_d and one time 100 mL of saturated brine solution were used for the described workup steps. Raw product **34** was used in the following synthesis steps with no further purification process, since the purity was subjectively considered to be sufficient for the next synthesis steps.

Yield and appearance: 27.9 g (83.9 mmol, 95%) as orange viscous oil.

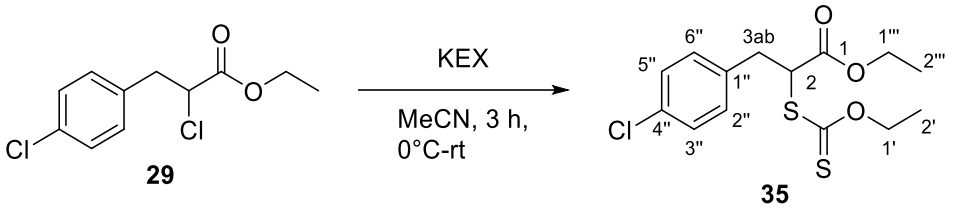
HRMS (EI): m/z = calculated for $[C_{14}H_{18}ClO_3S_2]^{\bullet+}$: 333.03804 (^{35}Cl), 335.0321 (^{37}Cl), found: 332.0400 (^{35}Cl), 335.0321 (^{37}Cl).

^{1}H NMR (500 MHz, Methylene Chloride-d2) δ: 7.29 – 7.21 (m, 3H, 2‘‘- and 4‘‘-, 5‘‘- or 6‘‘-CH), 7.17 – 7.14 (m, 1H, 4‘‘-, 5‘‘- or 6‘‘-CH), 4.66 – 4.58 (m, 2H, 1‘-CH_2), 4.56 (dd, J = 8.4, 6.9 Hz, 1H, 2-CH), 4.12 (q, J = 7.1 Hz, 2H, 1‘‘‘-CH_2), 3.23 (dd, J = 13.9, 8.4 Hz, 1H, 3a- or 3b-C$\underline{H}_2$), 3.14 (dd, J = 14.0, 6.9 Hz, 1H, 3a- or 3b-C$\underline{H}_2$), 1.40 (t, J = 7.1 Hz, 3H, 2‘-CH_3), 1.18 (t, J = 7.1 Hz, 3H, 2‘‘‘-CH_3).

^{13}C NMR (126 MHz, CD2Cl2) δ: 211.91 (C_qS), 170.29 (1-C_qO), 139.78 (1‘‘-C_q), 134.63 (3‘‘-C_q), 130.37 (2‘‘-, 4‘‘-, 5‘‘- or 6‘‘-CH), 129.81 (2‘‘-, 4‘‘-, 5‘‘- or 6‘‘-CH), 128.09 (4‘‘-, 5‘‘- or 6‘‘-CH), 127.79 (2‘‘-, 4‘‘-, 5‘‘- or 6‘‘-CH), 71.29 (1‘-CH_2), 62.42 (1‘‘‘-CH_2), 54.00 (2-CH), 37.76 (3ab-CH_2), 14.38 (2‘‘‘-CH_3), 14.00 (2‘-CH_3).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right]$ = 2981 w, 2937 w, 2900 w, 1730 s, 1598 w, 1574 w, 1475 w, 1441 w, 1388 w, 1367 w, 1329 w, 1217 s, 1174 m, 1148 m, 1110 m, 1095 m, 1079 m, 1042 s, 887 w, 856 m, 807 w, 779 m, 692 m, 682 m.

Ethyl 3-(4-chlorophenyl)-2-((ethoxycarbonothioyl)thio)propanoate (**35**)



Chemical Formula: $C_{14}H_{17}ClO_3S_2$ **Molecular Weight:** 332.8570 g/mol

Halide **29** (10.0 g, 41.2 mmol), KEX (14.5 g, 82.4 mmol) and 250 mL MeCN was used to synthesise the xanthate **35**, according to the general synthesis protocol B (see subchapter 7.2). After stirring the suspension for 3 h, 250 mL of CH_2Cl_2, two times 75 mL of H_2O_d and one time 50 mL of saturated brine solution were used for the described workup steps. Solvent was evaporated and the crude oil was purified by column chromatography with an acetone:isohexane (1:99) solvent mixture.

Yield and appearance: 10.0 g (30.6 mmol, 74%) as orange viscous oil.

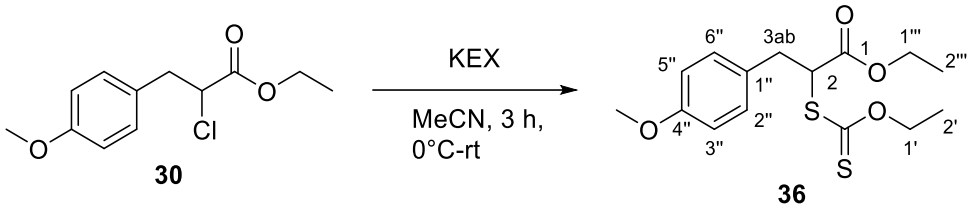
HRMS (EI): m/z = calculated for $[M]^{\cdot+}$ = $[C_{14}H_{17}ClO_3S_2]^{\cdot+}$: 332.03076 ($^{35}Cl$), 334.02781 ($^{37}Cl$), $[M\text{-}SCSOC_2H_5]^+$: 211.05258 (^{35}Cl), $[M\text{-}(CH(COOC_2H_5)(CSCOC_2H_5))]^+$: 125.01580 ($^{35}Cl$), found: $[M\text{-}SCSOC_2H_5]^+$: 211.0522 (^{35}Cl), $[M\text{-}(CH(COOC_2H_5)(CSCOC_2H_5))]^+$: 125.0154 ($^{35}Cl$).

^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.37 (ddd, *J* = 8.4, 2.2, 1.7 Hz, 2H, 3''- and 5''-CH), 7.27 (ddd, *J* = 8.4, 2.2, 1.7 Hz, 2H, 2''- and 6''-CH), 4.66 – 4.50 (m, 3H, 2-CH and 1'-CH_2), 4.08 (q, *J* = 7.1 Hz, 2H, 1'''-CH_2), 3.20 (dd, *J* = 13.9, 7.8 Hz, 1H, 3a- or 3b-C$\underline{H}_2$), 3.10 (dd, *J* = 13.9, 7.6 Hz, 1H, 3a- or 3b-C$\underline{H}_2$), 1.33 (t, *J* = 7.1 Hz, 3H, 2'-CH_3), 1.10 (t, *J* = 7.1 Hz, 3H, 2'''-CH_3).

^{13}C NMR (101 MHz, DMSO) δ: 210.74 (C_qS), 169.42 (1-C_qO), 135.81 (1''-C_q), 131.70 (4''-C_q), 131.05 (2''- and 6''-CH), 128.32 (3''- and 5''-CH), 70.82 (1'-CH_2), 61.40 (1''-CH_2), 52.42 (2-CH), 35.50 (3-CH_2), 13.85 (2'''-CH_3), 13.33 (2'-CH_3).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right]$ = 2981 w, 2936 w, 2903 w, 1728 s, 1596 w, 1492 m, 1442 w, 1408 w, 1389 w, 1367 m, 1291 w, 1217 s, 1173 m, 1148 s, 1110 m, 1092 s, 1043 s, 1014 s, 851 w, 808 m, 745 w, 717 w.

Ethyl 2-((ethoxycarbonothioyl)thio)-3-(4-methoxyphenyl)propanoate (**36**)



Chemical Formula: $C_{15}H_{20}O_4S_2$ **Molecular Weight:** 328.4410 g/mol

Halide **30** (8.03 g, 33.1 mmol), KEX (6.53 g, 37.1 mmol) and 150 mL MeCN was used synthesis of xanthate **36** according to general synthesis protocol B (see subchapter 7.2). After stirring the suspension for 3 h, 200 mL of CH_2Cl_2, two times with 100 mL of H_2O_d and one time with 50 mL of saturated brine solution were used for the described workup procedure. Raw product **36** was used in the following synthesis steps with no further purification process, since the purity was subjectively considered to be sufficient for the next synthesis steps.

Yield and appearance: 10.1 g (30.7 mmol, 93%) as yellow-orange oil.

HRMS (EI): m/z = calculated for $[C_{15}H_{20}O_4S_2]^{\bullet+}$: 328.08030, found: 328.0780.

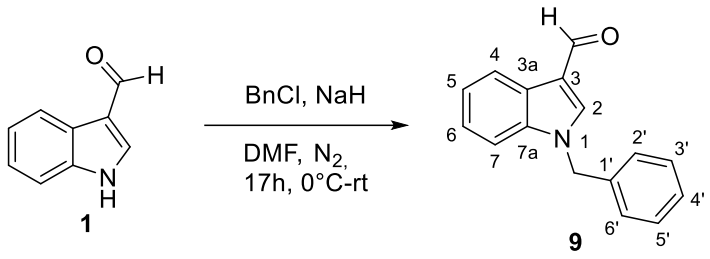
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.15 (ddd, *J* = 8.6, 2.5, 1.9 Hz, 2H, 2''- and 6''-CH), 6.82 (ddd, *J* = 8.6, 2.5, 1.9 Hz, 2H, 3''- and 5''-CH), 4.61 (qd, *J* = 7.1, 1.8 Hz, 2H, 1'-CH_2), 4.54 (dd, *J* = 8.4, 6.8 Hz, 1H, 2-CH), 4.13 (q, *J* = 7.1 Hz, 2H, 1'''-CH_2), 3.78 (s, 3H, -OCH_3), 3.19 (dd, *J* = 14.0, 8.4 Hz, 1H, 3a- or 3b-C$\underline{H}_2$), 3.10 (dd, *J* = 14.0, 6.8 Hz, 1H, 3a- or 3b-C$\underline{H}_2$), 1.40 (t, *J* = 7.1 Hz, 3H, 2'-CH_3), 1.19 (t, *J* = 7.1 Hz, 3H, 2'''-CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 211.98 (C_qS), 170.46 (1-C_qO), 158.83 (4''-C_q), 130.32 (2''- and 6''-CH), 129.08 (1''-C_q), 114.04 (3''- and 5''-CH), 70.47 (1'-CH_2), 61.79 (1'''-CH_2), 55.37 (-OCH_3), 54.06 (2-CH), 36.95 (3ab-CH_2), 14.19 (2'''-CH_3), 13.82 (2'-CH_3).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right]$ = 2979 w, 2935 w, 2834 w, 2031 w, 2000 w, 1730 m, 1611 mw, 1584 w, 1511 m, 1463 w, 1441 w, 1388 w, 1367 w, 1300 w, 1245 ms, 1218 ms, 1176 m, 1147 m, 1108 m, 1031 s, 849 mw, 819 m, 746 mw, 699 w.

7.3.3 Indole analogues

1-Benzyl-1*H*-indole-3-carbaldehyde (**9**)



1 **9**

Chemical Formula: $C_{16}H_{13}NO$ **Molecular Weight:** 235.2860 g/mol

The benzyl protected indole analogue **9** was synthesised in the style of Qinyuan Xu et al.[90]. Therefore, a one-neck flask, containing a 60% dispersion of NaH (372 mg, 9.30 mmol) and 15 mL of anhydrous DMF in a N_2-atmosphere, was cooled to 0°C. Indole-3-carbaldehyde (**1**) (1.00 g, 6.89 mmol), diluted in 15 mL of dry DMF, was added dropwise. The solution was stirred for 5 min, then benzyl bromide (1.60 mL, 2.30 g, 13.4 mmol) was added slowly to the flask and the suspension was allowed to gain room temperature. At room temperature it was stirred for further 17 h. The reaction was quenched with 100 mL H_2O_d and extracted three times with 150 mL of Et_2O. The combined organic layers were washes three times with 50 mL of H_2O_d, one time with 25 mL of a watery 5%-LiCl solution and one time with 20 mL of saturated brine solution, then dried over $MgSO_4$. After removing the solvent by rotary evaporator, pure product **9** could be isolated by means of column chromatography with an EtOAc:isohexane (2:8) solvent mixture.

Yield and appearance: 1.42 g (6.03 mmol, 88%) as white solid.

HRMS (ESI): m/z = calculated for $[C_{16}H_{14}NO]^+$: 236.10699, found: 236.10722.

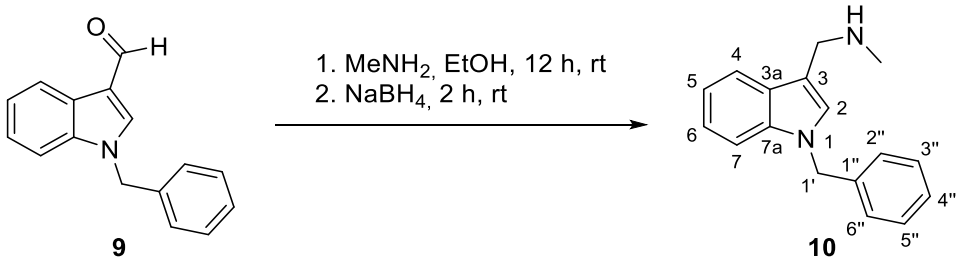
Melting area: 81.4 – 82.7°C

^{1}H NMR (500 MHz, $CDCl_3$) δ: 10.00 (s, 1H, -CHO), 8.37 – 8.28 (m, 1H, 4-CH), 7.72 (s, 1H, 2-CH), 7.40 – 7.27 (m, 6H, 3'-, 4'-, 5'-, 5-, 6- and 7-CH), 7.19 (dd, J = 7.7, 1.7 Hz, 2H, 2'- and 6'-CH), 5.37 (s, 2H, $-CH_2$).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 184.72 (-CHO), 138.65 (2-CH), 137.63 (7a-C_q), 135.41 (1'-C_q), 129.28 (3'- and 5'-CH), 128.56 (4'-CH), 127.38 (2'- and 6'-CH), 125.66 (3a-C_q), 124.33 (6-CH), 123.25 (5- or 7-CH), 122.34 (4-CH), 118.63 (3-C_q), 110.50 (5- or 7-CH), 51.10 ($-CH_2$).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right]$ = 3108 w, 3047 w, 2815 w, 1651 s, 1613 m, 1603 m, 1575 w, 1535 m, 1494 m, 1484 w, 1465 m, 1444 w, 1401 m, 1392 s, 1356 m, 1329 m, 1298 w, 1263 w, 1213 w, 1195 m, 1172 m, 1156 m, 1136 m, 1075 w, 1042 m, 1027 m, 1012 w, 977 w, 935 w, 878 m, 850 w, 812 w, 786 m, 774 w, 739 s, 730 s, 691 s.

1-(1-Benzyl-1*H*-indol-3-yl)-*N*-methylmethaneamine (**10**)



9 **10**

Chemical Formula: $C_{17}H_{18}N_2$ **Molecular Weight:** 250.34500 g/mol

The secondary amine **10** was generated using the synthesis protocol published in the year 2000 by Ferrarini et al.[89]. An 33%-ethanolic solution of H_2NMe (5.00 mL, 3.50 mg, 37.2 mmol) and the indole analogue **9** (500 mg, 2.13 mmol) was stirred at rt for 12 h. When TLC showed consumption of educts the solution was cooled on ice and $NaBH_4$ (121 mg, 3.19 mmol) was added in one portion. It was stirred at rt for 2 h then solvent was reduced by rotary evaporator and to the remaining solid 30 mL of saturated $NaHCO_3$ solution was added. It was extracted three times with 50 mL of CH_2Cl_2. The combined organic layers were washed with 15 mL of saturated brine solution, then dried over $NaSO_4$. Solvent was evaporated and column chromatography with MeCN:CH_2Cl_2 (5:95) with an 0.5% NEt_3 additive gave pure product **10**.

Yield and appearance: 300 mg (1.20 mmol, 56%) as brown oil.

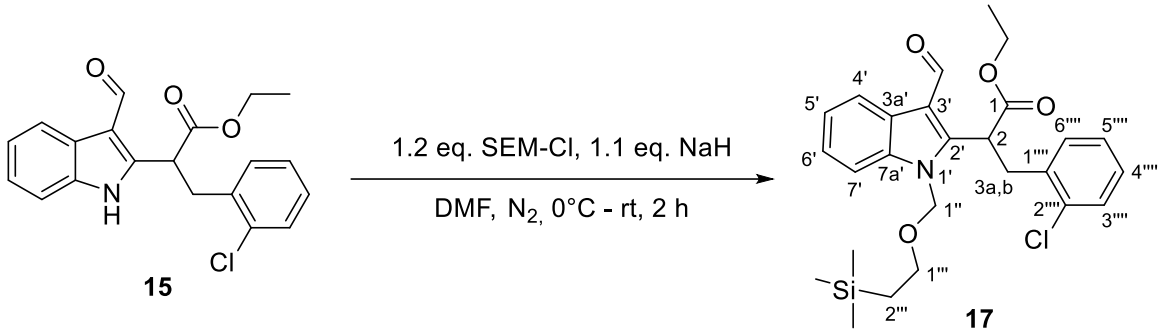
HRMS (EI): m/z = calculated for $[C_{17}H_{18}N_2]^{\bullet+}$: 250.1470, found: 250.1470.

^{1}H NMR (400 MHz, Chloroform-*d*) δ: 7.59 (dt, *J* = 7.7, 1.4, 0.8 Hz, 1H, 4-CH), 7.24 – 7.13 (m, 4H, 7-, 3''-, 4''- and 5''-CH), 7.10 (ddd, *J* = 8.2, 6.9, 1.4 Hz, 1H, 6-CH), 7.07 – 6.98 (m, 4H, 2-, 5-, 2''- and 6''-CH), 5.20 (s, 2H, 1'-CH_2), 3.89 (s, 2H, -CH_2), 2.55 (s, 1H, -N<u>H</u>CH_3) 2.42 (s, 3H, -NH<u>CH_3</u>).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 137.59 (1''-C_q), 136.83 (7a-C_q), 128.87 (3''- and 5''-CH), 127.92 (3a-C_q), 127.74 (4''-CH), 127.13 (2-CH), 126.99 (2''- and 6''-CH), 122.04 (6-CH), 119.50 (5-CH), 119.10 (4-CH), 113.36 (3-C_q), 109.92 (7-CH), 50.13 (1'-CH_2), 46.56 (-CH_2), 35.89 (-$NHCH_3$).

IR (ATR): $\tilde{\nu}\ \left[\frac{1}{cm}\right]$ = 3028 w, 2922 w, 2848 w, 2785 w, 2168 w, 2163 w, 2080 w, 1887 w, 1659 w, 1639 w, 1613 w, 1586 w, 1549 w,1495 w, 1480 w, 1452 m, 1465 m, 1452 m, 1377 m, 1355 m, 1330 m, 1300 w, 1271 w, 1253 w, 1199 w, 1175 m, 1130 w, 1095 w, 1076 w, 1027 m, 1012 m, 967 w, 926 w, 807 m, 735 s, 698 s.

Ethyl 3-(2-chlorophenyl)-2-(3-formyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indol-2-yl)propanoate (**17**)



Chemical Formula: $C_{26}H_{32}ClNO_4Si$ **Molecular Weight:** 486.08000 g/mol

Substance **17** was synthesised following the protocol of Muchowski et al.[95]. To a stirred solution of educt **15** (200 mg, 562 µmol) in 3 mL dry DMF was added sodium hydride (60% in mineral oil) (24.3 mg, 607 µmol). When the hydrogen evolution had ceased, [2-(trimethylsilyl)ethoxy]methyl chloride (125 µL, 117 mg, 669 µmol) was added dropwise at 0 °C. The reaction was stirred for 2 h at rt. When consumption of educt could be observed on TLC, the liquid was removed through a syringe and what remained of the sodium hydride dispersion was discarded. The solvent was evaporated and purification of **17** could be achieved through column chromatography with ethyl acetate/isohexane (1:9) with a 0.1% TEA additive.

Yield and appearance: 185 mg (381 µmol, 68%) as whiteish clear and viscous oil.

^{1}H NMR (400 MHz, Chloroform-d) δ: 10.29 (s, 1H, -CHO), 8.31 – 8.22 (m, 1H, 4'-CH), 7.41 – 7.36 (m, 1H, 7'-CH), 7.33 (dd, J = 8.0, 1.2 Hz, 1H, 3''''-CH), 7.32 – 7.28 (m, 2H, 5'- and 6'-CH), 7.11 (td, J = 8.0, 7.3, 1.9 Hz, 1H, 4''''-CH), 6.95 (td, J = 7.6, 1.2 Hz, 1H, 5''''-CH), 6.90 (dd, J = 7.6, 1.9 Hz, 1H, 6''''-CH), 5.31 (d, J = 11.4 Hz, 1H, 1''a- or 1''b-C$\underline{H}_2$), 5.16 (d, J = 11.4 Hz, 1H, 1''a- or 1''b-C$\underline{H}_2$), 4.76 (dd, J = 9.4, 5.8 Hz, 1H, 2-CH), 4.18 (qd, J = 7.1, 1.4 Hz, 2H, -CH_2), 3.96 (dd, J = 13.7, 5.8 Hz, 1H, 3a- or 3b-C$\underline{H}_2$), 3.48 (t, J = 8.2 Hz, 2H, 1'''-CH_2), 3.33 (dd, J = 13.7, 9.4 Hz, 1H, 3a- or 3b-C$\underline{H}_2$), 1.18 (t, J = 7.1 Hz, 3H, -CH_3), 0.88 (td, J = 8.3, 7.4, 1.7 Hz, 2H, 2'''-CH_2), -0.05 (s, 9H, Si(CH_3)$_3$).

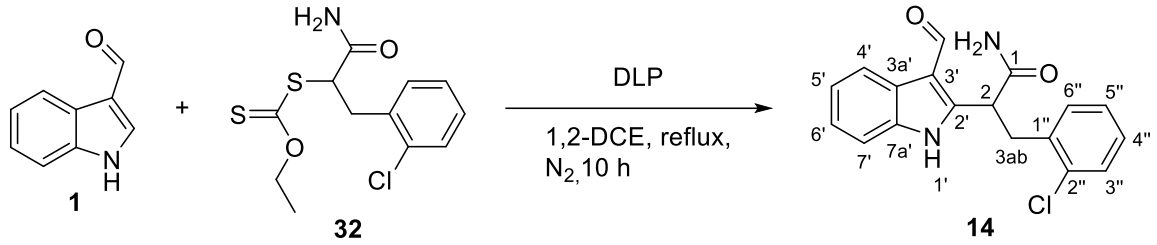
^{13}C NMR (101 MHz, $CDCl_3$) δ: 185.13 (-CHO), 170.58 (1-C_qO), 145.64 (2'-C_q), 136.92 (7a'-C_q), 135.68 (1''''-C_q), 134.06 (2''''-C_q), 131.74 (6''''-CH), 129.67 (3''''-CH), 128.70 (4''''-CH),

127.11 (5’’’-CH), 126.12 (3a’-C_q), 124.05 (6’-CH), 123.40 (5’-CH), 121.15 (4’-CH), 115.97 (3’-C_q), 110.26 (7’-CH), 72.44 (1’’-CH_2), 66.40 (1’’’-CH_2), 62.08 (-CH_2), 42.47 (2-CH), 36.47 (3ab-CH_2), 17.97 (2’’’-CH_2), 14.21 (-CH_3), 1.31 (-Si($\underline{C}H_3$)$_3$).

Due to the instability of the substance **17** the rest of the required data had regrettably not been able to be measured in due time before substance decomposition had taken place, therefore for the substance **17** only the NMR spectra are given as proof of its former existence.

7.3.4 Zard chemistry products 14-16 and 19-24

3-(2-Chlorophenyl)-2-(3-formyl-1*H*-indol-2-yl)propenamide (**14**)



1 32 14

Chemical Formula: $C_{18}H_{15}ClN_2O_2$ **Molecular Weight:** 326.7800 g/mol

The general protocol C (see subchapter 7.2) was used to synthesise the indole aldehyde derivative **14**. Indole-3-carboxaldehyde (**1**) (155 mg, 1.07 mmol), xanthate **32** (486 mg, 1.60 mmol), 20 mL 1,2-dichloroethane and dilauroyl peroxide (531 mg, 1.33 mmol) were used. Dilauroyl peroxide was added, as described, in portions of 53.1 mg/h at the beginning of each hour. It was stirred for 10 h. For the column chromatography purification of **14**, a CH_2Cl_2:MeOH (98:2) solvent mixture was used.

Yield and appearance: 113 mg (345 µmol, 32%) as white powdery solid.

HRMS (ESI): m/z = calculated for $[C_{18}H_{16}ClN_2O_2]^+$: 327.08948 (^{35}Cl), 329.08653 (^{37}Cl), 330.08989 (^{38}Cl), found: 327.08953 (^{35}Cl), 329.08670 (^{37}Cl), 330.09012 (^{38}Cl).

Melting area: 189.8 - 198.7°C

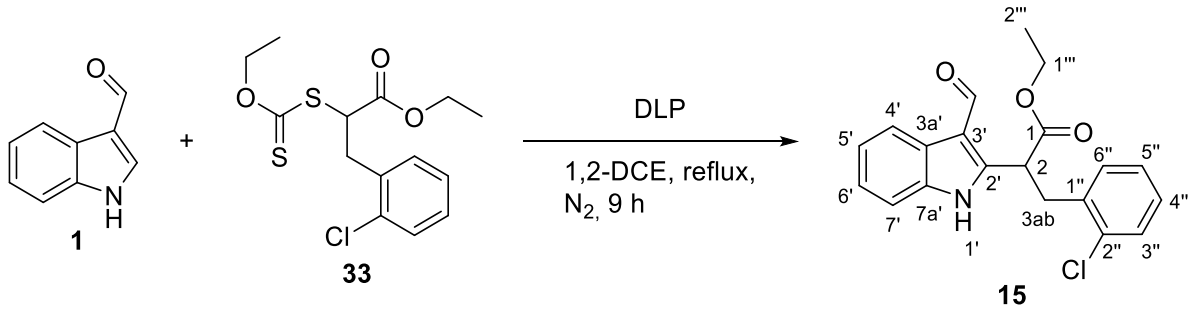
^{1}H NMR (400 MHz, DMSO-d6) δ: 12.04 (s, 1H, 1‘-NH), 9.99 (s, 1H, -CHO), 8.02 (d, J = 7.5 Hz, 1H, 4‘-CH), 7.78 (s, 1H, -NH_2), 7.51 (d, J = 7.9 Hz, 1H, 7‘-CH), 7.41 (d, J = 7.1 Hz, 1H, 6‘‘-CH), 7.29 – 7.09 (m, 6H, 3‘‘-, 4‘‘-, 5‘‘-, 5‘-, 6‘-CH and -NH_2), 4.74 (t, J = 7.7 Hz, 1H, 2-CH), 3.52 (dd, J = 13.6, 7.8 Hz, 1H, 3a- or 3b-C$\underline{H}_2$), 3.28 (dd, J = 13.1, 7.1 Hz, 1H, 3a- or 3b-C$\underline{H}_2$).

^{13}C NMR (101 MHz, DMSO) δ: 184.31 (-CHO), 171.28 (1-C_q), 147.82 (2‘-C_q), 135.95 (7a‘-C_q), 135.83 (1‘‘-C_q), 133.20 (2‘‘-C_q), 131.12 (6‘‘-CH), 129.28 (3‘‘-CH), 128.56 (4‘‘- or 5‘‘- or 5‘- or 6‘-CH), 127.09 (4‘‘- or 5‘‘- or 5‘- or 6‘-CH), 124.71 (3a‘-C_q), 123.05 (4‘‘- or 5‘‘- or 5‘- or 6‘-CH), 121.96 (4‘‘- or 5‘‘- or 5‘- or 6‘-CH), 120.38 (4‘-CH), 113.90 (3‘-C_q), 112.21 (7‘-CH), 42.03 (2-CH), 35.79 (3ab-CH_2).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right]$ = 3372 w, 3188 w, 3099 w, 2979 w, 2937 w, 2818 w, 2752 w, 1682 m, 1672 m, 1635 s, 1582 w, 1551 w, 1528 w, 1495 w, 1476 w, 1455 s, 1414 w, 1390 s, 1358 w, 1316 w,

1272 w, 1258 w, 1228 w, 1183 w, 1156 w, 1141 w, 1109 w, 1053 w, 1038 w, 1024 w, 1011 w, 985 w, 957 w, 938 w, 898 w, 864 w, 854 w, 835 w, 789 w, 750 s, 701 w, 670 m.

Ethyl 3-(2-chlorophenyl)-2-(3-formyl-1*H*-indol-2-yl)propanoate (**15**)



1 **33** **15**

Chemical Formula: $C_{20}H_{18}ClNO_3$ **Molecular Weight:** 355.8180 g/mol

The general protocol C (see subchapter 7.2) was used to synthesise the indole aldehyde derivative **15**. Indole-3-carboxaldehyde (**1**) (200 mg, 1.38 mmol), xanthate **33** (550 mg, 1.65 mmol), 20 mL 1,2-dichloroethane and dilauroyl peroxide (687 mg, 1.72 mmol) were used. Dilauroyl peroxide was added, as described, in portions of 76.3 mg/h at the beginning of each hour. It was stirred for 9 h. For the column chromatography purification of **15**, pure CH_2Cl_2 was used as solvent.

Yield and appearance: 168 mg (471 µmol, 34%) as orange-brown solid.

HRMS (ESI): m/z = calculated for $[C_{20}H_{19}O_3NCl]^+$: 356.10480 (^{35}Cl), 358.10185 (^{37}Cl), 359.10520 (^{38}Cl), found: 356.10504 (^{35}Cl), 358.10259 (^{37}Cl), 359.10579 (^{38}Cl).

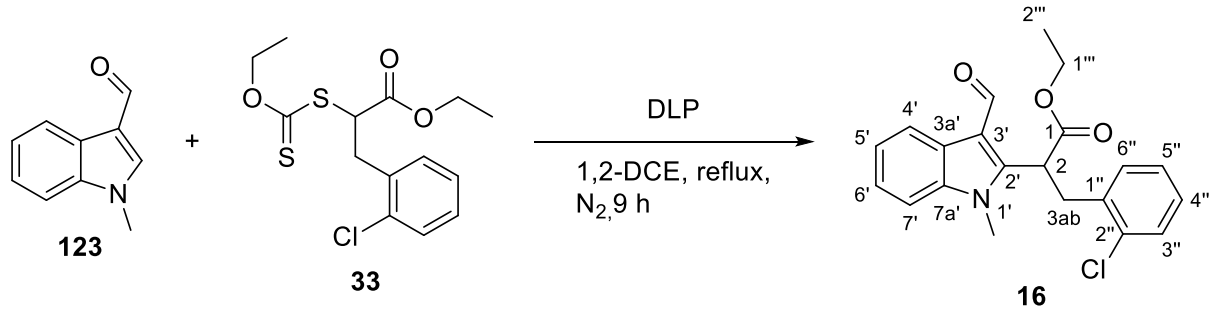
Melting area: 100.4 - 131.5°C

^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.28 (s, 1H, -NH), 9.97 (s, 1H, -CHO), 8.02 (d, *J* = 7.8 Hz, 1H, 4'-CH), 7.47 (dt, *J* = 8.0, 1.0 Hz, 1H, 7'-CH), 7.38 (dd, *J* = 8.1, 1.5 Hz, 1H, 3''-CH), 7.25 – 7.10 (m, 5H, 4''-, 5''-, 6''-, 5'- and 6'-CH), 4.95 (dd, *J* = 9.2, 6.9 Hz, 1H, 2-CH), 4.18 – 4.04 (m, 2H, 1'''-CH_2), 3.67 (dd, *J* = 13.9, 6.9 Hz, 1H, 3a- or 3b-C$\underline{H}_2$), 3.40 (dd, *J* = 13.9, 9.2 Hz, 1H, 3a- or 3b-C$\underline{H}_2$), 1.10 (t, *J* = 7.1 Hz, 3H, 2'''-CH_3).

^{13}C NMR (101 MHz, DMSO) δ: 183.97 (-CHO), 170.28 (1-OC_q), 145.16 (2'-C_q), 135.71 (7a'-C_q), 135.15 (1''-C_q), 133.15 (2''-C_q), 131.08 (6''-CH), 129.29 (3''-CH), 128.68 (4''- or 5''-CH), 127.13 (4''- or 5''-CH), 125.06 (3a'-C_q), 123.26 (5'- or 6'-CH), 122.09 (5'- or 6'-CH), 120.19 (4'-CH), 114.39 (3'-C_q), 112.03 (7'-CH), 61.35 (1'''-CH_2), 42.16 (2-CH), 34.81 (3ab-CH_2), 13.89 (2'''-CH_3).

IR (ATR): $\tilde{\nu}\ \left[\frac{1}{cm}\right]$ = 3179 w, 3070 w, 2981 w, 1727 m, 1626 s, 1580 w, 1551 w, 1530 w, 1493 w, 1475 w, 1453 s, 1382 m, 1341 w, 1310 w, 1291 w, 1272 w, 1239 m, 1183 s, 1156 m, 1124 w, 1098 w, 1053 w, 1035 m, 1020 w, 1003 w, 987 w, 959 w, 950 w, 858 w, 831 w, 806 w, 749 s, 715 m, 675 w.

Ethyl 3-(2-chlorophenyl)-2-(3-formyl-1-methyl-1*H*-indol-2-yl)propanoate (**16**)



Chemical Formula: $C_{21}H_{20}ClNO_3$ **Molecular Weight:** 369.8450 g/mol

The general protocol C (see subchapter 7.2) was used to synthesise the upper 1-methylindole aldehyde derivative **16**. 1-Methylindole-3-carboxaldehyde (**123**) (152 mg, 923 µmol), xanthate educt **33** (365 mg, 1.10 mmol), 20 mL 1,2-dichloroethane and dilauroyl peroxide (455 mg, 1.14 mmol) were used. Dilauroyl peroxide was added as described in portions of 50.6 mg/h at the beginning of each hour. It was stirred for 9 h. Product **16** was purified by column chromatography with an EtOAc:isohexane (2:8) solvent mixture.

Yield and appearance: 72.5 mg (196 µmol, 21%) as brown viscous oil.

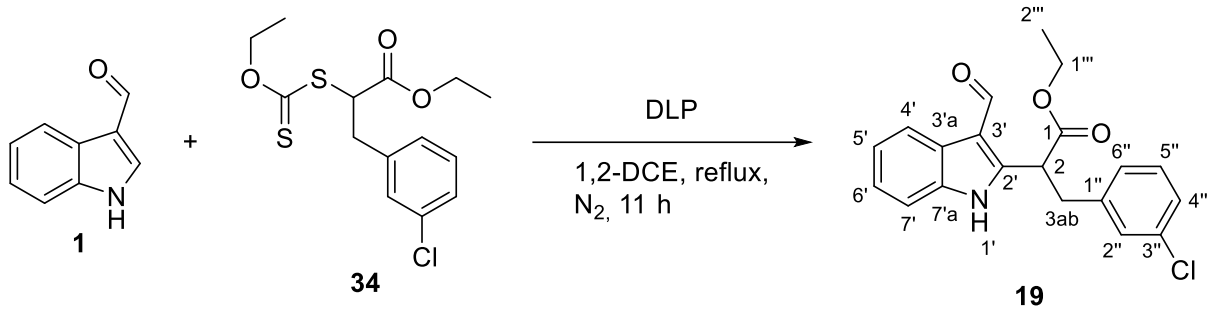
HRMS (ESI): m/z = calculated for $[C_{21}H_{21}ClNO_3]^+$: 370.12045 (^{35}Cl), found: 370.12096 (^{35}Cl).

^{1}H NMR (500 MHz, CD_2Cl_2) δ: 10.09 (s, 1H, -CHO), 8.20 – 8.14 (m, 1H, 4'-CH), 7.35 – 7.25 (m, 3H, 3''-, 6'- and 7'-CH), 7.30 – 7.23 (m, 1H, 5'-CH), 7.14 (ddd, *J* = 7.7, 7.6, 1.8 Hz, 1H, 4''-CH), 7.00 (td, *J* = 7.6, 1.3 Hz, 1H, 5''-CH), 6.92 (dd, *J* = 7.6, 1.8 Hz, 1H, 6''-CH), 4.75 (dd, *J* = 9.7, 5.7 Hz, 1H, 2-CH), 4.19 (qd, *J* = 7.1, 2.3 Hz, 2H, 1'''-CH_2), 3.92 (dd, *J* = 13.7, 5.7 Hz, 1H, 3a- or 3b-C<u>H</u>$_2$), 3.57 (s, 3H, 1'-NCH_3), 3.31 (dd, *J* = 13.7, 9.7 Hz, 1H, 3a- or 3b-C<u>H</u>$_2$), 1.18 (t, *J* = 7.1 Hz, 3H, 2'''-CH_3).

^{13}C NMR (126 MHz, CD_2Cl_2) δ: 184.29 (-CHO), 170.74 (1-C_qO), 145.65 (2'-C_q), 137.43 (7a'-C_q), 135.98 (1''-C_q), 134.27 (2''-C_q), 131.90 (6''-CH), 129.87 (3''-CH), 129.00 (4''-CH), 127.34 (5''-CH), 126.23 (3a'-C_q), 123.82 (6'-CH), 123.24 (5'-CH), 120.88 (4'-CH), 115.15 (3'-C_q), 110.30 (7'-CH), 62.38 (1'''-CH_2), 42.68 (2-CH), 35.89 (3ab-CH_2), 30.81 (1'-NCH_3), 14.27 (2'''-CH_3).

IR (ATR): $\tilde{\nu}\ \left[\frac{1}{cm}\right]$ = 3057 w, 2980 w, 2931 w, 2857 w, 1732 m, 1684 w, 1651 m, 1613 w, 1580 w, 1559 w, 1521 w, 1470 m, 1443 m, 1395 m, 1327 w, 1286 w, 1251 m, 1212 m, 1159 m, 1127 m, 1102 m, 1051 m, 1038 m, 1016 m, 940 w, 907 w, 862 w, 840 w, 814 w, 748 s, 696 m, 684 m, 667 m, 655 w.

Ethyl 3-(3-chlorophenyl)-2-(3-formyl-1*H*-indol-2-yl)propanoate (**19**)



1 **34** **19**

Chemical Formula: $C_{20}H_{18}ClNO_3$ **Molecular Weight:** 355.8180 g/mol

The general protocol C (see subchapter 7.2) was used to synthesise the indole aldehyde derivative **19**. Indole-3-carboxaldehyde (**1**) (200 mg, 1.35 mmol), xanthate **34** (1.05 g, 3.16 mmol), 20 mL 1,2-dichloroethane and dilauroyl peroxide (1.22 g, 3.06 mmol) were used. Dilauroyl peroxide was added as described in portions of 111 mg/h at the beginning of each hour. It was stirred for 11 h. Product **19** was purified by column chromatography with an EtOAc:isohexane (1:9-2:8) solvent mixture.

Yield and appearance: 209 mg (587 µmol, 43%) as red-brown viscous oil.

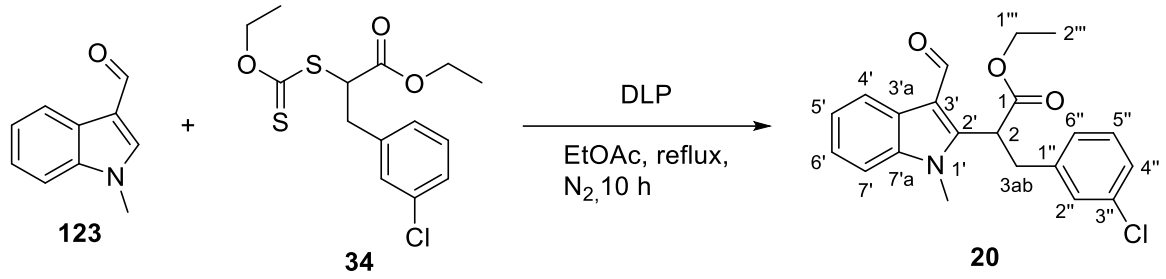
HRMS (ESI): m/z = calculated for $[C_{20}H_{17}ClNO_3]^-$: 354.09025 (^{35}Cl), 356.08730 (^{37}Cl), found: 354.0954 (^{35}Cl), 356.08779 (^{37}Cl).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 10.18 (s, 1H, -CHO), 9.75 (s, 1H, 1'-NH), 8.18 - 8.10 (m, 1H, 4'-CH), 7.46 – 7.38 (m, 1H, 7'-CH), 7.34 – 7.27 (m, 2H, 5'- and 6'-CH), 7.23 (ddd, *J* = 8.0, 1.9, 1.4 Hz, 1H, 4''-CH), 7.19 (dd, *J* = 8.0, 7.3 Hz, 1H, 5''-CH), 7.16 (dd, *J* = 1.9, 1.6 Hz, 1H, 2''-CH), 6.99 (ddd, *J* = 7.3, 1.6, 1.4 Hz, 1H, 6''-CH), 4.86 (t, *J* = 7.5 Hz, 1H, 2-CH), 4.14 (ddq, *J* = 39.9, 10.8, 7.2 Hz, 2H, 1'''-CH_2), 3.25 (d, *J* = 7.5 Hz, 2H, 3a- and 3b-C$\underline{H}_2$), 1.15 (t, *J* = 7.2 Hz, 3H, 2'''-CH_3).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 184.25 (-CHO), 173.08 (1-C_qO), 143.37 (2'-C_q), 138.97 (1''-C_q), 135.04 (7a'-C_q), 134.49 (3''-C_q), 130.00 (5''-CH), 129.20 (2''-CH), 127.61 (4''-CH), 127.32 (6''-CH), 126.41 (3a'-C_q), 124.02 (6'-CH), 123.00 (5'-CH), 120.02 (4'-CH), 114.11 (3'-Cq), 111.74 (7'-CH), 62.15 (1'''-CH_2), 44.75 (2-CH), 41.36 (3ab-CH_2), 14.07 (2'''-CH_3).

IR (ATR): $\tilde{\nu}\ \left[\frac{1}{cm}\right]$ = 3248 w, 3112 w, 3061 w, 2981 w, 2929 w, 2855 w, 2815 w, 2747 w, 2365 w, 2178 w, 2158 w, 2032 w, 2017 w, 1982 w, 1941 w, 1870 w, 1726 m, 1632 m, 1599 mw, 1583 mw, 1533 w, 1493 w, 1455 m, 1389 m, 1371 mw, 1339 mw, 1285 w, 1269 w, 1238 m, 1189 m, 1155 m, 1113 w, 1095 mw, 1079 mw, 1026 m, 1000 w, 961 w, 935 w, 855 w, 820 w, 780 m, 744 ms, 692 m, 681 m.

Ethyl 3-(3-chlorophenyl)-2-(3-formyl-1-methyl-1*H*-indol-2-yl)propanoate (**20**)



Chemical Formula: $C_{21}H_{20}ClNO_3$ **Molecular Weight:** 369.8450 g/mol

The general protocol C (see subchapter 7.2) was used to synthesise the 1-methylindole aldehyde derivative **20**. 1-Methylindole-3-carboxaldehyde (**123**) (226 mg, 1.38 mmol), xanthate **34** (1.15 g, 3.46 mmol), 20 mL EtOAc and dilauroyl peroxide (1.10 g, 2.75 mmol) were used. Dilauroyl peroxide was added as described in portions of 110 mg/h at the beginning of each hour. It was stirred for 10 h. The crude product **20** was purified by column chromatography with an EtOAc:isohexane (1:9) solvent mixture.

Yield and appearance: 125 mg (338 µmol, 25%) as pale orange solid.

HRMS (ESI): m/z = calculated for $[C_{21}H_{21}ClNO_3]^+$: 370.12045 (^{35}Cl), 372.11750 (^{37}Cl), found: 370.12035 (^{35}Cl), 372.11809 (^{37}Cl).

Melting area: 99.0 - 104.2°C

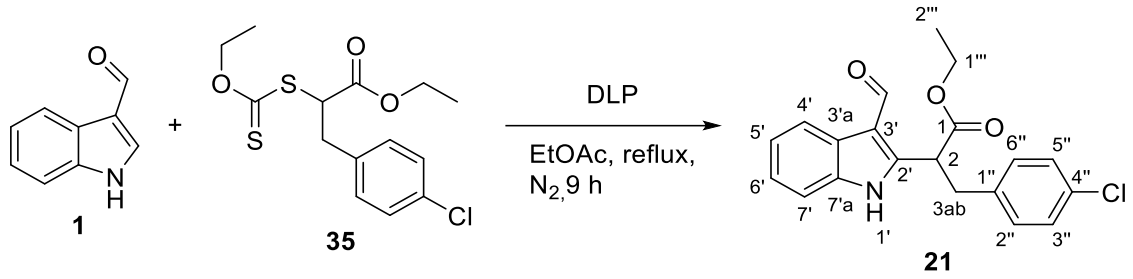
^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.23 (s, 1H, -CHO), 8.30 – 8.14 (m, 1H, 4'-CH), 7.36 – 7.28 (m, 3H, 5'-, 6'- and 7'-CH), 7.15 (ddd, *J* = 8.0, 2.1, 1.2 Hz, 1H, 4''-CH), 7.11 – 7.04 (m, 2H, 2''- and 5''-CH), 6.82 (dt, *J* = 7.6, 1.2 Hz, 1H, 6''-CH), 4.68 (t, *J* = 8.8, 6.0 Hz, 1H, 2-CH), 4.20 (qd, *J* = 7.1, 2.1 Hz, 2H, 1'''-CH_2), 3.70 (dd, *J* = 13.8, 6.0 Hz, 1H, 3a- or 3b-C$\underline{H}_2$), 3.48 (s, 3H, 1'-NCH_3), 3.20 (dd, *J* = 13.8, 8.8 Hz, 1H, 3a- or 3b-C$\underline{H}_2$), 1.20 (t, *J* = 7.1 Hz, 3H, 2'''-CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 184.37 (-CHO), 170.51 (1-C_qO), 144.84 (2'-C_q), 140.23 (1''-C_q), 137.06 (7a'-C_q), 134.46 (3''-C_q), 129.97 (2''- or 5''-CH), 129.20 (4''-CH), 127.29 (5'-, 6'-, 7'-, or 6''-CH), 127.26 (5'-, 6'-, 7'-, or 6''-CH), 126.39 (3a'-C_q), 123.74 (6'-CH), 123.23 (2''-CH),

120.37 (4'-CH), 114.45 (3'-C_q), 110.00 (5'-, 6'-, or 7'-CH), 62.16 (1'''-CH_2), 44.74 (2-CH), 37.60 (3ab-CH_2), 30.61 (1'-NCH_3), 14.25 (2'''-CH_3).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right]$ = 3183 w, 2917 w, 2164 w, 2083 w, 2000 w, 1735 m, 1630 m, 1599 w, 1585 w, 1497 w, 1455 m, 1441 m, 1378 mw, 1358 w, 1314 mw, 1236 m, 1215 w, 1158 m, 1141 m, 1113 w, 1096 w, 1078 w, 1020 m, 986 w, 967 w, 934 w, 889 w, 875 w, 860 w, 824 w, 772 m, 751 ms, 728 m, 693 m, 678 m, 669 mw.

Ethyl 3-(4-chlorophenyl)-2-(3-formyl-1*H*-indol-2-yl)propanoate (**21**)



Chemical Formula: $C_{20}H_{18}ClNO_3$ **Molecular Weight:** 355.8180 g/mol

The general protocol C (see subchapter 7.2) was used to synthesise the upper indole aldehyde derivative **21**. Indole-3-carboxaldehyde (**1**) (266 mg, 1.83 mmol), xanthate **35** (661 mg, 2.01 mmol), 20 mL ethyl acetate and dilauroyl peroxide (875 mg, 2.20 mmol) were used. Dilauroyl peroxide was added as described in portions of 97.2 mg/h at the beginning of each hour. It was stirred for 9 h. Product **21** was purified by column chromatography with an EtOAc:isohexane (2:8) solvent mixture.

Yield and appearance: 154 mg (432 µmol, 24%) as brown solid.

HRMS (ESI): m/z = calculated for $[C_{20}H_{19}ClNO_3]^+$: 356.10480 (^{35}Cl), 358.10185 (^{37}Cl), found: 356.10489 (^{35}Cl), 358.10219 (^{37}Cl).

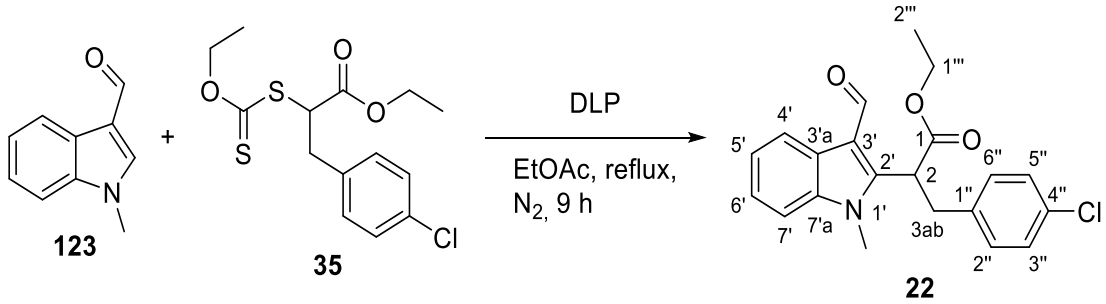
Melting area: 126.4 - 130.3°C

^{1}H NMR (500 MHz, CD_2Cl_2) δ: 10.09 (s, 1H, -CHO), 9.71 (s, 1H, 1'-NH), 8.16 – 8.09 (m, 1H, 4'-CH), 7.48 – 7.41 (m, 1H, 7'-CH), 7.29 (ddd, *J* = 7.6, 7.2, 1.6 Hz, 1H, 6'-CH), 7.27 (ddd, *J* = 7.5, 7.2, 1.5 Hz, 1H, 5'-CH), 7.23 (ddd, *J* = 8.4, 2.5, 2.0 Hz, 2H, 3''- and 5''-CH), 7.05 (ddd, *J* = 8.4, 2.5, 2.0 Hz, 2H, 2''- and 6''-CH), 4.80 (dd, *J* = 8.2, 6.9 Hz, 1H, 2-CH), 4.21 – 4.09 (m, 2H, 1'''-CH_2), 3.33 (dd, *J* = 13.5, 8.2 Hz, 1H, 3a- or 3b-C<u>H</u>$_2$), 3.25 (dd, *J* = 13.5, 6.9 Hz, 1H, 3a- or 3b-C<u>H</u>$_2$), 1.17 (t, *J* = 7.2 Hz, 3H, 2'''-CH_3).

^{13}C NMR (126 MHz, CD_2Cl_2) δ: 184.18 (-CHO), 172.87 (1-C_qO), 144.00 (2'-C_q), 136.05 (1''-C_q), 135.48 (7a'-C_q), 133.31 (4''-C_q), 130.81 (2''- and 6''-CH), 128.99 (3''- and 5''-CH), 126.37 (3a'-C_q), 124.15 (6'-CH), 123.07 (5'-CH), 120.47 (4'-CH), 114.62 (3'-C_q), 111.98 (7'-CH), 62.44 (1'''-CH_2), 44.95 (2-CH), 40.97 (3ab-CH_2), 14.17 (2'''-CH_3).

IR (ATR): $\tilde{\nu}\ \left[\frac{1}{cm}\right] =$ 3178 w, 2978 w, 2807 w, 2739 w, 2393 w, 2303 w, 2013 w, 1993 w, 1730 s, 1631 s, 1581 m, 1491 m, 1455 s, 1410 w, 1381 s, 1367 m, 1341 m, 1327 w, 1311 m, 1301 m, 1281 w, 1268 w, 1236 s, 1189 s, 1156 s, 1114 w, 1090 m, 1026 m, 1015 m, 969 w, 934 w, 875 w, 860 w, 847 w, 830 w, 806 m, 787 m, 751 s, 718 m, 706 m, 661 m.

Ethyl 3-(4-chlorophenyl)-2-(3-formyl-1-methyl-1*H*-indol-2-yl)propanoate (**22**)



Chemical Formula: $C_{21}H_{20}ClNO_3$ **Molecular Weight:** 369.8450 g/mol

The general protocol C (see subchapter 7.2) was used to synthesise the 1-methylindole aldehyde derivative **22**. 1-Methylindole-3-carboxaldehyde (**123**) (226 mg, 1.38 mmol), xanthate **35** (907 mg, 2.76 mmol), 20 mL EtOAc and dilauroyl peroxide (1.38 g, 3.45 mmol) were used. Dilauroyl peroxide was added as described in portions of 153 mg/h at the beginning of each hour. It was stirred for 9 h. The crude product **22** was purified by column chromatography with an EtOAc:isohexane (1.5:8.5) solvent mixture.

Yield and appearance: 172 mg (461 µmol, 33%) as brown viscous oil.

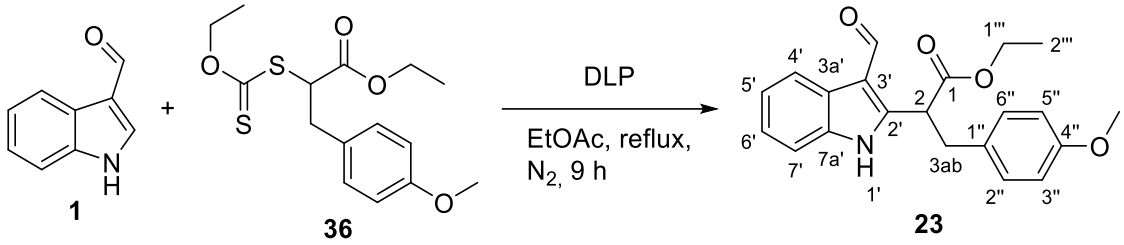
HRMS (ESI): m/z = calculated for [M]: 370.12045 (^{35}Cl), 372.11750 (^{37}Cl), found: 370.12071 (^{35}Cl), 372.11809 (^{37}Cl).

^{1}H NMR (400 MHz, CD_2Cl_2) δ: 10.16 (s, 1H, -CHO), 8.21 – 8.11 (m, 1H, 4'-CH), 7.36 – 7.25 (m, 3H, 5'-, 6'- and 7'-CH), 7.16 (ddd, *J* = 8.4, 2.6, 2.0 Hz, 2H, 3''- and 5''-CH), 6.97 (ddd, *J* = 8.4, 2.6, 2.0 Hz, 2H, 2''- and 6''-CH), 4.67 (dd, *J* = 9.3, 5.9 Hz, 1H, 2-CH), 4.17 (qd, *J* = 7.1, 3.1 Hz, 2H, 1'''-CH_2), 3.69 (dd, *J* = 13.9, 5.9 Hz, 1H, 3a- or 3b-CH), 3.50 (s, 3H, 1'-NCH_3), 3.21 (dd, *J* = 13.9, 9.3 Hz, 1H, 3a- or 3b-CH), 1.18 (t, *J* = 7.1 Hz, 3H, 2'''-CH_3).

^{13}C NMR (101 MHz, CD_2Cl_2) δ: 184.44 (-CHO), 170.77 (1-C_qO), 145.37 (2'-C_q), 137.39 (1''- or 7a'-C_q), 137.18 (1''- or 7a'-C_q), 132.97 (4''-C_q), 130.79 (2''- and 6''-CH), 128.96 (3''- and 5''-CH), 126.44 (3a'-Cq), 123.86 (5'-, 6'- or 7'-CH), 123.30 (5'-, 6'- or 7'-CH), 120.50 (4'-CH), 114.72 (3'-C_q), 110.41 (5'-, 6'- or 7'-CH), 62.37 (1'''-CH_2), 44.95 (2-CH), 37.40 (3ab-CH_2), 30.94 (1'-NCH_3), 14.29 (2'''-CH_3).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right]$ = 2977 w, 2925 w, 2853 w, 1728 m, 1649 w, 1580 w, 1520 mw, 1491 m, 1468 m, 1394 mw, 1366 mw, 1328 w, 1203 m, 1156 m, 1128 mw, 1091 m, 1076 m, 1035 m, 1014 m, 903 w, 832 m, 806 m, 770 w, 745 m, 674 w.

Ethyl 2-(3-formyl-1*H*-indol-2-yl)-3-(4-methoxyphenyl)propanoate (**23**)



1 **36** **23**

Chemical Formula: $C_{21}H_{21}NO_4$ **Molecular Weight:** 351.4020 g/mol

The general protocol C (see subchapter 7.2) was used to synthesise the upper indole aldehyde derivative **23**. Indole-3-carboxaldehyde (**1**) (200 mg, 1.38 mmol), xanthate **36** (905 mg, 2.76 mmol), 20 mL ethyl acetate and dilauroyl peroxide (1.37 g, 3.44 mmol) were used. Dilauroyl peroxide was added, as described, in portions of 153 mg/h at the beginning of each hour. It was stirred for 9 h. Product **23** was purified by column chromatography with an EtOAc:isohexane (3:7) solvent mixture.

Yield and appearance: 239 mg (679 µmol, 49 %) as brown-orange solid.

HRMS (ESI): m/z = calculated for $[C_{21}H_{22}NO_4]^+$: 352.15433, found: 352.15432.

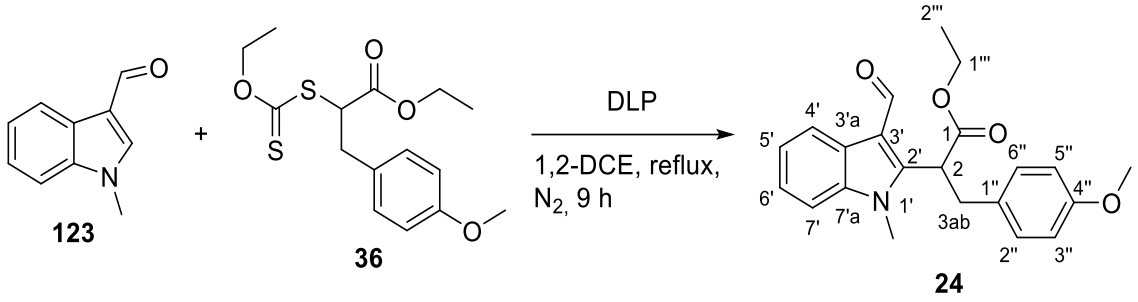
Melting area: 118.3 - 122.3°C

^{1}H NMR (400 MHz, CD_2Cl_2) δ: 10.04 (s, 1H, -CHO), 9.74 (s, 1H, 1'-NH), 8.2 – 8.10 (m, 1H, 4'-CH), 7.48 – 7.40 (m, 1H, 7'-CH), 7.33 – 7.21 (m, 2H, 5'- and 6'-CH), 6.99 (ddd, *J* = 8.7, 2.8, 2.2 Hz, 2H, 2''- and 6''-CH), 6.77 (ddd, *J* = 8.7, 2.8, 2.2 Hz, 2H, 3''- and 5''-CH), 4.75 (dd, *J* = 7.9, 7.0 Hz, 1H, 2-CH), 4.25 – 4.05 (m, 2H, 1'''-CH_2), 3.75 (s, 3H, -OCH_3), 3.32 (dd, *J* = 13.6, 7.9 Hz, 1H, 3a- or 3b-C$\underline{H}_2$), 3.21 (dd, *J* = 13.6, 7.0 Hz, 1H, 3a- or 3b-C$\underline{H}_2$), 1.18 (t, *J* = 7.1 Hz, 3H, 2'''-CH_3).

^{13}C NMR (101 MHz, CD_2Cl_2) δ: 184.20 (-CHO), 173.08 (1-C_qO), 159.24 (4''-C_q), 144.85 (2'-C_q), 135.55 (7a'-C_q), 130.37 (2''- and 6''-CH), 129.30 (1''-C_q), 126.24 (3a'-C_q), 124.08 (6'-CH), 123.01 (5'-CH), 120.76 (4'-CH), 114.76 (3'-C_q), 114.23 (3''- and 5''-CH), 111.92 (7'-CH), 62.33 (1'''-CH_2), 55.56 (-OCH_3), 45.29 (2-CH), 40.98 (3ab-CH_2), 14.20 (2'''-CH_3).

IR (ATR): $\tilde{\nu}\ \left[\frac{1}{cm}\right]$ = 3179 w, 2976 w, 2927 w, 2166 w, 2085 w, 2046 w, 2035 w, 2015 w, 1998 w, 1982 w, 1960 w, 1951 w, 1730 m, 1631 m, 1581 mw, 1512 m, 1454 m, 1378 m, 1341 w, 1297 w, 1234 m, 1188 m, 1178 m, 1155 m, 1107 mw, 1027 m, 969 w, 874 w, 861 w, 833 w, 818 w, 811 w, 797 w, 761 m, 746 m, 693 mw, 667 w, 656 mw.

Ethyl 2-(3-formyl-1-methyl-1*H*-indol-2-yl)-3-(4-methoxyphenyl)propanoate (**24**)



Chemical Formula: $C_{22}H_{23}NO_4$ **Molecular Weight:** 365.4290 g/mol

The general synthesis protocol C (see subchapter 7.2) was used to synthesise the 1-methylindole aldehyde derivative **24**. 1-Methylindole-3-carboxaldehyde (**123**) (406 mg, 2.47 mmol), xanthate educt **36** (934 mg, 2.84 mmol), 30 mL 1,2-dichloroethane and dilauroyl peroxide (1.18 g, 2.97 mmol) were used. Dilauroyl peroxide was added as described in portions of 131 mg/h at the beginning of each hour. It was stirred for 9 h. Column chromatography with an EtOAc:isohexane (2:8) solvent mixture yielded pure product **24**.

Yield and appearance: 137 mg (376 µmol, 15%) as yellow solid.

HRMS (ESI): m/z = calculated for $[C_{22}H_{24}NO_4]^+$: 366.16998, found: 366.17043.

Melting area: 83.5 - 86.3°C

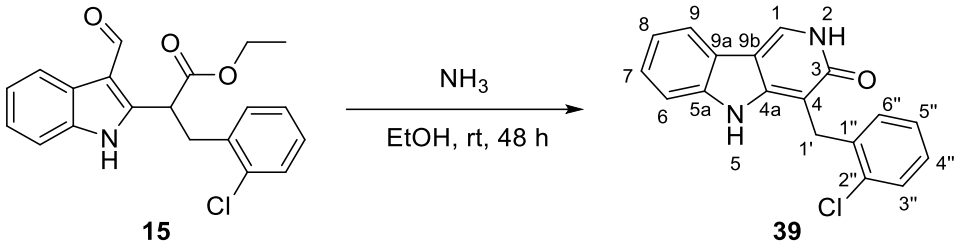
^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.20 (s, 1H, -CHO), 8.30 – 8.18 (m, 1H, 4'-CH), 7.34 – 7.26 (m, 3H, 5'-, 6'- and 7'-CH), 6.88 (dt, *J* = 8.7, 2.5 Hz, 2H, 2''- and 6''-CH), 6.69 (dt, *J* = 8.7, 2.5 Hz, 2H, 3''- and 5''-CH), 4.58 (dd, *J* = 9.2, 5.6 Hz, 1H, 2-CH), 4.19 (qd, *J* = 7.1, 1.2 Hz, 2H, 1'''-CH_2), 3.72 (s, 3H, -OCH_3), 3.66 (dd, *J* = 13.8, 5.6 Hz, 1H, 3a- or 3b-C<u>H</u>$_2$), 3.43 (s, 3H, 1'-NCH_3), 3.18 (dd, *J* = 13.8, 9.2 Hz, 1H, 3a- or 3b-C<u>H</u>$_2$), 1.20 (t, *J* = 7.1 Hz, 3H, 2'''-CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 184.47 (-CHO), 170.86 (1-C_qO), 158.63 (4''-C_q), 145.78 (2'-C_q), 137.04 (7a'-C_q), 130.05 (1''-C_q, 2''- and 6''-CH), 126.30 (3a'-C_q), 123.57 (5'-, 6'- or 7'-CH), 123.12 (5'-, 6'- or 7'-CH), 120.68 (4'-CH), 114.52 (3'-C_q), 114.11 (3''- and 5''-CH), 109.93 (5'-, 6'- or 7'-CH), 62.00 (1'''-CH_2), 55.34 (-OCH_3), 45.32 (2-CH), 37.33 (3ab-CH_2), 30.55 (1'-NCH_3), 14.26 (2'''-CH_3).

IR (ATR): $\tilde{\nu}\ \left[\frac{1}{cm}\right]$ = 3065 w, 2973 w, 2953 w, 2930 w, 2834 w, 2755 w, 1881 w, 1732 ms, 1644 s, 1609 m, 1579 w, 1530 w, 1512 m, 1470 m, 1440 m, 1420 w, 1414 w, 1398 m, 1375 w, 1366 w, 1325 w, 1314 w, 1301 w, 1265 m, 1242 m, 1214 m, 1174 m, 1161 m, 1126 mw, 1105 m, 1054 m, 1028 m, 1015 m, 943 w, 901 w, 872 w, 861 mw, 852 mw, 819 m, 798 w, 778 w, 763 w, 753 s, 747 s, 712 w, 684 w, 667 w.

7.3.5 3-Oxo-γ-carbolines 39 and 41-55

4-(2-Chlorobenzyl)-2,5-dihydro-3*H*-pyrido[4,3-*b*]indol-3-one (**39**)



15 **39**

Chemical Formula: $C_{18}H_{13}ClN_2O$ **Molecular Weight:** 308.7650 g/mol

3-Oxo-γ-carboline **39** was synthesised according to the general synthesis protocol D2 (see subchapter 7.2). The indol-3-carboxaldehyde derivative **15** (149 mg, 419 µmol), 10 mL of EtOH and a 25% watery NH_3-solution (9.00 mL, 8.10 g, 57.8 mmol) were used. It was stirred for 48 h. Product **39** could be successfully purified by column chromatography with pure EtOAc.

Yield and appearance: 49.4 mg (160 µmol, 38%) as white solid.

HRMS (ESI): m/z = calculated for $[C_{18}H_{14}ClN_2O]^+$: 309.07892 (^{35}Cl), 311.07597 (^{37}Cl), 312.07932 (^{38}Cl), found: 309.07889 (^{35}Cl), 311.07604 (^{37}Cl), 312.07955 (^{38}Cl).

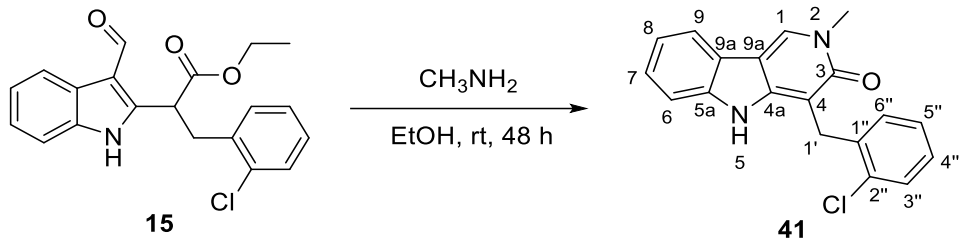
Melting area: 279.5 - 279.9°C

^{1}H NMR (500 MHz, DMSO-d_6) δ: 11.67 (s, 1H, 2-NH), 10.87 (s, 1H, 5-NH), 8.28 (s, 1H, 1-CH), 7.90 (dd, *J* = 7.7, 1.2 Hz, 1H, 9-CH), 7.47 (dd, *J* = 7.9, 1.5 Hz, 1H, 3''-CH), 7.25 (ddd, *J* = 7.8, 7.5, 1.2 Hz, 1H, 7-CH), 7.20 (ddd, *J* = 7.9, 7.7, 1.8 Hz, 1H, 4''-CH), 7.18 (dd, *J* = 7.8, 1.0-Hz, 1H, 6-CH), 7.13 (td, *J* = 7.7, 1.5 Hz, 1H, 5''-CH), 7.06 (td, *J* = 7.7, 7.5, 1.0 Hz, 1H, 8-CH), 6.80 (dd, *J* = 7.7, 1.8 Hz, 1H, 6''-CH), 3.98 (s, 2H, 1'-CH_2).

^{13}C NMR (126 MHz, DMSO) δ: 161.93 (3-C_qO), 149.87 (4a-C_q), 142.46 (5a-C_q), 137.24 (1''-C_q), 133.64 (2''-C_q), 128.91 (3''-CH), 128.32 (6''-CH), 127.41 (4''-CH), 127.32 (1-CH), 126.96 (5''-CH), 126.01 (7-CH), 122.45 (9a-C_q), 119.88 (8- or 9-CH), 119.83 (8- or 9-CH), 110.32 (6-CH), 109.73 (9b-C_q), 99.73 (4-C_q), 28.11 (1'-CH_2).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right]$ = 3060 w, 2926 w, 2807 w, 2325 w, 2206, 2166 w, 2161 w, 2062 w, 2046 w, 2015 w, 1982 w, 1967 w, 1941 w, 1658 mw, 1613 m, 1589 w, 1572 w, 1554 w, 1545 w, 1466 m, 1441 w, 1417 mw, 1347 w, 1321 w, 1278 w, 1270 w, 1235 m, 1201 w, 1157 w, 1124 w, 1104 w, 1047 w, 1038 w, 1013 w, 967 w, 867 w, 847 w, 810 w, 779 w, 770 w, 742 s, 715 w, 695 w, 666 w.

4-(2-Chlorobenzyl)-2-methyl-2,5-dihydro-3*H*-pyrido[4,3-*b*]indol-3-one (**41**)



Chemical Formula: $C_{19}H_{15}ClN_2O$ **Molecular Weight:** 322.7920 g/mol

For synthesising the 3-oxo-γ-carboline **41**, according to the general protocol D1 (see subchapter 7.2), the indol-3-carboxaldehyde derivative **15** (200 mg, 562 µmol), 10 mL of EtOH, and a 33% CH_3NH_2 in EtOH (15.0 mL, 10.5 g, 112 mmol) solution was used. It was stirred for 48 h. The supernatant was discarded and the precipitate was washed with EtOH and CH_2Cl_2, then dried in high vacuum. No further purification steps were necessary.

Yield and appearance: 123 mg (380 µmol, 68%) as white needles.

HRMS (ESI): m/z = calculated for $[C_{19}H_{16}ClN_2O]^+$: 323.09457 (^{35}Cl), 325.09162 (^{37}Cl), found: 323.09459 (^{35}Cl), 325.09206 (^{37}Cl).

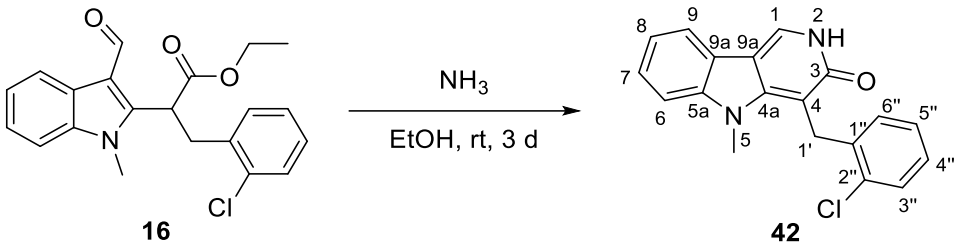
Melting area: 235.8 - 236.1 °C

^{1}H NMR (400 MHz, DMSO) δ: 10.90 (s, 1H, 5-NH), 8.65 (s, 1H, 1-CH), 7.82 (dd, *J* = 7.6, 1.0 Hz, 1H, 9-CH), 7.46 (dd, *J* = 7.7, 1.3 Hz, 1H, 3''-CH), 7.26 (ddd, *J* = 7.4, 7.2, 1.0 Hz, 1H, 7-CH), 7.20 (ddd, *J* = 7.7, 7.3, 1.7 Hz, 1H, 4''-CH), 7.19 (dd, *J* = 7.4, 1.1 Hz, 1H, 6-CH), 7.13 (ddd, *J* = 7.6, 7.3, 1.3 Hz, 1H, 5''-CH), 7.09 (ddd, *J* = 7.6, 7.2, 1.1 Hz, 1H, 8-CH), 6.79 (dd, *J* = 7.6, 1.7 Hz, 1H, 6''-CH), 4.02 (s, 2H, 1'-CH_2), 3.59 (s, 3H, 2-NCH_3).

^{13}C NMR (101 MHz, DMSO) δ: 161.25 (3-C_qO), 149.04 (4a-C_q), 142.31 (5a-C_q), 137.19 (1''-C_q), 133.59 (2''-C_q), 131.40 (1-CH), 128.89 (3''-CH), 128.45 (6''-CH), 127.40 (4''-CH), 126.92 (5''-CH), 126.09 (7-CH), 122.19 (9a-C_q), 119.96 (8-CH), 119.45 (9-CH), 110.40 (6-CH), 109.07 (9b-C_q), 99.29 (4-C_q), 37.84 (2-NCH_3), 28.68 (1'-CH_2).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right] =$ 3068 w, 2157 w, 2168 w, 1668 w, 1616 w, 1588 w, 1572 w, 1556 w, 1479 w, 1442 w, 1399 w, 1339 w, 1316 w, 1293 w, 1261 w, 1233 w, 1166 w, 1092 w, 1048 w, 1037 w, 1014 w, 922 w, 859 w, 844 w, 832 w, 810 w, 775 w, 754 w, 742 mw, 707 w, 685 mw, 661 w.

4-(2-Chlorobenzyl)-5-methyl-2,5-dihydro-3*H*-pyrido[4,3-*b*]indol-3-one (**42**)



Chemical Formula: $C_{19}H_{15}ClN_2O$ **Molecular Weight:** 322.7920 g/mol

Synthesis protocol D2 (subchapter 7.2) was applied to generate **42**. Educt **16** (123 mg, 333 µmol), a 25% watery NH_3-solution (3.30 mL, 2.97 g, 21.2 mmol) and 2 mL of iPrOH were used. The reaction solution was stirred for 3 d. The pure product **42** could be obtained through recrystallisation from pure CH_2Cl_2.

Yield and appearance: 48.0 mg (149 µmol, 45%) as yellowish white powder.

HRMS (ESI): m/z = calculated for $[C_{19}H_{16}ClN_2O]^+$: 323.09457 (^{35}Cl), 325.09162 (^{37}Cl), found: 323.09454 (^{35}Cl), 325.09165 (^{37}Cl).

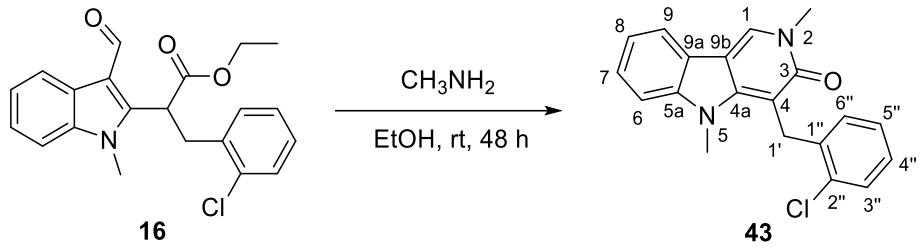
Melting area: 292.5 - 293.1 °C

^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.85 (s, 1H, 2-NH), 8.35 (s, 1H, 1-CH), 7.93 (dd, *J* = 7.5, 1.0 Hz, 1H, 9-CH), 7.50 (dd, *J* = 7.8, 1.5 Hz, 1H, 3''-CH), 7.32 (ddd, *J* = 8.2, 7.2, 1.0 Hz, 1H, 7-CH), 7.26 (dd, *J* = 8.2, 1.0 Hz, 1H, 6-CH), 7.23 (ddd, *J* = 7.8, 7.5, 1.6 Hz, 1H, 4''-CH), 7.18 (ddd, *J* = 7.5, 7.4, 1.5 Hz, 1H, 5''-CH), 7.12 (ddd, *J* = 7.5, 7.2, 1.0 Hz, 1H, 8-CH), 6.84 (dd, *J* = 7.4, 1.6 Hz, 1H, 6''-CH), 4.29 (s, 2H, 1'-CH_2), 3.50 (s, 3H, 5-NCH_3).

^{13}C NMR (101 MHz, DMSO) δ: 162.78 (3-C_qO), 149.11 (4a-C_q), 143.72 (5a-C_q), 138.82 (1''-C_q), 132.66 (2''-C_q), 129.08 (3''-CH), 128.94 (6''-CH), 127.64 (4''- or 5'' CH), 127.34 (4''- or 5''-CH), 126.98 (1-CH), 126.00 (7-CH), 121.86 (9a-C_q), 120.40 (8-CH), 119.27 (9-CH), 109.84 (9b-C_q), 108.79 (6-CH), 100.28 (4-C_q), 30.54 (5-NCH_3), 27.63 (1'-CH_2).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right]$ = 2917 w, 2691 w, 2006 w, 1926 w, 1657 w, 1620 m, 1608 m, 1564 w, 1476 m, 1468 m, 1443 m, 1421 mw, 1400 mw, 1370 w, 1346 w, 1312 w, 1277 mw, 1242 w, 1185 w, 1160 w, 1137 w, 1113 w, 1060 w, 1048 w, 1037 w, 1020 w, 993 w, 933 w, 886 w, 870 mw, 852 w, 810 w, 799 w, 774 w, 760 m, 742 ms, 710 w, 688 mw, 667 w.

4-(2-Chlorobenzyl)-2,5-dimethyl-2,5-dihydro-3*H*-pyrido[4,3-*b*]indol-3-one (**43**)



16 **43**

Chemical Formula: $C_{20}H_{17}ClN_2O$ **Molecular Weight:** 336.81900 g/mol

The 3-oxo-γ-carboline **43** was prepared according to the general synthesis protocol D1 (see subchapter 7.2). As educt, 1-methylindole-3-carboxaldehyde derivative **16** (50.0 mg, 135 µmol), 2 mL EtOH and an ethanolic 33% CH_3NH_2 solution (1.20 mL, 840 mg, 27.0 mmol) were used. It was stirred for 48 h. The product **43** was purified by column chromatography with pure EtOAc.

Yield and appearance: 20.0 mg (59.4 µmol, 44%) as pale orange-brown solid.

HRMS (ESI): m/z = calculated for $[C_{20}H_{18}ClN_2O]^+$: 337.11022 (^{35}Cl), 339.10727 (^{37}Cl), 340.11062 (^{38}Cl), found: 337.11019 (^{35}Cl), 339.10773 (^{37}Cl), 340.11109 (^{38}Cl).

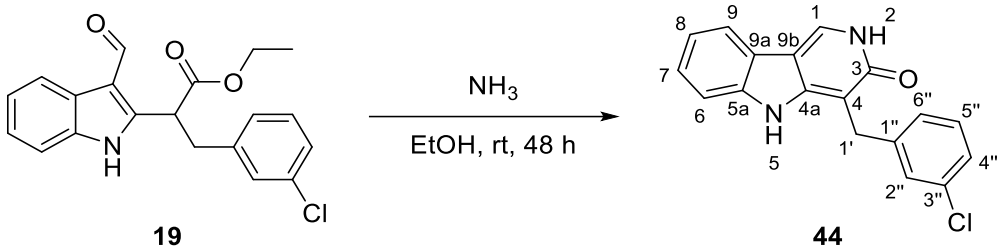
Melting area: 245.5 - 246.7°C

^{1}H NMR (400 MHz, Methylene Chloride-*d2*) δ: 8.08 (s, 1H, 1-CH), 7.73 (ddd, *J* = 7.6, 1.2, 0.6 Hz, 1H, 9-CH), 7.42 (dd, *J* = 7.9, 1.4 Hz, 1H, 3''-CH), 7.35 (ddd, *J* = 8.0, 7.4, 1.2 Hz, 1H, 7-CH), 7.18 – 7.12 (m, 2H, 4''- and 8-CH), 7.10 (d, *J* = 8.0 Hz, 1H, 6-CH), 7.09 (td, *J* = 7.7, 7.2, 1.4 Hz, 1H, 5''-CH), 6.91 (ddt, *J* = 7.7, 1.9, 1.0 Hz, 1H, 6''-CH), 4.43 (s, 2H, 1'-CH_2), 3.71 (s, 3H, 2-NCH_3), 3.51 (s, 3H, 5-NCH_3).

^{13}C NMR (101 MHz, CD_2Cl_2) δ: 163.54 (3-C_qO), 149.61 (4a-C_q), 144.85 (5a-C_q), 139.55 (1''- or 2''-C_q), 134.13 (1''- or 2''-C_q), 129.76 (1- or 3''- or 6''-CH), 129.65 (1- or 3''- or 6''-CH), 129.56 (1- or 3''- or 6''-CH), 127.84 (4''- or 5''-CH), 127.46 (4''- or 5''-CH), 126.91 (7-CH), 122.48 (9a-C_q), 121.09 (8-CH), 119.12 (9-CH), 110.86 (9b-C_q), 108.97 (6-CH), 102.00 (4-C_q), 39.27 (2-NCH_3), 31.45 (5-NCH_3), 29.24 (1'-CH_2).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right]$ = 2922 w, 1665 mw, 1612 w, 1582 w, 1563 mw, 1487 w, 1466 w, 1450 w, 1441 w, 1416 w, 1398 w, 1378 w, 1349 w, 1322 w, 1301 w, 1278 w, 1246 w, 1178 w, 1157 w, 1144 w, 1122 w, 1088 w, 1047 w, 1037 w, 1021 w, 981 w, 909 w, 874 w, 849 w, 806 w, 786 w, 773 w, 755 w, 740 w, m, 708 w, 699 w, 692 w, 676 w.

4-(3-Chlorobenzyl)-2,5-dihydro-3*H*-pyrido[4,3-*b*]indol-3-one (**44**)



Chemical Formula: $C_{18}H_{13}ClN_2O$ **Molecular Weight:** 308.7650 g/mol

The 3-oxo-γ-carboline **44** was prepared according to the general synthesis protocol D1 (see subchapter 7.2). Indole-3-carboxaldehyde derivative **19** (360 mg, 809 µmol) and a 25% NH_3 in EtOH solution (4.00 mL, 3.52 g, 51.7 mmol) were used. It was stirred for 48 h. Product **44** was purified by column chromatography with pure ethyl acetate.

Yield and appearance: 89.2 mg (289 µmol, 36%) as white powdery solid.

HRMS (ESI): m/z = calculated for $[C_{18}H_{14}ClN_2O]^+$: 309.07892 (^{35}Cl), 311.07597 (^{37}Cl), found: 309.07883 (^{35}Cl), 311.07584 (^{37}Cl).

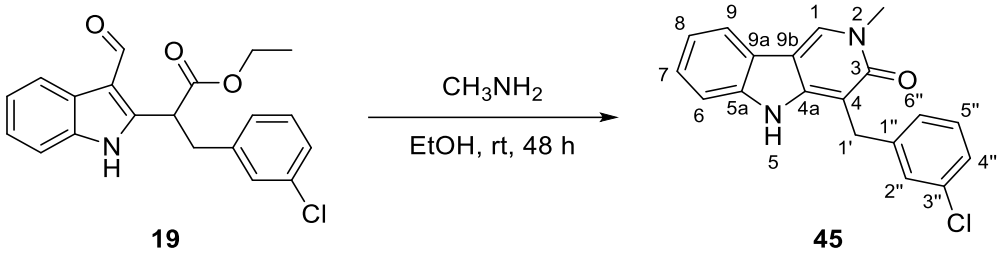
Melting area: 266.8 - 269.2°C

^{1}H NMR (500 MHz, DMSO) δ: 11.56 (s, 1H, 2-NH), 10.93 (s, 1H, 5-NH), 8.21 (s, 1H, 1-CH), 7.87 (d, *J* = 7.7 Hz, 1H, 9-CH), 7.41 (t, *J* = 1.5 Hz, 1H, 2''-CH), 7.34 (dd, *J* = 7.7, 1.5 Hz, 1H, 6''-CH), 7.31 – 7.22 (m, 3H, 5''-, 6- and 7-CH), 7.19 (dt, *J* = 8.3, 1.5 Hz, 1H, 4''-CH), 7.06 (ddd, *J* = 7.7, 6.3, 2.0 Hz, 1H, 8-CH), 3.93 (s, 2H, 1'-CH_2).

^{13}C NMR (126 MHz, DMSO) δ: 161.86 (3-C_qO), 148.80 (4a-C_q), 143.64 (1''-C_q), 142.35 (5a-C_q), 132.63 (3''-C_q), 129.89 (5''-CH), 128.00 (2''-CH), 127.03 (6''-CH), 126.99 (1-CH), 126.05 (7-CH), 125.62 (4''-CH), 122.39 (9a-C_q), 119.91 (8-CH), 119.83 (9-CH), 110.33 (6-CH), 109.77 (9b-C_q), 102.49 (4-C_q), 29.71 (1'-CH_2).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right]$ = 3096 w, 2897 w, 2799 w, 1900 w, 1658 m, 1610 ms, 1587 m, 1489 w, 1465 m, 1448 m, 1425 m, 1396 m, 1329 w, 1315 mw, 1292 w, 1270 mw, 1233 ms, 1209 mw, 1184 w, 1152 w, 1118 w, 1089 w, 1076 w, 1052 mw, 1013 w, 999 w, 965 w, 944 w, 930 w, 903 w, 880 w, 865 m, 850 w, 842 w, 793 m, 785 m, 771 m, 762 m, 754 m, 744 m, 738 m, 713 m, 695 m, 679 m, 667 m.

4-(3-Chlorobenzyl)-2-methyl-2,5-dihydro-3*H*-pyrido[4,3-*b*]indol-3-one (**45**)



19 **45**

Chemical Formula: $C_{19}H_{15}ClN_2O$ **Molecular Weight:** 322.7920 g/mol

The 3-oxo-γ-carboline **45** was prepared according to the general synthesis protocol D1 (see subchapter 7.2). As educt indole-3-carboxaldehyde derivative **19** (186 mg, 522 µmol), and a 2 M CH_3NH_2 in THF solution (6.40 mL, 5.76 g, 12.8 mmol) were used. It was stirred for 48 h, then product **45** was purified by column chromatography with pure ethyl acetate.

Yield and appearance: 87.0 mg (270 µmol, 52%) as pale brown powdery solid.

HRMS (ESI): m/z = calculated for $[C_{19}H_{16}ClN_2O]^+$: 323.09457 (^{35}Cl), 325.09162 (^{37}Cl), found: 323.09458 (^{35}Cl), 325.09186 (^{37}Cl).

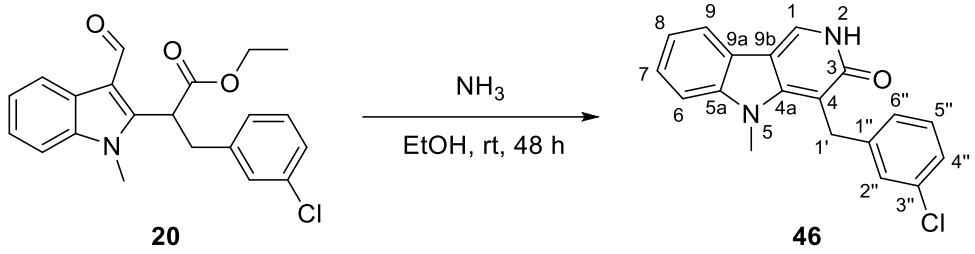
Melting area: 149.4 - 151.7 °C

^{1}H NMR (500 MHz, MeOD) δ: 8.44 (s, 1H, 1-CH), 7.84 (d, *J* = 7.7 Hz, 1H, 9-CH), 7.36 – 7.31 (m, 2H, 2''- and 7-CH), 7.30 (d, *J* = 7.6 Hz, 1H, 6-CH), 7.24 (d, *J* = 7.7 Hz, 1H, 6''-CH), 7.19 (dd, *J* = 7.8, 7.7 Hz, 1H, 5''-CH), 7.14 (ddd, *J* = 7.7, 6.9, 1.5 Hz, 1H, 8-CH), 7.13 (d, *J* = 7.8 Hz, 1H, 4''-CH), 4.09 (s, 2H, 1'-CH_2), 3.75 (s, 3H, 2-NCH_3).

^{13}C NMR (126 MHz, MeOD) δ: 163.69 (3-C_qO), 150.48 (4a-C_q), 143.93 (1''-C_q), 143.86 (5a-C_q), 135.05 (3''-C_q), 131.73 (1-CH), 130.70 (5''-CH), 129.37 (2''-CH), 127.95 (7-CH), 127.79 (6''-CH), 127.05 (4''-CH), 123.30 (9a-C_q), 121.73 (8-CH), 120.80 (9-CH), 113.07 (9b-C_q), 111.76 (6-CH), 104.32 (4-C_q), 39.31 (2-NCH_3), 31.49 (1'-CH_2).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right]$ = 3044 w, 1665 m, 1616 w, 1594 w, 1556 m, 1487 w, 1466 m, 1430 w, 1400 m, 1359 w, 1334 w, 1312 w, 1288 w, 1273 w, 1266 w, 1232 m, 1198 w, 1161 w, 1147 w, 1090 w, 1077 w, 1035 w, 1014 w, 998 w, 982 w, 930 w, 910 w, 873 w, 861 w, 834 w, 797 w, 776 mw, 757 mw, 738 m, 702 m, 684 m, 677 m, 661 w.

4-(3-Chlorobenzyl)-5-methyl-2,5-dihydro-3*H*-pyrido[4,3-*b*]indol-3-one (**46**)



Chemical Formula: $C_{19}H_{15}ClN_2O$ **Molecular Weight:** 322.7920 g/mol

The 3-oxo-γ-carboline **46** was prepared according to the general synthesis protocol D2 (see subchapter 7.2). As educt 1-methylindole-3-carboxaldehyde derivative **20** (213 mg, 577 µmol), 10 mL of iPrOH and a watery 25% NH_3 solution (5.30 mL, 3.18 g, 46.7 mmol) were used. It was stirred for 48 h. After having performed the in D2 described working up procedure, product **46** could be gained from recrystallisation from a CH_2Cl_2:isohexane (1:6) mixture.

Yield and appearance: 56.7 mg (176 µmol, 30%) as white powdery solid.

HRMS (ESI): m/z = calculated for $[C_{19}H_{16}ClN_2O]^+$: 323.09457 (^{35}Cl), 325.09162 (^{37}Cl), found: 323.09454 (^{35}Cl), 325.09164 (^{37}Cl).

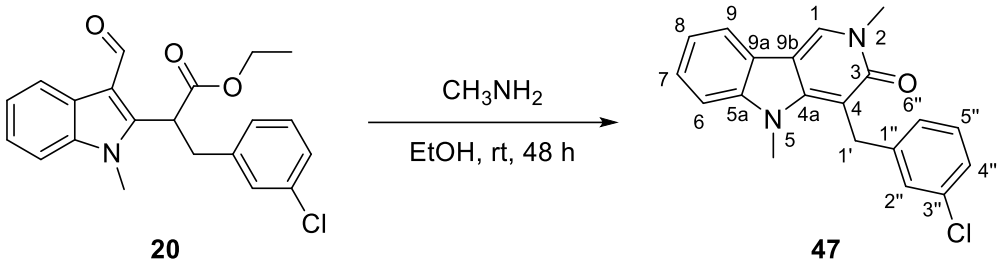
Melting area: 280.0 - 280.9°C

^{1}H NMR (400 MHz, DMSO) δ: 11.82 (s, 1H, 2-NH), 8.32 (s, 1H, 1-CH), 7.92 (dt, *J* = 7.8, 1.0 Hz, 1H, 9-CH), 7.36 – 7.25 (m, 3H, 5‘‘-, 6- and 7-CH), 7.25 – 7.18 (m, 2H, 2‘‘- and 4’’-CH), 7.14 (dt, *J* = 7.7, 1.4 Hz, 1H, 6’’-CH), 7.11 (ddd, *J* = 7.8, 6.5, 2.2 Hz, 1H, 8-CH), 4.31 (s, 2H, 1‘-CH_2), 3.62 (s, 3H, 5-NCH_3).

^{13}C NMR (101 MHz, DMSO) δ: 162.96 (3-C_qO), 148.76 (4a-C_q), 144.88 (1’’-C_q), 143.75 (5a-C_q), 133.04 (3’’-C_q), 130.26 (5’’-CH), 127.50 (2’’- or 4’’-CH), 126.83 (1-CH), 126.46 (6’’-CH), 126.02 (7-CH), 125.68 (2’’- or 4’’-CH), 121.84 (9a-C_q), 120.38 (8-CH), 119.25 (9-CH), 109.87 (9b-C_q), 108.84 (6-CH), 101.88 (4-C_q), 31.22 (5-NCH_3), 29.03 (1’-CH_2).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right]$ = 3210 w, 3066 w, 2927 w, 2778 w, 2676 w, 1892 w, 1817 w, 1760 w, 1736 w, 1657 m, 1615 s, 1607 s, 1593 m, 1572 mw, 1464 m, 1441 m, 1417 m, 1397 m, 1364 w, 1341 w, 1322 w, 1305 mw, 1272 m, 1258 w, 1240 m, 1201 w, 1184 w, 1165 w, 1133 m, 1116 w, 1093 w, 1074 w, 1057 w, 1019 mw, 972 w, 942 w, 929 w, 901 w, 888 m, 877 mw, 849 ms, 796 mw, 781 m, 768 m, 745 s, 705 w, 700 w, 679 m.

4-(3-Chlorobenzyl)-2,5-dimethyl-2,5-dihydro-3*H*-pyrido[4,3-*b*]indol-3-one (**47**)



20 **47**

Chemical Formula: $C_{20}H_{17}ClN_2O$ **Molecular Weight:** 336.8190 g/mol

The 3-oxo-γ-carboline **47** was prepared according to the general synthesis protocol D1 (see subchapter 7.2). As educts, 1-methylindole-3-carboxaldehyde derivative **20** (1.00 g, 2.70 mmol) and a 33% CH_3NH_2 in EtOH solution (9.00 mL, 6.81 g, 72.3 mmol) were used. It was stirred for 48 h, then product **47** was purified by column chromatography with pure EtOAc.

Yield and appearance: 411 mg (1.22 mmol, 45%) as pale-yellow solid.

HRMS (ESI): *m/z* = calculated for $[C_{20}H_{18}ClN_2O]^+$: 337.11022 (^{35}Cl), 339.10727 (^{37}Cl), 340.11062 (^{38}Cl), found: 337.11044 (^{35}Cl), 339.10786 (^{37}Cl), 340.11132 (^{38}Cl).

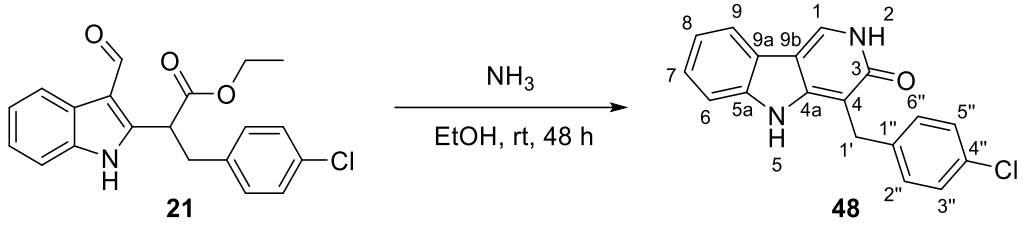
Melting area: 148.3 - 149.2°C

^{1}H NMR (400 MHz, CD_2Cl_2) δ: 8.06 (s, 1H, 1-CH), 7.72 (dq, *J* = 7.6, 0.8 Hz, 1H, 9-CH), 7.36 (td, *J* = 7.8, 1.3 Hz, 1H, 7-CH), 7.21 (td, *J* = 7.5, 0.8 Hz, 1H, 5''-CH), 7.20 – 7.09 (m, 5H, 2''-, 4''-, 6''-, 6- and 8-CH), 4.40 (s, 2H, 1'-CH_2), 3.71 (s, 3H, 2-NCH_3), 3.63 (s, 3H, 5-NCH_3).

^{13}C NMR (101 MHz, CD_2Cl_2) δ: 163.43 (3-C_qO), 149.21 (4a-C_q), 144.68 (1''-C_q), 144.64 (5a-C_q), 134.59 (3''-C_q), 130.13 (5''-CH), 129.33 (1-CH), 128.27 (2''-, 4''-, or 6''-CH), 126.76 (2''-, 4''-, 6''- or 7-CH), 126.74 (2''-, 4''-, 6''- or 7-CH), 126.35 (2''-, 4''-, or 6''-CH), 122.34 (9a-C_q), 120.95 (8-CH), 118.96 (9-CH), 110.76 (9b-C_q), 108.82 (6-CH), 102.72 (4-C_q), 39.10 (2-NCH_3), 31.80 (5-NCH_3), 30.83 (1'-CH_2).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right]$ = 3053 w, 1694 w, 1665 w, 1609 w, 1574 w, 1570 w, 1557 w, 1453 w, 1472 w, 1446 w, 1418 w, 1397 w, 1374 w, 1346 w, 1321 w, 1301 w, 1267 w, 1236 w, 1197 w, 1172 w, 1161 w, 1135 w, 1086 w, 1078 w, 1048 w, 1098 w, 987 w, 928 w, 900 w, 873 w, 791 w, 773 w, 753 w, 715 w, 707 w, 700 w, 683 w, 667 w.

4-(4-Chlorobenzyl)-2,5-dihydro-3*H*-pyrido[4,3-*b*]indol-3-one (**48**)



Chemical Formula: $C_{18}H_{13}ClN_2O$ **Molecular Weight:** 308.7650 g/mol

The 3-oxo-γ-carboline **48** was prepared according to the general synthesis protocol D1 (see subchapter 7.2). As educt indole-3-carboxaldehyde derivative **21** (190 mg, 534 µmol) and a 2 M NH_3 in MeOH solution (24.0 mL, 14.4 g, 48.0 mmol) were used. It was stirred for 48 h. Product **48** could be gained from recrystallisation from CH_2Cl_2.

Yield and appearance: 52.9 mg (171 µmol, 32%) as white powder.

HRMS (ESI): *m/z* = calculated for $[C_{18}H_{14}ClN_2O]^+$: 309.07892 (^{35}Cl), 311.07597 (^{37}Cl), found: 309.07875 (^{35}Cl), 311.07595 (^{37}Cl).

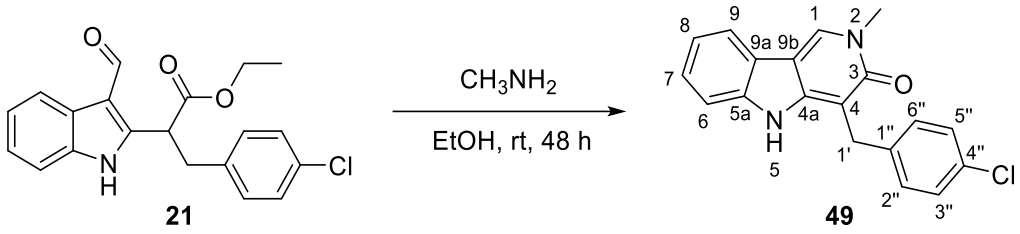
Melting area: 230.4 - 231.5°C

^{1}H NMR (500 MHz, DMSO) δ: 11.61 (s, 1H, 2-NH), 10.90 (s, 1H, 5-NH), 8.19 (s, 1H, 1-CH), 7.86 (d, *J* = 7.9 Hz, 1H, 9-CH), 7.37 (ddd, *J* = 8.5, 2.5, 2.0 Hz, 2H, 2''- and 6''-CH), 7.28 (ddd, *J* = 8.5, 2.5, 2.0 Hz, 2H, 3''- and 5''-CH), 7.28 – 7.20 (m, 2H, 6- and 7-CH), 7.05 (ddd, *J* = 7.9, 7.0, 1.7 Hz, 1H, 8-CH), 3.91 (s, 2H, 1'-CH_2).

^{13}C NMR (126 MHz, DMSO) δ: 161.83 (3-C_qO), 148.76 (4a-C_q), 142.37 (5a-C_q), 140.02 (1''-Cq), 130.16 (4''-C_q), 130.09 (2''- and 6''-CH), 127.90 (3''- and 5''-CH), 126.84 (1-CH), 126.01 (7-CH), 122.39 (9a-C_q), 119.85 (8-CH), 119.79 (9-CH), 110.29 (6-CH), 109.77 (9b-C_q), 102.77 (4-Cq), 29.37 (1'-CH_2).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right]$ = 3063 w, 2900 w, 2781 w, 2361 w, 1880 w, 1734 w, 1700 w, 1659 m, 1620 mw, 1605 m, 1587 mw, 1488 w, 1467 mw, 1449 w, 1426 mw, 1320 w, 1293 w, 1277 w, 1247 mw, 1236 m, 1220 w, 1199 w, 1175 w, 1116 w, 1091 w, 1052 w, 1016 w, 965 w, 949 w, 940 w, 928 w, 871 w, 860 m, 852 w, 828 w, 815 w, 800 w, 785 m, 774 m, 757 w, 740 m, 734 ms, 716 w, 686 w, 671 w, 653 w.

4-(4-Chlorobenzyl)-2-methyl-2,5-dihydro-3*H*-pyrido[4,3-*b*]indol-3-one (**49**)



Chemical Formula: $C_{19}H_{15}ClN_2O$ **Molecular Weight:** 322.7920 g/mol

The 3-oxo-γ-carboline **49** was prepared according to the general synthesis protocol D1 (see subchapter 7.2). As educts, indole-3-carboxaldehyde derivative **21** (95.4 mg, 268 µmol) and a 2 M CH_3NH_2 in THF solution (9.00 mL, 8.10 g, 18.0 mmol) were used. It was stirred for 48 h, then product **49** was purified by column chromatography with pure EtOAc.

Yield and appearance: 34.6 mg (107 µmol, 40%) yellowish white powder.

HRMS (ESI): *m/z* = calculated for $[C_{19}H_{16}ClN_2O]^+$: 323.09457 (^{35}Cl), 325.09162 (^{37}Cl), found: 323.09444 (^{35}Cl), 325.09186 (^{37}Cl).

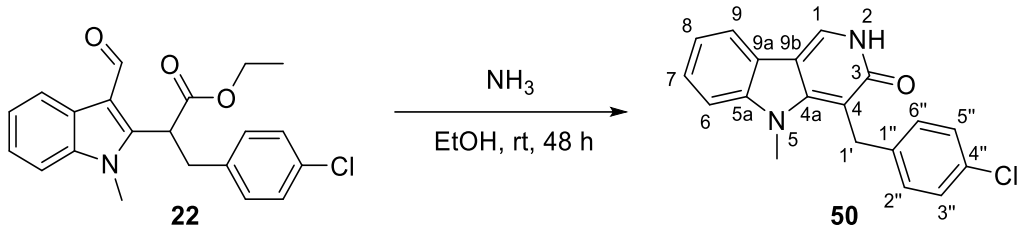
Melting point: 206.8 - 208.5°C

^{1}H NMR (500 MHz, DMSO) δ: 10.94 (s, 1H, 5-NH), 8.57 (s, 1H, 1-CH), 7.79 (d, *J* = 7.8 Hz, 1H, 9-CH), 7.36 (ddd, *J* = 8.6, 2.5, 2.1 Hz, 2H, 2''- and 6''-CH), 7.31 – 7.22 (m, 4H, 3''-, 5''-, 6- and 7-CH), 7.08 (ddd, *J* = 7.8, 6.8, 1.6 Hz, 1H, 8-CH), 3.94 (s, 2H, 1'-CH_2), 3.58 (s, 3H, 2-NCH_3).

^{13}C NMR (126 MHz, DMSO) δ: 161.22 (3-C_qO), 147.97 (4a-C_q), 142.25 (5a-C_q), 139.92 (1''-C_q), 130.95 (1-CH), 130.19 (4''-C_q), 130.15 (2''- and 6''-CH), 127.90 (3''- and 5''-CH), 126.11 (7-CH), 122.15 (9a-C_q), 119.95 (8-CH), 119.42 (9-CH), 110.38 (6-CH), 109.12 (9b-C_q), 102.25 (4-C_q), 37.84 (2-NCH_3), 29.96 (1'-CH_2).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right]$ = 3853 w, 3126 w, 2922 w, 2361 w, 1734 w, 1700 w, 1662 mw, 1616 w, 1587 w, 1545 mw, 1488 w, 1467 w, 1436 w, 1403 w, 3163 w, 1336 w, 1315 w, 1295 w, 1236 mw, 1162 w, 1110 w, 1090 w, 1012 w, 924 w, 876 w, 860 w, 839 w, 799 w, 782 w, 775 w, 750 w, 742 mw, 704 w, 668 w.

4-(4-Chlorobenzyl)-5-methyl-2,5-dihydro-3*H*-pyrido[4,3-*b*]indol-3-one (**50**)



Chemical Formula: $C_{19}H_{15}ClN_2O$ **Molecular Weight:** 322.7920 g/mol

The 3-oxo-γ-carboline **50** was prepared according to the general synthesis protocol D1 (see subchapter 7.2). As educt 1-methylindole-3-carboxaldehyde derivative **22** (300 mg, 811 µmol) and a 2 M NH_3 in MeOH solution (15.0 mL, 9.00 g, 30.0 mmol) were used. It was stirred for 48 h, then product **50** was purified by column chromatography with pure EtOAc.

Yield and appearance: 75.0 mg (232 µmol, 29%) as white powder.

HRMS (ESI): m/z = calculated for $[C_{19}H_{16}ClN_2O]^+$: 323.09457 (^{35}Cl), 325.09162 (^{37}Cl), found: 323.09447 (^{35}Cl), 325.09189 (^{37}Cl).

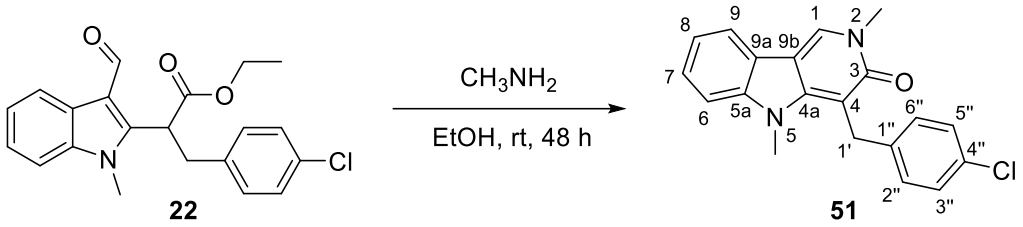
Melting area: 288.5 - 289.2°C

^{1}H NMR (400 MHz, DMSO) δ: 11.81 (s, 1H, 2-NH), 8.31 (s, 1H, 1-CH), 7.91 (d, *J* = 7.4 Hz, 1H, 9-CH), 7.38 – 7.24 (m, 4H, 6-, 7-, 3''- and 5''-CH), 7.18 (d, *J* = 8.1 Hz, 2H, 2''- and 6''-CH), 7.11 (dd, *J* = 7.4, 7.2 Hz, 1H, 8-CH), 4.29 (s, 2H, 1'-CH_2), 3.61 (s, 3H, 5-NCH_3).

^{13}C NMR (101 MHz, DMSO) δ: 162.93 (3-C_qO), 148.73 (4a-C_q), 143.76 (5a-C_q), 141.19 (1''-C_q), 130.15 (4''-C_q), 129.58 (2''- and 6''-CH), 128.29 (3''- and 5''-CH), 126.69 (1-CH), 125.99 (7-CH), 121.85 (9a-C_q), 120.34 (8-CH), 119.22 (9-CH), 109.88 (9b-C_q), 108.80 (6-CH), 102.20 (4-C_q), 31.15 (5-NCH_3), 28.68 (1'-CH_2).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right]$ = 3099 w, 2982 w, 2875 w, 1654 m, 1615 ms, 1573 w, 1476 m, 1440 m, 1432 w, 1418 w, 1405 w, 1396 mw, 1361 w, 1341 w, 1324 w, 1314 w, 1275 mw, 1261 w, 1235 w, 1176 w, 1158 w, 1134 w, 1116 w, 1091 w, 1057 w, 1025 w, 1012 w, 920 w, 888 w, 864 w, 848 w, 824 w, 813 w, 805 w, 777 w, 763 m, 752 w, 741 m, 706 w, 658 w.

4-(4-Chlorobenzyl)-2,5-dimethyl-2,5-dihydro-3*H*-pyrido[4,3-*b*]indol-3-one (**51**)



Chemical Formula: $C_{20}H_{17}ClN_2O$ **Molecular Weight:** 336.8190 g/mol

The 3-oxo-γ-carboline **51** was prepared according to the general synthesis protocol D1 (see subchapter 7.2). 1-Methylindole-3-carboxaldehyde derivative **22** (100 mg, 270 µmol) and a 33% CH_3NH_2 in EtOH solution (2.00 mL, 1.40 g, 14.9 mmol) were used. It was stirred for 48 h. Product **51** was purified by column chromatography with pure EtOAc.

Yield and appearance: 30.0 mg (89.1 µmol, 33%) as beige-white powder.

HRMS (ESI): m/z = calculated for $[C_{20}H_{18}ClN_2O]^+$: 337.11022 (^{35}Cl), 339.10727 (^{37}Cl), found: 337.11039 (^{35}Cl), 339.10785 (^{37}Cl).

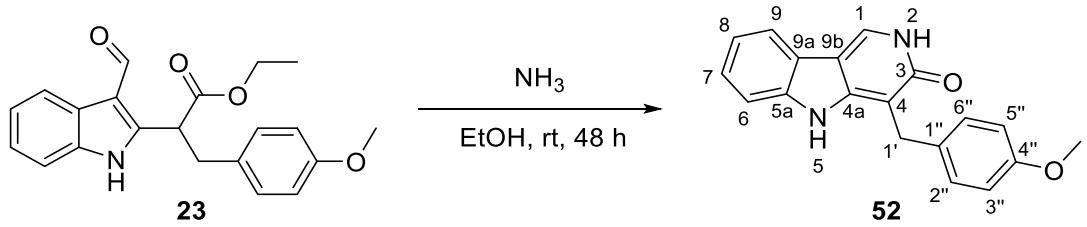
Melting area: 220 - 221.5°C

^{1}H NMR (500 MHz, Acetone) δ: 8.49 (s, 1H, 1-CH), 7.82 (dt, *J* = 7.6, 1.0 Hz, 1H, 9-CH), 7.33 (ddd, *J* = 8.2, 7.6, 1.0 Hz, 1H, 7-CH), 7.27 (m, 4H, 2''-, 3''-, 5''-, 6''-CH), 7.24 (dt, *J* = 8.2, 1.0 Hz, 1H, 6-CH), 7.12 (td, *J* = 7.6, 1.0 Hz, 1H, 8-CH), 4.43 (s, 2H, 1'-CH_2), 3.72 (s, 3H, 5-NCH_3), 3.68 (s, 3H, 2-NCH_3).

^{13}C NMR (126 MHz, Acetone) δ: 163.70 (3-C_qO), 149.38 (4a-C_q), 145.19 (5a-C_q), 142.35 (1''-C_q), 131.70 (4''-C_q), 130.73 (1-CH), 130.63 (2''- and 6''-CH), 129.12 (3''- and 5''-CH), 127.01 (7-CH), 123.12 (9a-C_q), 121.29 (8-CH), 119.54 (9-CH), 110.70 (9b-C_q), 109.44 (6-CH), 103.32 (4-C_q), 38.58 (2-NCH_3), 31.79 (5-CH_3), 30.53 (1'-CH_2).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right]$ = 3853 w, 3744 w, 3665 w, 3628 w, 3048 w, 2360 w, 1772 w, 1717 w, 1734 w, 1700 w, 1665 m, 1612 w, 1583 w, 1564 m, 1506 w, 1488 w, 1473 w, 1449 w, 1419 w, 1408 w, 1398 w, 1377 w, 1350 w, 1307 w, 1294 w, 1278 w, 1225 w, 1176 w, 1160 w, 1143 w, 1087 mw, 1049 w, 1021 w, 1014 w, 982 w, 932 w, 918 w, 896 w, 869 w, 837 w, 822 w, 803 w, 773 w, 741 m, 709 w, 680 w, 668 w, 655 w.

4-(4-Methoxybenzyl)-2,5-dihydro-3*H*-pyrido[4,3-*b*]indol-3-one (**52**)



23 **52**

Chemical Formula: $C_{19}H_{16}N_2O_2$ **Molecular Weight:** 304.3490 g/mol

The 3-oxo-γ-carboline **52** was prepared according to the general synthesis protocol D1 (see subchapter 7.2). Indole-3-carboxaldehyde derivative **23** (250 mg, 711 µmol) and a 2 M NH_3 in MeOH solution (7.00 mL, 4.20 g, 14.0 mmol) were used. It was stirred for 48 h, then product **52** was purified by column chromatography with a MeOH:CH_2Cl_2 (1:99-3:97) solvent mixture.

Yield and appearance: 55.0 mg (181 µmol, 25%) as beige-white powder.

HRMS (ESI): m/z = calculated for $[C_{19}H_{17}N_2O_2]^+$: 305.12845, found: 305.12840.

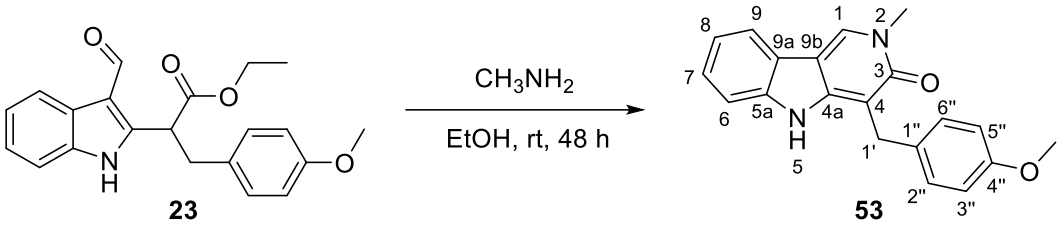
Melting area: 266.6 - 267.4°C

^{1}H NMR (500 MHz, MeOD) δ: 8.16 (s, 1H, 1-CH), 7.85 (dt, *J* = 7.9, 1.1 Hz, 1H, 9-CH), 7.33 (ddd, *J* = 8.1, 6.8, 1.1 Hz, 1H, 7-CH), 7.30 (dd, *J* = 8.1, 1.5 Hz, 1H, 6-CH), 7.22 (ddd, *J* = 8.7, 3.0, 2.0 Hz, 2H, 2''- and 6''-CH), 7.13 (ddd, *J* = 7.9, 6.8, 1.5 Hz, 1H, 8-CH), 6.78 (ddd, *J* = 8.7, 3.0, 2.0 Hz, 2H, 3''- and 5''-CH), 4.04 (s, 2H, 1'-CH_2), 3.71 (s, 3H, -OCH_3).

^{13}C NMR (126 MHz, MeOD) δ: 164.08 (3-C_qO), 159.46 (4''-C_q), 151.34 (4a-C_q), 144.12 (5a-C_q), 133.22 (1''-C_q), 130.20 (2''- and 6''-CH), 127.93 (7-CH), 126.72 (1-CH), 123.39 (9a-C_q), 121.72 (8-CH), 120.90 (9-CH), 114.68 (3''- and 5''-CH), 113.71 (9b-Cq), 111.80 (6-CH), 105.98 (4-Cq), 55.61 (-OCH_3), 30.21 (1'-CH_2).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right]$ = 3091 w, 2901 w, 2832 w, 1900 w, 1738 w, 1655 m, 1611 m, 1581 m, 1506 m, 1490 w, 1465 m, 1451 mw, 1427 mw, 1417 m,1396 m, 1328 w, 1329 w, 1297 w, 1282 w, 1265 w, 1231 m, 1179 mw, 1169 w, 1110 w, 1089 w, 1053 w, 1033 mw, 1015 w, 961 w, 936 w, 923 w, 880 w, 863 m, 854 mw, 839 w, 816 w, 792 mw, 782 mw, 746 m, 720 mw, 708 m, 698 mw, 661 w.

4-(4-Methoxybenzyl)-2-methyl-2,5-dihydro-3*H*-pyrido[4,3-*b*]indol-3-one (**53**)



23 **53**

Chemical Formula: $C_{20}H_{18}N_2O_2$ **Molecular Weight:** 318.3760 g/mol

The 3-oxo-γ-carboline **53** was prepared according to the general synthesis protocol D1 (see subchapter 7.2). Indole-3-carboxaldehyde derivative **23** (150 mg, 427 µmol) and a 2 M CH_3NH_2 in THF solution (2.50 mL, 2.25 g, 4.99 mmol) were used. It was stirred for 48 h. Product **53** was purified by column chromatography with a MeOH:CH_2Cl_2 (1:99-3:97) solvent mixture.

Yield and appearance: 46.6 mg (146 µmol, 34%) as yellowish white powder.

HRMS (ESI): m/z = calculated for $[C_{20}H_{19}N_2O_2]^+$: 319.14410, found: 319.14399.

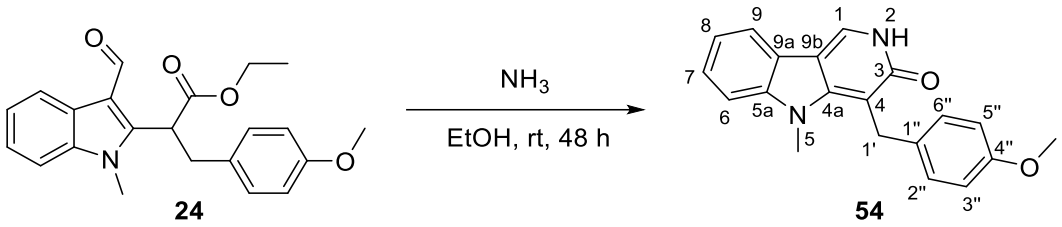
Melting area: 242.6 - 244°C

^{1}H NMR (400 MHz, MeOD) δ: 8.42 (s, 1H, 1-CH), 7.83 (dt, *J* = 7.7, 1.0 Hz, 1H, 9-CH), 7.32 (ddd, *J* = 8.0, 6.8, 1.0 Hz, 1H, 7-CH), 7.29 (ddd, *J* = 8.0, 1.6, 0.8 Hz, 1H, 6-CH), 7.21 (ddd, *J* = 8.8, 3.0, 2.1 Hz, 2H, 2''- and 6''-CH), 7.12 (ddd, *J* = 7.7, 6.8, 1.6 Hz, 1H, 8-CH), 6.77 (ddd, *J* = 8.8, 3.0, 2.1 Hz, 2H, 3''- and 5''-CH), 4.04 (s, 2H, 1'-CH_2), 3.75 (s, 3H, 2-NCH_3), 3.71 (s, 3H, -OCH_3).

^{13}C NMR (101 MHz, MeOD) δ: 163.75 (3-C_qO), 159.46 (4''-C_q), 150.35 (4a-C_q), 143.98 (5a-C_q), 133.33 (1''-C_q), 131.25 (1-CH), 130.25 (3''- and 5''-CH), 127.88 (7-CH), 123.30 (9a-C_q), 121.59 (8-CH), 120.75 (9-CH), 114.67 (2''- and 6''-CH), 113.13 (9a-C_q), 111.72 (6-CH), 105.68 (4-C_q), 55.62 (-OCH_3), 39.31 (2-NCH_3), 30.85 (1'-CH_2).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right]$ = 3065 w, 2990 w, 2832 w, 1664 mw, 1618 w, 1588 w, 1582 w, 1556 m, 1507 mw, 1468 mw, 1440 w, 1404 w, 1364 w, 1342 w, 1315 w, 1297 w, 1268 w, 1235 m, 1174 w, 1150 w, 1109 w, 1094 w, 1030 w, 933 w, 920 w, 875 w, 836 w, 821 w, 808 w, 800 w, 786 w, 757 w, 749 mw, 664 w, 703 w, 682 w.

4-(4-Methoxybenzyl)-5-methyl-2,5-dihydro-3*H*-pyrido[4,3-*b*]indol-3-one (**54**)



24 **54**

Chemical Formula: $C_{20}H_{18}N_2O_2$ **Molecular Weight:** 318.3760 g/mol

The 3-oxo-γ-carboline **54** was prepared according to the general synthesis protocol D2 (see subchapter 7.2). 1-Methylindole-3-carboxaldehyde derivative **24** (70.0 mg, 192 µmol), 5 mL of iPrOH and an aqueous 25%-solution of NH_3 (1.50 mL, 1.35 g, 9.62 mmol) were used. It was stirred for 48 h. Product **54** was purified by column chromatography with a MeOH:CH_2Cl_2 (1:99-3:97) solvent mixture.

Yield and appearance: 15.0 mg (47.1 µmol, 25%) as white powder.

HRMS (ESI): *m/z* = calculated for $[C_{20}H_{19}N_2O_2]^+$: 319.14410, found: 319.14407.

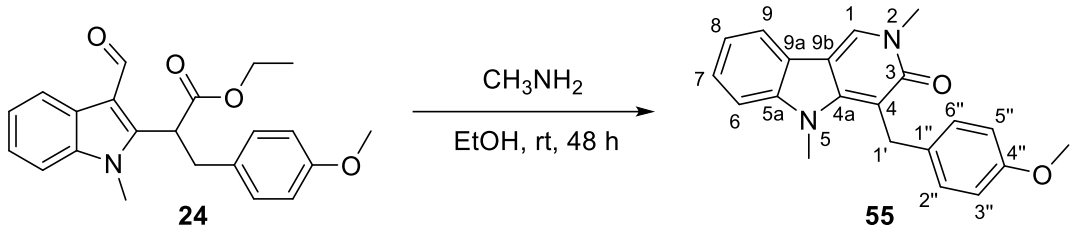
Melting area: 259.9 - 260.3°C

^{1}H NMR (500 MHz, DMSO-d_6) δ: 11.67 (s, 1H, 2-NH), 8.28 (s, 1H, 1-CH), 7.90 (dd, *J* = 7.7, 1.1 Hz, 1H, 9-CH), 7.30 (ddd, *J* = 7.9, 7.5, 1.1 Hz, 1H, 7-CH), 7.26 (dd, *J* = 7.9, 1.2 Hz, 1H, 6-CH), 7.10 (ddd, *J* = 7.7, 7.5, 1.2 Hz, 1H, 8-CH), 7.06 (ddd, *J* = 8.6, 3.0, 2.1 Hz, 2H, 2''- and 6''-CH), 6.82 (ddd, *J* = 8.6, 3.0, 2.1 Hz, 2H, 3''- and 5''-CH), 4.23 (s, 2H, 1'-CH_2), 3.69 (s, 3H, -OCH_3), 3.62 (s, 3H, 5-CH_3).

^{13}C NMR (126 MHz, DMSO) δ: 163.20 (3-C_qO), 157.26 (4''-C_q), 148.60 (4a-C_q), 143.72 (5a-C_q), 133.95 (1''-C_q), 128.60 (2''- and 6''-CH), 126.74 (1-CH), 125.84 (7-CH), 121.91 (9a-C_q), 120.20 (8-CH), 119.11 (9-CH), 113.79 (3''- and 5''-CH), 109.80 (9b-C_q), 108.69 (6-CH), 102.98 (4-C_q), 54.95 (-OCH_3), 31.09 (5-CH_3), 28.31 (1'-CH_2).

IR (ATR): $\tilde{\nu}\ \left[\frac{1}{cm}\right]$ = 2926 w, 2645 w, 1919 w, 1663 w, 1626 mw, 1610 w, 1580 w, 1507 w, 1476 mw, 1440 mw, 1425 w, 1415 w, 1404 w, 1348 w, 1318 w, 1285 w, 1271 w, 1240 mw, 1205 w, 1174 w, 1162 w, 1138 w, 1116 w, 1108 w, 1060 w, 1033 w, 976 w, 930 w, 917 w, 877 mw, 836 w, 814 w, 798 w, 782 w, 743 m, 731 w, 715 w, 700 w, 682 w.

4-(4-Methoxybenzyl)-2,5-dimethyl-2,5-dihydro-3*H*-pyrido[4,3-*b*]indol-3-one (**55**)



24 **55**

Chemical Formula: $C_{21}H_{20}N_2O_2$ **Molecular Weight:** 332.4030 g/mol

The 3-oxo-γ-carboline **55** was prepared according to the general synthesis protocol D1 (see subchapter 7.2). 1-Methylindole-3-carboxaldehyde derivative **24** (133 mg, 364 µmol) and a 2 M CH_3NH_2 in THF solution (1.00 mL, 901 mg, 2.00 mmol) were used. It was stirred for 48 h. Product **55** was purified by column chromatography with a MeOH:CH_2Cl_2 (1:99-3:97) solvent mixture.

Yield and appearance: 53.0 mg (159 µmol, 44%) as yellow powder.

HRMS (ESI): m/z = calculated for $[C_{21}H_{21}N_2O_2]^+$: 333.15975, found: 333.15963.

Melting area: 203.6 - 204.3°C

^{1}H NMR (400 MHz, DMSO) δ: 8.65 (s, 1H, 1-CH), 7.82 (ddd, *J* = 7.9, 1.2, 1.0 Hz, 1H, 9-CH), 7.32 (dddd, *J* = 7.7, 7.6, 1.2, 1.0 Hz, 1H, 7-CH), 7.28 (dt, *J* = 7.7, 1.0 Hz, 1H, 6-CH), 7.12 (ddd, *J* = 7.9, 7.6, 1.0 Hz, 1H, 8-CH), 7.05 (ddd, *J* = 8.7, 2.9, 2.1 Hz, 2H, 2''- and 6''-CH), 6.82 (ddd, *J* = 8.7, 2.9, 2.1 Hz, 2H, 3''- and 5''-CH), 4.26 (s, 2H, 1'-CH_2), 3.68 (s, 3H, -OCH_3), 3.63 (s, 3H, 5-NCH_3), 3.62 (s, 3H, 2-NCH_3).

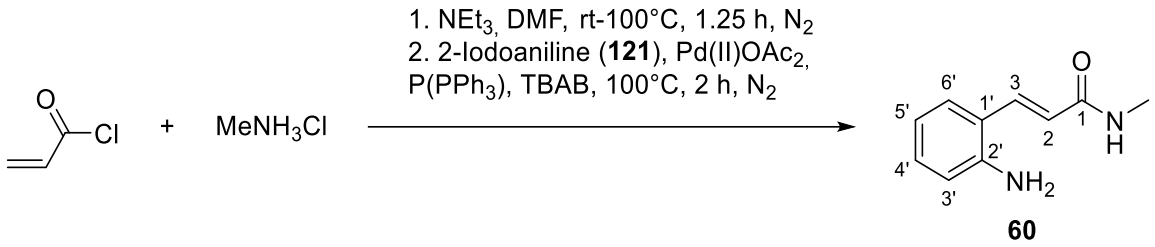
^{13}C NMR (101 MHz, DMSO) δ: 162.34 (3-C_qO), 157.29 (4''-C_q), 147.86 (4a-C_q), 143.70 (5a-C_q), 133.77 (1''-C_q), 130.40 (1-CH), 128.61 (2''- and 6''-CH), 126.03 (7-CH), 121.66 (9a-C_q), 120.32 (8-CH), 118.78 (9-CH), 113.79 (3''- and 5''-CH), 109.11 (9b-C_q), 108.80 (6-CH), 102.60 (4-C_q), 54.94 (-OCH_3), 38.12 (2-NCH_3), 31.05 (5-NCH_3), 28.88 (1'-CH_2).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right]$ = 3056 w, 3028 w, 2988 w, 2944 w, 2831 w, 1841 w, 1736 w, 1667 m, 1611 m, 1585 w, 1578 w, 1557 m, 1508 m, 1488 w, 1478 w, 1467 m, 1451 mw, 1441 mw, 1418 m, 1401 m, 1378 m, 1348 m, 1338 w, 1324 w, 1301 m, 1284 m, 1262 m, 1241 ms, 1203 w, 1177 m, 1172 m, 1160 w, 1144 w, 1128 w, 1110 w, 1090 m, 1049 w, 1030 m, 1020 m, 986 w, 924 mw, 911 w, 866 w, 824 w, 816 w, 805 m, 785 m, 754 w, 743 ms, 730 mw, 714 mw, 707 mw, 671 w, 667 w.

7.4 Data of sythesised compounds – project β-carbolines 57-64

7.4.1 Heck reactions and their educts

(*E*)-3-(2-aminophenyl)-*N*-methylacrylamide (**60**)



60

Chemical Formula: $C_{10}H_{12}N2O$ **Molecular Weight:** 176.2190 g/mol

The preparation of amine **60** was performed in the style of Priebbenow et al.[115], with the difference of using DMF as solvent and NEt_3 as a base. For that, 2-propenoyl chloride (6.00 mL, 6.69 g, 70.9 mmol) and methylammonium chloride (4.89 g, 70.9 mmol) were added to a 250 mL two-neck flask and the air was exchanged to nitrogen. 100 mL of dry DMF and subsequently dry NEt_3 (27.0 mL, 19.6 g, 194 mmol) were added successively by syringe and it was stirred for 1 h at room temperature. The flask was heated up to 100°C and it was stirred for another 15 min, before adding the remaining reaction components at that temperature. 2-Iodoaniline (**121**) (6.02 g, 26.9 mmol), tetrakis(triphenylphosphane)palladium(0) (321 mg, 269 µmol), triphenylphosphine (713 mg, 269 µmol) and tetrabutylammonium bromide (2.20 g, 6.82 mmol) were premixed and then added in portions by spatula while degassing the reaction solution with N_2 gas. The suspension was stirred at 100°C for 2 h in a nitrogen atmosphere. After allowing the solution to cool down to room temperature, 200 mL of H_2O_d were added, the pH was adjusted to 3, using 2 M watery HCl solution. It was washed three times with 300 mL of methylene chloride and the organic layers were discarded. The water-DMF solution was then adjusted to pH 9 by adding solid K_2CO_3, while controlling the pH by using indicator paper. The solution was extracted three times with 300 mL of methylene chloride. The organic layers were washed five times with 100 mL of H_2O_d, one time with 50 mL of 5%-LiCl solution, then one last time with 50 mL of saturated brine solution. The methylene chloride layer was dried over dry $MgSO_4$ and concentrated *in vacuo*. Product **60** could be isolated by column chromatography with pure EtOAc with an 0.1% NEt_3 additive.

Yield and appearance: 725 mg (4.12 mmol, 15%) as beige-white solid.

HRMS (CI): m/z = calculated for $[C_{10}H_{12}N_2O]^{\bullet+}$: 176.09496, found: 176.0943.

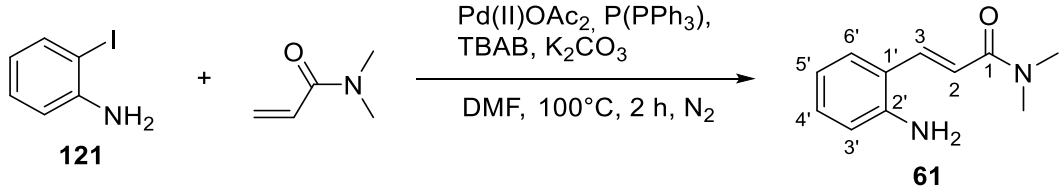
Melting area: 106.3 - 109.8°C

^{1}H NMR (400 MHz, Chloroform-d): δ 7.76 (d, J = 15.4 Hz, 1H, 3-CH), 7.32 (dd, J = 7.8, 1.5 Hz, 1H, 6'-CH), 7.13 (ddd, J = 8.0, 7.2, 1.5 Hz, 1H, 4'-CH), 6.73 (ddd, J = 7.8, 7.2, 1.2 Hz, 1H, 5'-CH), 6.68 (dd, J = 8.0, 1.2 Hz, 1H, 3'-CH), 6.30 (d, J = 15.4 Hz, 1H, 2-CH), 5.85 (s, 1H, -N<u>H</u>CH_3), 3.97 (s, 2H, -NH_2), 2.93 (d, J = 4.9 Hz, 3H, -NHC<u>H_3</u>).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 166.98 (1-C_q), 145.49 (2'-C_q), 136.45 (3-CH), 130.72 (4'-CH), 127.84 (6'-CH), 121.00 (2-CH), 120.49 (1'-C_q), 118.85 (5'-CH), 116.66 (3'-CH), 26.64 (-$NHCH_3$).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right]$ = 3411 w, 3327 w, 3274 mw, 3089 w, 2928 w, 2875 w, 2124 w, 1901 w, 1642 ms, 1603 m, 1562 m, 1489 m, 1455 m, 1438 m, 1411 m, 1384 m, 1345 m, 1309 m, 1257 m, 1230 m, 1156 m, 1119 m, 1093 m, 1056 mw, 1037 mw, 991 m, 979 m, 957 m, 878 m, 854 m, 814 w, 752 m, 745 m, 722 m, 711 m, 693 m, 661 m.

<u>(*E*)-3-(2-aminophenyl)-*N*,*N*-dimethylacrylamide (**61**)</u>



Chemical Formula: $C_{11}H_{14}N_2O$ **Molecular Weight:** 190.2460 g/mol

Heck reaction product **61** was synthesised according to the general synthesis protocol E (see subchapter 7.2), but the working up process differed from the, in the general instructions described, method. 2-Jodoaniline (**121**) (4.52 g, 20.2 mmol), palladium(II) acetate (270 mg, 1.20 mmol), triphenylphosphine (670 mg, 2.53 mmol), tetrabutylammonium bromide (1.63 g, 5.06 mmol) and K_2CO_3 (3.36 g, 20.2 mmol), 50 mL of dry DMF and *N*,*N*-dimethyl acrylamide (5.00 mL, 4.81 g, 48.5 mmol) were used. After letting the reaction solution cool down to room temperature 200 mL of H_2O_d was added to the flask. The pH was adjusted to 3 (with 2 M HCl solution) and the suspension was washed two times with 250 mL of ethyl acetate. The ethyl acetate phase was discarded and the pH of the watery solution was adjusted with solid Na_2CO_3 to pH 10. The pH was controlled by using pH paper. The alkaline watery layer was extracted five times with 250 mL EtOAc again and the combined organic layers were washed four times with 100 mL of H_2O_d, one time with 30 mL of a 5%-LiCl solution, then with 30 mL of saturated brine solution. The extracted solution was dried over $MgSO_4$ and concentrated *in vacuo*. Product **61** was successfully purified by means of column chromatography with a MeOH:CH_2Cl_2 (1:99-3:97, + 1% NEt_3 additive) solvent gradient.

Yield and appearance: 3.67 g (19.3 mmol, 95%) as light-yellow powder.

HRMS (ESI): m/z = calculated for $[C_{11}H_{15}N_2O]^+$: 191.11789, found: 191.11790.

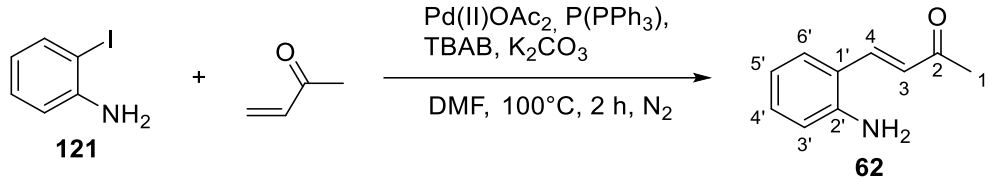
Melting area: 141.6 - 142.1°C

^{1}H NMR (400 MHz, Chloroform-d) δ: 7.80 (d, J = 15.2 Hz, 1H, 3-CH), 7.36 (dd, J = 7.8, 1.5 Hz, 1H, 6'-CH), 7.14 (td, J = 7.7, 1.6 Hz, 1H, 4'-CH), 6.80 (d, J = 15.2 Hz, 1H, 2-CH), 6.75 (td, J = 7.5, 1.2 Hz, 1H, 5'-CH), 6.69 (dd, J = 8.1, 1.2 Hz, 1H, 3'-CH), 3.97 (s, 2H, -NH_2), 3.15 (s, 3H, -N($\underline{CH_3}$)$_2$), 3.06 (s, 3H, -N($\underline{CH_3}$)$_2$).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 166.95 (1-C_qO), 145.41 (2'-C_q), 137.96 (3-CH), 130.64 (4'-CH), 127.83 (6'-CH), 121.08 (1'-C_q), 118.79 (5'-CH), 118.03 (2-CH), 116.58 (3'-CH), 37.51 (-N($\underline{CH_3}$)$_2$), 36.07 (-N($\underline{CH_3}$)$_2$).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right] =$ 3454 w, 3316 w, 3205 w, 3033 w, 2917 w, 1641 m, 1601 m, 1585 m, 1485 m, 1455 m, 1409 w, 1391 m, 1318 w, 1295 w, 1256 w, 1141 m, 1062 w, 1032 w, 975 m, 953 w, 930 w, 886 w, 855 w, 772 w, 749 w, 738 s, 665 w.

(*E*)-4-(2-aminophenyl)but-3-en-2-one (**62**)



Chemical Formula: $C_{10}H_{11}NO$ **Molecular Weight:** 161.2040 g/mol

Heck reaction product **62** was synthesised according to the general synthesis protocol E (see subchapter 7.2). 2-Jodoaniline (**121**) (2.05 g, 9.17 mmol), 3-buten-2-one (820 µL, 708 mg, 10.1 mmol), palladium(II) acetate (125 mg, 546 µmol), triphenylphosphine (304 mg, 1.15 mmol), tetrabutyl-ammonium bromide (739 mg, 2.29 mmol), potassium carbonate (1.52 g, 9.17 mmol) and 30 mL of dry DMF were used. Product **62** could be purified by column chromatography with CH_2Cl_2:MeOH (99:1 + 0.1% NEt_3 additive).

Yield and appearance: 465 mg (2.88 mmol, 32%) as grey-brownish oil.

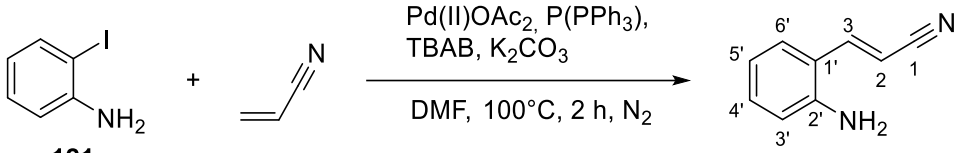
HRMS (ESI): *m/z* = calculated for $[C_{10}H_{12}NO]^+$: 162.09134, found: 162.09153.

^{1}H NMR (400 MHz, Chloroform-*d*) δ: 7.68 (d, *J* = 16.0 Hz, 1H, 4-CH), 7.39 (dd, *J* = 7.9, 1.6 Hz, 1H, 6'-CH), 7.18 (ddd, *J* = 8.0, 7.7, 1.6 Hz, 1H, 4'-CH), 6.78 (ddd, *J* = 7.9, 7.7, 1.2 Hz, 1H, 5'-CH), 6.71 (dd, *J* = 8.0, 1.2 Hz, 1H, 3'-CH), 6.67 (d, *J* = 16.0 Hz, 1H, 3-CH), 3.99 (s, 2H, -NH_2), 2.36 (s, 3H, 1-CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 198.30 (2-C_qO), 145.99 (2'-C_q), 138.73 (4-CH), 131.68 (4'-CH), 128.32 (6'-CH), 126.93 (3-CH), 120.03 (1'-C_q), 119.23 (5'-CH), 117.01 (3'-CH), 28.23 (1-CH_3).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right]$ = 4053 w, 3211 w, 3054 w, 2919 w, 2851 w, 2166 w, 2136 w, 2034 w, 1999 w, 1956 w, 1823 w, 1710 w, 1659 w, 1599 m, 1489 m, 1456 mw, 1435 m, 1373 mw, 1310 m, 1247 m, 1220 w, 1178 m, 1158 m, 1117 m, 1094 m,1070 m, 1027 m, 997 m, 974 m, 851 w, 820 m, 783 m, 745 ms, 719 s, 693 ms.

(*E*)-3-(2-aminophenyl)acrylonitrile (**63**)



Chemical Formula: $C_9H_8N_2$ **Molecular Weight:** 144.1770 g/mol

Heck reaction product **63** was synthesised according to the general synthesis protocol E (see subchapter 7.2). 2-Iodoaniline (**121**) (10.0 g, 45.7 mmol), acrylonitrile (2.80 mL, 5.13 g, 95.7 mmol), palladium(II) acetate (314 mg, 1.37 mmol), triphenylphosphine (1.81 g, 6.85 mmol), potassium carbonate (7.58 g, 45.7 mmol), tetrabutylammonium bromide (1.84 g, 5.71 mmol) and 100 mL of dry DMF were used. Product purification by column chromatography with a MeOH:CH_2Cl_2 (1:99-3:97, + 0.1% NEt_3) solvent gradient yielded pure product **63**.

Yield and appearance: 2.63 g (18.2 mmol, 40%) as pale brown crystals.

HRMS (ESI): *m/z* = calculated for $[C_9H_9N_2]^+$: 145.07602, found: 145.07598.

Melting area: 129.7 - 130.8°C

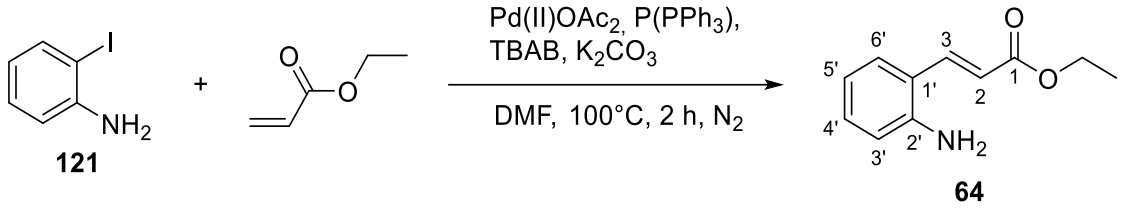
^{1}H NMR (400 MHz, Methylene Chloride-d2) δ: 7.88 (d, J = 8.8 Hz, 1H, 3-CH), 7.63 (dd, J = 8.1, 1.5 Hz, 1H, 6'-CH), 7.60 (dd, J = 8.4, 1.4 Hz, 1H, 3'-CH), 7.53 (ddd, J = 8.4, 6.8, 1.5 Hz, 1H, 4'-CH), 7.24 (ddd, J = 8.1, 6.8, 1.3 Hz, 1H, 5'-CH), 6.74 (d, J = 8.8 Hz, 1H, 2-CH), 4.88 (s, 2H, -NH_2).

^{13}C NMR (101 MHz, CD_2Cl_2) δ: 157.74 (1-C_qN), 148.46 (2'-C_q), 138.30 (3-CH), 130.03 (4'-CH), 128.01 (6'-CH), 126.56 (3'-CH), 124.21 (1'-C_q), 122.97 (5'-CH), 112.21 (2-CH).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right]$ = 3437 m, 3293 w, 3240 w, 3143 m, 3042 m, 2824 w, 2745 w, 2219 w, 2059 w, 1951 w, 1633 s, 1610 s, 1602 m, 1564 m, 1528 w, 1505 s, 1483 m, 1429 s, 1392 s, 1352 s,

1302 m, 1264 m, 1247 w, 1222 w, 1210 m, 1152 m, 1141 m, 1124 m, 1023 m, 975 m, 946 m, 914 m, 869 m, 819 s, 779 m, 770 m, 757 s, 728 m, 683 m.

Ethyl (*E*)-3-(2-aminophenyl)acrylate (**64**)



Chemical Formula: $C_{11}H_{13}NO_2$ **Molecular Weight:** 191.2300 g/mol

Heck reaction product **64** was synthesised according to the general synthesis protocol E (see subchapter 7.2). 2-Iodoaniline (**121**) (5.00 g, 22.8 mmol), ethyl acrylate (5.00 mL, 4.59 g, 45.9 mmol), palladium(II) acetate (157 mg, 685 µmol), triphenylphosphine (907 mg, 3.42 mmol), K_2CO_3 (3.79 g, 22.8 mmol), tetrabutylammonium bromide (920 mg, 2.85 mmol) and 50 mL of dry DMF were used. Product **64** was purified by column chromatography with a MeOH:CH_2Cl_2 (1:99-3:97, + 0.1% NEt_3) solvent gradient.

Yield and appearance: 4.18 g (21.9 mmol, 96%) as pale brown crystalline solid.

HRMS (ESI): *m/z* = calculated for $[C_{11}H_{14}NO_2]^+$: 192.10191, found: 192.10191.

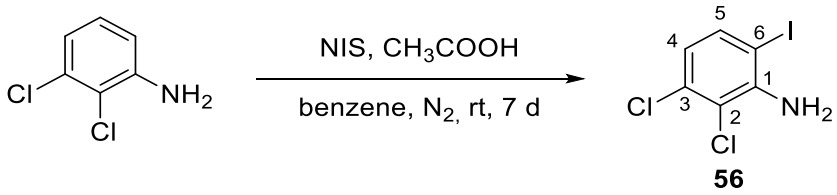
Melting area: 76.7 - 78.7 °C

^{1}H NMR (400 MHz, Chloroform-*d*) δ: 7.82 (d, *J* = 15.8 Hz, 1H, 3-CH), 7.38 (dd, *J* = 7.9, 1.5 Hz, 1H, 6'-CH), 7.17 (ddd, *J* = 8.1, 7.3, 1.5 Hz, 1H, 4'-H), 6.77 (ddd, *J* = 7.9, 7.3, 1.3 Hz, 1H, 5'-H), 6.70 (dd, *J* = 8.1, 1.3 Hz, 1H, 3'-H), 6.35 (d, *J* = 15.8 Hz, 1H, 2-H), 4.26 (q, *J* = 7.1 Hz, 2H, -CH_2), 3.96 (s, 2H, -NH_2), 1.34 (t, *J* = 7.1 Hz, 3H, -CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 167.41 (1-C_qO), 145.64 (2'-C_q), 140.16 (3-CH), 131.38 (4'-CH), 128.29 (6'-CH), 120.11 (1'-C_q), 119.11 (5'-CH), 118.41 (2-CH), 116.85 (3'-CH), 60.60 (-CH_2), 14.50 (-CH_3).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right]$ = 3465 w, 3368 w, 3229 w, 3061 w, 3032 w, 2992 w, 2979 w, 2936 w, 2906 w, 2871 w, 1687 s, 1633 m, 1615 s, 1603 m, 1570 m, 1490 m, 1463 m, 1444 w, 1394 w, 1363 m, 1334 m, 1322 m, 1304 m, 1264 w, 1202 m, 1180 m, 1159 s, 1116 m, 1030 m, 978 m, 969 m, 885 m, 860 m, 808 m, 751 s, 722 m, 702 m, 672 w.

2,3-Dichloro-6-iodoaniline (**56**)



56

Chemical Formula: $C_6H_4Cl_2IN$ **Molecular Weight:** 287.9095 g/mol

2,3-Dichloro-6-iodoaniline (**56**) was prepared with variations following the protocol of Shen et al.[77]. 2,3-Dichloroaniline (15.9 mL, 21.7 g, 134 mmol) was put in a three-neck flask and the air was exchanged to nitrogen, then 400 mL of dry benzene was added. While stirring, the reaction was started by adding dried acidic acid (9.10 mL, 9.55 g, 158 mmol) *via* syringe, then *N*-Iodosuccinimide (30.2 g, 134 mmol) was added in portions, while degassing. It was stirred under N_2-atmosphere for 7 days at room temperature, then the solution was quenched with 150 mL of H_2O_d and after 10 min of stirring, the phases were separated with the help of a separation funnel. The organic layers were washed one time with 75 mL of saturated brine solution, then the organic layer was dried over $MgSO_4$ and the excess of solvent was removed by rotary evaporation. Product **56** was purified by column chromatography with EtOAc:isohexane (0.5:9.5 + an 0.5% NEt_3-additive).

Yield and appearance: 35.7 g (124 mmol, 93%) as white needles.

HRMS (EI): *m/z* = calculated for [$C_6H_4N_1Cl_2I$]: 286.87655 (^{35}Cl, ^{35}Cl), 288.87360 (^{35}Cl, ^{37}Cl), 289.87695 (^{35}Cl, ^{38}Cl or ^{36}Cl, ^{37}Cl), found: 286.8767 (^{35}Cl, ^{35}Cl), 288.8767 (^{35}Cl, ^{37}Cl), 289.8797 (^{35}Cl, ^{38}Cl or ^{36}Cl, ^{37}Cl).

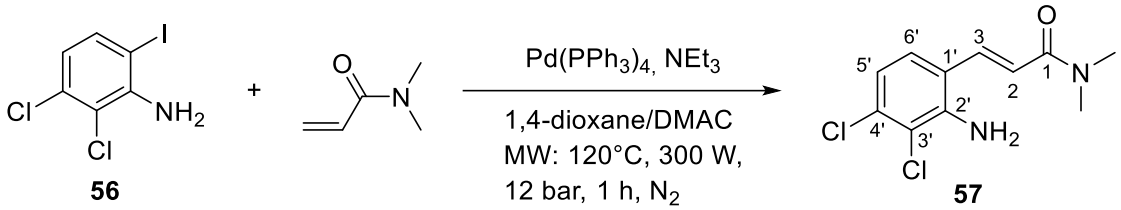
Melting area: 71.7 - 72.8°C (Lit. ref.: **M. a. :** 71-72°C[101])

^{1}H NMR (400 MHz, Chloroform-d) δ: 7.46 (d, J = 8.5 Hz, 1H, 5-CH), 6.61 (d, J = 8.5 Hz, 1H, 4-CH), 4.68 (s, 2H, -NH_2). (Lit. ref.: **^{1}H NMR (400 MHz, $CDCl_3$) δ:** 7.46 (d, J = 8.5 Hz, 1 H), 6.61 (d, J = 8.5 Hz, 1 H), 4.68 ppm (br s, 2 H).[101])

^{13}C NMR (101 MHz, $CDCl_3$) δ: 144.88 (1-C_q), 137.03 (5-CH), 133.65 (2- or 3-C_q), 120.37 (4-CH), 116.41(2- or 3-C_q), 80.31 (6-C_q). (Lit. ref.: **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 144.7, 136.9, 133.5, 120.2, 116.2, 80.1[101])

IR (ATR): $\tilde{\nu}\ \left[\frac{1}{cm}\right]$ = 3303 w, 1600 m, 1558 w, 1444 w, 1406 w, 1285 w, 1257 w, 1198 w, 1131 w, 1078 w, 1046 w, 910 w, 792 w, 781 s, 754 w, 714 w. (Lit. ref.: **IR (solid):** $\tilde{\nu}\ \left[\frac{1}{cm}\right]$ = 3419, 3307, 1600, 1444, 1408, 1086, 1046, 911, 783, 756.[101])

(*E*)-3-(2-amino-3,4-dichlorophenyl)-*N*,*N*-dimethylacrylamide (**57**)



Chemical Formula: $C_{11}H_{12}Cl_2N_2O$ **Molecular Weight:** 259.1300 g/mol

Heck reaction product **57** was synthesised using an improved microwave assisted method[107] developed by Dr. Ong, which was originally based on a method he found in a reference book named "Organikum"[108]. Following his instructions, the aniline **56** (2.63 g, 9.13 mmol) and tetrakis(triphenyl-phosphine)palladium(0) (528 mg, 457 µmol) were put in a 35 mL synthesis microwave tube and diluted in 10 mL of dry 1,4-dioxane. 10 mL of dry DMAC, *N*,*N*-dimethylacrylamide (2.00 mL, 1.92 g, 19.4 mmol) and triethylamine (1.30 mL, 944 mg, 9.33 mmol) were added by syringe right before the reaction was started. The mixture was heated in a synthesis microwave for 1 h at 130 °C (300 W, 12 bar). The reaction solution was added to 100 mL of H_2O_d, and extracted three times with 250 mL of EtOAc. The combined organic layers were washed five times with 75 mL of H_2O_d, one time with 30 mL of a 5%-LiCl solution, then one time with 30 mL of saturated brine solution. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography with a MeOH:DCM (2.5:97.5 + NEt_3 0.1 % additive) solvent mixture yielded product **57**.

Yield and appearance: 2.10 g (8.10 mmol, 89%) as light beige powder.

HRMS (ESI): *m/z* = calculated for $[C_{11}H_{13}Cl_2N_2O]^+$: 259.03994 (^{35}Cl), found: 259.04006 (^{35}Cl).

Melting area: 146.6 - 150.5°C

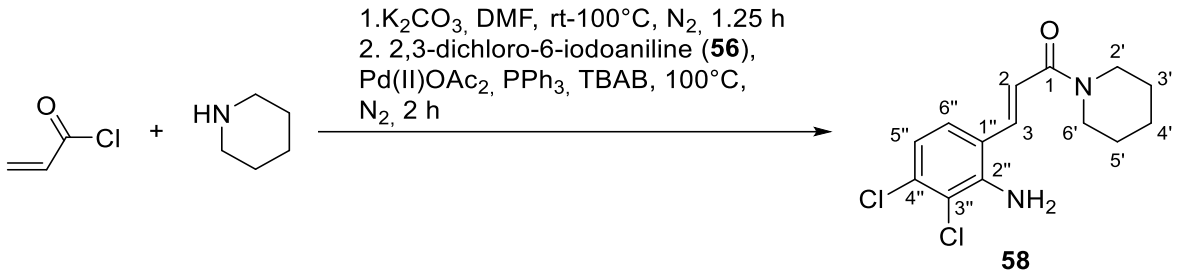
^{1}H NMR (500 MHz, DMSO-d6) δ: 7.66 (d, J = 15.1 Hz, 1H, 3-CH), 7.52 (d, J = 8.5 Hz, 1H, 6'-CH), 7.02 (d, J = 15.1 Hz, 1H, 2-CH), 6.80 (d, J = 8.5 Hz, 1H, 5'-CH), 5.90 (s, 2H, -NH_2), 3.13 (s, 3H, -N($\underline{CH_3}$)$_2$), 2.93 (s, 3H, -N($\underline{CH_3}$)$_2$).

^{13}C NMR (126 MHz, DMSO) δ: 165.61 (1-C_qO), 144.65 (1'-C_q), 135.64 (3-CH), 132.38 (4'-C_q), 126.44 (6'-CH), 119.73 (3'-C_q), 119.34 (2-CH), 116.91 (5'-CH), 116.40 (2'-C_q), 36.92 (-N($\underline{CH_3}$)$_2$), 35.30 (-N($\underline{CH_3}$)$_2$).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right]$ = 3423 w, 3314 w, 3206 w, 3024 w, 2934 w, 1724 w, 1636 s, 1589 s, 1551 w, 1484 m, 1457 m, 1425 m, 1412 m, 1394 s, 1318 m, 1293 w, 1258 m, 1208 w, 1182 w, 1145 m,

1136 m, 1120 m, 1103 m, 1057 w, 989 m, 936 w, 921 m, 885 w, 860 m, 827 w, 791 s, 747 m, 720 m, 707 m, 697 m, 667 w.

(*E*)-3-(2-amino-3,4-dichlorophenyl)-1-(piperidin-1-yl)prop-2-en-1-one (**58**)



Chemical Formula: $C_{14}H_{16}Cl_2N_2O$ **Molecular Weight:** 299.19500 g/mol

The synthesis of **58** was carried out as reported by Priebbenow et al.[115], instead of toluol though, DMF was used as a solvent. Piperidine (8.00 mL, 6.90 g, 81.0 mmol) and potassium carbonate (2.45 g, 14.7 mmol) were submitted to a three-neck flask and the air was exchanged to N_2, then 150 mL of dry and degassed DMF was added. At room temperature, acryloyl chloride (3.40 mL, 3.79 g, 40.2 mmol) was added by syringe and the solution was stirred for 1 h at room temperature. The solution was then heated up to 100°C and it was stirred for another 15 min, when the other premixed reaction components were added. The mixture of solids, containing aniline **56** (4.33 g, 14.7 mmol), palladium(II) acetate (169 mg, 737 µmol), triphenylphosphine (488 mg, 1.84 mmol) and tetrabutylammonium bromide (1.19 g, 3.68 mmol), was added spoon wise to the flask while degassing with N_2. The reaction solution was stirred for another 2 h at 100°C under protective gas. After cooling down to room temperature, 100 mL of H_2O_d were added and the solution was extracted one time with 200 mL of EtOAc. The EtOAc phase was washed four times with 100 mL of water, two times with 50 mL of a 5%-LiCl solution, then finally with 50 mL of saturated brine solution. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Product **58** was successfully isolated after performing column chromatography with an isohexane:EtOAc (1:1-0:1, + 0.1% NEt_3 as additive) solvent gradient.

Yield and appearance: 3.01 g (10.1 mmol, 68%) as pale-yellow solid.

HRMS (ESI): m/z = calculated for $[C_{14}H_{17}Cl_2N_2O]^+$: 299.07124 (^{35}Cl, ^{35}Cl), 301.06829 (^{35}Cl, ^{37}Cl), 302.07165 (^{35}Cl, ^{38}Cl, or ^{36}Cl, ^{37}Cl), found: 299.07176 (^{35}Cl, ^{35}Cl), 301.06899 (^{35}Cl, ^{37}Cl), 302.07220 (^{35}Cl, ^{38}Cl, or ^{36}Cl, ^{37}Cl).

Melting area: 145.3 – 146.8°C

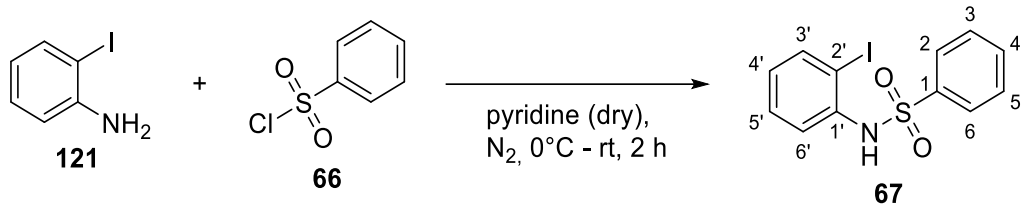
^{1}H NMR (400 MHz, Chloroform-*d*) δ: 7.69 (d, *J* = 15.1 Hz, 1H, 3-CH), 7.18 (dd, *J* = 8.4, 0.6 Hz, 1H, 6''-CH), 6.83 (dd, *J* = 8.4, 0.6 Hz, 1H, 5''-CH), 6.80 (d, *J* = 15.1 Hz, 1H, 2-CH), 4.60 (s, 2H, -NH_2), 3.66 (dd, *J* = 5.5, 4.7 Hz, 2H, 2'- or 6'-CH_2), 3.56 (dd, *J* = 5.5, 4.7 Hz, 2H, 2'- or 6'-CH_2), 1.73 – 1.65 (m, 2H, 4'-CH_2), 1.65 – 1.57 (m, 4H, 3'- and 5'-CH_2).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 165.08 (1-C_qO), 143.18 (2''-C_q), 136.84 (3-CH), 133.99 (4''-C_q), 126.05 (6''-CH), 120.47 (1''-C_q), 119.85 (2-CH), 119.08 (5''-CH), 118.44 (3''-C_q), 47.16 (2'- or 6'-CH_2), 43.60 (2'- or 6'-CH_2), 26.89 (3'- or 5'-CH_2), 25.73 (3'- or 5'-CH_2), 24.72 (4'-CH_2).

IR (ATR): $\tilde{\nu}$ $\left[\frac{1}{cm}\right]$ = 3474 w, 3332 w, 3198 w, 2939 w, 2854 w, 1632 w, 1596 w, 1578 w, 1461 w, 1444 w, 1422 w, 1349 w, 1300 w, 1241 w, 1218 w, 1207 w, 1187 w, 1136 w, 1120 w, 1080 w, 1019 w, 986 w, 977 w, 957 w, 925 w, 901 w, 880 w, 851 w, 801 w, 783 w, 706 w, 694 w.

7.4.2 Sulfonamides syntheses 67-76

N-(2-iodophenyl)benzenesulfonamide (**67**)



67

Chemical Formula: $C_{12}H_{10}INO_2S$ **Molecular Weight:** 359.1815 g/mol

Sulfonamide **67** was synthesised according to the general synthesis protocol F in subchapter 7.2. 2-Iodoaniline (**121**) (4.43 g, 20.2 mmol), benzenesulfonyl chloride (**66**) (2.60 mL, 3.59 g, 20.3 mmol), dry pyridine (7.00 mL, 6.84 g, 86.5 mmol) and glacial acetic acid (5.00 mL, 5.25 g, 87.4 mmol) were used. 250 mL of CH_2Cl_2, then 75 mL of H_2O_d were added after stopping the reaction and the workup was further performed as described in the general protocol. Product **67** could be isolated by means of column chromatography with a MeOH:CH_2Cl_2 (1:99 + 1% glacial acetic acid additive) solvent mixture.

Yield and appearance: 7.17 g (20.0 mmol, 99%) as pale brown solid.

HRMS (ESI): m/z = calculated for $[C_{12}H_9INO_2S]^-$: 357.94042, found: 357.94065.

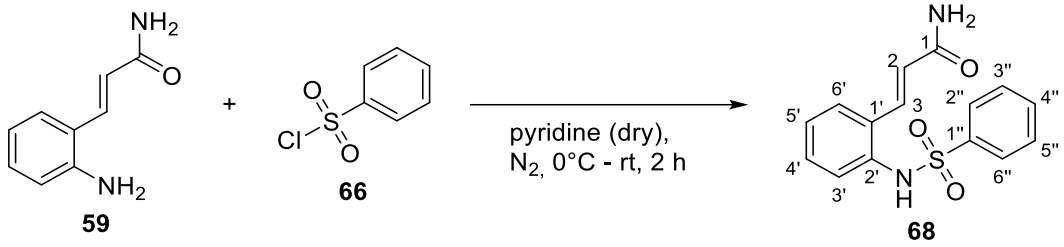
Melting area: 107.6 - 110.3°C

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.74 (dd, *J* = 8.3, 1.3 Hz, 2H, 2- and 6-CH), 7.67 (dd, *J* = 8.1, 1.6 Hz, 1H, 6‘-CH), 7.64 (dd, *J* = 8.0, 1.5 Hz, 1H, 3‘-CH), 7.55 (tt, *J* = 7.5, 1.3 Hz, 1H, 4-CH), 7.43 (ddt, *J* = 8.3, 7.5, 1.3 Hz, 2H, 3- and 5-CH), 7.32 (tt, *J* = 8.1, 7.5, 1.5 Hz, 1H, 5‘-CH), 6.84 (td, *J* = 8.0, 7.5, 1.6 Hz, 1H, 4‘-CH), 6.79 (s, 1H, -NH).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 139.26 (3‘-CH), 138.95 (1-C_q), 137.49 (1‘-C_q), 133.44 (4-CH), 129.69 (5‘-CH), 129.18 (3- and 5-CH), 127.55 (2- and 6-CH), 127.20 (4‘-CH), 123.00 (6‘-CH), 92.69 (2‘-C_q).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right]$ = 3825 w, 3257 m, 3080 w, 3053 w, 2166 w, 1999 w, 1978 w, 1961 w, 1927 w, 1901 w, 1818 w, 1771 w, 1666 w, 1613 w, 1579 w, 1567 w, 1466 m, 1445 m, 1394 m, 1331 m, 1308 m, 1294 w, 1264 w, 1215 w, 1167 m, 1155 m, 1118 mw, 1089 m, 1070 mw, 1044 w, 1017 m, 1003 mw, 997 mw, 982 w, 944 mw, 927 w, 898 m, 883 mw, 862 w, 845 w, 819 w, 755 m, 720 m, 709 m, 685 m, 668 w.

(*E*)-3-(2-(phenylsulfonamido)phenyl)acrylamide (**68**)



Chemical Formula: $C_{15}H_{14}N_2O_3S$ **Molecular Weight:** 302.3480 g/mol

The sulfonamide **68** was synthesised according to the general synthesis protocol F in subchapter 7.2. (*E*)-3-(2-aminophenyl)acrylamide (**59**) (700 mg, 4.32 mmol), benzenesulfonyl chloride (**66**) (600 µL, 831 mg, 4.70 mmol), dry pyridine (4.00 mL, 3.91 g, 49.5 mmol) and glacial acetic acid (3.00 mL, 3.15 g, 52.4 mmol) were used. 100 mL of CH_2Cl_2, then 25 mL of H_2O_d were added after stopping the reaction and the workup was further performed as described in the general protocol. Product **68** was purified by column chromatography with an EtOAc:MeOH (100:0-95:5 + 1% acetic acid additive) solvent gradient.

Yield and appearance: 1.03 g (3.41 mmol, 79%) as white-beige solid.

HRMS (ESI): m/z = calculated for $[C_{15}H_{15}O_3N_2S]^+$: 303.07979, found: 303.07985.

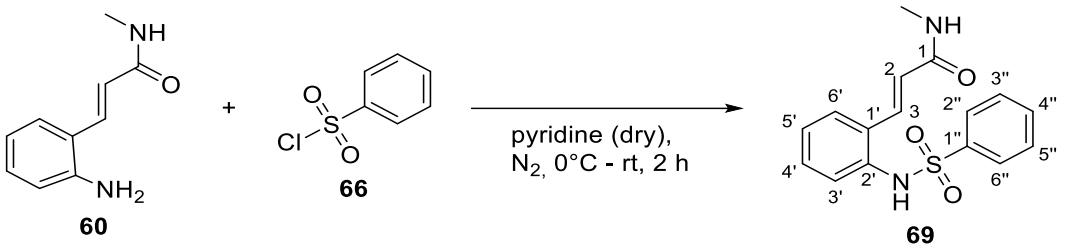
Melting area: 211.0 - 217.8°C

^{1}H NMR (500 MHz, DMSO-d_6) δ: 9.98 (s, 1H, $PhSO_2$-NH-), 7.70 – 7.64 (m, 3H, 2- or 3-CH, 2''- and 6''-CH), 7.64 – 7.59 (m, 1H, 4''-CH), 7.58 – 7.55 (m, 1H, 3'- or 6'-CH), 7.55 – 7.50 (m, 2H, 3''- and 5''-CH), 7.44 (s, 1H, -NH_2), 7.28 – 7.21 (m, 2H, 4'- and 5'-CH), 7.08 (s, 1H, -NH_2), 6.89 – 6.84 (m, 1H, 3'- or 6'-CH), 6.42 (d, *J* = 15.8 Hz, 1H, 2- or 3-CH).

^{13}C NMR (126 MHz, DMSO) δ: 166.44 (1-OC_q), 139.85 (1''-C_q), 134.94 (2- or 3-CH), 134.93 (1'- or 2'-C_q), 132.79 (4''-CH), 132.10 (1'- or 2'- C_q), 129.68 (4'- or 5'-CH), 129.15 (3''- and 5''-CH), 127.00 (4'- or 5'-CH), 126.88 (3'- or 6'-CH), 126.67 (2''- and 6''-CH), 126.44 (3'- or 6'- CH), 123.44 (2- or 3-CH).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right]$ = 3399 w, 3323 w, 3204 w, 3006 w, 2750 w, 2034 w, 1999 w, 1662 mw, 1639 w, 1581 mw, 1489 w, 1462 w, 1443 w, 1406 w, 1326 m, 1304 w, 1294 w, 1286 w, 1232 w, 1174 w, 1152 m, 1122 w, 1090 mw, 1071 w, 1050 w, 1022 w, 999 w, 974 w, 957 w, 936 w, 868 w, 856 w, 769 w, 754 mw, 717 w, 669 w, 689 m.

(*E*)-*N*-methyl-3-(2-(phenylsulfonamido)phenyl)acrylamide (**69**)



Chemical Formula: $C_{16}H_{16}N_2O_3S$ **Molecular Weight:** 316.3750 g/mol

The sulfonamide **69** was synthesised according to the general synthesis protocol F in subchapter 7.2. Educt **60** (616 mg, 3.50 mmol), benzenesulfonyl chloride (**66**) (500 µL, 692 mg, 3.92 mmol), dry pyridine (4.50 mL, 4.40 g, 55.6 mmol) and glacial acetic acid (5.00 mL, 5.25 g, 86.5 mmol) were used. 75 mL of CH_2Cl_2, then 25 mL of H_2O_d were added after stopping the reaction and the workup was further performed as described in the general protocol. Product **69** could be recrystallized from a CH_2Cl_2:isohexane (1:5, + 1% acetic acid additive) solvent mixture.

Yield and appearance: 525 mg (1.66 mmol, 47%) as whitish clear crystals.

HRMS (ESI): m/z = calculated for $[C_{16}H_{15}N_2O_3S]^-$: 315.08089, found: 315.08102.

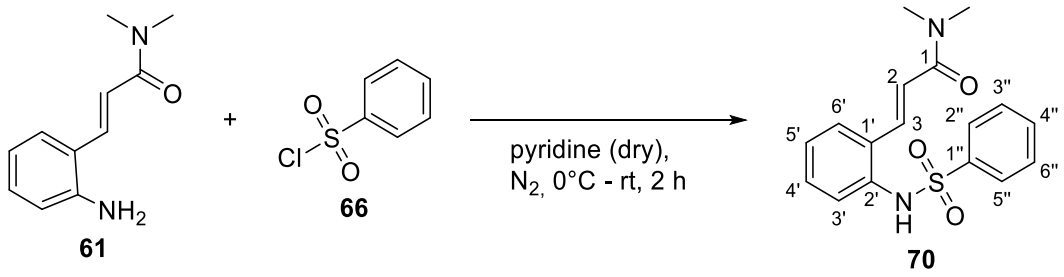
Melting area: 238.6 - 239.9°C

^{1}H NMR (500 MHz, DMSO-d_6) δ: 10.00 (s, 1H, $PhSO_2$-NH-), 7.96 (q, *J* = 4.7 Hz, 1H, -N<u>H</u>CH_3), 7.65 (ddd, *J* = 7.0, 1.9, 1.5 Hz, 2H, 2''- and 6''-CH), 7.65 (d, *J* = 15.8 Hz, 1H, 3-CH), 7.61 (tt, *J* = 7.5, 1.9 Hz, 1H, 4''-CH), 7.57 – 7.52 (m, 1H, 6'-CH), 7.52 (ddt, *J* = 7.5, 7.0, 1.7 Hz, 2H, 3''- and 5''-CH), 7.27 – 7.19 (m, 2H, 4'- and 5'-CH), 6.90 – 6.82 (m, 1H, 3'-CH), 6.38 (d, *J* = 15.8 Hz, 1H, 2-CH), 2.71 (d, *J* = 4.7 Hz, 3H, -NHC<u>H</u>$_3$).

^{13}C NMR (126 MHz, DMSO) δ: 165.27 (1-C_qO), 139.88 (1''-C_q), 134.88 (2'-C_q), 134.19 (3-CH), 132.77 (4''-CH), 132.29 (1'-C_q), 129.60 (4'-CH), 129.14 (3''- and 5''-CH), 127.03 (3'- or 5'-CH), 126.99 (3'- or 5'-CH), 126.66 (2''- and 6''-CH), 126.40 (6'-CH), 123.33 (2-CH), 25.67 (-NH<u>C</u>H_3).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right]$ = 3291 w, 3093 w, 2822 w, 2165 w, 1999 w, 1646 w, 1602 w, 1595 w, 1546 w, 1488 w, 1447 w, 1424 w, 1403 w, 1335 w, 1309 w, 1284 w, 1269 w, 1225 w, 1164 mw, 1151 mw, 1088 mw, 1063 w, 1046 w, 1024 w, 979 mw, 963 w, 950 w, 919 w, 887 w, 858 w, 824 w, 770 w, 749 w, 726 mw, 679 m.

(*E*)-*N*,*N*-dimethyl-3-(2-(phenylsulfonamido)phenyl)acrylamide (**70**)



61 **66** **70**

Chemical Formula: $C_{17}H_{18}N_2O_3S$ **Molecular Weight:** 330.4020 g/mol

The sulfonamide **70** was synthesised according to the general synthesis protocol F in subchapter 7.2. Educt **61** (3.35 g, 17.6 mmol), benzenesulfonyl chloride (**66**) (2.30 mL, 3.18 g, 18.0 mmol), dry pyridine (8.50 mL, 8.32 g, 105 mmol) and glacial acetic acid (7.00 mL, 7.34 g, 122 mmol) were used. 200 mL of CH_2Cl_2, then 75 mL of H_2O_d were added after stopping the reaction and the workup was further performed as described in the general protocol. Performing a column chromatography purification with a MeOH:CH_2Cl_2 (1:99 + 1% glacial acetic acid additive) solvent mixture yielded pure product **70**.

Yield and appearance: 5.54 g (16.8 mmol, 95%) as white powder.

HRMS (EI): m/z = calculated for $[C_{17}H_{18}O_3N_2S_1]^{\bullet+}$: 330.10381, found: 330.1026.

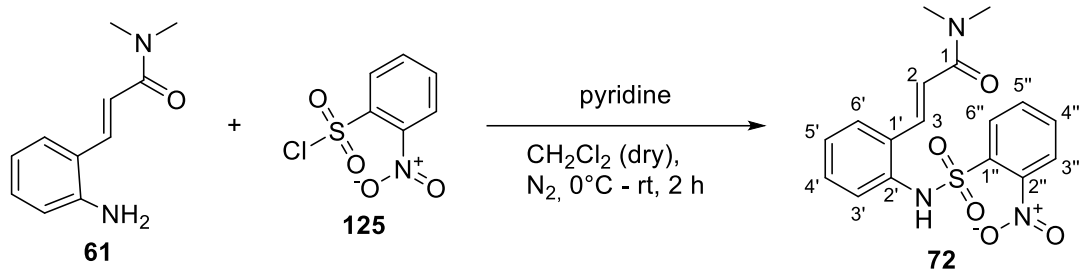
Melting area: 203.8 - 204.2°C

^{1}H NMR (400 MHz, Chloroform-*d*) δ: 8.87 (s, 1H, -NH), 7.87 (d, *J* = 15.1 Hz, 1H, 3-CH), 7.69 – 7.63 (m, 2H, 2''- and 6''-CH), 7.56 (dd, *J* = 8.0, 1.2 Hz, 1H, 3'-CH), 7.42 – 7.32 (m, 3H, 4'-, 6'- and 4''-CH), 7.32 – 7.27 (m, 2H, 3''- and 5''-CH), 7.22 – 7.17 (m, 1H, 5'-CH), 6.40 (d, *J* = 15.1 Hz, 1H, 2-CH), 3.09 (s, 3H, -N($\underline{CH_3}$)$_2$), 3.05 (s, 3H, -N($\underline{CH_3}$)$_2$).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 166.31 (1-C_qO), 139.65 (1''-C_q), 137.99 (3-CH), 135.00 (2'-C_q), 132.32 (4''-CH), 132.06 (1'-C_q), 130.23 (4'-CH), 128.88 (3''- and 5''-CH), 128.35 (3'-CH), 127.44 (2''- and 6''-CH), 127.05 (6'-CH), 127.01 (5'-CH), 120.09 (2-CH), 37.76 (-N($\underline{CH_3}$)$_2$), 36.70 (-N($\underline{CH_3}$)$_2$).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right]$ = 3464 w, 3369 m, 3228 w, 3061 w, 3032 w, 2992 w, 2979 w, 2936 w, 2906 w, 1687 s, 1658 w, 1633 w, 1614 s, 1603 s, 1571 w, 1490 m, 1463 m, 1444 w, 1394 w, 1363 m, 1334 m, 1322 m, 1304 m, 1264 w, 1202 m, 1181 s, 1160 s, 1116 m, 1030 m, 977 m, 969 m, 885 m, 860 m, 807 w, 751 s, 722 m, 702 w, 671 w.

(*E*)-*N*,*N*-dimethyl-3-(2-((2-nitrophenyl)sulfonamido)phenyl)acrylamide (**72**)



61 + **125** → **72**

Chemical Formula: $C_{17}H_{17}N_3O_5S$ **Molecular Weight:** 375.3990 g/mol

The sulfonamide **72** was synthesised according to the general synthesis protocol F in subchapter 7.2. Educt **61** (1.50 g, 7.88 mmol), dissolved in 6 mL of CH_2Cl_2, 2-nitrobenzenesulfonyl chloride (**125**) (1.7 g, 8.04 mmol), dissolved in 3 mL of dry CH_2Cl_2, dry pyridine (9.57 mL, 9.36 g, 118 mmol) and glacial acetic acid (9.00 mL, 9.45 g, 157 mmol) were used. 100 mL of CH_2Cl_2, then 25 mL of H_2O_d were added after stopping the reaction and the workup was further performed as described in the general protocol. Performing a column chromatography purification with a MeOH:CH_2Cl_2 (1:99-3:97 + 1% glacial acetic acid additive) solvent gradient yielded pure product **72**.

Yield and appearance: 425 mg (1.13 mmol, 14%) as beige-white powder.

HRMS (ESI): m/z = calculated for $[C_{17}H_{18}N_3O_5S]^+$: 376.09617, found: 376.09677.

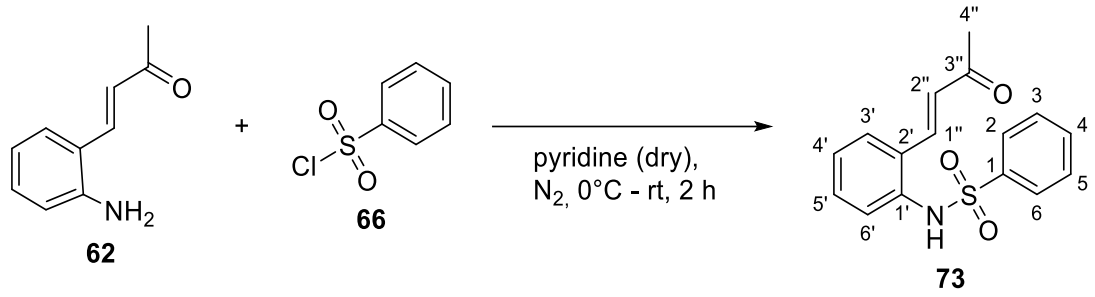
Melting area: 244.8 - 246.8°C

^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.30 (s, 1H, -NH), 7.92 (dd, *J* = 7.9, 1.6 Hz, 1H, 3‘‘-CH), 7.86 – 7.77 (m, 2H, 4‘‘- and 6‘-CH), 7.73 (ddd, *J* = 7.8, 7.2, 1.6 Hz, 1H, 5‘‘-CH), 7.68 (dd, *J* = 7.8, 1.6 Hz, 1H, 6‘‘-CH), 7.65 (d, *J* = 15.4 Hz, 1H, 3-CH), 7.36 – 7.29 (m, 2H, 4‘- and 5‘-CH), 7.08 – 7.00 (m, 1H, 3‘-CH), 6.88 (d, *J* = 15.4 Hz, 1H, 2-CH), 3.05 (s, 3H, -NCH_3), 2.89 (s, 3H, -NCH_3).

^{13}C NMR (101 MHz, DMSO) δ: 165.09 (1-C_q), 147.36 (2‘‘-C_q), 136.25 (3-CH), 134.28 (4‘‘-CH), 133.87 (2‘-C_q), 133.57 (1‘-C_q), 132.53 (5‘‘-CH), 132.05 (1‘‘-C_q), 129.99 (4‘- or 6‘‘-CH), 129.87 (4‘- or 6‘‘-CH), 129.01 (3‘-CH), 127.84 (5’-CH), 127.17 (6‘-CH), 124.80 (3‘‘-CH), 120.10 (2-CH), 36.83 (-NCH_3), 35.28 (-NCH_3).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right]$ = 3033 w, 2989 w, 2801 w, 2751 w, 1643 w, 1596 w, 1572 w, 1538 w, 1512 w, 1486 w, 1442 w, 1432 w, 1405 w, 1371 w, 1350 w, 1283 w, 1257 w, 1232 w, 1187 w, 1170 m, 1128 w, 1093 w, 1060 w, 989 w, 957 w, 933 w, 891 w, 871 w, 858 w, 850 w, 795 w, 765 m, 749 w, 733 w.

(*E*)-*N*-(2-(3-oxobut-1-en-1-yl)phenyl)benzenesulfonamide (**73**)



Chemical Formula: $C_{16}H_{15}NO_3S$ **Molecular Weight:** 301.3600 g/mol

Sulfonamide **73** was synthesised according to the general synthesis protocol F in subchapter 7.2. Educt **62** (233 mg, 1.44 mmol), benzenesulfonyl chloride (**66**) (500 µL, 692 mg, 3.92), dry pyridine (3.50 mL, 3.42 g, 43.2 mmol) and glacial acetic acid (5.00 mL, 5.25 g, 87.4 mmol) were used. 75 mL of CH_2Cl_2, then 15 mL of H_2O_d were added after stopping the reaction and the workup was further performed as described in the general protocol. Performing a column chromatography purification with pure EtOAc (+ 1% glacial acetic acid additive) as solvent yielded pure product **73**.

Yield and appearance: 385 mg (1.28 mmol, 89%) as yellowish white crystals.

HRMS (ESI): m/z = calculated for $[C_{16}H_{14}NO_3S]^-$: 300.06999, found: 300.07000.

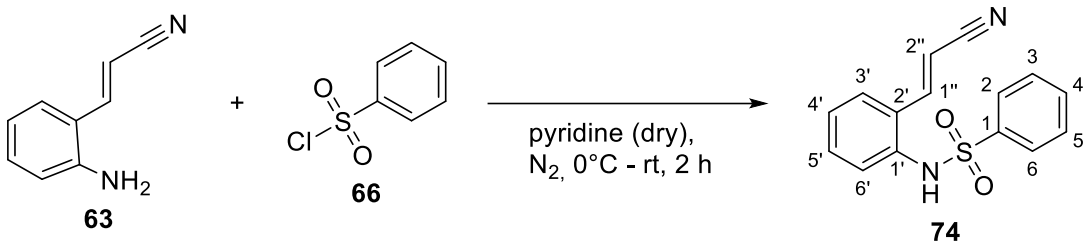
Melting area: 159.5 – 173.4°C

^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.10 (s, 1H, -NH), 7.72 (dd, *J* = 7.9, 1.6 Hz, 1H, 3'-CH), 7.63 – 7.56 (m, 3H, 2-, 4- and 6-CH), 7.53 (d, *J* = 16.3 Hz, 1H, 1''-CH), 7.55 – 7.46 (m, 2H, 3- and 5-CH), 7.38 (ddd, *J* = 7.8, 7.6, 1.6 Hz, 1H, 5'-CH), 7.28 (ddd, *J* = 7.9, 7.6, 1.4 Hz, 1H, 4'-CH), 7.12 (dd, *J* = 7.8, 1.4 Hz, 1H, 6'-CH), 6.48 (d, *J* = 16.3 Hz, 1H, 2''-CH), 2.19 (s, 3H, 4''-CH_3).

^{13}C NMR (101 MHz, DMSO) δ: 197.94 (3''-C_qO), 139.38 (1-C_q), 138.50 (1''-CH), 135.38 (1'-C_q), 132.93 (4-CH), 131.03 (2'-Cq), 130.89 (5'-CH), 129.26 (3- and 5-CH), 128.27 (6'-CH), 128.16 (2''-CH), 127.29 (4'-CH), 126.90 (3'-CH), 126.57 (2- and 6-CH), 26.87 (4''-CH_3).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right]$ = 3166 w, 2916 w, 1965 w, 1672 w, 1638 m, 1623 mw, 1598 w, 1569 w, 1481 w, 1457 w, 1447 w, 1415 w, 1367 w, 1328 m, 1311 w, 1298 w, 1286 w, 1265 m, 1227 w, 1191 w, 1181 w, 1166 m, 1158 m, 1090 m, 1070 w, 1027 w, 1015 w, 1000 w, 988 m, 983 mw, 950 w, 915 w, 881 w, 844 w, 814 w, 752 m, 760 m, 752 m, 732 m, 721 m, 688 m, 666 m.

(*E*)-*N*-(2-(2-cyanovinyl)phenyl)benzenesulfonamide (**74**)



Chemical Formula: $C_{15}H_{12}N_2O_2S$ **Molecular Weight:** 284.3330 g/mol

The sulfonamide **74** was synthesised according to the general synthesis protocol F in subchapter 7.2. Educt **63** (1.15 g, 8.00 mmol), benzenesulfonyl chloride (**66**) (1.50 mL, 2.08 g, 11.8 mmol), dry pyridine (6.00 mL, 5.87 g, 74.2 mmol), glacial acetic acid (7.50 mL, 7.86 g, 131 mmol) were used. 100 mL of CH_2Cl_2, then 25 mL of H_2O_d were added after stopping the reaction and the workup was further performed as described in the general protocol. Product **74** could be recrystallized from an EtOAc:CH_3COOH:isohexane (1:1:10) solvent mixture.

Yield and appearance: 1.10 g (3.87 mmol, 48 %) greyish white crystals.

HRMS (ESI): m/z = calculated for $[C_9H_9N_2]^+$: 145.07602, found: 145.07625.

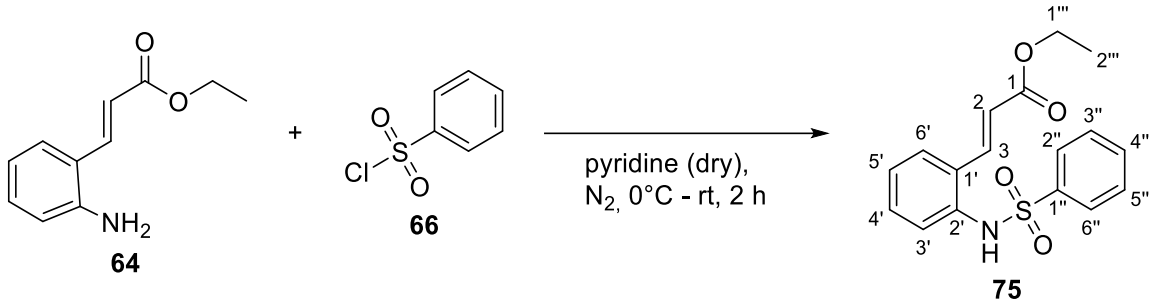
Melting area: 170.9 - 171.1°C

^{1}H NMR (400 MHz, Chloroform-*d*) δ: 11.94 (s, 1H, -NH), 8.01 (dt, *J* = 6.8, 1.5 Hz, 2H, 2- and 6-CH), 7.87 (d, *J* = 9.4 Hz, 1H, 1''-CH), 7.65 – 7.59 (m, 2H, 3'- and 4'-CH), 7.54 – 7.44 (m, 4H, 4-, 6'-, 3- and 5-CH), 7.36 (td, *J* = 8.0, 7.6, 1.1 Hz, 1H, 5'-CH), 6.97 (d, *J* = 9.4 Hz, 1H, 2''-CH).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 154.53 (-C_qN), 142.95 (1-C_q), 141.00 (1''-CH), 136.51 (1'-C_q), 132.22 (4-CH), 131.93 (6'-CH), 128.94 (3- and 5-CH), 128.28 (3'-CH), 126.36 (2- and 6-CH), 124.93 (5'-CH), 121.54 (2'-C_q), 121.17 (2''-CH), 117.46 (3'-CH).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right]$ = 3115 w, 3040 w, 2952 w, 2889 w, 2845 w, 2386 w, 2351 w, 1628 m, 1606 m, 1595 m, 1526 m, 1481 w, 1458 w, 1446 w, 1406 w, 1380 m, 1358 m, 1332 m, 1295 m, 1265 m, 1221 w, 1180 w, 1162 w, 1140 m, 1128 m, 1087 s, 1030 w, 1008 w, 943 w, 915 w, 861 w, 829 m, 767 w, 746 m, 737 m, 707 m, 690 m.

Ethyl (*E*)-3-(2-(phenylsulfonamido)phenyl)acrylate (**75**)



Chemical Formula: $C_{17}H_{17}NO_4S$ **Molecular Weight:** 331.3860 g/mol

Sulfonamide **75** was synthesised according to the general synthesis protocol F in subchapter 7.2. Educt **64** (7.20 g, 37.6 mmol), benzenesulfonyl chloride (**66**) (5.55 mL, 7.69 g, 43.1 mmol), dry pyridine (35.0 mL, 34.2 g, 433 mmol) and glacial acetic acid (30.0 mL, 31.5 g, 525 mmol) were used. 350 mL of CH_2Cl_2, then 100 mL of H_2O_d were added after stopping the reaction and the workup was further performed as described in the general protocol. Product **75** was purified by means of column chromatography with a MeOH:CH_2Cl_2 (+ 0.1% glacial acetic acid additive) solvent mixture.

Yield and appearance: 9.05 g (27.3 mmol, 73 %) as beige-white solid.

HRMS (ESI): m/z = calculated for $[C_{17}H_{16}NO_4S]^-$: 330.08055, found: 330.08054.

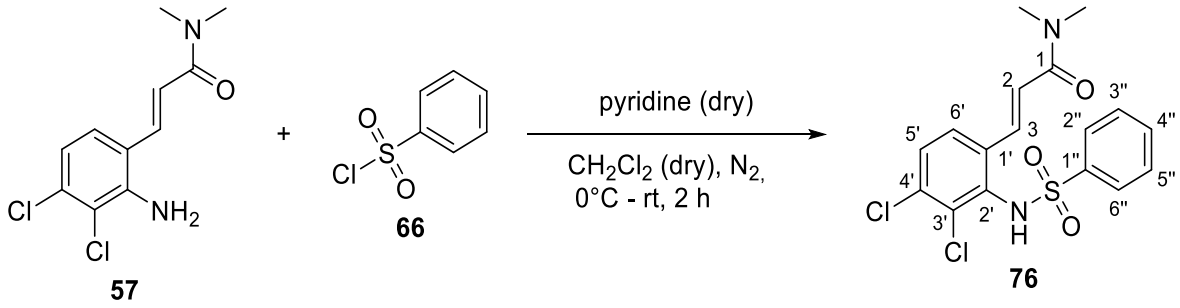
Melting area: 126.8 - 127.3°C

^{1}H NMR (400 MHz, CD_2Cl_2) δ: 7.70 – 7.64 (m, 2H, 2''- and 6''-CH), 7.54 (d, *J* = 15.8 Hz, 1H, 3-CH), 7.54 (tt, *J* = 8.1, 1.9 Hz, 1H, 4''-CH), 7.51 (dd, *J* = 7.8, 1.5 Hz, 1H, 6'-CH), 7.47 – 7.38 (m, 2H, 3''- and 5''-CH), 7.36 (ddd, *J* = 8.1, 6.8, 1.5 Hz, 1H, 4'-CH), 7.33 (ddd, *J* = 8.1, 1.9, 0.6 Hz, 1H, 3'-CH), 7.27 (dddd, *J* = 7.8, 6.8, 1.9, 0.6 Hz, 1H, 5'-CH), 6.95 (s, 1H, -NH), 6.17 (d, *J* = 15.8 Hz, 1H, 2-CH), 4.21 (q, *J* = 7.1 Hz, 2H, 1'''-CH_2), 1.31 (t, *J* = 7.1 Hz, 3H, 2'''-CH_3).

^{13}C NMR (101 MHz, CD_2Cl_2) δ: 166.57 (1-C_qO), 139.27 (1''-C_q), 138.83 (3-CH), 134.86 (2'-C_q), 133.50 (4''-CH), 131.21 (1'-C_q), 131.17 (4'-CH), 129.52 (3''- and 5''-CH), 127.87 (3'- or 5'-CH), 127.84 (3'- or 5'-CH), 127.57 (2''-, 6''- and 6'-CH), 121.33 (2-CH), 61.08 (1'''-CH_2), 14.49 (2'''-CH_3).

IR (ATR): $\tilde{\nu}\ \left[\frac{1}{cm}\right]$ = 3201 w, 2988 w, 2523 w, 1692 m, 1636 w, 1601 w, 1572 w, 1485 w, 1448 w, 1415 w, 1370 w, 1343 w, 1319 s, 1295 w, 1267 w, 1231 w, 1190 m, 1166 s, 1118 w, 1090 w,1029 w, 999 w, 980 m, 954 w, 910 w, 890 w, 862 w, 838 w, 797 w, 767 m, 758 w, 747 w, 722 m, 686 w.

(*E*)-3-(3,4-Dichloro-2-(phenylsulfonamido)phenyl)-*N*,*N*-dimethylacrylamide (**76**)



Chemical Formula: $C_{17}H_{16}Cl_2N_2O_3S$ **Molecular Weight:** 399.2860 g/mol

The sulfonamide **76** was synthesised according to the general synthesis protocol F in subchapter 7.2. Educt **57** (4.90 g, 18.9 mmol), dissolved in 50 mL of CH_2Cl_2, benzenesulfonyl chloride (**66**) (2.50 mL, 3.46 g, 19.6 mmol), dry pyridine (6.60 mL, 6.45 g, 81.6 mmol) and glacial acetic acid (7.00 mL, 7.35 g, 122 mmol) were used. 200 mL of CH_2Cl_2, then 75 mL of H_2O_d were added after stopping the reaction and the workup was further performed as described in the general protocol. Product **76** could be gained from recrystallisation from EtOAc with an 1% glacial acetic acid additive.

Yield and appearance: 3.24 g (8.11 mmol, 43%) as white powder.

HRMS (ESI): m/z = calculated for $[C_{17}H_{15}Cl_2N_2O_3S]^-$: 397.01859 ($^{35}Cl$, ^{35}Cl), 399.01564 (^{35}Cl, ^{37}Cl), 401.01269 (^{37}Cl, ^{37}Cl), found: 397.01940 (^{35}Cl, ^{35}Cl), 399.01663 (^{35}Cl, ^{37}Cl), 401.01367 (^{37}Cl, ^{37}Cl).

Melting area: 251.6 - 253.6°C

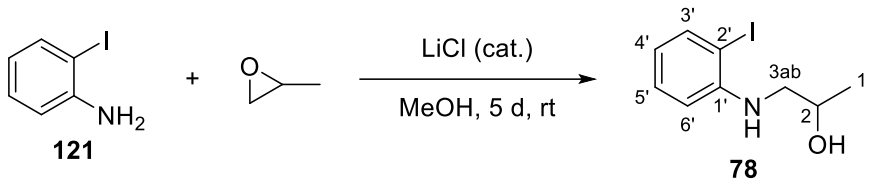
^{1}H NMR (400 MHz, DMSO) δ: 10.21 (s, 1H, -NH), 7.88 (d, *J* = 8.7 Hz, 1H, 6'-CH), 7.66 – 7.57 (m, 4H, 5'-, 2''-, 4''- and 6''-CH), 7.52 (d, *J* = 15.5 Hz, 1H, 3-CH), 7.56 – 7.46 (m, 2H, 3''- and 5''-CH), 7.04 (d, *J* = 15.5 Hz, 1H, 2-CH), 3.09 (s, 3H, -N($\underline{CH_3}$)$_2$), 2.91 (s, 3H, -N($\underline{CH_3}$)$_2$).

^{13}C NMR (101 MHz, DMSO) δ: 164.95 (1-C_qO), 140.62 (1''-C_q), 136.52 (1'-C_q), 135.76 (3-CH), 133.56 (2'-C_q), 133.06 (3'-C_q), 132.79 (4''-CH), 132.46 (4'-C_q), 129.52 (5'-CH), 129.18 (3''- and 5''-CH), 126.64 (2''- and 6''-CH), 126.45 (6'-CH), 121.41 (2-CH), 36.89 (-N($\underline{CH_3}$)$_2$), 35.27 (-N($\underline{CH_3}$)$_2$).

IR (ATR): $\tilde{\nu}\ \left[\frac{1}{cm}\right]$ = 3060 w, 2795 w, 1642 m, 1591 m, 1582 m, 1547 w, 1458 m, 1442 mw, 1414 w, 1393 m, 1315 m, 1304 mw, 1299 mw, 1262 mw, 1246 w, 1200 w, 1153 m, 1126 m, 1087 m, 1068 w, 1022 w, 976 m, 955 w, 935 m, 899 mw, 870 mw, 844 mw, 817 m, 762 m, 751 m 725 mw, 685 ms, 666 w.

7.4.3 Alcohol derivatives 78-80

1-((2-Iodophenyl)amino)propan-2-ol (**78**)



Chemical Formula: $C_9H_{12}INO$ **Molecular Weight:** 277.1055 g/mol

The alcohol **78** was synthesised according to the general synthesis protocol G in subchapter 7.2. Iodoaniline (**121**) (1.24 g, 5.53 mmol), (±)-propylene oxide (400 µL, 332 mg, 5.72 mmol), LiBr (49.0 mg, 564 µmol), 2.5 mL of MeOH and 150 mL of CH_2Cl_2 were used. It was stirred for 5 days. Product **78** could by isolated after performing column chromatography with an EtOAc:isohexane (1:4 with a 0.1% NEt_3 additive) solvent mixture.

Yield and appearance: 344 mg (1.24 mmol, 22.4 %) as brown oil.

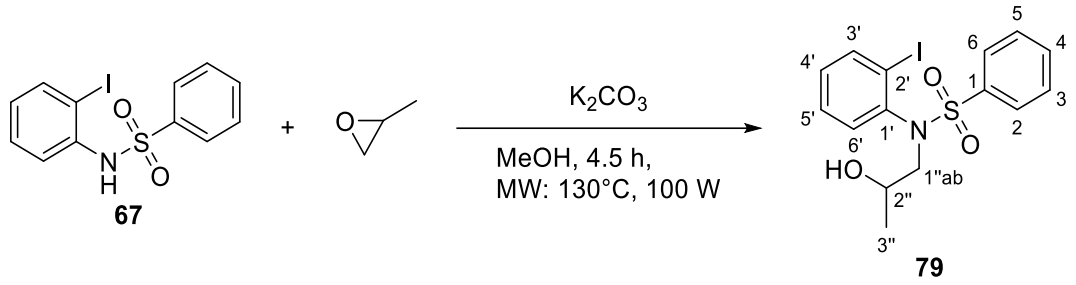
HRMS (ESI): m/z = calculated for $[C_9H_{13}INO]^+$: 278.00363, found: 278.00393.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.67 (dd, *J* = 7.6, 1.5 Hz, 1H, 3'-CH), 7.21 (ddd, *J* = 8.2, 7.4, 1.5 Hz, 1H, 5'-CH), 6.61 (dd, *J* = 8.2, 1.4 Hz, 1H, 6'-CH), 6.47 (ddd, *J* = 7.6, 7.4, 1.4 Hz, 1H, 4'-CH), 4.48 (s, 1H, -NH), 4.14 – 4.02 (m, 1H, 2-CH), 3.27 (dd, *J* = 12.9, 2.2 Hz, 1H, 3a-C<u>H</u>$_2$ or 3b-C<u>H</u>$_2$), 3.08 (dd, *J* = 12.9, 8.3 Hz, 1H, 3a-C<u>H</u>$_2$ or 3b-C<u>H</u>$_2$), 1.93 (s, 1H, -OH), 1.30 (d, *J* = 6.3 Hz, 3H, 1-CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 147.38 (1'-C_q), 139.29 (3'-CH), 129.56 (5'-CH), 119.25 (4'-CH), 111.14 (6'-CH), 86.09 (2'-C_q), 66.38 (2-CH), 51.91 (3ab-CH_2), 21.03 (1-CH_3).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right]$ = 3364 m, 3060 w, 2970 w, 2914 m, 2834 w, 2251 w, 2168 w, 2140 w, 2009 w, 1870 w, 1832 w, 1748 w, 1665 w, 1588 s, 1501 s, 1448 s, 1428 s, 1373 m, 1318 m, 1299 m, 1281 m, 1246 w, 1213 m, 1163 m, 1147 m, 1138 m, 1094 m, 1075 s, 1041 s, 1004 s, 958 w, 923 m, 865 m, 837 w, 824 m, 740 s, 731 s, 702 m, 687 m, 671 m.

N-(2-hydroxypropyl)-*N*-(2-iodophenyl)benzenesulfonamide (**79**)



Chemical Formula: $C_{15}H_{16}INO_3S$ **Molecular Weight:** 417.26147 g/mol

The alcohol **79** was synthesised, with variations though, in the style of a previously described method of Shyh-Ming et al.[105]. Substance **67** (4.38 g, 4.38 mmol) and K_2CO_3 (1.46 g, 8.76 mmol) were therefore put in a synthesis microwave reaction vessel and 25 ml of EtOH was added. (±)-Propylene oxide (900 µl, 747 mg, 12.9 mmol) was added shortly before the reaction was started in a synthesis microwave (4.5 h, 130°C, 100 W). The reaction solvent was evaporated and the crude solid was redissolved with 250 mL of CH_2Cl_2. The organic layer was washed three times with 50 mL of H_2O, then one time with 30 mL of brine solution. The organic phase was dried over $MgSO_4$, then solvent was removed with the help of a rotary evaporator. Purification of **79** was achieved by means of column chromatography with CH_2Cl_2:MeOH (99:1, + 0.1 % NEt_3) as solvent mixture.

Yield and appearance: 1.40 g (3.36 mmol, 77%) as yellowish clear viscous oil.

HRMS (ESI): m/z = calculated for $[C_{15}H_{17}INO_3S]^+$: 417.99683, found: 417.99705.

Rotamer 1 – NMR data:

^{1}H NMR (500 MHz, Chloroform-*d*) δ: 7.95 (dd, *J* = 8.0, 1.5 Hz, 1H, 3'-CH), 7.77 – 7.71 (m, 2H, 2- and 6'-CH), 7.64 (tt, *J* = 7.5, 1.7 Hz, 1H, 4-CH), 7.53 (ddt, *J* = 8.3, 7.5, 1.8 Hz, 2H, 3- and 5-CH), 7.28 (ddd, *J* = 8.0, 7.5, 1.5 Hz, 1H, 5'-CH), 7.06 (ddd, *J* = 8.0, 7.5, 1.6 Hz, 1H, 4'-CH), 6.79 (dd, *J* = 8.0, 1.6 Hz, 1H, 6'-CH), 3.85 – 3.75 (m, 1H, 2''-CH), 3.71 (dd, *J* = 13.6, 9.4 Hz, 1H, 1''a-C$\underline{H}_2$ or 1''b-C$\underline{H}_2$), 3.16 (dd, *J* = 13.6, 1.9 Hz, 1H, 1''a-C$\underline{H}_2$ or 1''b-C$\underline{H}_2$), 2.92 (dd, *J* = 2.3, 0.9 Hz, 1H, -OH), 1.11 (dd, *J* = 6.3, 0.6 Hz, 3H, 2''-CH_3).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 142.71 (1'-C_q), 140.71 (3'-CH), 138.08 (1-C_q), 133.43 (4-CH), 130.37 (4'-CH), 129.42 (5'-CH), 129.21 (3- and 5-CH), 129.10 (6'-CH), 128.51 (2- and 6-CH), 104.09 (2'-C_q), 65.02 (2''-CH), 60.81 (1''ab-CH_2), 19.74 (3''-CH_3).

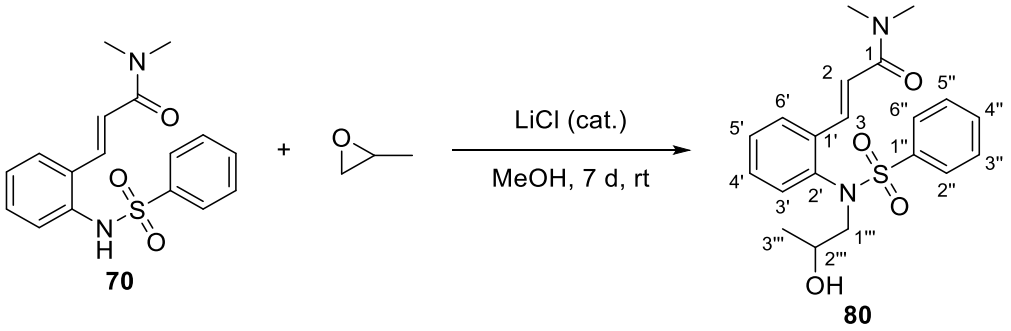
Rotamer 2 – NMR data:

^{1}H NMR (500 MHz, Chloroform-*d*) δ: 7.88 (dd, *J* = 7.9, 1.5 Hz, 1H, 3'-CH), 7.77 – 7.71 (m, 2H, 2- and 6-CH), 7.61 (tt, *J* = 7.5, 1.2 Hz, 1H, 4-CH), 7.50 (ddt, *J* = 8.3, 7.5, 1.7 Hz, 2H, 3- and 5-CH), 7.33 (ddd, *J* = 8.0, 7.5, 1.5 Hz, 1H, 5'-CH), 7.15 (dd, *J* = 8.0, 1.6 Hz, 1H, 6'-CH), 7.04 (ddd, *J* = 7.9, 7.5, 1.6 Hz, 1H, 4'-CH), 3.99 – 3.90 (m, 1H, 2''-CH), 3.60 (dd, *J* = 14.7, 3.3 Hz, 1H, 1''a- or 1''b-C$\underline{H}_2$), 3.48 (dd, *J* = 14.7, 8.8 Hz, 1H, 1''a- or 1''b-C$\underline{H}_2$), 2.55 (d, *J* = 4.6 Hz, 1H, -OH), 1.18 (d, *J* = 6.3 Hz, 3H, 3''-CH_3).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 141.81 (1'-C_q), 140.72 (3'-CH), 139.01 (1-C_q), 133.25 (4-CH), 132.10 (6'-CH), 130.24 (4'-CH), 129.10 (3- and 5-CH), 129.06 (5'-CH), 128.39 (2- and 6-CH), 101.23 (2'-C_q), 65.77 (2''-CH), 59.39 (1''ab-CH_2), 20.78 (3''-CH_3).

IR (ATR): $\tilde{\nu}\ \left[\frac{1}{cm}\right]$ = 3532 w, 3061 w, 2972 w, 2928 w, 1577 w, 1464 m, 1446 m, 1426 w, 1378 w, 1346 m, 1310 m, 1292 w, 1272 w, 1220 w, 1157 s, 1087 s, 1069 m, 1037 m, 1017 m, 999 w, 943 m, 858 m, 830 m, 769 m, 757 m, 740 m, 720 s, 699 m, 687 s.

(*E*)-3-(2-(*N*-(2-hydroxypropyl)phenylsulfonamido)phenyl)-*N*,*N*-dimethylacrylamide (**80**)



70 **80**

Chemical Formula: $C_{20}H_{24}N_2O_4S$ **Molecular Weight:** 388.4820 g/mol

The alcohol **80** was synthesised according to the general synthesis protocol G in subchapter 7.2. Sulfonamide **70** (311 mg, 941 µmol), (±)-propylene oxide (700 µL, 581 mg, 9.90 mmol), LiBr (20.4 mg, 235 µmol), 15 mL MeOH and 50 mL CH_2Cl_2 were used. The reaction was stirred for 7 days. After having performed the described workup processes, product **80** was separated from the residues of epoxide by performing column chromatography with pure EtOAc as solvent.

Yield and appearance: quantitative as white solid.

HRMS (ESI): m/z = calculated for $[C_{20}H_{25}N_2O_4S^+]$: 389.15295, found: 389.15297.

Melting area: 85.5 - 89.4°C

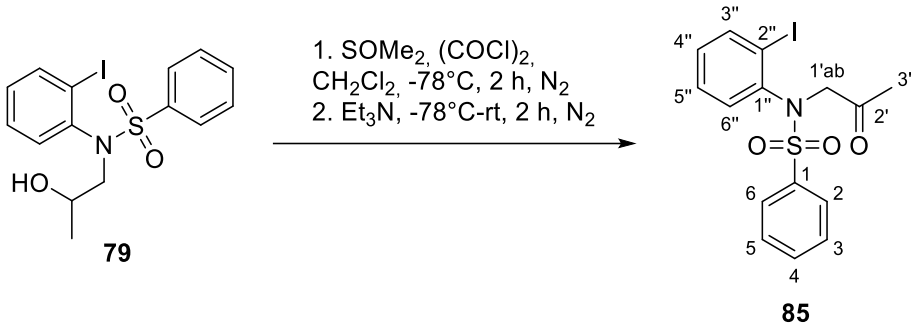
^{1}H NMR (400 MHz, DMSO, 373K) δ: 7.84 (dd, *J* = 7.7, 1.6 Hz, 1H, 6'-CH), 7.73 (d, *J* = 15.7 Hz, 1H, 3-CH), 7.68 (tt, *J* = 7.3, 1.5 Hz, 1H, 4''-CH), 7.65 (dt, *J* = 7.7, 2.1, 1.5 Hz, 2H, 2''- and 6''-CH), 7.57 (dddd, *J* = 7.7, 7.3, 1.9, 1.5 Hz, 2H, 3''- and 5''-CH), 7.37 (ddd, *J* = 7.7, 7.6, 1.1 Hz, 1H, 5'-CH), 7.30 (ddd, *J* = 7.9, 7.6, 1.6 Hz, 1H, 4'-CH), 7.00 (d, *J* = 15.7 Hz, 1H, 2-CH), 6.86 (dd, *J* = 7.9, 1.1 Hz, 1H, 3'-CH), 4.23 (s, 1H, -OH), 3.66 – 3.30 (m, 3H, 1'''-CH_2 and 2'''-CH), 3.05 (s, 6H, -N(CH_3)$_2$), 1.04 (d, *J* = 5.8 Hz, 3H, 3'''-CH_3).

^{13}C NMR (101 MHz, DMSO, 373K) δ: 165.21 (1-C_qO), 138.27 (2'-C_q), 138.01 (1''-C_q), 136.18 (3-CH), 135.83 (1'-C_q), 132.43 (4''-CH), 128.88 (4'-CH), 128.65 (3'-CH), 128.51 (3''- and 5''-CH), 127.86 (5'-CH), 127.08 (2''- and 6''-CH), 126.75 (6'-CH), 120.23 (2-CH), 63.91 (2'''-CH), 58.59 (1'''-CH_2), 35.78 (-N(CH_3)$_2$), 20.76 (3'''-CH_3).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right] =$ 3348 m, 3068 w, 2987 w, 2940 w, 2862 w, 1650 m, 1592 m, 1550 w, 1494 w, 1462 w, 1445 m, 1413 w, 1399 w, 1380 w, 1350 s, 1309 w, 1294 w, 1262 w, 1213 w, 1171 m, 1091 s, 1052 m, 1040 m, 986 m, 940 m, 887 m, 877 m, 863 w, 854 m, 804 w, 752 m, 730 s, 706 m, 688 s, 670 w.

7.4.4 Swern products and 2-alkylacylindoles syntheses products 89-96

N-(2-iodophenyl)-*N*-(2-oxopropyl)benzenesulfonamide (**85**)



Chemical Formula: $C_{15}H_{14}INO_3S$ **Molecular Weight:** 415.2455 g/mol

Ketone **85** was synthesised with variations according to the original synthesis description of Omura et al.[106]. Dry $SOMe_2$ (1.50 mL, 1.65 g, 21.1 mmol) was put in a flask with 50 mL of dry CH_2Cl_2 and cooled down to -75°C. Oxalyl chloride (750 µL, 1.13 g, 8.86 mmol), dissolved in 5 mL of dry CH_2Cl_2, was added dropwise and it was stirred for 20 min at -75°C. Alcohol **79** (3.11 g, 7.44 mmol), dissolved in 45 mL of dry CH_2Cl_2, was also added dropwise by syringe to the reaction flask. It was stirred for 2 h at -75°C then NEt_3 (3.40 mL, 2.47 g, 24.4 mmol) was added and the solution was allowed to warm to rt. It was stirred for another hour at room temperature, then the reaction solution was quenched with 20 mL of H_2O_d and it was stirred for another 10 min. The organic and watery layer were separated with help of a separation funnel, then the watery layer was extracted one more time with 10 mL of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and the solvent was removed *in vacuo*. The resulting crude product **85** was purified by means of column chromatography with pure CH_2Cl_2.

Yield and appearance: 2.20 g (5.30 mmol, 71%) as white solid.

HRMS (ESI): m/z = calculated for $[C_{15}H_{15}INO_3S]^+$: 415.98118, found: 415.98149.

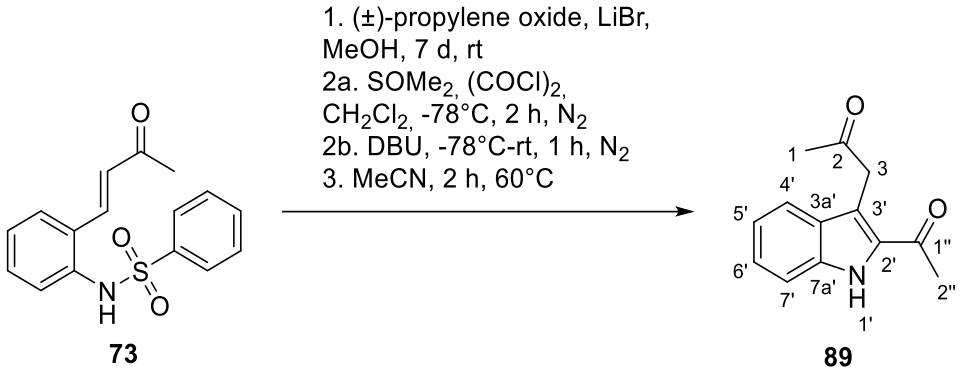
Melting area: 92 - 95.6°C

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.82 (dd, *J* = 7.8, 1.5 Hz, 1H, 3‘‘-CH), 7.66 (ddd, *J* = 7.5, 2.0, 1.6 Hz, 2H, 2- and 6-CH), 7.59 (tt, *J* = 7.8, 1.6 Hz, 1H, 4-CH), 7.56 (dd, *J* = 8.0, 1.6 Hz, 1H, 6‘‘-CH), 7.47 (ddt, *J* = 7.8, 7.5, 1.6 Hz, 2H, 3- and 5-CH), 7.32 (ddd, *J* = 8.0, 7.5, 1.5 Hz, 1H, 5‘‘-CH), 7.02 (ddd, *J* = 7.8, 7.5, 1.6 Hz, 1H, 4‘‘-CH), 4.84 (d, *J* = 18.6 Hz, 1H, 1’a- or 1‘b-C$\underline{H}_2$), 4.13 (d, *J* = 18.6 Hz, 1H, 1’a- or 1‘b-C$\underline{H}_2$), 2.19 (s, 3H, 3’-CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 202.55 (2‘-C_qO), 141.40 (1‘‘-C_q), 140.42 (3‘‘-CH), 139.84 (1-C_q), 133.87 (6‘‘-CH), 133.14 (4-CH), 130.42 (4‘‘-CH), 129.12 (5‘‘-CH), 128.99 (3- and 5-CH), 128.17 (2- and 6-CH), 100.51 (2‘‘-C_q), 60.71 (1’ab-CH_2), 27.07 (3‘-CH_3).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right] =$ 3054 w, 2975 w, 2896 w, 1726 w, 1688 w, 1665 w, 1642 w, 1574 w, 1551 w, 1529 w, 1479 w, 1462 w, 1448 w, 1423 w, 1351 m, 1333 m, 1312 w, 1265 w,1232 w, 1176 w, 1161 m, 1119 m, 1091 w, 1068 w, 1035 w, 1021 w, 974 w, 950 w, 933 w, 863 w, 805 w, 774 w, 753 m, 743 m, 722 s, 701 w, 687 m.

1-(2-Acetyl-1*H*-indol-3-yl)propan-2-one (**89**)



73 **89**

Chemical Formula: $C_{13}H_{13}NO_2$ **Molecular Weight:** 215.25200 g/mol

The indole analogue **89** was prepared according to the general synthesis protocol H (see subchapter 7.2). The sulfonamide **73** (253 mg, 840 µmol), (±)-propylene oxide (1.00 mL, 830 mg, 14.3 mmol), LiBr (23.6 mg, 269 µmol) and 10 mL of MeOH as solvent were used for the first step. The workup was performed as described. For step 2., $SOMe_2$ (250 µL, 275 mg, 3.53 mmol), oxalyl chloride (150 µL, 225 mg, 1.77 mmol), DBU (380 µL, 387 mg, 2.54 mmol) and a total of 50 mL of CH_2Cl_2 as solvent were used. 15 mL of MeCN and glacial acetic acid (250 µL, 262 mg, 4.37 mmol) were used for the 3. step. Again, the workup was performed, as described. Column chromatography with EtOAc:isohexane (1:1-1:0) yielded pure product **89**.

Yield and appearance: 94.0 mg (437 µmol, 52%) as brown solid.

HRMS (ESI): m/z = calculated for $[C_{13}H_{12}NO_2]^-$: 214.08735, found: 214.08725.

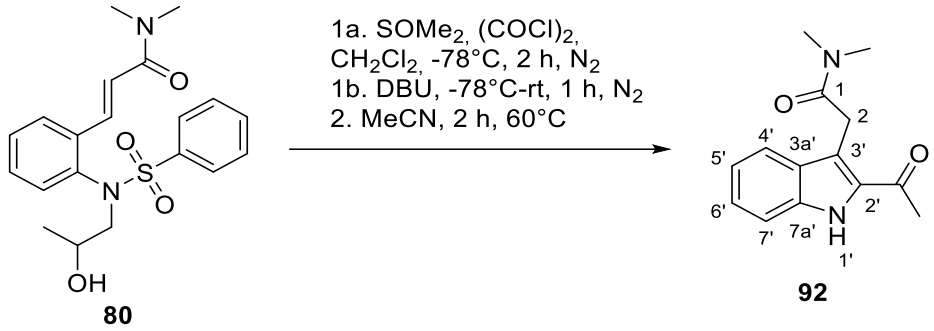
Melting area: 72.8 - 87.9°C

^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.08 (s, 1H, 1’-NH), 7.62 (dd, *J* = 8.1, 1.0 Hz, 1H, 4’-CH), 7.39 – 7.31 (m, 2H, 6’- and 7’-CH), 7.17 (ddd, *J* = 8.1, 5.8, 2.2 Hz, 1H, 5’-CH), 4.21 (s, 2H, 3-CH_2), 2.50 (s, 3H, 2‘‘-CH_3), 2.26 (s, 3H, 1-CH_3).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 205.82 (2-C_qO), 190.35 (1''-C_qO), 136.07 (7a'-C_q), 132.90 (2'-C_q), 128.37 (3a'-C_q), 126.75 (6'-CH), 121.11 (5'-CH), 120.80 (4'-CH), 115.15 (3'-C_q), 112.48 (7'-CH), 40.84 (3-CH_2), 29.69 (1-CH_3), 28.30 (2''-CH_3).

IR (ATR): $\tilde{\nu}\ \left[\frac{1}{cm}\right]$ = 3327 w, 2923 w, 2873, 1718 mw, 1655 w, 1575 w, 1539 w, 1489 w, 1457 w, 1444 w, 1397 w, 1386 w, 1363 w, 1335 m, 1325 m ,1306 w, 1293 w, 1254 w, 1241 w, 1155 m, 1136 w, 1114 mw, 1088 w, 1076 m, 1052 w, 1043 w, 1010 w, 995 w, 960 w, 926 w, 891 w, 873 w, 858 w, 850 w, 810 w, 778 w, 764 m, 755 m, 733 m, 692 m.

2-(2-Acetyl-1*H*-indol-3-yl)-*N*,*N*-dimethylacetamide (**92**)



80 **92**

Chemical Formula: $C_{14}H_{16}N_2O_2$ **Molecular Weight:** 244.2940 g/mol

Indole **92** was synthesised with variations according to the synthesis protocols of K. Omura et al.[106] and A. Kim et al.[48]. Dry $SOMe_2$ (150 µL, 164 mg, 2.11 mmol) was put in a flask with 25 mL of dry CH_2Cl_2 and cooled down to -75°C. Oxalyl chloride (100 µL, 150 mg, 1.18 mmol), dissolved in 5 mL of dry CH_2Cl_2, was added dropwise and it was stirred for 20 min at -75°C. Alcohol **80** (398 mg, 1.02 mmol), dissolved in 10 mL of dry CH_2Cl_2, was also added dropwise by syringe to the reaction flask. It was stirred for 2 h at -75°C then DBU (600 µL, 611 mg, 4.01 mmol) was added as well and the solution was allowed to warm to rt. The flask was opened, and 15 mL of MeCN was added. The solution was stirred in an open flask at 65°C for 2 h, then the remaining solvent was removed by rotary evaporator and the resulting crude solid was redissolved in 50 mL of CH_2Cl_2 again and glacial acetic acid (240 µL, 252 mg, 4.20 mmol) was added by syringe. The organic layer was washed three times with 20 mL of H_2O_d and one time with 20 mL of brine solution. The combined organic layers were dried over $MgSO_4$ and the solvent was removed *in vacuo*. Product **92** was recrystallized from pure EtOAc.

Yield and appearance: 214 mg (876 mmol, 86%) as pale brown crystals.

HRMS (ESI): m/z = calculated for $[C_{14}H_{17}N_2O_2]^+$: 245.12845, found: 245.12861.

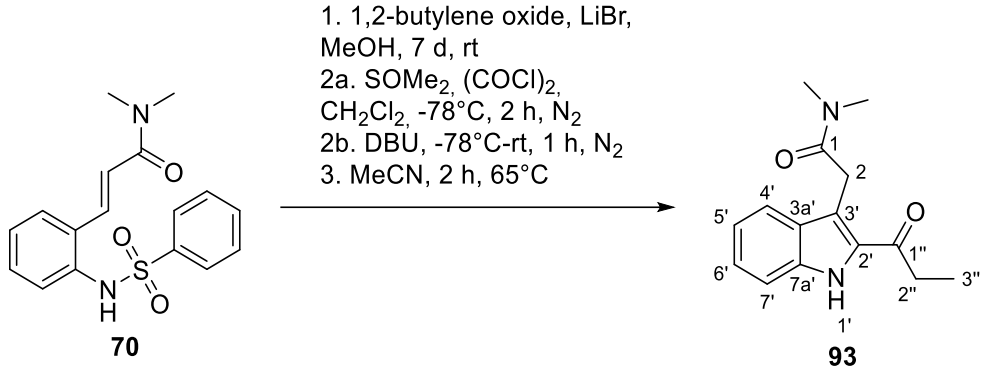
Melting area: 220.1 - 222.0°C

^{1}H NMR (400 MHz, Methylene Chloride-d2) δ: 9.75 (s, 1H, 1‘-NH), 7.58 (dd, J = 8.1, 0.9 Hz, 1H, 4‘-CH), 7.27 – 7.16 (m, 2H, 6‘- and 7‘-CH), 7.09 (ddd, J = 8.1, 6.6, 1.3 Hz, 1H, 5‘-CH), 4.14 (s, 2H, 2-CH_2), 3.24 (s, 3H, -N($\underline{CH_3}$)$_2$), 3.07 (s, 3H, -N($\underline{CH_3}$)$_2$), 2.03 (s, 3H, $COCH_3$).

^{13}C NMR (101 MHz, CD_2Cl_2) δ: 191.34 ($\underline{C_q}OCH_3$), 171.38 (1-C_qO), 136.72 (7‘a-C_q), 133.39 (2‘-C_q), 129.01 (3‘a-C_q), 126.17 (6‘-CH), 120.80 (4‘- and 5‘-CH), 116.75 (3‘-C_q), 113.49 (7‘-CH), 37.99 (-N($\underline{CH_3}$)$_2$), 36.25 (-N($\underline{CH_3}$)$_2$), 30.62 (2-CH_2), 27.81 (CO$\underline{C}H_3$).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right]$ = 3170 w, 2909 w, 1661 m, 1630 m, 1574 w, 1538 w, 1501 w, 1450 w, 1402 w, 1393 w, 1349 w, 1318 w, 1298 w, 1259 m, 1225 w, 1173 w, 1145 w, 1017 w, 1006 w, 988 w, 935 w, 890 w, 847 w, 826 w, 813 w, 742 s, 702 w, 673 w.

N,*N*-dimethyl-2-(2-propionyl-1*H*-indol-3-yl)acetamide (**93**)



Chemical Formula: $C_{15}H_{18}N_2O_2$ **Molecular Weight:** 258.32100 g/mol

The indole **93** was prepared according to the general synthesis protocol H (see subchapter 7.2). The sulfonamide **70** (156 mg, 472 µmol), 1,2-butylene oxide (1.00 mL, 829 mg, 11.5 mmol), LiBr (12.4 mg, 142 µmol) and 15 mL of MeOH as solvent were used for the step 1.. It was stirred for 7 d. The workup was performed as described. For step 2., $SOMe_2$ (100 µL, 110 mg, 1.41 mmol), oxalyl chloride (50.0 µL, 75.1 mg, 591 µmol), DBU (250 µL, 254 mg, 1.67 mmol) and a total of 35 mL of CH_2Cl_2 as solvent were used. 20 mL of MeCN and glacial acetic acid (100 µL, 105 mg, 1.75 mmol) were used for the step 3.. Again, the workup was performed, as described in the general protocol. Product **93** was successfully purified by means of column chromatography with a MeOH:CH_2Cl_2 (2:98-3:97) solvent gradient.

Yield and appearance: 120 mg (465 µmol, 98%) as beige-white solid.

HRMS (ESI): m/z = calculated for $[C_{15}H_{19}N_2O_2]^+$: 259.14410, found: 257.12953.

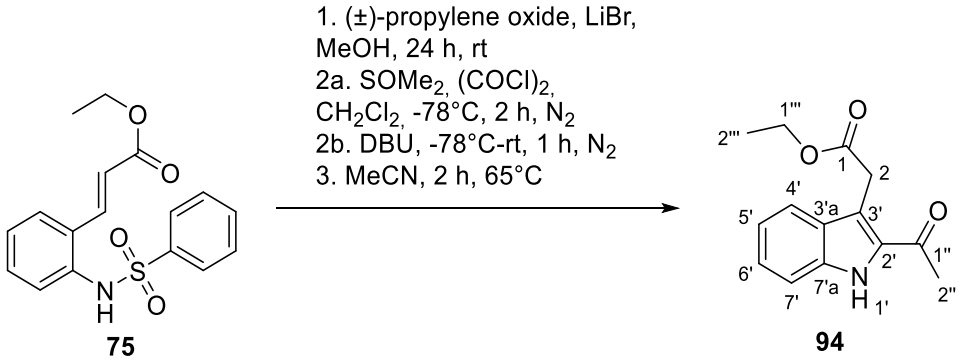
Melting area: 191.8 - 195.6°C

^{1}H NMR (400 MHz, CD_2Cl_2) δ: 9.64 (s, 1H, 1'-NH), 7.52 (dt, *J* = 8.0, 1.0 Hz, 1H, 4'-CH), 7.22 – 7.10 (m, 2H, 6'- and 7'-CH), 7.03 (ddt, *J* = 8.0, 6.5, 1.2 Hz, 1H, 5'-CH), 4.09 (s, 2H, 2-CH_2), 3.19 (s, 3H, -N($\underline{CH_3}$)$_2$), 3.02 (s, 3H, -N($\underline{CH_3}$)$_2$), 2.35 (qd, *J* = 7.2, 0.9 Hz, 2H, 2''-CH_2), 0.84 (td, *J* = 7.2, 0.9 Hz, 3H, 3''-CH_3).

^{13}C NMR (101 MHz, CD_2Cl_2) δ: 194.17 (1''-C_q), 171.45 (1-C_qO), 136.67 (7a'-C_q), 133.10 (2'-C_q), 128.92 (3a'-C_q), 126.02 (6'-CH), 120.73 (4'- or 5'-CH), 120.71 (4'- or 5'-CH), 116.31 (3'-C_q), 113.42 (7'-CH), 37.99 (-N($\underline{CH_3}$)$_2$), 36.25 (-N($\underline{CH_3}$)$_2$), 33.28 (2''-CH_2), 30.73 (2-CH_2), 7.72 (3''-CH_3).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right]$ = 3176 w, 2936 w, 1669 w, 1631 mw, 1573 w, 1545 w, 1457 w, 1401 w, 1341 w, 1295 w, 1265 w, 1242 w, 1219 w, 1168 w, 1140 w, 1031 w, 924 w, 888 w, 846 w, 828 w, 807 w, 739 mw, 691 w.

Ethyl 2-(2-acetyl-1*H*-indol-3-yl)acetate (**94**)



75 **94**

Chemical Formula: $C_{14}H_{15}NO_3$ **Molecular Weight:** 245.2780 g/mol

The indole **94** was prepared according to the general synthesis protocol H (see subchapter 7.2). The sulfonamide **75** (2.29 g, 6.92 mmol), (±)-propylene oxide (5.00 mL, 4.15 g, 71.5 mmol), LiBr (328 mg, 3.77 mmol) and 30 mL of MeOH as solvent were used for the first step. It was stirred for 24 h. The workup was performed as described. For step 2., $SOMe_2$ (1.00 mL, 1.10 g, 14.1 mmol), oxalyl chloride (700 µL, 1.05 g, 8.27 mmol), DBU (4.00 mL, 4.07 g, 26.7 mmol) and a total of 35 mL of CH_2Cl_2 as solvent were used. 100 mL of MeCN and glacial acetic acid (1.60 mL, 1.68 g, 28.0 mmol) were used for the step 3.. Again, the workup was performed, as described in the general protocol. Product **94** was successfully purified by means of column chromatography with a EtOAc:isohexane (1:3 + 0.1% NEt_3 additive) solvent mixture.

Yield and appearance: 1.17 g (4.77 mmol, 69%) as yellowish white solid.

HRMS (ESI): m/z = calculated for $[C_{14}H_{14}NO_3]^-$: 244.09792, found: 244.09777.

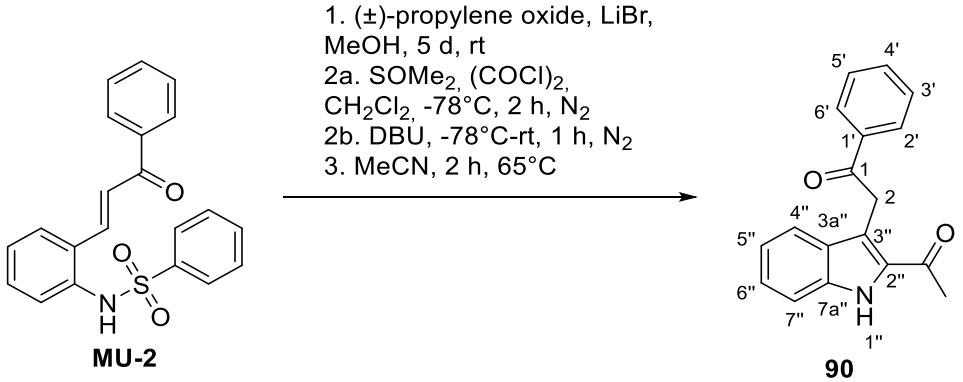
Melting area: 106.4 - 108.6°C

^{1}H NMR (400 MHz, Chloroform-*d*) δ: 9.05 (s, 1H, 1'-NH), 7.72 (dd, *J* = 8.2, 0.9 Hz, 1H, 4'-CH), 7.40 – 7.30 (m, 2H, 6'- and 7'-CH), 7.17 (ddd, *J* = 8.2, 5.8, 2.1 Hz, 1H, 5'-CH), 4.18 (q, *J* = 7.1 Hz, 2H, 1'''-CH_2), 4.13 (s, 2H, 2-CH_2), 2.64 (s, 3H, 2''-CH_3), 1.26 (t, *J* = 7.1 Hz, 3H, 2'''-CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 190.43 (1''-C_q), 170.83 (1-C_q), 135.86 (7a'-C_q), 132.99 (2'-C_q), 128.50 (3a'-C_q), 126.68 (6'-CH), 121.25 (4'-CH), 120.92 (5'-CH), 114.46 (3'-C_q), 112.21 (7'-CH), 61.39 (1'''-CH_2), 31.63 (2-CH_2), 28.54 (2''-CH_3), 14.33 (2'''-CH_3).

IR (ATR): $\tilde{\nu}\ \left[\frac{1}{cm}\right] =$ 3336 w, 3055 w, 2978 w, 2937 w, 1723 m, 1639 m, 1620 w, 1575 w, 1531 w, 1456 w, 1435 m, 1410 w, 1389 w, 1368 w, 1346 m, 1330 m, 1298 w, 1252 m, 1217 w, 1181 m, 1157 m, 1095 w, 1019 m, 1009 w, 969 m, 940 w, 918 w, 890 w, 873 w, 808 w, 776 w, 744 s, 716 w, 682 m.

2-(2-acetyl-1*H*-indol-3-yl)-1-phenylethan-1-one (**90**)



Chemical Formula: $C_{18}H_{15}NO_2$ **Molecular Weight:** 277.32300 g/mol

The indole **90** was prepared according to the general synthesis protocol H (see subchapter 7.2). Sulfonamide **MU-2** (429 mg, 1.18 mmol), (±)-propylene oxide (460 µL, 381 mg, 6.57 mmol), LiBr (27.6 mg, 315 µmol) and 15 mL of MeOH as solvent were used for the first step. It was stirred for 5 days. The workup was performed as described. For step 2., $SOMe_2$ (250 µL, 275 mg, 3.53 mmol), oxalyl chloride (150 µL, 224 mg, 1.77 mmol), DBU (700 µL, 713 mg, 4.68 mmol) and a total of 25 mL of CH_2Cl_2 as solvent were used. 20 mL of MeCN and glacial acetic acid (300 µL, 315 mg, 5.25 mmol) were used for the step 3.. Again, the workup was performed, as described in the general protocol. Product **90** could be purified *via* performing column chromatography with CH_2Cl_2:MeOH (99:1-98:2) as solvent mixture.

Yield and appearance: 196 mg (707 µmol, 60%) as beige powdery solid.

HRMS (ESI): m/z = calculated for $[C_{18}H_{14}NO_2]^-$: 276.10300, found: 276.10299.

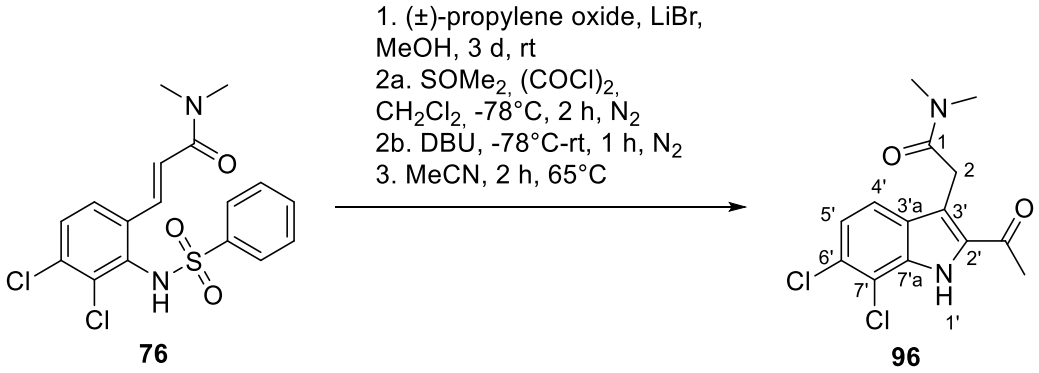
Melting area: 188.4 – 189.5°C

^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.72 (s, 1H, 1''-NH), 8.11 (ddd, *J* = 6.9, 1.8, 1.4 Hz, 2H, 2'- and 6'-CH), 7.71 – 7.63 (m, 2H, 4'- and 4''-CH), 7.56 (ddd, *J* = 8.2, 6.9, 1.3 Hz, 2H, 3'- and 5'-CH), 7.48 (dt, *J* = 8.3, 0.9 Hz, 1H, 7''-CH), 7.30 (ddd, *J* = 8.3, 6.9, 1.1 Hz, 1H, 6''-CH), 7.06 (ddd, *J* = 8.0, 6.9, 0.9 Hz, 1H, 5''-CH), 4.89 (s, 2H, 2-CH_2), 2.51 (s, 3H, -CH_3).

^{13}C NMR (101 MHz, DMSO) δ: 197.12 (1-C_qO), 191.05 (C_qO), 136.85 (1'-C_q), 136.20 (7a'-C_q), 133.15 (4'-CH), 132.34 (2''-C_q), 128.71 (3'- and 5'-CH), 128.10 (2'- and 6'-CH), 128.08 (3a''-C_q), 125.39 (6''-CH), 120.91 (4''-CH), 119.84 (5''-CH), 115.35 (3''-C_q), 112.58 (7''-CH), 35.29 (2-CH_2), 28.22 (-CH_3).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right]$ = 3318 mw, 3057 w, 2894 w, 1674 mw, 1643 m, 1619 w, 1594 w, 1572 w, 1532 w, 1454 w, 1435 w, 1409 w, 1388 w, 1370 w, 1340 mw, 1331 mw, 1253 mw, 1213 m, 1182 w, 1159 w, 1141 w, 1074 w, 1018 w, 1007 w, 1000 w, 990 mw, 972 mw, 936 w, 888 w, 854 w, 833 w, 809 w, 763 w, 735 ms, 700 m, 686 m, 664 m.

2-(2-Acetyl-6,7-dichloro-1*H*-indol-3-yl)-*N*,*N*-dimethylacetamide (**96**)



Chemical Formula: $C_{14}H_{14}Cl_2N_2O_2$ **Molecular Weight:** 313.1780 g/mol

The indole **96** was prepared according to the general synthesis protocol H (see subchapter 7.2). The sulfonamide **76** (468 mg, 1.17 mmol), (±)-propylene oxide (800 µL, 687 mg, 11.8 mmol), LiBr (25.7 mg, 293 µmol) and 45 mL of a methylene chloride/MeOH (6:1) solvent mixture was used for the first step. It was stirred for 3 days. The workup was performed as described in the general protocol. For step 2., $SOMe_2$ (200 µL, 220 mg, 2.81 mmol), oxalyl chloride (120 µL, 180 mg, 1.42 mmol), DBU (700 µL, 713 mg, 4.68 mmol) and a total of 25 mL of CH_2Cl_2 as solvent were used. 20 mL of MeCN and glacial acetic acid (300 µL, 315 mg, 5.24 mmol) were used for the step 3.. Again, the workup was performed, as described in the general protocol. Product **96** could be isolated after purification by column chromatography with pure EtOAc as solvent.

Yield and appearance: 95.0 mg (303 µmol, 26%) as white powder.

HRMS (ESI): m/z = calculated for $[C_{14}H_{15}Cl_2N_2O_2]^+$: 313.05051 ($^{35}Cl$, ^{35}Cl), 315.04756 (^{35}Cl, ^{37}Cl), found: 313.05066 (^{35}Cl, ^{35}Cl), 315.04777 (^{35}Cl, ^{37}Cl).

Melting area: 240.6 - 243.6°C

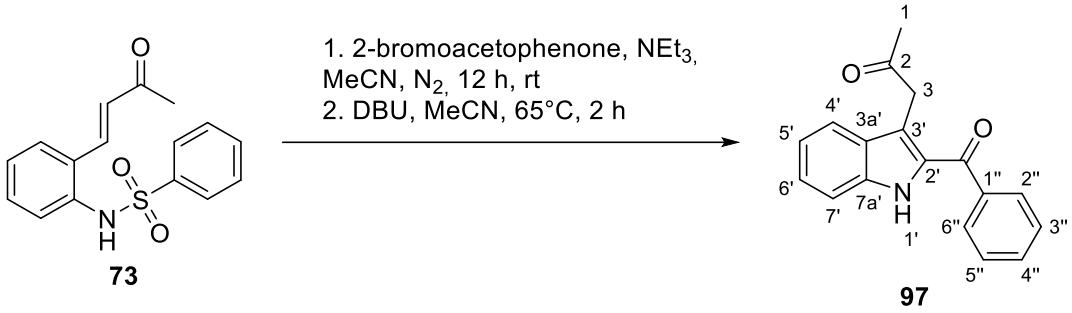
^{1}H NMR (400 MHz, Methylene Chloride-d_2) δ: 10.03 (s, 1H, 1'-NH), 7.42 (dd, *J* = 8.7, 0.6 Hz, 1H, 4'-CH), 7.13 (dd, *J* = 8.7, 0.6 Hz, 1H, 5'-CH), 4.06 (s, 2H, -CH_2), 3.21 (s, 3H, -N($\underline{CH_3}$)$_2$), 3.04 (s, 3H, -N($\underline{CH_3}$)$_2$), 2.42 (s, 3H, -C_qO$\underline{CH_3}$).

^{13}C NMR (101 MHz, CD_2Cl_2) δ: 191.18 (-$\underline{C_q}$OCH_3), 170.41 (1-C_qO), 134.67 (2'-C_q), 134.65 (7a'- or 6'-C_q), 129.38 (7a'- or 6'-C_q), 128.34 (3a'-Cq), 122.43 (5'-CH), 120.38 (4'-CH), 117.87 (3'-C_q), 115.91 (7'-C_q), 37.84 (-N($\underline{CH_3}$)$_2$), 36.08 (-N($\underline{CH_3}$)$_2$), 30.49 (2-CH_2), 28.48 (-$C_q\underline{CH_3}$).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right]$ = 3156 w, 3036 w, 3002 w, 2936 w, 2901 w, 1665 m, 1624 m, 1556 w, 1538 m, 1488 w, 1449 w, 1412 w, 1399 w, 1362 m, 1341 w, 1289 m, 1258 m, 1249 s, 1220 w, 1183 w, 1144 m, 1130 m, 1098 w, 1060 w, 1021 w, 1001 w, 943 w, 924 m, 896 w, 832 w, 799 w, 789 w, 747 w, 707 w, 667 w.

7.4.5 2-Benzoylindoles syntheses products 97-104

1-(2-Benzoyl-1*H*-indol-3-yl)propan-2-one (**97**)



73 **97**

Chemical Formula: $C_{18}H_{15}NO_2$ **Molecular Weight:** 277.32300 g/mol

The indole **97** was synthesised according to the general synthesis protocol I, that is elaborated in subchapter 7.2. The sulfonamide **73** (302 mg, 1.00 mmol), 2-bromoacetophenone (222 mg, 1.10 mmol), NEt_3 (350 µL, 254 mg, 2.51 mmol), DBU (300 µL, 305 mg, 2.0 mmol), glacial acetic acid (280 µL, 294 mg, 4.84 mmol) and 20 mL of dry MeCN were used. Three times 15 mL of H_2O_d, and one time 10 mL of saturated brine solution were used in the working up process. Column chromatography with CH_2Cl_2:MeOH (99:1) yielded pure product **97**.

Yield and appearance: 230 mg (828 µmol, 83%) as beige solid.

HRMS (ESI): m/z = calculated for $[C_{18}H_{16}NO_2]^+$: 278.11755, found: 278.11785.

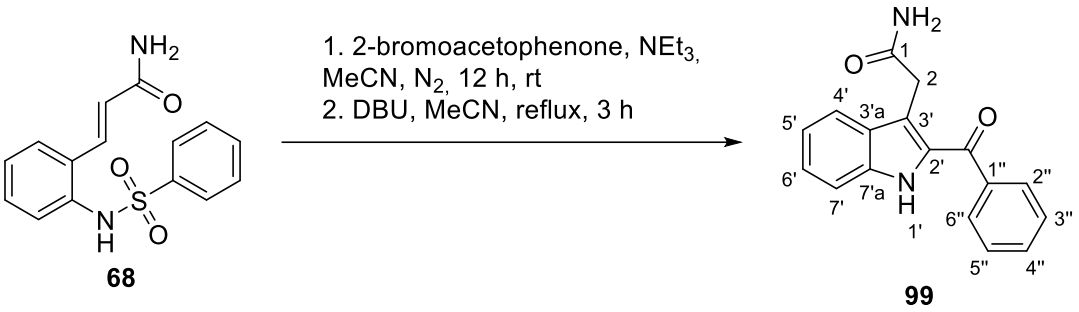
Melting area: 159.6 - 163.1°C

^{1}H NMR (400 MHz, Acetone) δ: 10.73 (s, 1H, 1'-NH), 7.78 (ddd, *J* = 7.0, 2.1, 1.4 Hz, 2H, 2''- and 6''CH), 7.69 – 7.61 (m, 2H, 4'- and 4''-CH), 7.60 – 7.50 (m, 3H, 7'-, 3''- and 5''-CH), 7.33 (ddd, *J* = 8.3, 6.9, 1.2 Hz, 1H, 6'-CH), 7.13 (ddd, *J* = 8.0, 6.9, 1.0 Hz, 1H, 5'-CH), 4.06 (s, 2H, 3-CH_2), 2.07 (s, 3H, 1-CH_3).

^{13}C NMR (101 MHz, Acetone) δ: 204.99 (2-C_qO), 189.20 (C_qO), 140.36 (1''-C_q), 137.86 (7a'-C_q), 133.08 (2'-C_q), 132.89 (4''-CH), 129.62 (2''- and 6''-CH), 129.46 (3''- and 5''-CH), 129.27 (3a'-C_q), 126.52 (6'-CH), 121.73 (4'-CH), 121.12 (5'-CH), 117.90 (3'-C_q), 113.45 (7'-CH), 40.64 (3-CH_2), 29.33 (-CH_3).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right]$ = 3312 m, 3061 w, 1936 w, 1718 mw, 1609 m, 1571 mw, 1525 mw, 1493 w, 1447 w, 1431 w, 1405 w, 1384 w, 1369 w, 1337 m, 1316 mw, 1268 m, 1243 w, 1212 w, 1180 w, 1160 m, 1153 m, 1136 w, 1040 w, 1027 w, 1001 w, 984 w, 961 w, 936 w, 929 w, 906 w, 853 w, 796 w, 786 w, 754 w, 745 m, 738 m, 707 m, 688 m, 671 m.

2-(2-Benzoyl-1*H*-indol-3-yl)acetamide (**99**)



68 **99**

Chemical Formula: $C_{17}H_{14}N_2O_2$ **Molecular Weight:** 278.31100 g/mol

The indole **99** was synthesised according to the general synthesis protocol I, that is elaborated in subchapter 7.2. The sulfonamide **68** (257 mg, 851 µmol), 2-bromoacetophenone (188 mg, 937 mmol), NEt_3 (350 µL, 254 mg, 2.51 mmol), DBU (370 µL, 377 mg, 2.47 mmol), glacial acetic acid (500 µL, 524 mg, 8.65 mmol) and 20 mL of dry MeCN were used. Three times 15 mL of H_2O_d, and one time 10 mL of saturated brine solution were used in the working up process. Colum chromatography with a CH_2Cl_2:MeOH (99:1) solvent mixture yielded pure product **99**.

Yield and appearance: 146 mg (525 µmol, 62%) as light-yellow powder.

HRMS (ESI): m/z = calculated for $[C_{17}H_{13}N_2O_2]^-$ m/z: 277.09825, found: 277.09823.

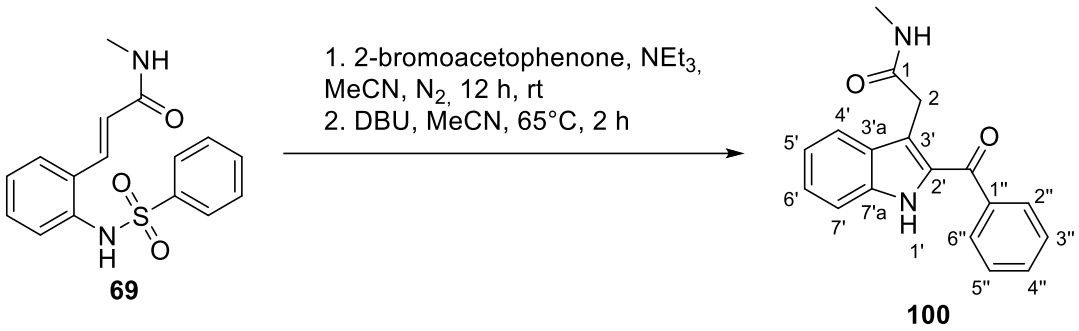
Melting area: 211.0 - 211.5°C

^{1}H NMR (400 MHz, DMSO) δ: 11.55 (s, 1H, 1'-NH), 7.84 – 7.76 (m, 2H, 2''- and 6''-CH), 7.72 – 7.63 (m, 2H, 4'- and 4''-CH), 7.61 – 7.52 (m, 2H, 3''- and 5''-CH), 7.45 (dt, *J* = 8.3, 1.0 Hz, 1H, 7'-CH), 7.29 (ddd, *J* = 8.3, 6.9, 1.2 Hz, 1H, 6'-CH), 7.24 (s, 1H, -N$\underline{H}_2$), 7.09 (ddd, *J* = 8.0, 6.9, 1.0 Hz, 1H, 5'-CH), 6.84 (s, 1H, -N$\underline{H}_2$), 3.64 (s, 2H, 2-CH_2).

^{13}C NMR (101 MHz, DMSO) δ: 188.54 (C_qO), 171.64 (1-C_qO), 138.84 (1''-C_q), 136.66 (7a'-C_q), 132.28 (4''-CH), 132.08 (2'-C_q), 129.03 (2''- and 6''-CH), 128.54 (3''- and 5''-CH), 127.70 (3a'-C_q), 125.27 (6'-CH), 120.93 (4'-CH), 119.79 (5'-CH), 117.23 (3'-C_q), 112.64 (7'-CH), 32.03 (2-CH_2).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right]$ = 3377 w, 3311 w, 3186 w, 1655 mw, 1611 mw, 1573 w, 1524 w, 1445 w, 1417 w, 1396 w, 1369 w, 1337 w, 1268 w, 1244 w, 1216 w, 1174 w, 1154 w, 1137 w, 1009 w, 991 w, 941 w, 934 w, 891 w, 881 w, 852 w, 804 w, 755 w, 746 w, 712 w, 691 mw, 675 w.

2-(2-Benzoyl-1*H*-indol-3-yl)-*N*-methylacetamide (**100**)



69 **100**

Chemical Formula: $C_{18}H_{16}N_2O_2$ **Molecular Weight:** 292.33800 g/mol

The indole **100** was synthesised according to the general synthesis protocol I, that is elaborated in subchapter 7.2. The sulfonamide **69** (254 m, 803 µmol), 2-bromoacetophenone (178 mg, 883 µmol), NEt_3 (300 µL, 218 mg, 2.15 mmol), DBU (350 µL, 356 mg, 2.34 mmol), glacial acetic acid (350 µL, 367 mg, 5.99 mmol) and 20 mL of dry MeCN were used. Three times 15 mL of H_2O_d, and one time 10 mL of saturated brine solution were used in the working up process. Pure product **100** could be isolated by means of column chromatography with CH_2Cl_2:MeOH (99:1).

Yield and appearance: 81.5 mg (279 µmol, 35%) as beige white solid.

HRMS (ESI): m/z = calculated for $[C_{18}H_{17}N_2O_2]^+$: 293.12845, found: 293.12862.

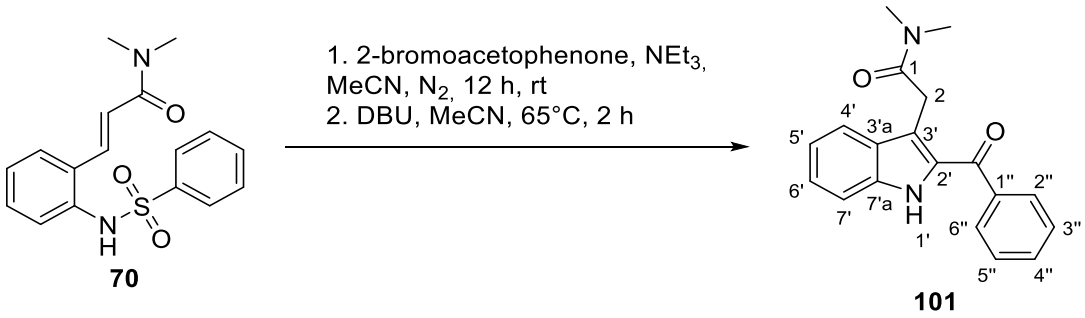
Melting area: 218.0 - 218.5°C

^{1}H NMR (400 MHz, DMSO) δ: 11.57 (s, 1H, 1, 1'-NH), 7.79 (dt, *J* = 7.1, 2.1, 1.4 Hz, 2H, 2''- and 6''-CH), 7.70 – 7.60 (m, 3H, -CONH, 4'- and 4''-CH), 7.56 (tt, *J* = 7.8, 7.1, 1.8, 1.4 Hz, 2H, 3''- and 5''-CH), 7.45 (dt, *J* = 8.3, 1.0 Hz, 1H, 7'-CH), 7.29 (ddd, *J* = 8.3, 6.9, 1.1 Hz, 1H, 6'-CH), 7.08 (ddd, *J* = 8.0, 6.9, 1.0 Hz, 1H, 5'-CH), 3.64 (s, 2H, -CH_2), 2.52 (d, *J* = 4.6 Hz, 3H, -CH_3).

^{13}C NMR (101 MHz, DMSO) δ: 188.56 (C_qO), 169.97 (1-C_qO), 138.85 (1''-C_q), 136.65 (7a'-C_q), 132.25 (4''-CH), 132.14 (2'-C_q), 129.00 (2''- and 6''-CH), 128.52 (3''- and 5''-CH), 127.68 (3a'-C_q), 125.26 (6'-CH), 120.89 (4'-CH), 119.84 (5'-CH), 116.90 (3'-C_q), 112.65 (7'-CH), 32.14 (2-CH_2), 25.74 (-NCH_3).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right]$ = 3312 mw, 3056 w, 2941 w, 2111 w, 2038 w, 2015 w, 1991 w, 1931 w, 1652 mw, 1614 m, 1598 w, 1574 w, 1529 mw, 1451 w, 1431 w, 1403 w, 1384 w, 1369 w, 1338 mw, 1267 mw, 1254 w, 1243 mw, 1211 w, 1180 w, 1155 w, 1138 w, 1053 w, 1010 w, 999 w, 992 w, 939 w, 931 w, 908 w, 891 w, 852 w, 799 w, 786 w, 752 w, 738 m, 702 wm, 688 m, 670 mw.

2-(2-Benzoyl-1*H*-indol-3-yl)-*N*,*N*-dimethylacetamide (**101**)



70 **101**

Chemical Formula: $C_{19}H_{18}N_2O_2$ **Molecular Weight:** 306.3650 g/mol

The indole **101** was synthesised according to the general synthesis protocol I, that is elaborated in subchapter 7.2. The sulfonamide **70** (2.50 g, 7.57 mmol), 2-bromoacetophe-none (1.54 g, 7.72 mmol), NEt_3 (2.00 mL, 1.45 g, 14.4 mmol), DBU (2.50 mL, 2.55 g, 16.7 mmol), glacial acetic acid (2.00 mL, 2.09 g, 34.9 mmol) and 100 mL of dry MeCN were used. Three times 50 mL of H_2O_d, and one time 25 mL of saturated brine solution were used in the working up process. Product **101** purification could be achieved by performing column chromatography with a CH_2Cl_2:MeOH (99:1-97:3) solvent mixture.

Yield and appearance: 1.67 g (5.46 mmol, 72%) as yellowish white crystalline solid.

HRMS (ESI): m/z = calculated for $[C_{19}H_{19}N_2O_2]^+$: 307.14410, found: 307.14427.

Melting area: 159.3 - 161.2°C

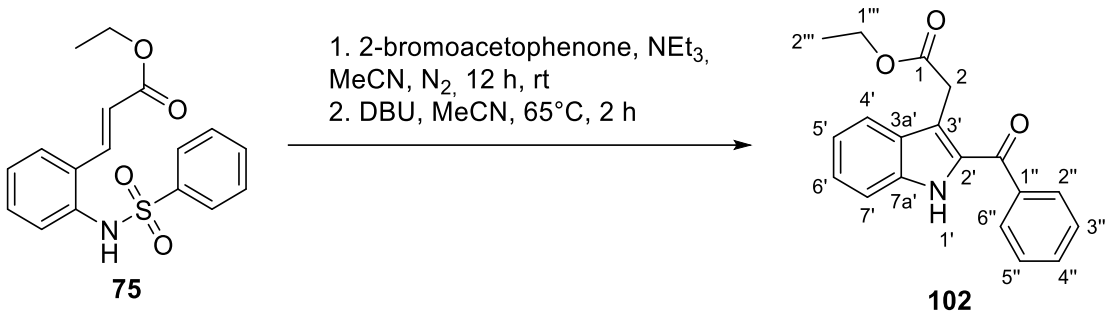
^{1}H NMR (500 MHz, Methylene Chloride-d2) δ: 8.97 (s, 1H, 1‘-NH), 7.74 (dd, J = 8.1, 1.1 Hz, 2H, 2‘‘- and 6‘‘-CH), 7.67 (dd, J = 8.2, 1.1 Hz, 1H, 4‘-CH), 7.61 (tt, J = 7.4, 1.3 Hz, 1H, 4‘‘-CH), 7.50 (dd, J = 8.4, 7.1 Hz, 2H, 3‘‘- and 5‘‘-CH), 7.42 (dt, J = 8.4, 1.0 Hz, 1H, 7‘-CH), 7.35 (ddd, J = 8.2, 6.9, 1.1 Hz, 1H, 6‘-CH), 7.15 (ddd, J = 8.0, 6.8, 1.0 Hz, 1H, 5‘-CH), 3.77 (s, 2H, 2-CH_2), 2.88 (s, 3H, -N($\underline{CH_3}$)$_2$), 2.80 (s, 3H, -N($\underline{CH_3}$)$_2$).

^{13}C NMR (126 MHz, CD2Cl2) δ: 189.26 (C_qO), 170.35 (1-$\underline{C_q}$ON(CH_3)$_2$), 139.99 (1‘‘-C_q), 136.96 (7a‘-C_q), 132.56 (4‘‘-CH), 132.51 (2‘-C_q), 129.42 (3a‘-C_q), 129.20 (2‘‘- and 6‘‘-CH), 129.03 (3‘‘- and 5‘‘-CH), 126.83 (6‘-CH), 122.21 (4‘-CH), 121.11 (5‘-CH), 118.82 (3‘-C_q), 112.51 (7‘-CH), 37.54 (-N($\underline{CH_3}$)$_2$), 35.89 (-N($\underline{CH_3}$)$_2$), 31.30 (2-CH_2).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right]$ = 3852 w, 3744 w, 3314 mw, 3055 w, 2922 w, 2359 w, 1733 w, 1700 w, 1683 w, 1647 mw, 1606 m, 1572 mw, 1558 w, 1524 w, 1486 w, 1449 w, 1431 w, 1422 w, 1390 mw, 1372 w,

1336 mw, 1305 w, 1264 mw, 1246 mw, 1215 w, 1175 w, 1152 w, 1128 w, 1072 w, 1057 w, 1007 w, 990 w, 968 w, 938 w, 921 w, 892 w, 830 w, 799 w, 761 w, 748 mw, 736 m, 695 m, 674 mw.

Ethyl 2-(2-benzoyl-1*H*-indol-3-yl)acetate (**102**)



75 **102**

Chemical Formula: $C_{19}H_{17}NO_3$ **Molecular Weight:** 307.3490 g/mol

The indole analogue **102** was synthesised according to the general synthesis protocol I, that is elaborated in subchapter 7.2. The sulfonamide **75** (2.21 g, 6.66 mmol), 2-bromoacetophenone (1.37 g, 6.79 mmol), NEt_3 (2.00 mL, 1.45 g, 14.3 mmol), DBU (2.00 mL, 2.04 g, 13.4 mmol), glacial acetic acid (1.70 mL, 1.78 g, 29.7 mmol) and 100 mL of dry MeCN were used. Three times 50 mL of H_2O_d, and one time 20 mL of saturated brine solution were used in the working up process. Product purification *via* column chromatography with CH_2Cl_2:MeOH (99:1-97:3) yielded product **102**.

Yield and appearance: 1.00 g (3.26 mmol, 49%) as yellowish white powder.

HRMS (ESI): m/z = calculated for $[C_{19}H_{16}NO_3]^-$: 306.11357, found: 306.11365.

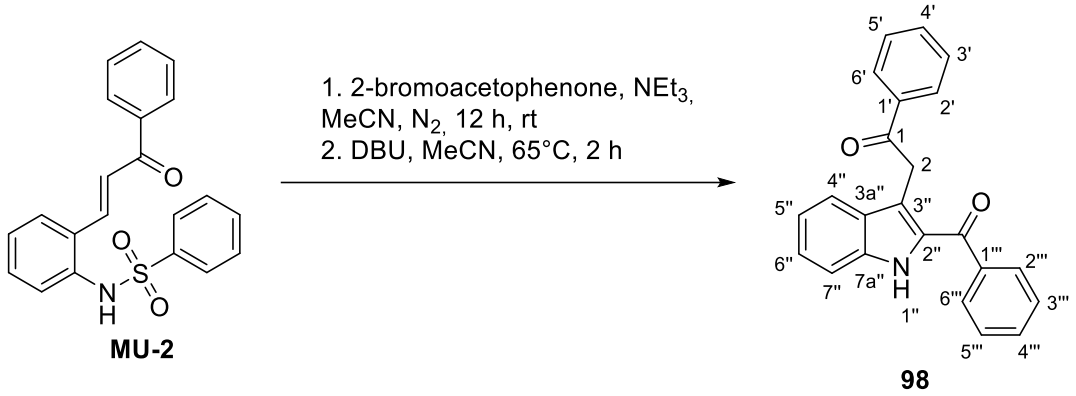
Melting area: 140.2 - 140.5°C

^{1}H NMR (400 MHz, Acetone) δ: 10.76 (s, 1H, 1'-NH), 7.81 (ddd, *J* = 7.3, 1.8, 1.5 Hz, 2H, 2''- and 6''-CH), 7.72 (dt, *J* = 8.1, 1.1 Hz, 1H, 4'-CH), 7.66 (tt, *J* = 7.5, 1.5 Hz, 1H, 4''-CH), 7.56 (dddd, *J* = 7.5, 7.3, 1.8, 1.5 Hz, 2H, 3''- and 5''-CH), 7.55 (dd, *J* = 8.2, 1.0 Hz, 1H, 7'-CH), 7.34 (ddd, *J* = 8.2, 6.9, 1.1 Hz, 1H, 6'-CH), 7.14 (ddd, *J* = 8.1, 6.9, 1.0 Hz, 1H, 5'-CH), 4.05 (q, *J* = 7.1 Hz, 2H, 1'''-CH_2), 3.92 (s, 2H, 2-CH_2), 1.17 (t, *J* = 7.1 Hz, 3H, 2'''-CH_3).

^{13}C NMR (101 MHz, Acetone) δ: 189.26 (C_qOPh), 171.35 (1-C_qO), 140.30 (1''-C_q), 137.75 (7a'-C_q), 133.21 (2'-C_q), 132.96 (4''-CH), 129.65 (2''- and 6''-CH), 129.45 (3''- and 5''-CH), 129.12 (3a'-Cq), 126.46 (6'-CH), 121.71 (4'-CH), 121.13 (5'-CH), 116.69 (3'-C_q), 113.41 (7'-CH), 61.02 (1'''-CH_2), 31.44 (2-CH_2), 14.52 (2'''-CH_3).

IR (ATR): $\tilde{\nu}\ \left[\frac{1}{cm}\right]$ = 3304 mw, 3054 w, 2978 w, 2895 w, 2166 w, 2083 w, 1973 w, 1913 w, 1729 m, 1609 m, 1597 m, 1572 mw, 1529 w, 1495 w, 1476 w, 1448 w, 1431 w, 1420 w, 1383 w, 1366 w, 1328 m, 1268 m, 1217 m, 1203 w, 1181 w, 1174 w, 1159 w, 1153 mw, 1112 w, 1074 w, 1030 mw, 1025 mw, 1010 mw, 1001 w, 991 w, 943 w, 930 w, 893 w, 873 w, 856 w, 809 w, 799 w, 778 w, 756 w, 732 m, 698 m, 674 m.

2-(2-Benzoyl-1*H*-indol-3-yl)-1-phenylethan-1-one (**98**)



Chemical Formula: $C_{23}H_{17}NO_2$ **Molecular Weight:** 339.39400 g/mol

The indole **98** was synthesised according to the general synthesis protocol I, that is elaborated in subchapter 7.2. The sulfonamide **MU-2** (330 mg, 909 µmol), 2-bromoacetophe-none (274 mg, 1.36 mmol), NEt_3 (260 µL, 189 mg, 1.86 mmol), DBU (500 µL, 509 g, 3.35 mmol), glacial acetic acid (350 µL, 367 mg, 5.99 mmol) and 25 mL of dry MeCN were used. Three times 20 mL of H_2O_d, and one time 15 mL of saturated brine solution were used in the working up process. Column chromatography with a EtOAc:MeOH (100:0-98:2) as eluent solvent mixture yielded in pure product **98**.

Yield and appearance: 174 mg (513 µmol, 57%) as yellow-brown needles.

HRMS (ESI): m/z = calculated for $[C_{23}H_{18}NO_2]^+$: 340.13320, found: 340.13344.

Melting area: 159.6 - 165.3°C

^{1}H NMR (400 MHz, CD_2Cl_2) δ: 8.95 (s, 1H, 1''-NH), 7.90 (dt, *J* = 7.7, 1.9, 1.4 Hz, 2H, 2'-CH and 6'-CH), 7.73 (ddd, *J* = 6.9, 1.9, 1.1 Hz, 2H, 2'''- and 6'''-CH), 7.62 – 7.53 (m, 2H, 4'- and 4''-CH), 7.54 – 7.33 (m, 7H, 3'-CH, 5'-CH, 6''-CH, 7''-CH, 3'''-CH, 4'''-CH and 5'''-CH), 7.16 (ddd, *J* = 8.0, 6.9, 1.0 Hz, 1H, 5''-CH), 4.54 (s, 2H, 2-CH_2).

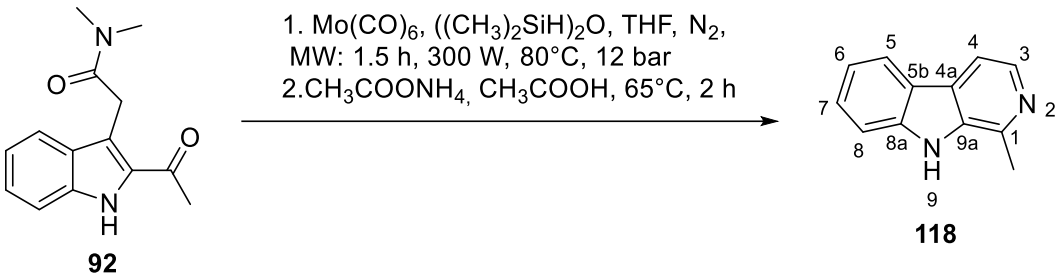
^{13}C NMR (101 MHz, CD_2Cl_2) δ: 197.01 (1-CqO), 188.99 (CqO), 139.59 (1'''-Cq), 137.20 (1'-Cq), 136.77 (7a''-Cq), 133.47 (4'-CH), 132.55 (2''-Cq), 132.45 (4'''-CH), 129.09 (3a''-Cq),

129.05 (3’’’- and 5’’’-CH), 128.93 (3’- and 5’-CH), 128.91 (2’’’- and 6’’’-CH), 128.46 (2’- and 6’-CH), 126.78 (6’’-CH), 121.64 (4’’-CH), 121.16 (5’’-CH), 117.77 (3’’-Cq), 112.52 (7’’-CH), 36.18 (2-CH_2).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right] =$ 3312 mw, 1687 mw, 1614 mw, 1594 w, 1573 w, 1527 w, 1447 w, 1434 w, 1406 w, 1384 w, 1364 w, 1336 mw, 1258 mw, 1247 w, 1218 w, 1203 w, 1174 w, 1154 w, 1009 w, 1000 w, 994 w, 976 w, 930 w, 918 w, 802 w, 744 mw, 735 m, 705 w, 687 mw, 675 mw, 662 w.

7.4.6 β-Carbolines 105-119

Harmane or 1-methyl-9*H*-pyrido[3,4-*b*]indole (**118**)



Chemical Formula: $C_{12}H_{10}N_2$ **Molecular Weight:** 182.22600 g/mol

The chemoselective amide reduction, next to a more reactive keto-group, equated to the first part of the Harman (**118**) synthesis. It was synthesized according to a method of Trillo et al.[116] but the reaction was performed with THF instead of EtOAc, that was reported by Volkov et al.[81] to work just as well with this particular reaction. The subsequent condensation reaction, induced by the addition of CH_3COONH_4/CH_3COOH, had been performed following the previously described condensation reaction, carried out by Kamlah et al.[31]. For the reduction reaction, indole **92** (67.8 mg, 278 µmol) and $Mo(CO)_6$ (3.74 mg, 13.9 µmol) were put in a synthesis microwave reaction flask and the air was exchanged for nitrogen. Tetramethyldisiloxane (130 µL, 98.8 mg, 713 µmol) and 2 mL of dry THF were added by syringe and the reaction mixture was heated at 85°C for 10 min until the components were dissolved. Another 2 mL of dry THF were added and the reaction was performed using a synthesis microwave device (1.5 h, 300 W, 80 °C, 12 bar). For the following in-situ condensation reaction, CH_3COONH_4 (629 mg, 8.16 mmol), dissolved in 1.00 mL glacial acetic acid, was added dropwise and the reaction was stirred at 65°C for 2 h. Residues of THF were removed by rotary evaporator and the remaining acetic acid phase was redissolved in 10 mL of water. The mixture was extracted three times with 20 mL of methylene chloride. The combined organic layers were washed three times with 5 mL of H_2O_d, then one time with 5 mL of saturated brine solution. After removing the excess solvent by rotary evaporator again, the crude product **118** was purified by means of flash column chromatography with EtOAc (+ 0.1% NEt_3 additive).

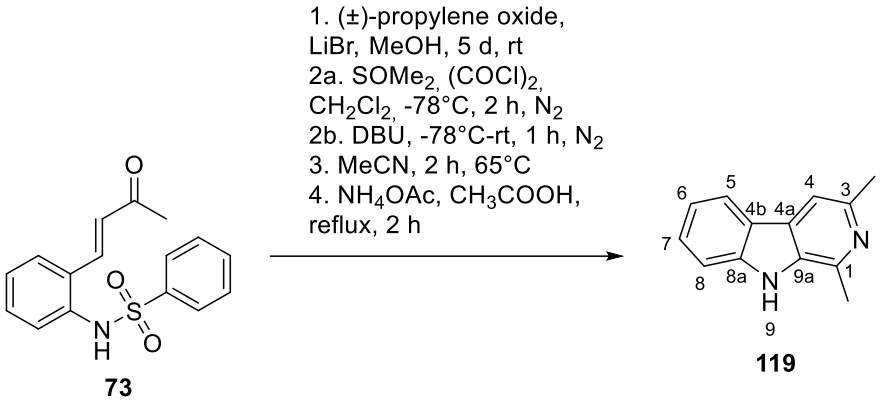
Yield and appearance: 17.0 mg (93.3 µmol, 34%) as brown solid.

Melting area: 221.2 - 238.5°C (Lit. ref.: 234 - 236°C[134])

HRMS (ESI): m/z = calculated for $[C_{12}H_{11}N_2]^+$: 183.09167, found: 183.09159. (Lit. ref.: $[C_{12}H_{11}N_2]^+$: 183.0922, found: 183.0924.[135])

^{1}H NMR (500 MHz, Chloroform-*d*) δ: 8.51 (s, 1H, 9-NH), 8.34 (d, *J* = 5.4 Hz, 1H, 3-CH), 8.11 (dt, *J* = 8.0, 1.0 Hz, 1H, 5-CH), 7.82 (d, *J* = 5.4 Hz, 1H, 4-CH), 7.57 – 7.50 (m, 2H, 7- and 8-CH), 7.29 (ddd, *J* = 8.0, 6.5, 1.6 Hz, 1H, 6-CH), 2.81 (s, 3H, 1-C_qCH_3). (Lit. ref.: **^{1}H NMR (500 MHz, Chloroform-*d*) δ:** 8.52 (1H, s, H-9), 8.35 (1H, d, J = 4.5, H-3), 8.10 (1H, d, J = 8.0, H-5), 7.80 (1H, d, J = 5.0, H-4), 7.55 (2H, m, H-7 and H-8), 7.30 (1H, td, J = 7.5, 4.0, H-6), 2.86 (3H, s, H-1).[134])

3-Methylharmane or 1,3-dimethyl-9*H*-pyrido[3,4-*b*]indole (**119**)



Chemical Formula: $C_{13}H_{12}N_2$ **Molecular Weight:** 196.25300 g/mol

The reaction steps 1. to 3. To substance **119** were carried out, following the general synthesis protocol H in subchapter 7.2. The sulfonamide **73** (347 mg, 1.15 mmol), (±)-propylene oxide (800 µL, 664 mg, 11.4 mmol), LiBr (49.9 mg, 575 µmol), 15 mL of MeOH were used for the first step. It was stirred for 5 days. For the second (2a. and 2b.) step, dry $SOMe_2$ (200 µL, 220 mg, 2.82 mmol), 20 mL of dry CH_2Cl_2 and oxalyl chloride (120 µL, 180 mg, 1.42 mmol), dissolved in 5 mL of dry CH_2Cl_2, were used. The crude solid from the first reaction step was dissolved in 10 mL of dry CH_2Cl_2 and added dropwise to the reaction solution. DBU (500 µL, 509 mg, 3.35 mmol) was added to abort the Swern oxidation and 20 mL of MeCN were added for the 3rd step. It was stirred for 2 h, then instead of proceeding to the solvent removing and workup procedure, that is mentioned in the general protocol, it was directly proceeded to the step 4., that was again performed following the previously described condensation reaction, carried out before by Kamlah et al.[31]. 3.5 mL glacial acetic acid, containing NH_4OAc (2.20 g, 28.5 mmol), was added by syringe. The reaction solution was refluxed for another two hours. Remaining organic solvent was removed by rotary evaporator, then the crude solid was redissolved in 30 mL CH_2Cl_2 again. The organic layer was washed two times with 15 mL of H_2O_d. The watery layer was extracted one more time with 10 mL of methylene chloride. The combined organic layers were washed one time with 10 mL of saturated brine solution. The organic layer was dried over $MgSO_4$ and the solvent was removed *in vacuo*. Product **119** was purified by means of column chromatography with pure methylene chloride.

Yield and appearance: 19.2 mg (9.78 µmol, 9%) as brown solid.

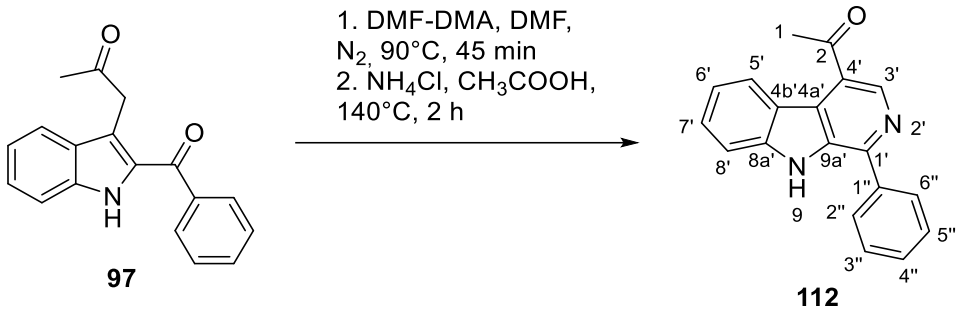
Melting area: 175.5 - 187.3°C

HRMS (ESI): m/z = calculated for $[C_{13}H_{13}N_2]^+$: 197.10732, found: 197.10741.

^{1}H NMR (500 MHz, Methylene Chloride-d_2) δ: 8.72 (s, 1H, 9-NH), 8.07 (dt, *J* = 7.9, 1.0 Hz, 1H, 5-CH), 7.64 (s, 1H, 4-CH), 7.54 – 7.49 (m, 2H, 7- and 8-CH), 7.25 (ddd, *J* = 7.9, 4.9, 3.2 Hz, 1H, 6-CH), 2.75 (s, 3H, 1-C_qCH_3), 2.64 (s, 3H, 3-C_qCH_3).

^{13}C NMR (126 MHz, CD_2Cl_2) δ: 146.88 (3-C_q), 141.18 (8a-C_q), 141.03 (1-C_q), 133.28 (9a-C_q), 129.70 (4a-C_q), 128.56 (7-), 122.12 (4b-C_q), 122.05 (5-CH), 120.19 (6-CH), 112.00 (8-CH), 111.80 (4-CH), 23.90 (3-$C_q\underline{C}H_3$), 20.12 (1-$C_q\underline{C}H_3$).

1-(1-Phenyl-9*H*-pyrido[3,4-*b*]indol-4-yl)ethan-1-one (**112**)



97 **112**

Chemical Formula: $C_{19}H_{14}N_2O$ **Molecular Weight:** 286.33400 g/mol

The β-carboline **112** was synthesised using the general synthesis protocol J in subchapter 7.2. Indole **97** (179 mg, 633 µmol), *N*,*N*-dimethylformamide dimethyl acetal (200 µL, 172 mg, 876 µmol), NH_4Cl (2.37 g, 44.3 mmol), glacial acetic acid (1.00 mL, 1.05 g, 17.5 mmol) and 6 mL of dry DMF were used for the reaction. The temperature in the first reaction step was 90°C. 30 mL of CH_2Cl_2, five times 15 mL of H_2O_d, one time 15 mL of a watery 5%-LiCl solution, and one time 10 mL of saturated brine solution were used in the reaction workup process. Pure product **112** could be isolated after performing column chromatography with pure EtOAc as solvent.

Yield and appearance: 116 mg (405 µmol, 64%) as golden sparkling solid.

HRMS (ESI): m/z = calculated for $[C_{19}H_{15}N_2O]^+$: 287.11789, found: 287.11803.

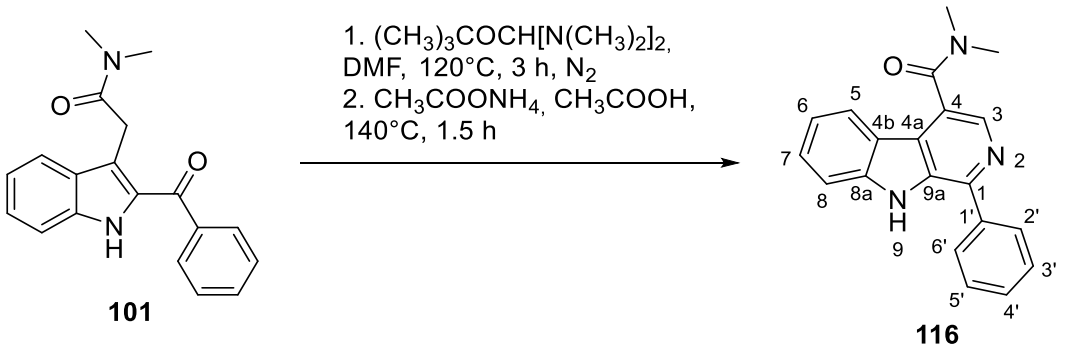
Melting area: 80.0 - 85.7°C

^{1}H NMR (400 MHz, CD_2Cl_2) δ: 9.23 (s, 1H, 9'-NH), 9.01 (s, 1H, 3'-CH), 8.97 (d, *J* = 8.3 Hz, 1H, 5'-CH), 7.96 (ddd, *J* = 7.0, 1.9, 1.4 Hz, 2H, 2''- and 6''-CH), 7.62 – 7.51 (m, 3H, 7'-, 3''- and 5''-CH), 7.54 – 7.45 (m, 2H, 8'- and 4''-CH), 7.30 (ddd, *J* = 8.3, 6.9, 1.2 Hz, 1H, 6'-CH), 2.83 (s, 3H, 1-CH_3).

^{13}C NMR (101 MHz, CD_2Cl_2) δ: 199.80 (2-C_q), 147.07 (1'-C_q), 142.75 (3'-CH), 142.03 (8a'-C_q), 138.33 (1''-C_q), 134.42 (9a'-C_q), 130.01 (4''-CH), 129.86 (7'-CH), 129.70 (3''- and 5''-CH), 129.04 (2''- and 6''-CH), 127.70 (5'-CH), 127.57 (4'- or 4a'-C_q), 127.44 (4'- or 4a'-C_q), 121.69 (4b'-C_q), 120.84 (6'-CH), 111.82 (8'-CH), 29.27 (1-CH_3).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right]$ = 3053 w, 1673 mw, 1618 w, 1588 w, 1566 w, 1536 mw, 1493 w, 1455 w, 1445 w, 1397 w, 1376 w, 1354 w, 1327 w, 1319 w, 1291 mw, 1245 w, 1226 mw, 1178 w, 1157 w ,1136 mw, 1111 w, 1074 w, 1018 w, 1001 w, 923 w, 893 w, 854 w, 801 w, 768 w, 741 m, 721 mw, 698 m, 675 mw.

N,*N*-Dimethyl-1-phenyl-9*H*-pyrido[3,4-*b*]indole-4-carboxamide (**116**)



Chemical Formula: $C_{20}H_{17}N_3O$ **Molecular Weight:** 315.37600 g/mol

The β-carboline **116** was synthesised using the general synthesis protocol J in subchapter 7.2. Indole **101** (391 mg, 1.28 mmol), *tert*-butoxy bis(dimethylamino)methane (400 µL, 337 mg, 1.93 mmol), CH_3COONH_4 (12.0 g, 156 mmol), glacial acetic acid (1.00 mL, 1.05 g, 17.5 mmol) and 20 mL of dry DMF were used for the reaction. The temperature in the first reaction step was 120°C. 50 mL of CH_2Cl_2, five times 20 mL of H_2O_d, one time 20 mL of a watery 5%-LiCl solution, and one time 15 mL of saturated brine solution were used in the reaction workup process. Pure product **116** could be isolated after performing column chromatography with pure EtOAc as solvent.

Yield and appearance: 285 mg (904 mmol, 71%) as yellow powdery solid.

HRMS (ESI): m/z = calculated for $[C_{20}H_{18}N_3O]^+$: 316.14444, found: 316.14453.

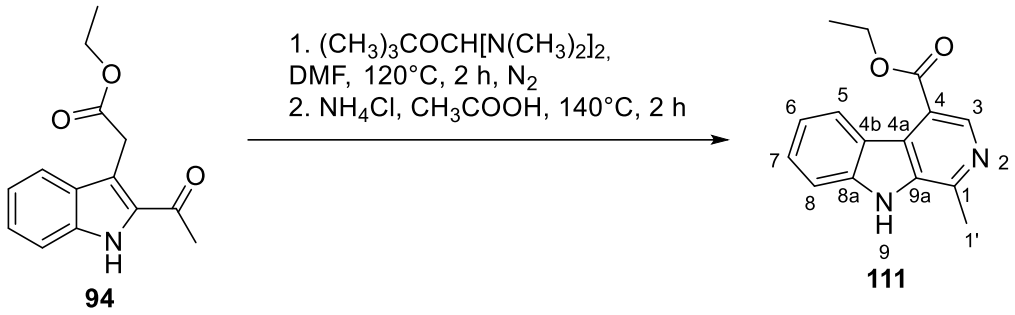
Melting area: 247.3 - 248.0°C

^{1}H NMR (400 MHz, DMSO) δ: 11.75 (s, 1H, 9-NH), 8.36 (s, 1H, 3-CH), 8.08 – 8.01 (m, 2H, 2'- and 6'-CH), 7.85 (d, *J* = 7.8 Hz, 1H, 5-CH), 7.69 (d, *J* = 8.1 Hz, 1H, 8-CH), 7.63 (ddd, *J* = 7.6, 1.0 Hz, 2H, 3'- and 5'-CH), 7.58 (dd, *J* = 8.1 Hz, 1H, 7-CH), 7.55 (dddd, *J* = 7.4, 1.9, 1.0 Hz, 1H, 4'-CH), 7.27 (t, *J* = 7.8 Hz, 1H, 6-CH), 3.23 (s, 3H, (-N($\underline{CH_3}$)$_2$)), 2.88 (s, 3H, -N($\underline{CH_3}$)$_2$).

^{13}C NMR (101 MHz, DMSO) δ: 167.84 (C_qO), 142.54 (1-C_q), 141.36 (8a-C_q), 137.87 (1'-C_q), 135.59 (3-CH), 132.64 (9a-C_q), 128.81 (4'-CH), 128.79 (3'- and 5'-CH), 128.51 (7-, 2'- and 6'-CH), 125.04 (4a-C_q), 124.09 (4-C_q), 122.06 (5-CH), 120.09 (6-CH), 119.42 (4b-C_q), 112.70 (8-CH), 38.00 (-N($\underline{CH_3}$)$_2$), 34.38 (-N($\underline{CH_3}$)$_2$).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right]$ = 3239 w, 3067 w, 2924 w, 2005 w, 1651 w, 1619 mw, 1590 w, 1572 w, 1543 w, 1495 w, 1455 w, 1444 w, 1396 w, 1382 w, 1323 w, 1301 w, 1273 w, 1241 w, 1219 w, 1175 w, 1155 w, 1132 w, 1110 w, 1073 w, 1042 w, 1021 w, 968 w, 956 w, 925 w, 905 w, 897 w, 881 w, 842 w, 801 w, 772 w, 759 w, 745 w, 733 m, 716 w, 699 mw, 667 w, 655 w.

Ethyl 1-methyl-9*H*-pyrido[3,4-*b*]indole-4-carboxylate (**111**)



Chemical Formula: $C_{15}H_{14}N_2O_2$ **Molecular Weight:** 254.28900 g/mol

The β-carboline **111** was synthesised using the general synthesis protocol J in subchapter 7.2. Indole **94** (200 mg, 815 µmol), *tert*-butoxy bis(dimethylamino)methane (250 µL, 211 mg, 1.21 mmol), NH_4Cl (603 mg, 11.3 mmol), glacial acetic acid (500 µL, 525 mg, 8.66 mmol) and 20 mL of dry DMF were used for the reaction. The temperature in the first reaction step was 120°C. 30 mL of CH_2Cl_2, five times 15 mL of H_2O_d, one time 15 mL of a watery 5%-LiCl solution, and one time 10 mL of saturated brine solution were used in the reaction workup process. Pure product **111** could be isolated after performing column chromatography with pure EtOAc as solvent.

Yield and appearance: 37.2 mg (146 µmol, 18%) as beige powdery solid.

HRMS (EI): m/z = calculated for $[C_{15}H_{14}N_2O_2]^{\bullet+}$: 254.10553, found: 254.1050.

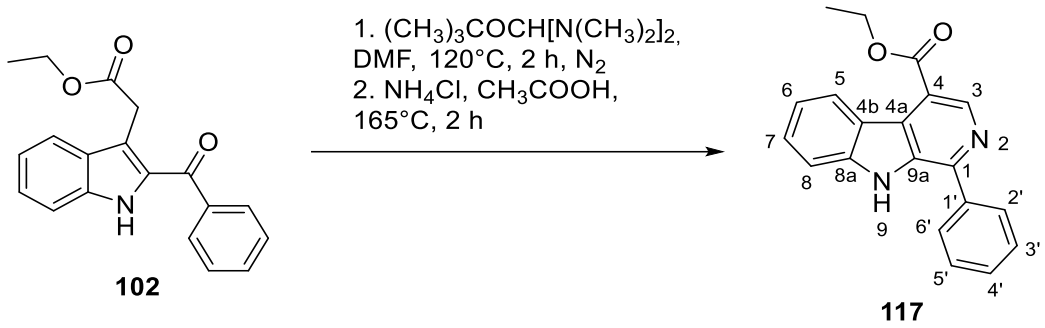
Melting area: 164.0 - 166.2°C

^{1}H NMR (400 MHz, Acetone) δ: 9.01 (dd, *J* = 8.3, 1.2 Hz, 1H, 5-CH), 8.88 (s, 1H, 3-CH), 7.64 (dd, *J* = 8.2, 1.3 Hz, 1H, 8-CH), 7.58 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H, 7-CH), 7.28 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H, 6-CH), 4.52 (q, *J* = 7.1 Hz, 2H, -CH_2), 2.87 (s, 3H, 1'-CH_3), 1.48 (t, *J* = 7.1 Hz, 3H, -CH_3).

^{13}C NMR (101 MHz, Acetone) δ: 167.53 (C_qO), 147.56 (1-C_q), 142.32 (8a-C_q), 141.96 (3-CH), 135.63 (9a-C_q), 129.54 (7-CH), 127.72 (5-CH), 126.58 (4a-C_q), 121.56 (4b-C_q), 120.51 (6-CH), 119.23 (4-C_q), 112.49 (8-CH), 61.61 (-CH_2), 20.97 (1'-CH_3), 14.66 (-CH_3).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right]$ = 3079 w, 2976 w, 2919 w, 2194 w, 2031 w, 1992 w, 1724 mw, 1647 w, 1620 w, 1604 w, 1548 w, 1509 w, 1473 w, 1449 w, 1417 w, 1391 w, 1330 w, 1308 mw, 1300 w, 1288 w, 1236 mw, 1196 mw, 1156 w, 1130 w, 1097 mw, 1035 w, 984 w, 949 w, 914 w, 867 w, 827 w, 797 w, 760 mw, 743 m.

Ethyl 1-phenyl-9*H*-pyrido[3,4-*b*]indole-4-carboxylate (**117**)



Chemical Formula: $C_{20}H_{16}N_2O_2$ **Molecular Weight:** 316.36000 g/mol

The β-carboline **117** was synthesised using the general synthesis protocol J in subchapter 7.2. Indole analogue **102** (252 mg, 819 µmol), *tert*-butoxy bis(dimethylamino)methane (250 µL, 211 mg, 1.21 mmol), NH_4Cl (3.46 g, 64.7 mmol), glacial acetic acid (600 µL, 630 mg, 10.4 mmol) and 10 mL of dry DMF were used. The temperature in the first reaction step was 120°C, for the second it was 165°C. 25 mL of CH_2Cl_2, five times 10 mL of H_2O_d, one time 10 mL of a watery 5%-LiCl solution, and one time 10 mL of saturated brine solution were used in the reaction workup process. Pure product **117** could be isolated after performing column chromatography with CH_2Cl_2:MeOH (100:0 – 98:2) as solvent mixture.

Yield and appearance: 196 mg (620 µmol, 81%) as yellow sparkling crystals.

HRMS (ESI): m/z = calculated for $[C_{20}H_{17}N_2O_2]^+$: 317.12845, found: 317.12863.

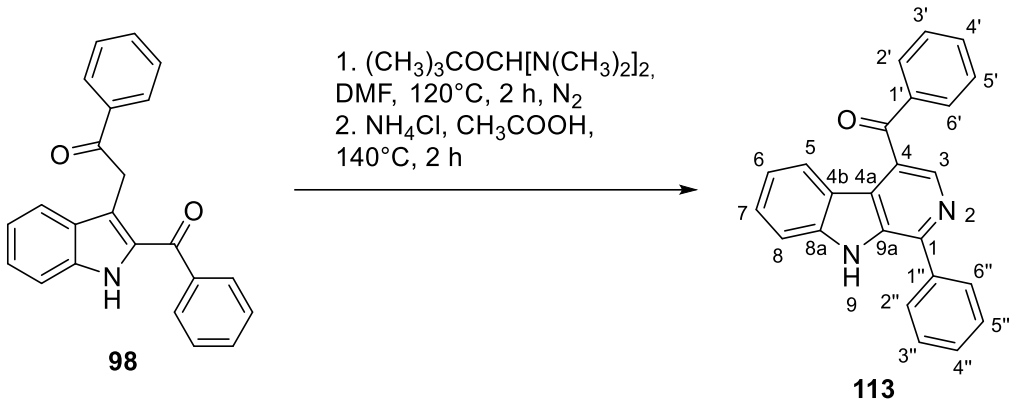
Melting area: 69.5 - 72.7°C

^{1}H NMR (500 MHz, CD_2Cl_2) δ: 9.11 (s, 1H, 3-CH), 9.01 (dq, *J* = 8.2, 0.9 Hz, 1H, 5-CH), 8.99 (s, 1H, 9-NH), 8.00 – 7.94 (m, 2H, 2'- and 6'-CH), 7.63 – 7.56 (m, 3H, 7-, 3'- and 5'-CH), 7.54 (dt, *J* = 8.4, 1.1 Hz, 1H, 8-CH), 7.53 (tt, *J* = 7.5, 1.3 Hz, 1H, 4'-CH), 7.33 (ddd, *J* = 8.2, 6.9, 1.1 Hz, 1H, 6-CH), 4.57 (q, *J* = 7.1 Hz, 2H, -CH_2), 1.52 (t, *J* = 7.1 Hz, 3H, -CH_3).

^{13}C NMR (126 MHz, CD_2Cl_2) δ: 167.32 (C_qO), 146.75 (1-C_q), 142.80 (3-CH), 141.85 (8a-C_q), 138.47 (1'-C_q), 134.19 (4a-C_q), 129.95 (4'-CH), 129.79 (7-CH), 129.74 (3'- and 5'-CH), 129.01 (2'- and 6'-CH), 128.68 (4'- or 9a-C_q), 127.59 (5-CH), 121.39 (4b-C_q), 120.94 (6-CH), 119.88 (4'- or 9a-C_q), 111.85 (8-CH), 61.90 (-CH_2), 14.76 (-CH_3).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right]$ = 3141 w, 2983 w, 2928 w, 1962 w, 1898 w, 1817 w, 1719 m, 1622 w, 1595 w, 1569 w, 1547 w, 1504 w, 1474 w, 1455 w, 1445 w, 1412 w, 1387 w, 1364 w, 1327 w, 1295 w, 1268 w, 1251 m, 1232 mw, 1187 m, 1158 w, 1135 m, 1108 m, 1075 w, 1044 mw, 1029 m, 1018 mw, 1012 mw, 994 w, 940 w, 911 w, 895 w, 873 w, 849 w, 834 w, 805 w, 771 w, 759 m, 735 m, 714 w, 693 m, 659 w.

Phenyl(1-phenyl-9*H*-pyrido[3,4-*b*]indol-4-yl)methanone (**113**)



Chemical Formula: $C_{24}H_{16}N_2O$ **Molecular Weight:** 348.40500 g/mol

The β-carboline **113** was synthesised using the general synthesis protocol J in subchapter 7.2. Indole **98** (75.0 mg, 221 µmol), *N*,*N*-dimethylformamide diethyl acetal (80.0 µL, 68.8 mg, 350 µmol), NH_4Cl (1.00 g, 18.8 mmol), glacial acetic acid (2.00 mL, 2.10 g, 34.6 mmol) and 3 mL of dry DMF were used for the reaction. The temperature in the first reaction step was 120°C. 15 mL of CH_2Cl_2, five times 5 mL of H_2O_d, one time 5 mL of a watery 5%-LiCl solution, and one time 5 mL of saturated brine solution were used in the reaction workup process. Pure product **113** could be isolated after performing column chromatography with EtOAc:MeOH (100:0-97:3) as solvent mixture.

Yield and appearance: 44.0 mg (126 µmol, 57%) as golden sparkling solid.

HRMS (ESI): m/z = calculated for $[C_{24}H_{17}N_2O]^+$: 349.13354, found: 349.13380.

Melting area: 82.9 - 85.7°C

^{1}H NMR (400 MHz, CD_2Cl_2) δ: 8.99 (s, 1H, 9-NH), 8.62 (s, 1H, 3-CH), 8.10 (dq, *J* = 8.2, 0.9 Hz, 1H, 5-CH), 8.02 (ddd, *J* = 7.0, 2.0, 1.5 Hz, 2H, 2''- and 6''-CH), 8.00 (ddd, *J* = 7.1, 1.8 Hz, 2H, 2'- and 6'-CH), 7.68 (tt, *J* = 7.4, 1.8 Hz, 1H, 4'-CH), 7.62 (ddt, *J* = 7.4, 7.1, 1.5 Hz, 2H, 3'- and 5'-CH), 7.58 – 7.51 (m, 5H, 7-, 8-, 3''-, 4''- and 5''-CH), 7.18 (ddd, *J* = 8.2, 4.8, 3.3 Hz, 1H, 6-CH).

^{13}C NMR (101 MHz, CD_2Cl_2) δ: 196.34 (CqO), 145.76 (1-Cq), 141.67 (3-CH), 141.42 (8a-Cq), 138.38 (1'- or 1''-Cq), 138.34 (1'- or 1''-Cq), 133.98 (9a-Cq), 133.78 (4'-CH), 130.79 (2'- and 6'-CH), 129.79 (4''-CH), 129.63 (3'- and 5'-CH), 129.45 (7-CH), 129.02 (3''- and 5''-CH), 128.79 (2''- and 6''-CH), 128.04 (4a-Cq), 127.02 (4-Cq), 125.54 (5-CH), 121.11 (4b-Cq), 120.76 (6-CH), 111.94 (8-CH).

IR (ATR): $\tilde{\nu}\left[\frac{1}{cm}\right]$ = 3057 w, 2923 w, 2853 w, 1737 w, 1651 w, 1621 w, 1595 w, 1577 w, 1566 w, 1549 w, 1494 w, 1470 w, 1446 w, 1394 w, 1320 w, 1266 mw, 1226 w, 1193 w, 1175 w, 1147 w, 1119 w, 1074 w, 1055 w, 1024 w, 1010 w, 1000 w, 970 w, 913 w, 893 w, 870 w, 807 w, 794 w, 767 w, 741 m, 725 m, 695 m.

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10 List of Tables

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