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MASTERARBEIT

Titel der Masterarbeit

„Investigations towards the total synthesis of ibogamine; A fast and convenient approach to *iboga*-alkaloids“

verfasst von

Nino Trattnig BSc

angestrebter akademischer Grad

Master of Science (MSc)

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Studienkennzahl lt. Studienblatt:	A 066 862
Studienrichtung lt. Studienblatt:	Masterstudium Chemie
Betreut von:	Ass.- Prof. Dipl.-Chem. Dr. Lothar Brecker, Privatdoz.

universität wien

MASTER THESIS

Title of the Thesis

„Investigations towards the total synthesis of ibogamine; A fast and convenient approach to *iboga*-alkaloids“

written by

Nino Trattnig BSc

Submitted in partial fulfillment of the requirements for the degree

Master of Science (MSc)

Vienna, June 2014

Studienkennzahl lt. Studienblatt:	A 066 862
Supervisor (formal)	Ass. Prof. Dipl.-Chem. Dr. Lothar Brecker, Privatdoz.
Supervisor (external)	Univ.Prof. Dipl.-Ing. Dr.techn. Marko D. Mihovilovic

Für alle die mich unterstützt haben und einen Teil zu diesem Erfolg beigetragen haben.

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The year I worked for my thesis was one of the most intense and exciting in my life. The path between excitement about efficient reactions and frustration about not working things was always small, but there were several people who were guiding me through that time and I want to take the chance to thank them.

At first I want to thank Prof. Marko Mihovilovic for giving me the chance to work on such an interesting but also challenging task and for his trust in me solving all problems under his professional supervision.

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A big thank goes to all the operators measuring hundreds of NMRs, dozens of HPLCs for me and helping me with devices when I needed help.

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My deepest thanks are going to my family including my parents, my grandmother, my aunt and uncle. They always supported me during my education and made it possible for me to conduct a study like this by giving me financial but also emotional support.

Last but not least I want to thank my girlfriend Bettina, for her support and brighten words when I needed some.

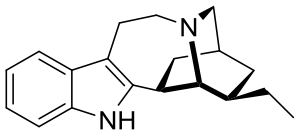
Key

All compounds prepared in this thesis are labeled with bold Arabic numbers. Compounds unknown to the literature are additionally underlined. Literature citations are indicated by superscript Arabic numbers.

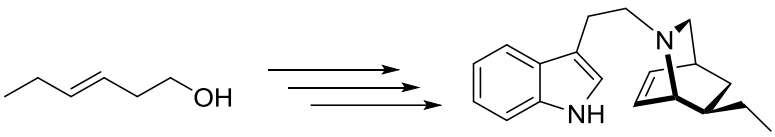
Abstract

Iboga-alkaloids are a class of compounds having a long history. Isolated from the root bark of the plant *Tabernanthe iboga* and initially used just by the natives in Gabon to treat hunger, thirst and fatigue, the potential for the treatment of addictions caused by drugs like heroin, opioids, alcohol and nicotine was recognized very soon. This compound class is interacting with a large number of receptors, ion channels and other proteins including: N-methyl-D-aspartate-receptors, opioid-receptors, serotonin- and dopamine-transporters and acetyl-choline-receptors. Prominent *iboga*-alkaloids like ibogaine show side effects so the search for new derivatives to use them in drug addiction therapy is still a challenging task.

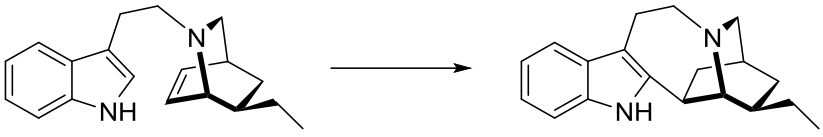
The aim of this thesis was to find a fast approach to *iboga*-alkaloids, which is simple and gives high yields, so that it is suitable for creating a substance library. A synthesis for racemic ibogamine was designed obtaining an overall yield of 5 % over 9 steps.



An approach which was published by Trost et al. was used for the synthesis of the isoquinuclidine-precursor. This precursor was synthesized over 6 steps with 16 % overall yield starting from commercially available 3-hexenol.



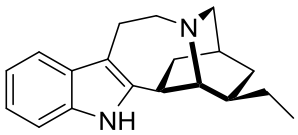
The isoquinuclidine precursor was then subjected to several metal-assisted C-C bond formation reactions, to find a suitable route to obtain the target compound ibogamine



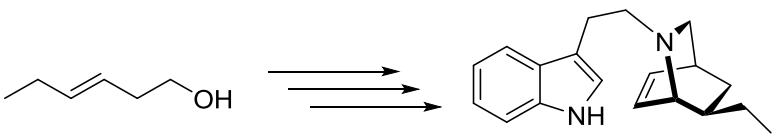
Deutsche Kurzfassung

Iboga-Alkaloide sind eine Klasse von Substanzen, die eine lange Geschichte aufweisen können. Isoliert aus der Wurzelrinde der Pflanze *Tabernanthe iboga* wurden die Alkaloide anfangs nur von den Ureinwohnern Gabons konsumiert, um Hunger, Durst und Müdigkeit zu behandeln. Später wurde ein möglicher Anwendungsbereich für die Therapie von Drogensucht, verursacht durch Heroin, Opioide, Alkohol und Nikotin entdeckt. *Iboga*-Alkaloide wechselwirken mit einer großen Anzahl an verschiedensten Rezeptoren, Ionenkanälen und anderen Proteinen wie: NMDA-Rezeptoren, Opioid-Rezeptoren, Serotonin- und Dopamin-Transporter und Acetyl-cholin-Rezeptoren. Die bekanntesten Iboga-Alkaloide wie Ibogain verursachen jedoch Nebenwirkungen, daher ist die Suche nach anderen Derivaten für die Drogenersatztherapie immer noch eine interessante Aufgabe.

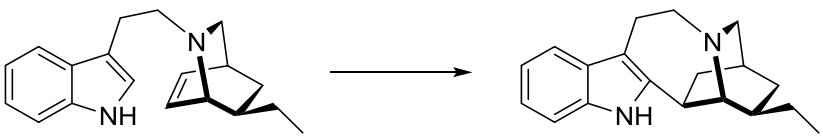
Das Ziel dieser Arbeit war es, einen schnellen Zugang zu *Iboga*-Alkaloiden zu finden, welcher möglichst einfach ist und sich durch gute Ausbeuten auszeichnet, um damit eine Substanz-Bibliothek aufzubauen. Es wurde eine Synthese für racemisches Ibogamin entwickelt, wobei eine Ausbeute von 5 % über 9 Schritte erhalten wurde.



Für die Synthese der Isoquinuclidin-Vorstufe wurde eine Route verwendet, die von Trost et al. publiziert wurde. Diese Vorstufe wurde über 6 Stufen mit einer Gesamtausbeute von 16 % synthetisiert, wobei der billige Alkohol 3-Hexenol als Ausgangsmaterial benutzt wurde.



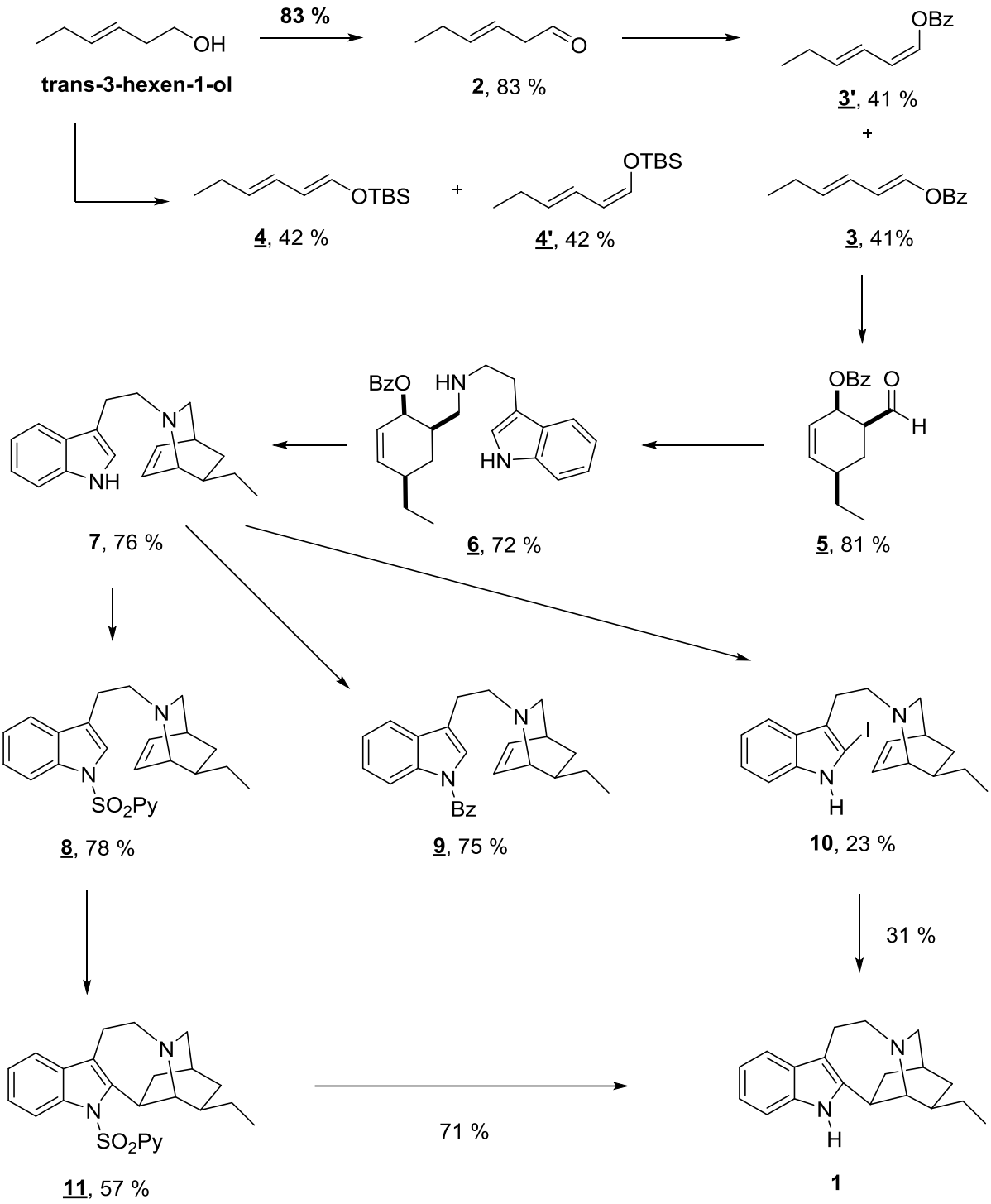
Die Isoquinuclidine-Vorstufe wurde dann verschiedenen metallassistierten Reaktionsbedingungen zur C-C Bindungsbildung unterworfen, um Zugang zu der Zielsubstanz zu bekommen.



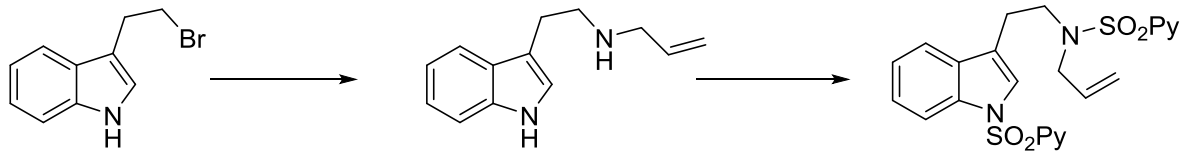
Content

General schemes

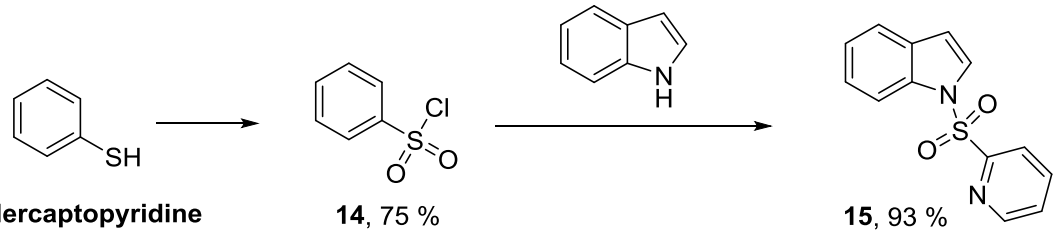
Total synthesis of ibogamine



Synthesis of CH-activation precursors

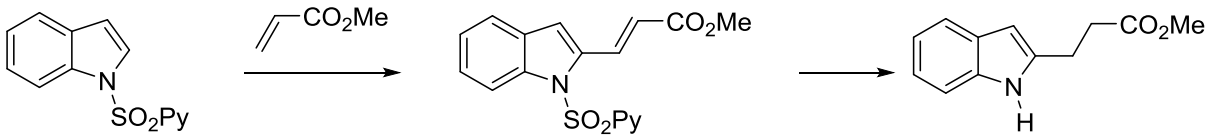


3(2-bromoethyl)indole **12**, **84 %** **13**, 50 %

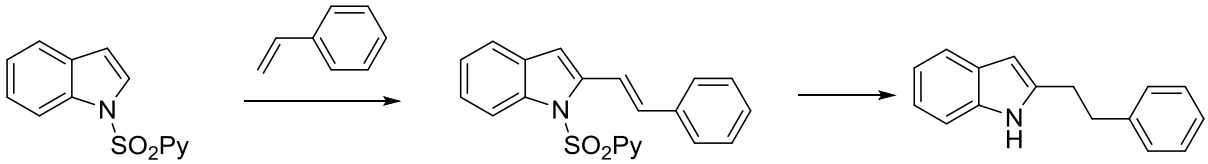


2-Mercaptopyridine **14**, 75 % **15**, 93 %

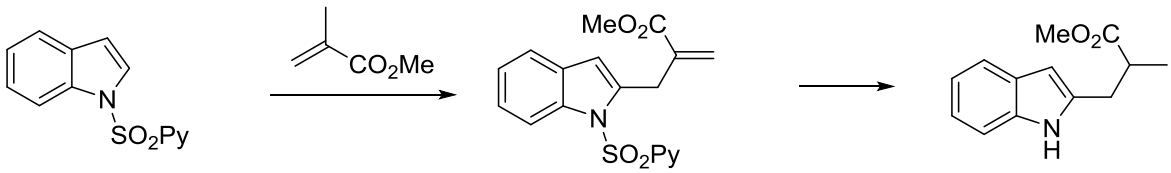
C2-Alkenylations of indole derivatives



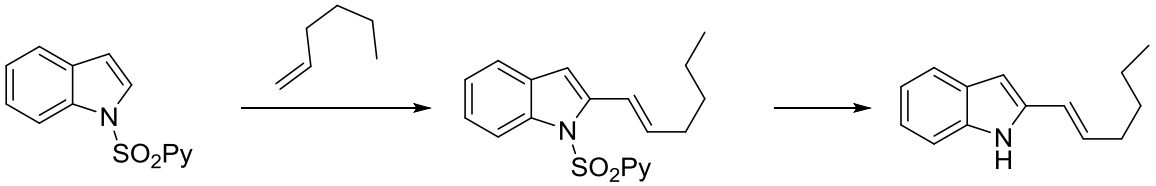
15 **16**, 53 % **23**, 57 %



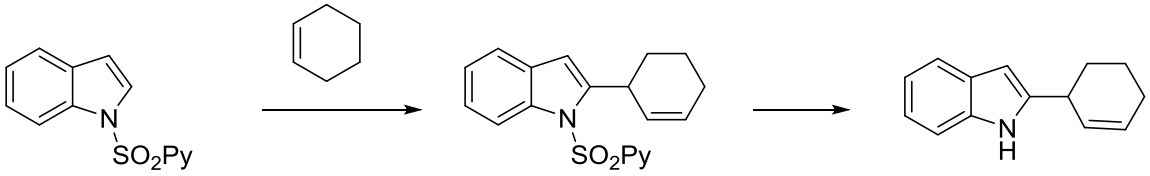
15 **17**, 72 % **24**, 52 %



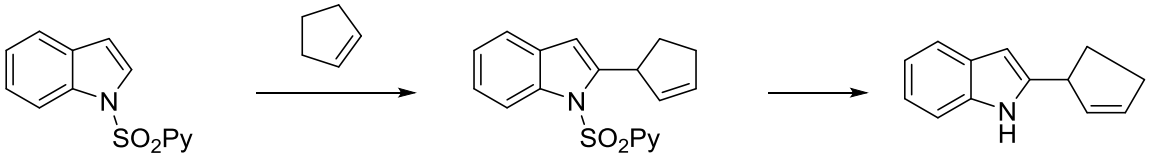
15 **18**, 72 % **25**, 57 %



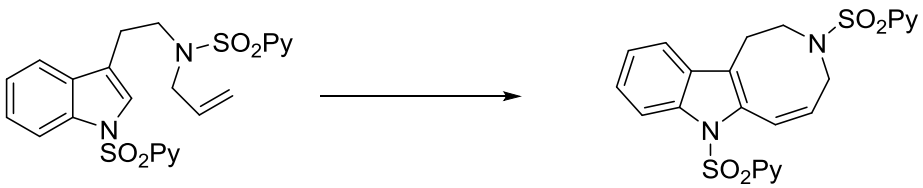
15 **19**, 71 % **26**, 87 %



15 **20**, 16 % **27**, 88 %



15 **21**, 53 % **28**, 80 %



13 **22**, 9 %

I. Introduction

1. Abbreviations

AcCl	acetyl chloride
AgOTf	silver triflate
aqu.	aqueous
broad s	broad singlet
BzCl	benzoyl chloride
Cu(OAc)2	Copper(2)acetate
cy	cyclohexyl
d	doublet (NMR)
DBU	1,8-Diazabicyclo[5.4.0]undec-7-en
DCE	1,2-dichloroethane
DCM	dichloromethane
dd	doublet of doublets (NMR)
ddd	doublet of doublets of doublets (NMR)
DIPEA	diisopropylethylamine
DMAc	dimethylacetamide
DMAP	4-(dimethylamino)pyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
dppf	1,1′-bis(diphenylphosphino)ferroce
dppp	1,3-bis(diphenylphosphino)propan
dt	doublet of triplets (NMR)
EI	electron impact
Et_2O	diethylether
EtOAc	ethyl acetate
equ.	equivalent
GC-MS	gas chromatography - mass spectrometry
HR-MS	high resolution mass spectrometry
J	coupling constant (NMR)
KOtBu	Potassium tert-butanolate
LG	leaving group

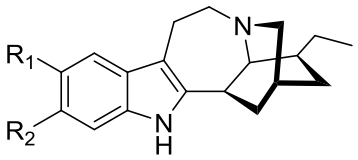
m	multiplet (NMR)
MeCN	acetonitrile
MeOH	methanol
MPLC	medium pressure liquid chromatography
NEt_3	triethylamine
NIS	N-iodo succinimide
NMR	nuclear magnetic resonance
PCC	pyridinium chloro chromate
PE	light petroleum (boiling point approx. 40 – 60 °C)
PhMe	toluene
PhI	iodobenzene
$PhI(OAc)_2$	(diacetoxyiodo)benzene
ppm	parts per million (NMR)
PTSA	p-toluene-sulfonic acid
2-$PySO_2Cl$	2-pyridine-sulfonylchloride
rel	relative
R_f	retention factor (TLC)
rt	room temperature
s	singlet (NMR)
satd.	saturated
Sphos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
T	temperature
t	triplet (NMR)
TBSOTf	tert-butyldimethylsilyl triflate
tBuMePhos	2-di-tert-butylphosphino-2′-methylbiphenyl
TEMPO	2,2,6,6-tetramethylpiperidinoxyl
THF	tetrahydrofuran
TLC	thin layer chromatography
q	quartet (NMR)

2. Iboga alkaloids

2.1. Historical Background

Iboga alkaloids were first described in the year 1864. French sailors collected some samples from a plant called *Tabernanthe iboga (T. iboga)*(**Figure 2**) in Gabon and brought them to France.[1] This plant, which belongs to the *Apocynaceae* family, triggered their interest, because it was and is still commonly eaten by natives in the western African region due to its different effects. The root bark of this plant is frequently eaten there in small doses, to treat hunger, thirst and fatigue. People belonging to a religion called Bwiti are using the plant in higher doses for religious ceremonies, for instance to celebrate the entrance of children into adulthood, or to communicate with deceased ancestors.[2] The first isolation of *iboga* alkaloids was conducted 1901 providing 6-10 g *iboga* alkaloids from 1 kg of dried root bark of *T. iboga.*[2] The root bark contains by far the biggest amount of the interesting alkaloids compared to other parts of the plant. The isolated alkaloids from the root bark are a mixture of different *iboga* alkaloids with most abundant constituents ibogaine (approx. 80 %), ibogaline (approx. 15 %) and ibogamine (approx. 5 %) (**Figure 1**).[3] Based on chemical methods a structure of the most prominent *iboga* alkaloid ibogaine was suggested 1957 by Taylor *et al,*[4] which was confirmed 1960 by X-ray analysis.[5]

Figure 2: *Tabernanthe iboga*



Ibogamine: R_1=H, R_2=H
Ibogaine: R_1=OMe, R_2=H
Ibogaline: R_1=OMe, R_2=OMe

Figure 1: Three prominent *iboga Alkaloids*

Having the structure in hand the first racemic total synthesis was performed by Büchi and co-workers 1966.[6] The first commercial sale of ibogaine started 1939 in France where it was sold for more than 40 years as a drug called “Lambarene” to treat fatigue depression and infectious diseases.[7] In the year 1962 Howard Lotsof made an interesting surveillance. Lotsof was a habitual heroin user who was always interested in new drugs. In the private laboratory of a friend he found a sample of the root bark of *T. Iboga* and self-administered himself the whole sample. What he reported was a “trip” comparable to psychedelics like LSD or psilocybin. It is noteworthy, that after the “trip” he had no more cravings to heroin which he took at this time regularly every day. He stopped taking Heroin immediately and also suffered no withdrawals.[8]

He recognized the potential of *iboga* alkaloids for anti-addictive therapy. In the same year he administered the ibogaine containing plant up to 19 mg/kg to a group of 20 people, of which seven were addicted to heroin. Five of seven addicts reported that they stayed abstinent from heroin for at least 6 month, suffering neither withdrawals nor cravings in the first months.[7,9] In the year 1968 the possession of ibogaine was made illegal in the U.S. and ibogaine was classified as a schedule 1 drug.[7] Howard Lotsof spent much time to spread and inform about the potential of ibogaine in anti-addictive therapy and 1985 he published his first patent for the application of ibogaine and its salts in opioid therapy.[9] The next years 4 more patents regarding ibogaine followed, concerning also suggestions for the anti-addictive therapy of alcohol and nicotine.[1] In 1986 he founded a company called NDA International to fund and obtain funds for research studies with ibogaine (e. g. animal studys).[1,7] In the early 90's a few studies where published which reported about the diminished self-administration of opioids and heroin after the exposure of rats with ibogaine.[7,10] In 1993 the first human trials were executed by Nash *et al,* who administered doses of 1, 2 and 3 mg/kg of ibogaine.[11] In the same year the National Institute of Drug Abuse (NIDA) and advisors were discussing about protocols to use ibogaine in different phase 1 and phase 2 studies, but due to a lot of criticism they disagreed to fund any trials concerning ibogaine.[1] Nowadays, ibogaine is more prominent in alternate medicine but the search is still ongoing to develop new derivatives with less side-effects (e. g. hallucination). There are still clinics in Mexico or the Netherlands which are using ibogaine in anti-addictive therapy.[1]

2.2. Biological activity

2.2.1. General comments

The biological activity of ibogaine and its derivatives noribogaine and 18-methoxycornaridine (18-MC) was reviewed a couple of times.[1,7,8,12] Although the type of activity of the different *iboga* alkaloids is very similar, the magnitude of the affinities and interactions to active sites during *in vitro* tests differ. In this part only the biological activity of ibogaine will be discussed because it's the most prominent *iboga* alkaloid.

Several experiments have shown that ibogaine is a very promising compound for application in anti-addictive therapy. A single dose of ibogaine can avoid withdrawal symptoms of opioids (e. g. heroin, morphine) and can reduce or even avoid cravings caused by opioids, cocaine, alcohol and nicotine. Evidence was given by several *in vitro* studies and by *in vivo* experiments in mice, rats and monkeys. Although a few protocols for phase I and II studies were developed and discussed and also the interest and willingness from the scientific community to conduct these studies with humans was given, none of these studies were started, due to not

completely understandable reasons. Therefore, there is very little scientifically accepted knowledge about *in vivo* activity of ibogaine in humans. The mode of action of ibogaine with respect to its anti-addictive properties is not fully understood, yet. That's mainly due to the fact that the effect of ibogaine cannot be explained with any known model for anti-addictive compounds. Ibogaine shows a lot of different interactions with transporters, receptors and ion channels and it's not completely clear which of these interactions are playing the most important part in the drug-replacement therapy, or if the mixture of them all together makes it so effective. The best known interactions, that ibogaine undergoes *in vitro,* are discussed here shortly.

2.2.2. Antagonist of NMDA-receptors

N-methyl-D-aspartate-(NMDA) glutamate receptors are located in the central nerve system (CNS) in the nerve-cell membranes. They regulate the flow of ions like Na^+ and Ca^{2+} into the cell **(Figure 3**). The name originates from the effective activator N-methyl-D-aspartate, which is naturally not occurring. *In vivo* these receptors are activated by glutamate (**Figure 4**).[13] Ibogaine is an antagonist of these receptors and inhibits them noncompetitively. The effect of some anti-addictive drugs is due to their ability to inhibit these receptors, so it was suggested that it could be the same case with ibogaine.

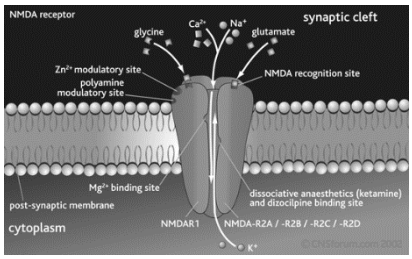
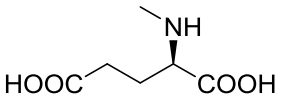
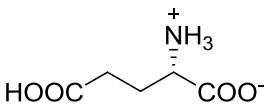


Figure 3: NMDA-receptor located in the cell-membrane[14]



A N-Methyl-D-aspartate



B L-Glutamate

Figure 4: Synthetic (A) and natural ligand of NMDA-receptor

2.2.3. Agonist in opioid receptors

There are several different types of opioid receptors including δ, κ, μ and nociception receptors, which are again arranged in subtypes. They are G-protein coupled membrane-receptor-proteins located in the CNS. Endogenous ligands are opioid peptides like endorphins, but also much smaller molecules like morphine are able to activate these receptors. Activation of these transmembrane proteins leads to a cascade of effects. After activation, the adenylate-cyclase gets inhibited. As a result of that potassium ion channels are activated and current dependent calcium-ion-channels are inhibited.[15] There is evidence that ibogaine has a high affinity to κ- and μ- opioid receptors. Ibogaine binds to μ-receptors with a binding affinity (K_i) between 0.13-26 μM and to κ-receptors (**Figure 5**) with 2.2-30 μM. There are suggestions that reduced opioid withdrawals and reduced opioid craving can be explained due to these interactions.

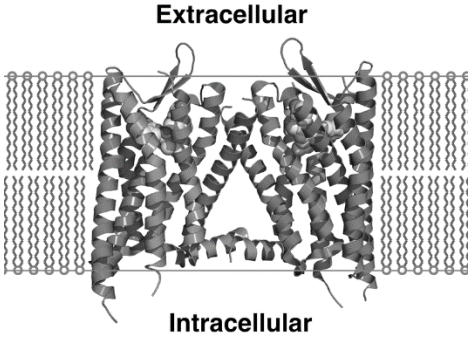


Figure 5: Crystallographic structure of the human κ1-opioid receptor homo dimer[16]

2.2.4. Inhibition of serotonin transporters

If the neurotransmitter serotonin is released from the nerve cell into the synaptic cleft, the effect of serotonin is appreciable. To end this effect, serotonin has to be transported back into the cell. For this purpose a serotonin transporter which is located in the synaptic cleft, is binding to a molecule of serotonin and locking it back into the nerve-cell. If these transporters are blocked, serotonin re-uptake is not possible and therefore the serotonin level is enhanced outside the cell.[17] If the structure of ibogaine is viewed closer, the serotonin structure can be recognized within it (**Figure 6**). It's therefore no surprise, that ibogaine binds to serotonin transporters with high affinity (K_i = 0.5-10 μM) and inhibits them efficiently. There are suggestions that ibogains hallucinogenic effect results from an enhanced serotonin level outside the cell. These interactions are making *iboga*-alakloids also interesting for other diseases like depressions.

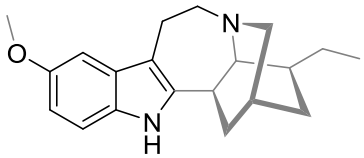


Figure 6: Structure of Ibogamine (grey+black),
structure of serotonin (black)

2.2.5. Other interactions

Ibogaine inhibits dopamine transporters. These transporters are re-uptaking released dopamine in a similar manner, like serotonin transporters do with serotonin. Dopamine contains a benzene ring instead of an indole as an aromatic moiety, which would explain why the affinity of ibogaine to these transporters is 10-50 times lower compared to serotonin transporters.

Some papers were published, reporting about the interaction between ibogaine and acetylcholine receptors.[1,7,12] These receptors are divided into nicotinic acetylcholine receptors (they are ionotropic which means they are ion channels themselves), and muscarinic acetylcholine receptors (they are metabotropic which means they are G-protein coupled and they are effecting ion channels after a signal cascade).[18]

An affinity to $Sigma_2$ receptors (K_i=0.01-1.8 µM) and $Sigma_1$ receptors (K_i=2-100 times weaker as $Sigma_2$) was reported.

Also an affinity of ibogaine to sodium channels was reported, but there is no evidence that this interaction plays any role in ibogains anti-addictive effect.

2.2.6. Side effects

Considering that ibogaine was illegalized in the USA very early and appreciating the fact that there is no admitted medicine based on *iboga* alkaloids, although it was proven that it can be very helpful in the therapies of different addictions, one may expect that this compound must have a drawback like severe side-effects. The truth is there is less known about side-effects. After taking a dose of ibogaine patients were reporting about hallucinations during their “trip” which can be indeed an awkward side-effect, but it is not concerning the physically health at all. In addition, there are suggestions that this “trip” including hallucinations are an important part in the treatment of addictions using ibogaine. The only known toxicity of ibogaine is a weak

neurotoxicity. This is a result of the interaction of ibogaine with with sigma-receptors. Only hypotheses can be made about the reasons why *iboga*-alkaloids are not used more often.

3. Previous synthesis of *iboga*-alkaloids

C. Frauenfelder summarized former total syntheses of *iboga* alkaloids for her dissertation in 1999.[19] An even more extensive review was published by Jana *et al.*[20] This work is not intended to provide another comprehensive survey on total syntheses of the natural compound, but will rather emphasize on different methods for dehydroazepane ring formation. This key step is the last important step in most of the syntheses and in this work the most time and also a lot of ideas were spent on this step. The synthesis of oxidized *iboga* alkaloids (e. g. Coronaridine) and even more complex *iboga* alkaloids are not considered in this overview.

The majority of strategies are working with a similar concept. The first aim is to arrange the complex isoquinuclidine ring system, which is obtained *via* many different paths (exeption: **Figure 7,** strategy 4). The introduction of the 3-ethyl indole moiety is sometimes involved in the isoquinculidine ring formation, but mostly it's introduced *via* substitution. In the most strategies the last key step contains a direct connection of the isoquinuclidine ring with the indole part to form the 7-membered dehydroazepane ring (exeption: **Figure 7**, strategy 6).

Figure 7 gives an overview about the different ring closing strategies. Each strategy is described in more detail and a few examples applying these strategies are given.

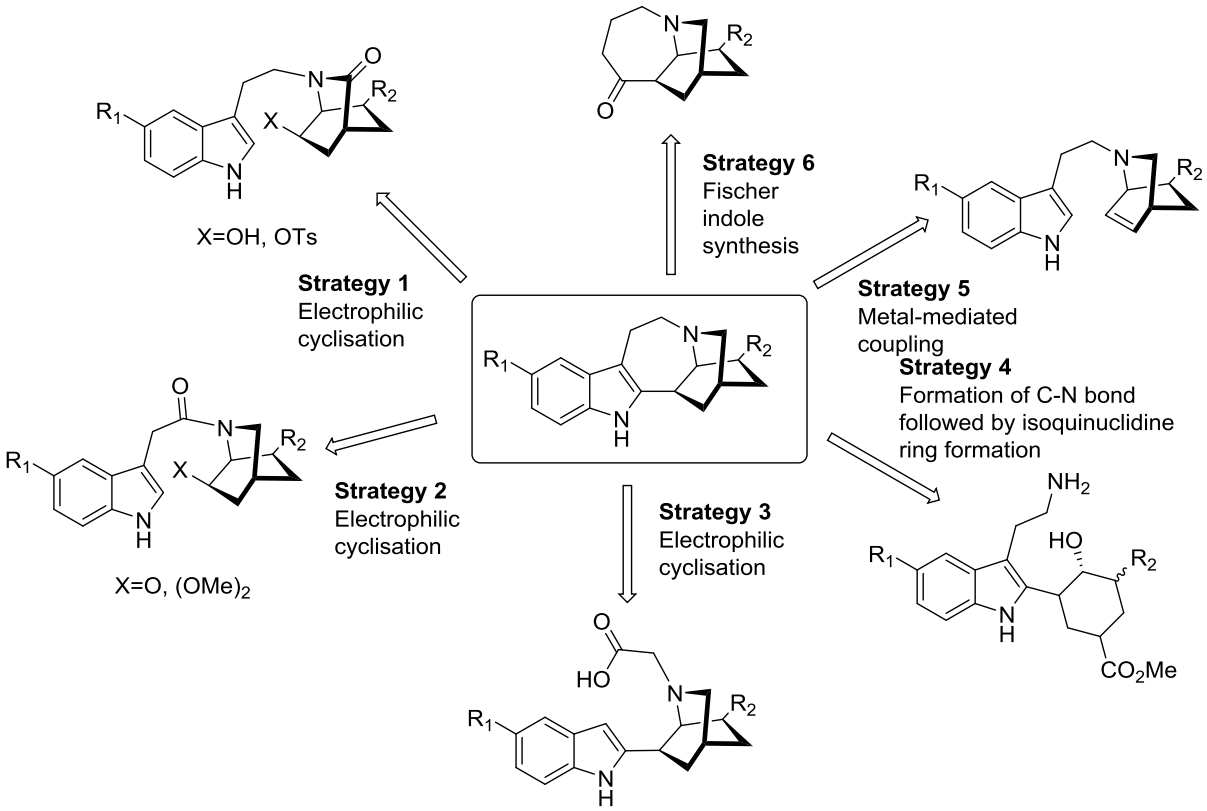
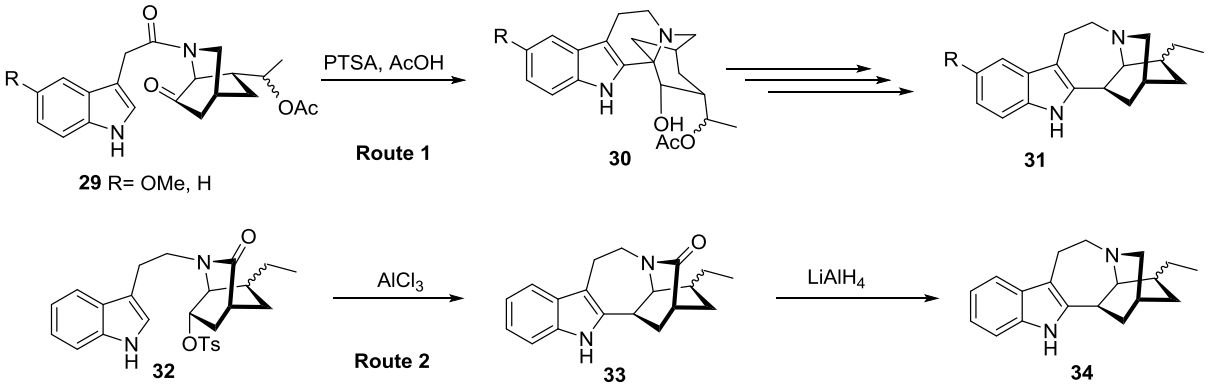


Figure 7: Different strategies to build the ibogaine-ring system

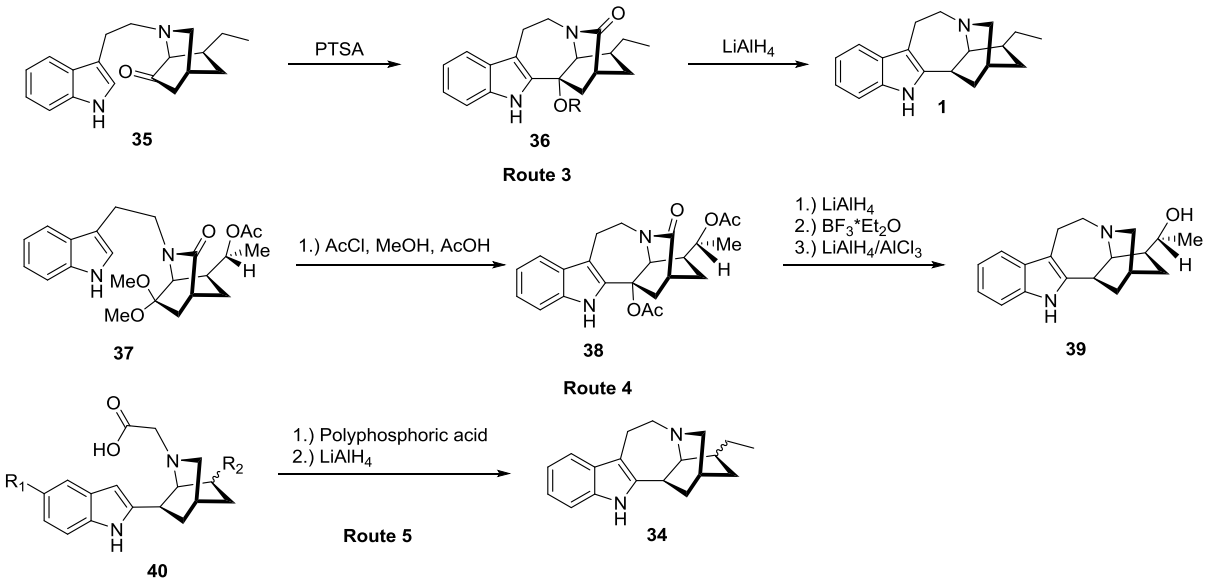
Electrophilic cyclisation: The strategy that is applied in the most cases of *iboga* alkaloid syntheses, is electrophilic cyclisation, where the electrophilic carbons of the indole are attacking the already installed isoquinuclidine ring. This can be achieved *via* attack of either C2 or C3 of the indole.

Büchi and coworkers published the first total synthesis of racemic ibogaine and ibogamine.[6] They proposed an electrophilic substitution-rearrangement cascade, to obtain at first a six membered ring which rearranges in the last step under Wolf-Kishner conditions to the desired dehydroazepane ring (**Scheme 1**, route 1). Huffman *et al and Kühne et al* used similar approaches for their synthesis of racemic ibogamine and derivatives.[21,22] In the end, both groups received the final ring system after substitution of a tosyl residue by the indole moiety (**Scheme 1**, route 2).



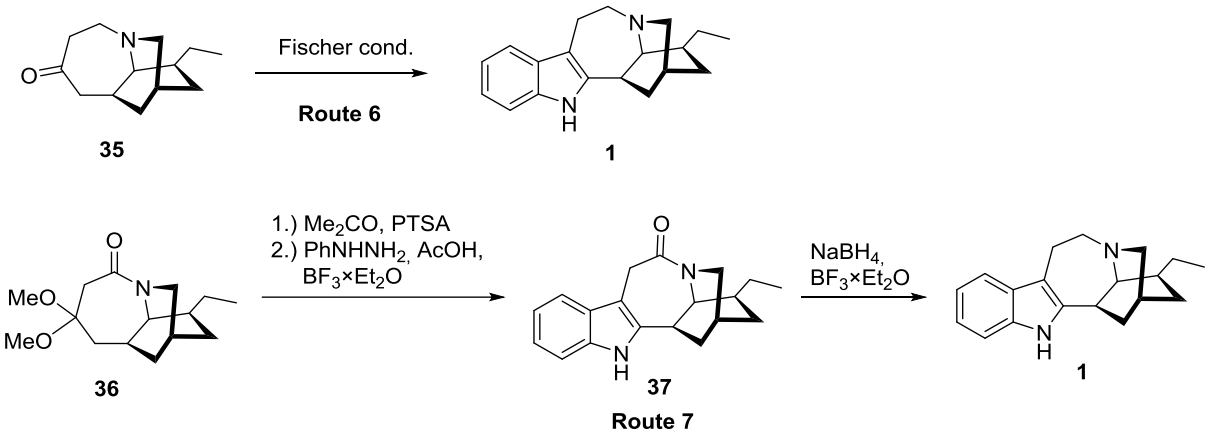
Scheme 1

Starting from different substrates the syntheses of Nagata *et al* and Imanishi *et al* were leading both to ketone **35** which was treated with PTSA to obtain racemic ibogamine after reduction (**Scheme 2**, route 3). [23,24] Boschberg *et al* published 2006 an enantioselective synthesis for (-)-ibogamine-19-ol, using also acid catalyzed cyclisation (**Scheme 2**, route 4).[25] Rosenmund and his group tried for their synthesis of racemic ibogamine and ibogaine to initiate cyclisation *via* an attack of the C3 of the indole under acid catalysis and succeed (**Scheme 2**, route 5).[26]



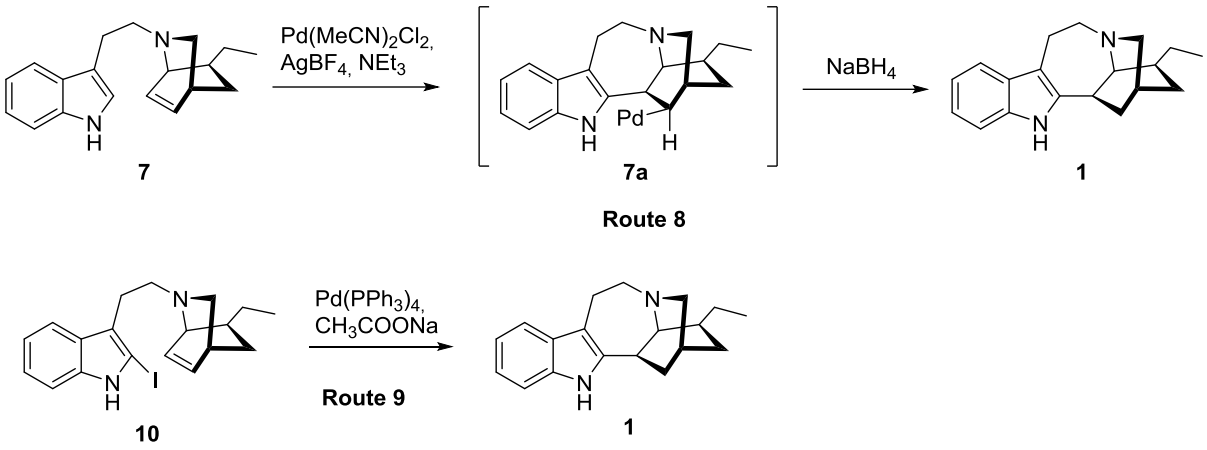
Scheme 2

Fischer Indolisation: The Fischer indolisation strategy is very popular. Commonly, the first challenge is to build a unit, where the isoquinuclidine ring is fused with an azepane ring. Using slightly different conditions the product is formed in the last step *via* Fischer indole synthesis.
Sallay and his group published 1967 the first Fischer indolisation approach to receive racemic ibogamine (**Scheme 3**, route 6).[27] In the year 2000 White *et al* designed a synthesis using a similar Fischer indolisation giving enantioenriched ibogamine (**Scheme 3**, route 7). The enantioselectivity was implemented in an early stage of the synthesis, performing a chiral Diels-Alder reaction with a chiral catalyst.[28]



Scheme 3

Metal-Mediated Cyclisation: Metal-mediated cyclisation represents a very elegant method to connect the C2 of the indole-moiety with the isoquinuclidine ring.
Trost and his group published a total synthesis for ibogamine in 1968 using a newly designed method.[29,30] They treated compound **7** with 2 equ. Pd-catalyst, 4 equ. silver salt and 1 equ. NEt_3 and reduced the *in situ* formed metal-carbon species with $NaBH_4$ afterwards (**Scheme 4**, route 8). Also an enantioselective route was designed by them, using methyl-mandelic acid as a chiral auxiliar in an earlier chiral Diels-Alder reaction.

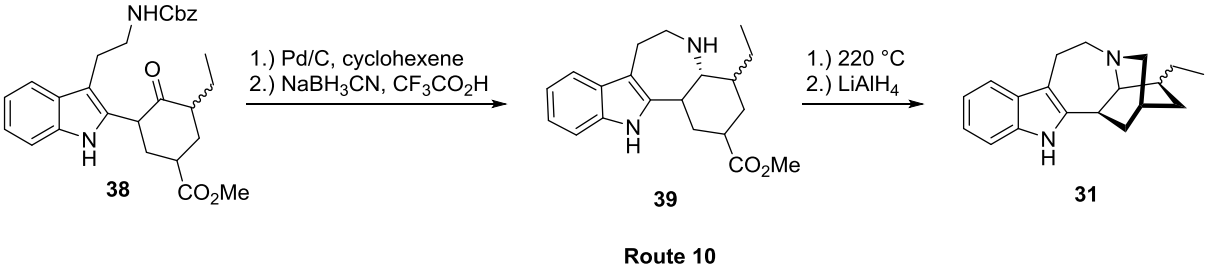


Scheme 4

This cyclisation was used in a lot of other total syntheses of *iboga* alkaloids for instance by Hodgson *et al* to synthesize enantiopure (+)-ibogamine[31] or by Sinha *et al* to receive different racemic iboga alkaloids.[32]

Another metal mediated coupling was reported by Jana *et al*.[33,34] They performed an intramolecular Heck coupling where the Pd-C species was reduced *in situ* by the mild reductant CH_3COONa (**Scheme 4**, route 9). Therefore, they were able to avoid the usage of stoichiometric amounts of Pd which were needed by Trost.

Formation of C-N bond followed by isoquinuclidine ring formation: A completely different approach to ibogamine was reported by Grieco and coworkers.[35] They closed the dehydroazepane ring *via* reductive amination followed by temperature induced isoquinuclidine formation. After reduction they received a mixture of racemic ibogamine and epiibogamine (**Scheme 5**, route 10)



Scheme 5

4. C-C Bond formation at C2 in indoles applying C-H activation

4.1. General comments

Indoles are a very important class of molecules. They can be found in proteins as amino acids (tryptophane), in the human body as neurotransmitters (e. g. serotonin), or in nature as indol-alkaloids (e.g. strychnine)(**Figure 8**).

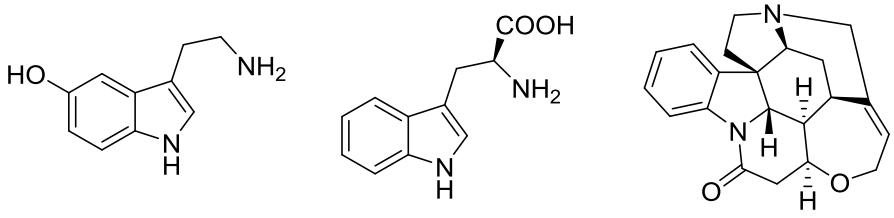
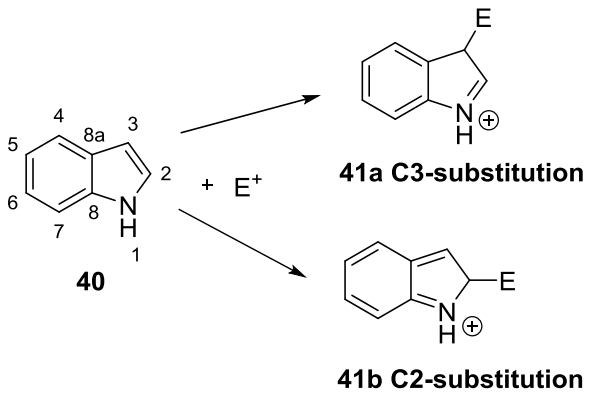


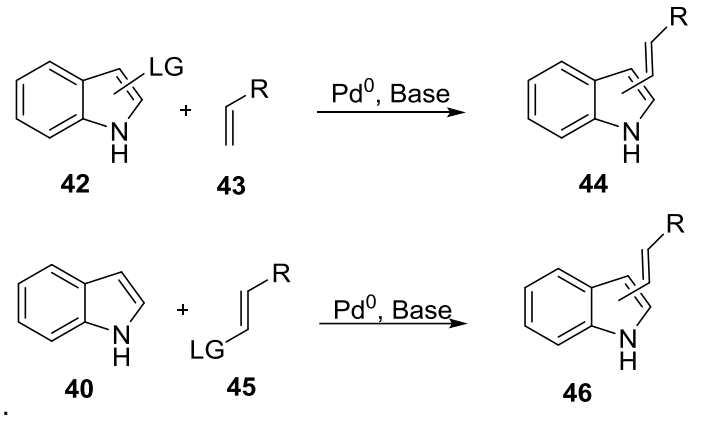
Figure 8: (from left to right) Serotonin, Tryptophane, Strychnine

Due to the importance of indoles for natural product and drug synthesis, new methods to substitute indoles selectively are of great interest. If an indole reacts with an electrophile (E^+), two products are probable. The pyrrole moiety of the indole is much more electrophilic then the benzene moiety and so possible attacks are from position 2 and 3 (**Scheme 6**). The favored attack usually commences in position 3 and this can be explained by considering the positively charged intermediates (**Scheme 6**). If the attack starts from position 3, the benzene ring is not involved in electron migration and therefore the aromaticity is not disturbed at all. Starting an attack from position 2 involves the benzene ring into electron migration and the aromaticity is disturbed.[36] Therefore it is an even bigger challenge to find procedures to substitute selectively on position 2.



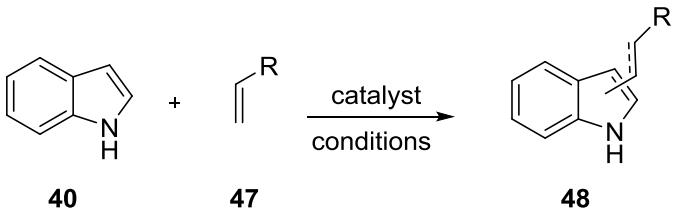
Scheme 6

For the connection of two carbons there are several methods known. Considering metal assisted C-C bond formation, Heck coupling is a very efficient way and has the advantage that a Pd-catalyst but no additional metal (in stoichiometric amounts) is needed, in contrast to many other coupling reactions (e.g. Stille coupling).[37] A disadvantage is, that one of the substrates has to be functionalized with a good leaving group (e. g. halide, tosyl) to perform Heck reaction (**Scheme 7**)



Scheme 7

An even more elegant method to connect two carbons with each other is a C-H activation with not functionalized alkenes/arenes. The big advantage of this chemistry is, that substrates don't have to be functionalized with halides or heteroatoms to perform a C-C bond formation (**Scheme 8**). The general theory of C-H activation was reviewed repeatedly.[38-40] Here it will be focused on C-H activation reactions providing substitution on inactivated C2 of indole.



Scheme 8

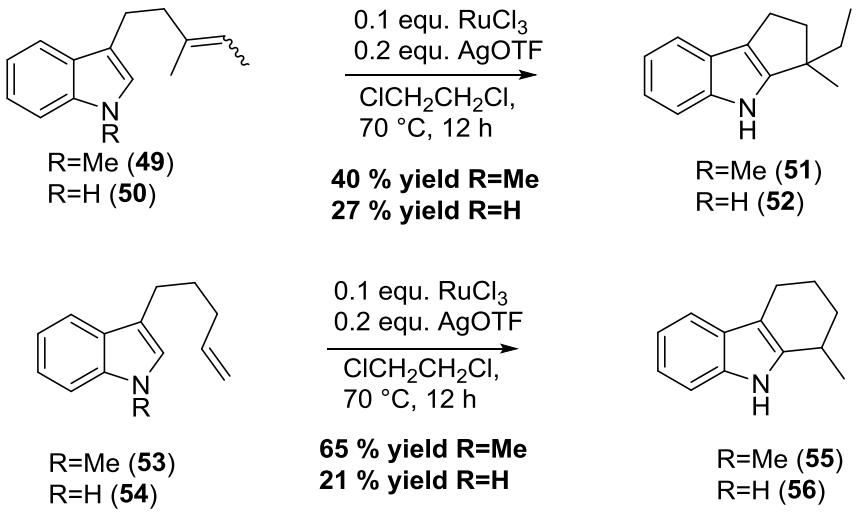
As already mentioned, substitution on C3 is more probable so strategies are needed to change selectivity. This can be done using different strategies:

- Block the C3 position so it cannot attack
- Use reaction conditions (e. g. special solvents) which provide C2 substitution
- Use a directing group that directs the electrophile to C2

Talking about C-H activation on indole in position 2, two different kinds of reaction have to be discussed. In the first method simple alkenes are used to alkylate indoles. The second method is called Fujiwara-Moritani reaction where the addition of alkenes/arenes and indoles are leading to arene or alkene substituted indoles.

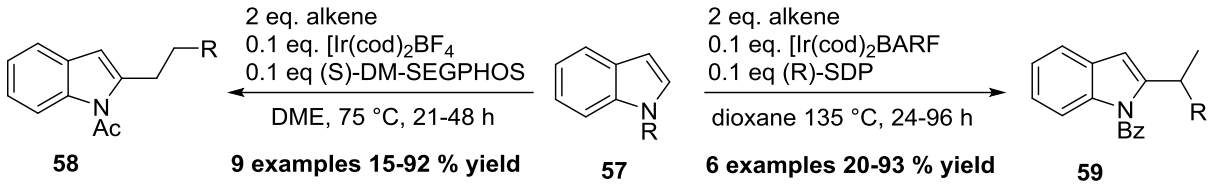
4.2. Alkylation of indoles using alkenes

In 2004 Youn *et al* were trying to alkylate different arenes intramolecularly using attached alkene residues as alkylating sources.[41] After catalyst and additive screening they developed a suitable system using $RuCl_3$ as catalyst and AgOTf as additive. The concept was also working on indole derivatives, which was demonstrated by two examples (**Scheme 9**)



Scheme 9

Shibata *et al* published selective C2 alkylation of indoles in 2012 applying an Ir^{I}-catalyst. By using different protecting groups and ligands they achieved selective reaction to the branched or linear alkylated indole (**Scheme 10**).[42] With this reaction conditions, the reaction was even working using relatively unreactive alkenes like nonene.



Scheme 10

The proposed mechanism for these alkylations is shown in **Figure 9**. At first the metal catalyst inserts into the C-H bond. This can happen for instance *via* [1,1] σ-bond metathesis. In the next step the alkene inserts into the C-M bond and in the end reductive elimination occurs, releasing the alkylating product.[42]

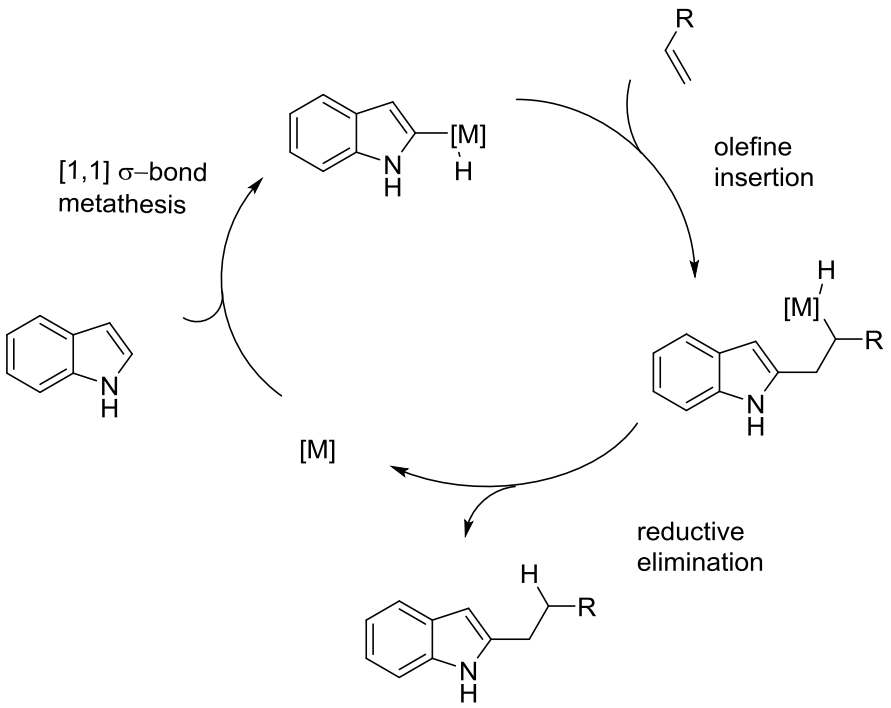


Figure 9: Mechanism of the alkylation of indole using alkenes

4.3. Fujiwara-Moritani type indol alkenylation

In 1969 Fujiwara, Moritani and coworkers reported the reaction of not functionalised benzene with alkenes under Pd^{II} catalysis giving alkenyl-phenyls.[43] A co-oxidant like $Cu(OAc)_2$ was necessary, to oxidise emerging Pd^0 back to Pd^{II} after the reaction. This newly developed reaction was then called Fujiwara-Moritani reaction or oxidative Heck reaction. The proposed mechanism for the indole alkenylation under Fujiwara-Moritani conditions is shown in **Figure 10**. At first the Pd-indole bond is formed. This can work either *via* an one step [1,1]-σ-bond metathesis or *via* electrophilic attack of the catalyst followed by rearomatisation. In the next step the alkene inserts into the C-M bond and then β-hydride elimination occurs. In the last step the metal has to be re-oxidised to the active catalyst by a co-oxidant.[44-46]

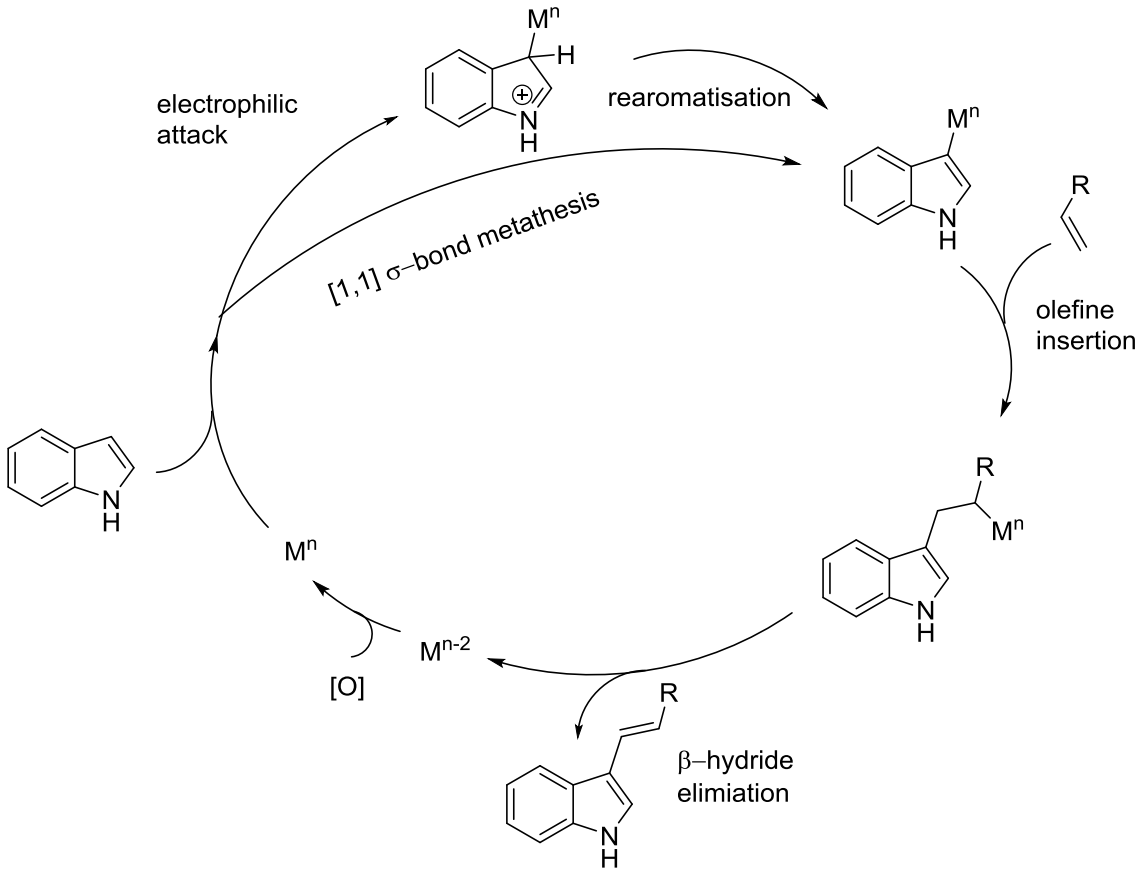
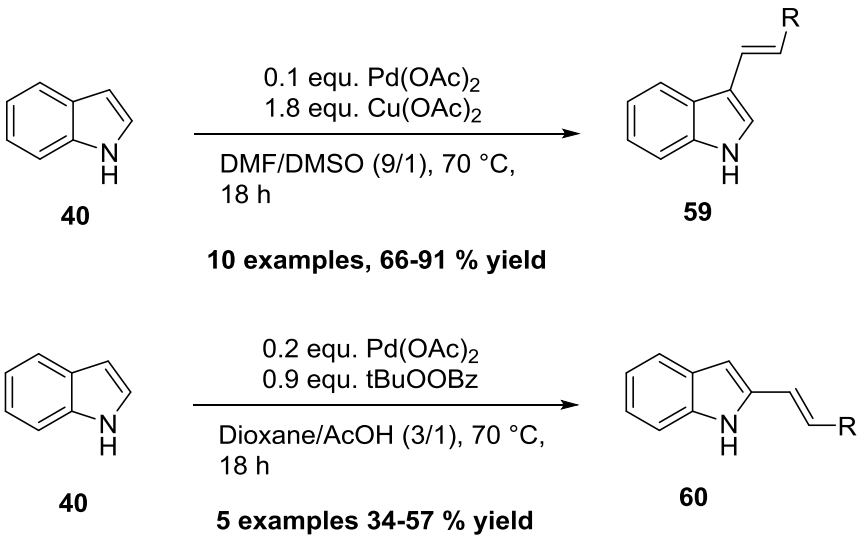


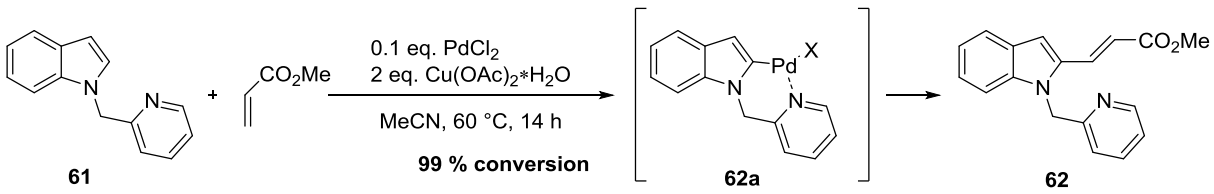
Figure 10: Mechanism of the Fujiwara-Moritani reaction

Grimster *et al* recognized the potential of this method for indole substitution.[44] Screening different solvents and co-oxidants they were able to promote selective C2 or C3 substitution using α,β-unsaturated esters as alkene sources (**Scheme 11**).



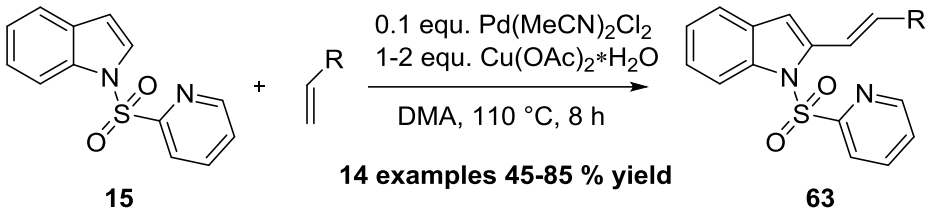
Scheme 11

Capito *et al* applied a different strategy to provide C2-alkenylation on indoles. They protected the indole nitrogen using a pyridylmethyl protecting group which serves as a directing group, leading to selective substitution in position 2. They proposed that this selectivity is due to a six membered transition state where the nitrogen of the pyridine is coordinated to Pd (***Scheme 12***).[47] One big drawback of this method is the hardly removable protecting group.



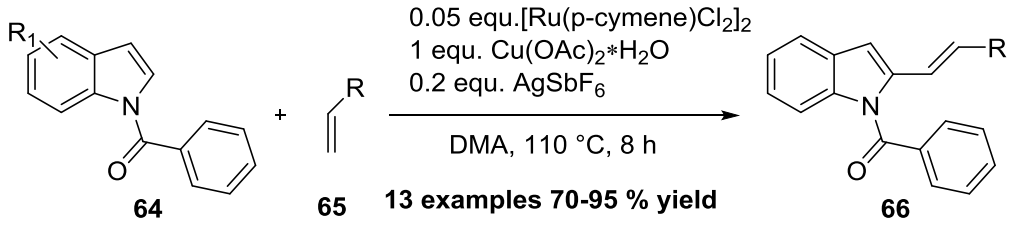
Scheme 12

Garcia-Rubia *et al* tried to improve this idea by finding a suitable but also easily removable protecting group. They protected the indole nitrogen with different groups and performed Fujiwara-Moritani reactions using methacrylate as alkene source, $Pd(MeCN)_2Cl_2$ as catalyst and $Cu(OAc)_2 \times H_2O$ as the co-oxidant. They succeeded using 2-pyridylsulfonyl as directing group and proved the efficiency of the reaction on several examples (several indole derivatives and several alkenes) getting good to excellent yields (**Scheme 13**).[45,48] The protecting group was easy removable using Zn or Mg in MeOH.



Scheme 13

A similar concept was elaborated by the group of Lanke using Ru catalysts instead of Pd catalysts. Following the same strategy like Garcia-Rubia *et al*, they used a model reaction, screened for a suitable directing group, screened for co-oxidants, reaction conditions and ended in the conditions shown in **Scheme 14**.[49] The wide scope of the reaction was proven on several examples.



Scheme 14

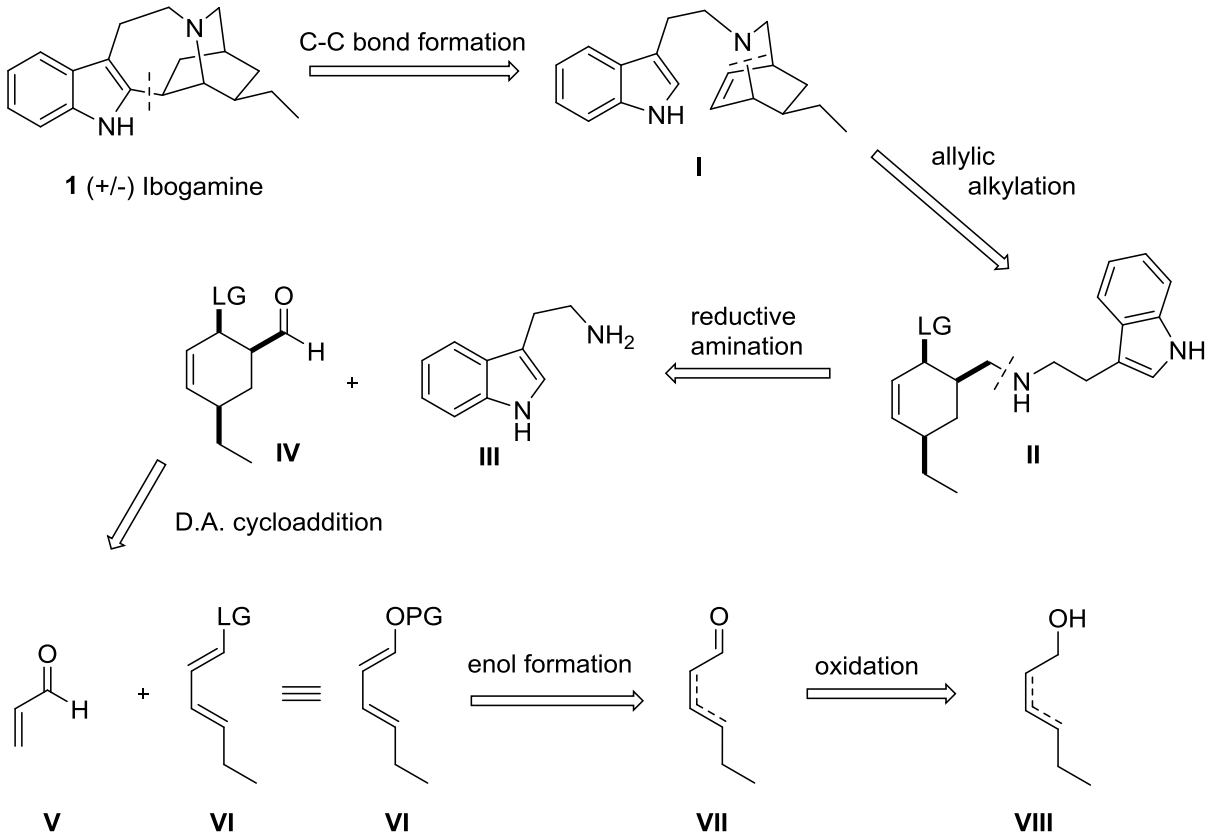
5. Objective

Although *iboga* alkaloids are known for a long period of time, they are still bearing a lot of potential. Due to the versatile biological activity there is already reasonable application known but maybe a lot of possible applications are still unknown. A major drawback of most *iboga* alkaloids like ibogaine are still side effects and so the search for even more active compounds showing less side effects is a challenging task. A lot of total syntheses to that class of alkaloids were developed but the most are very tedious with low yields and were carried out just in racemic form. To obtain a viable basis for constructing a substance library, it is important to find a short, effective and enantioselective synthesis which can be easily modified yielding in different *iboga* alkaloids. Considering all these points, the most convenient synthesis is the total synthesis of ibogamine that was outlined by Trost *et al*.[29] The main task was to reproduce this synthesis and increase the yields. The last step of the synthesis was reported with 2 equ. Pd, 4 equ. silver salt and only poor yields. To avoid this uneconomic step, a C-H activation by Garcia-Rubia *et al*[48] should be examined in respect to its scope and utility for the route done by Trost.

II. Results and Discussion

1. Retrosynthetic analysis

For the strategy applied, the synthesis conducted by Trost and coworkers[29] was used as a model strategy. **Scheme 15** shows the retrosynthetic approach to racemic ibogamine.



Scheme 15

The analysis of target compound **1** shows, that an indole moiety is fused together with an isoquinuclidine ring system, leading to a dehydroazepine ring. Disconnecting the bond at C2 of the indole from the isoquinuclidine ring leads in compound **I**. There are some metal assisted methods known, which should provide this connection. The C-N bridge of the isoquinuclidine ring system can be established using the Tsuji-Trost reaction, which leads us to amine **II**. LG represents here a leaving group. The better the leaving group, the better the Tsuji-Trost reaction will work. The tryptamine residue can be introduced *via* reductive amination and that leads to aldehyde **IV**. Cyclohexene **IV** looks like a typical Diels-Alder product and this would be indeed the method of choice to get to the aldehyde, using acrolein and diene **VI**. Due to the

high regio- and stereoselectivity of Diels-Alder cycloadditions the choice of the right diene isomere and appropriate conditions should lead to only one enantiomeric pair of products. Considering the *endo* selectivity of Diels-Alder reactions and utilizing a diene bearing both double bonds in an *E*-configuration, a Diels-Alder product should be achievable where all side chains are *syn* to each other. If the leaving is a substituted alcohol, diene **VI** is accessible by enol formation of 2-hexenal or 3-hexenal followed by substitution on the oxygen. The aldehydes are both accessible by oxidation of the corresponding alcohols which are both commercially available.

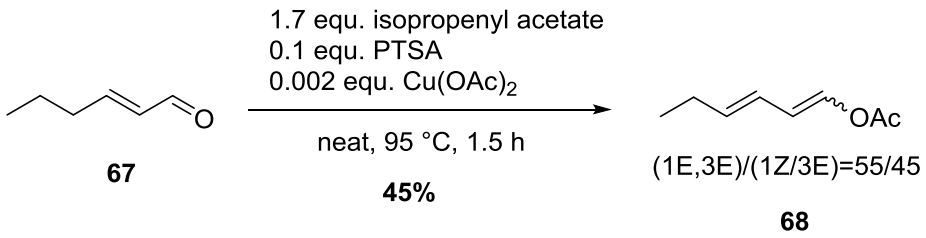
2. Synthesis of the isoquinuclidine ring system as precursor for *iboga* alkaloids

2.1. Choice of the appropriate starting material

When starting this work, the first important question was, which starting material to take. For the synthesis planned, a substrate was required which lead to hex-1,3-diene-1-ol substituted on the alcohol moiety. Concerning the diene, it is important to consider two properties in detail: The substituent of the alcohol and the configuration of the double bonds. To obtain syn geometry of the side chains in the resulting Diels-Alder cycloaddition product, *E*-conformation of both double bonds is necessary.[50] The substituent on the alcohol has to satisfy the following criteria:

- It should be easy to install
- It should be commercially available or easy to prepare
- It has to convert the alcohol into a good leaving group to support smooth reaction and good yields in the later Tsuji-Trost reaction
- A method enabling installation of an achiral and a chiral protecting group in a similar manner would be favorable.[51]

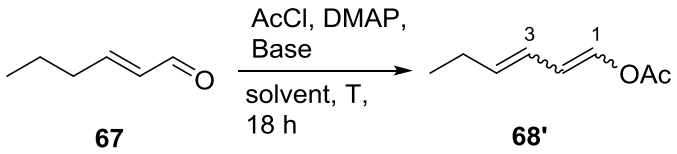
Trost and coworkers were using in the achiral version an acetyl protected diene for their total synthesis of ibogamine, which was prepared from trans-2-hexenal (**Scheme 16**).[29]



Scheme 16

For the chiral version of their synthesis they used the O-methyl-mandeloyl protected diene which they synthesized over 4 steps starting from tricyclo[4.2.5.1.0]non-7-ene-3-one.[29,52] As described before, a route was envisioned where a chiral and achiral protecting group could be installed in the same way, so the Trost diene preparation was not first choice. It was decided to take the acetyl group like Trost *et al* did as an achiral protecting group, but using acetyl

chloride instead of isopropenyl acetate to prepare the diene. The aim of this exchange was, to improve the yield and amount of desired (*1E,3E*)-isomere. Additionally, a chiral auxiliary such as a mandeloyl derivative should be easily installed in the same way (using mandeloyl chloride derivatives). With this considerations in hand acetyl protected diene was synthesized starting from 2-hexenal (**Scheme 17**)



Scheme 17

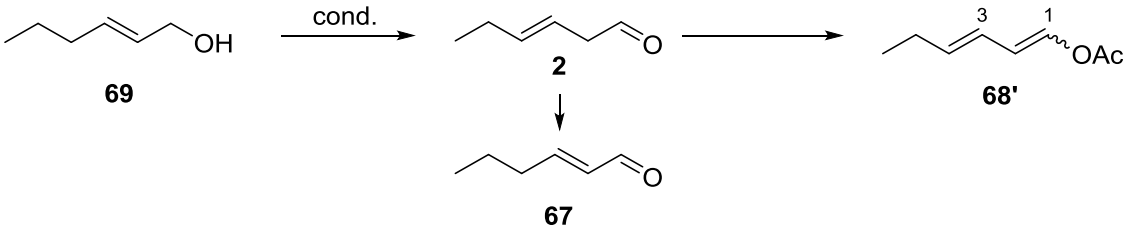
Adding AcCl followed by dry NEt3 at -10 °C via a syringe to a mixture of 2-hexenal and DMAP in dry DCM and stirring at room temperature provided the required product just in traces. After changing the solvent and stirring at 80 °C overnight, yields were increased to about 67 %. Unfortunately GC-MS and 1H-NMR analysis of the product always showed isomeric mixtures of all four possible isomers, containing the desired (1E,3E)-isomere only as a minor part. Surprisingly, sterically more hindered bases like DIPEA afforded formation of the undesired (3Z)-isomers only **(Table 1)**

Entry	T [°C]	Solvent	Base	Base + AcCl	Isomers (1E3Z/1Z3E/1E3Z/1Z3Z)	Yield
1	-10-25	DCM	NEt_3	1.2 equ.	n.d.	traces
2	-10-80	PhH	NEt_3	1.2 equ.	n.d.	traces
3	-10-80	DMF	NEt_3	1.2 equ.	n.d.	20
4	-10-80	DMF	NEt_3	1.7 equ.	1/1.6/2.3/2.3	67
5	-10-80	DMF	DIPEA	2 equ.	0/0/1/1	41

Table 1: Several conditions for the diene formation

To avoid the formation of all four isomers, the starting material was changed. 3-Hexenol contains already one double bond at position three in the desired (*E*)-conformation, so it was

assumed that after oxidation followed by the reaction with AcCl a less complex mixture of two isomers would be obtained (**Scheme 18**). Its known that β,γ-unsatured aldehyds are not very stable and undergo isomerisation yielding the α,β-unsaturated aldehyde **67** easily.[53,54]



Scheme 18

However, oxidation using Swern or PCC conditions did not lead to the desired product or gave product just in traces (

Table 2).

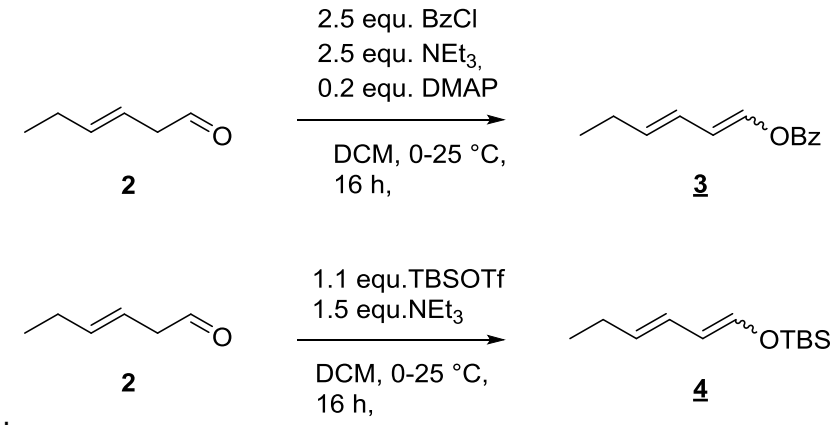
Entry	Cond.	Isomerisation	Yield
1	Swern	full	20%
2	PCC	yes	traces
3	TEMPO, $PhI(OAc)_2$	traces	83

Table 2: different oxidation conditions

In 2006 Vugts *et al* investigated a very mild way to oxidise β,γ-unsaturated aldehydes.[54] They used TEMPO (0.1 equ.) as oxidant and $PhI(OAc)_2$ (1.1 equ.) as co-oxidant in a mixture of DCM/pentane as solvent and reported high yields without isomerisation. The protocol was applied to the current problem and yields up to 83 % were reached including just traces of isomerisation product. The instability of the β,γ-unsaturated aldehyde occured already during work-up. Evaporation at temperatures >30 °C led to higher amounts of isomerisation product and purification methods using column chromatography or distillation were not suitable at all. ^{1}H-NMR analysis showed that the product implied high purity containing just one main impurity (iodobenzene) which did not have a detrimental effect in the next step. With the crude aldehyde in hand acetylation was performed in up to 80% yields. Unfortunately, this method still gave a mixture of two isomers (*1E/3E* + *1Z/3E*) and also applying different solvents and more sterically hindered bases (DIPEA) did not change this isomeric distribution. During the purification some

problems showed up. Distillation gave a mixture of iodobenzene and product. Using column chromatography for the separation yielded in significant loss of product during evaporation due to the volatility of the product. Due to these problems, other substituents on the alcohol were considered. At the one hand larger esters namely benzoylchloride were investigated to avoid a too volatile product. At the other hand a bulky siliyl-protecting group namely tert-butyl-dimetyl silyl was used to figure out if this very bulky group would lead to an enrichment of the (*1E*)-product.

Using conditions which were already optimized for AcCl, the benzoylated derivative **3** was obtained with 82 % yield but still in an isomeric mixture of 1/1 = (*1E,3E*)/(*1Z,3E*) (**Scheme 19**); also here modification of conditions didn't enhance the amount of the desired isomere.



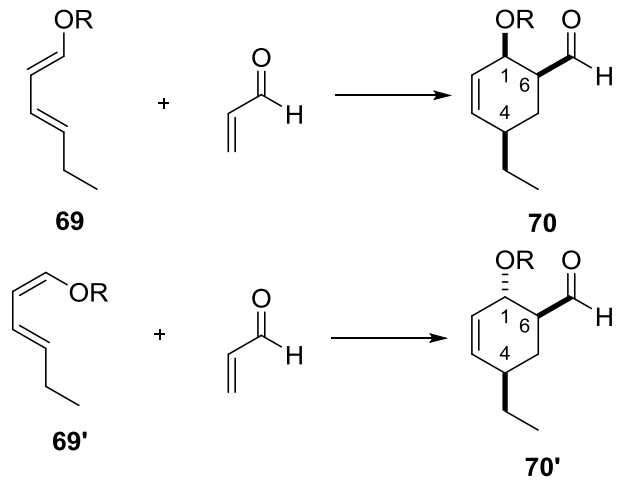
Scheme 19

The reaction of aldehyde **2** with TBSOTf in the presence of NEt_3 in dry DCM gave TBSO substituted diene in 85 % yield. Also here it was quite a surprise that with the very bulky TBS-protecting group an enrichment of the desired (*1E,3E*)-isomere was not possible. Additionally, the volatile product could not be separated from present iodobenzene. Nevertheless two protected dienic mixtures were synthesized in excellent yields and the Diels-Alder cycloaddition was performed with both of them.

2.2. Diels-Alder cycloadditon

The Diels-Alder cycloaddition is a powerful reaction in organic chemistry.[50] It displays very high selectivity in matters of regio- and stereochemistry and even four new stereocenters can be created in one step.[50] Theoretical studies are able to predict the regio- and stereoselectivity of a product with high probability.[55] The magnitude of orbitals can be measured using

computational methods. The regiochemistry is determined by the magnitude of the numeric solution of the orbitals, meaning that orbitals which having a bigger value are overlapping favored with other orbitals having big values. Considering that, the reaction should lead in only one regioisomere (ortho or para).[56] Due to the high *endo* selectivity of Diels-Alder cycloadditions, the *endo*-product should be formed predominantly. Considering these selectivities and applying the Diels-Alder reaction to a dienic mixture of **69** + **69'**, for each isomere one major product can be expected (**70 +70',Scheme 20**).



Scheme 20

Taking the benzoyl protected dienes and stirring them with acrolein and a Lewis-acid ($BF_3 \times Et_2O$) in dry DCM at -60 °C for 2 h, gave **5** in 86 % crude yield. Thankfully (*1Z,3E*)-diene **3'** was not reactive enough to undergo Diels-Alder cycloaddition under applied conditions due to steric reasons and product **5** was received as only product isomer, accompanied by traces of the *exo* product. Due to its acidic proton at C6 product **5** is not very stable and undergoes elimination (loosing benzoic acid) easily. Different separation methods like column chromatography using different stationary phases (Silica gel, deactivated silica gel, Al_2O_3, Florisil) or distillation yielded in high amounts of elimination product and therefore were not suitable.

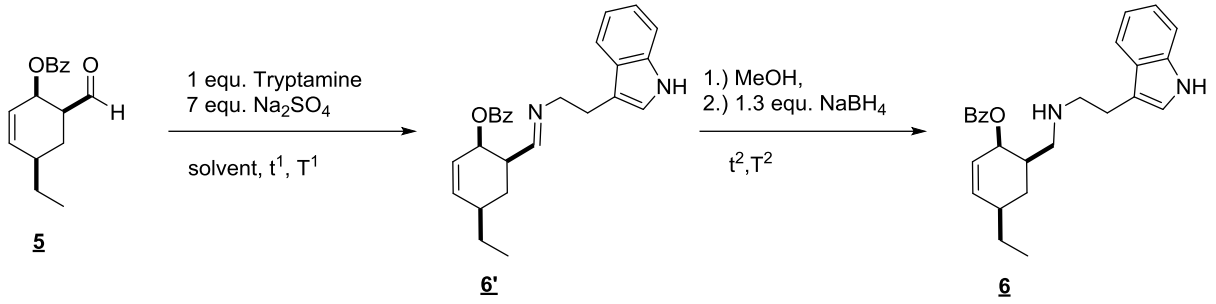
Stirring TBS protected dienes, acrolein and $BF_3 \times Et_2O$ in dry DCM at -78 °C for 1.5 h gave a mixture of two diasteriomeric products in 50 % yield. If it was stirred for 2 h more, none of the substrate isomers were present anymore, so it was concluded that the TBS protected (*1Z,3E*)-isomer is reactive enough to undergo cycloaddition with acrolein and always a product mixture

of two diastereomers was obtained which was not separable. Absence of Lewis-acid at room temperature did not facilitate the cycloaddition and at 110 °C a mixture of 4 isomers was again observed. Using other Lewis acids like $AlCl_3$, $ZnCl_2$ or $TiCl_4$ gave no product or worse results compared to $BF_3 \times Et_2O$. After the experiments with the two differently substituted dienes, it was decided to continue in later reactions with the crude product **5** which had some advantages compared to the TBS-subsituted product:

- Higher yield
- Only one isomere is reacting, therefore just one enatiomeric pair of products
- Higher yield in the later Tsuji-Trost reaction can be assumed due to the fact that BzO^- is a better leaving group than $TBSO^-$

2.3. Reductive amination

For the reductive amination, Trost conditions were at first applied. They reported a yield of 93 % using acetylated substrate instead of benzoylated using the following conditions.[29] The crude mixture of aldehyde 5 was suspended with $MgSO_4$ in dry toluene and tryptamine was added in dry MeOH at -20 °C. The reaction solution was stirred for 4 h at -15 °C to facilitate imine formation, then dry MeOH and $NaBH_4$ were added and the mixture was further stirred for 1 h before being quenched with water. Unfortunately, just 24 % yield was obtained and some side products were formed using these conditions. The side products were identified as elimination products of the substrate and the product (majority component) as well as reduced alcohol. This indicated that the reductive amination is working in principal, applying the Trost conditions but facilitated elimination before or even after substrate was reacted. Therefore milder reaction conditions were required. In the first attempts the slightly acidic $MgSO_4$ was changed to Na_2SO_4 and different reaction temperatures were investigated conducting the reaction in DCM. Temperatures around -78 °C were not suitable because a large part of substrate was not reacting and around -30 °C the problems with elimination started leading in both cases just poor yields (**Table 3)**. Within addition to temperature screenings the polarity of solvent was also investigated for the given reaction, considering that a different polarity of the solvent may reduce or avoid elimination. As Et_2O is slightly more apolar than DCM,[57] this solvent was applied alternatively at -25 °C. Elimination was still recognized but the solvent change gave also a higher yield. Using Et_2O and going down in temperature, finally resulted in reaction conditions which avoided elimination and yielded the desired product in 72 % (**Scheme 21**).



5 **6'** **6**

Scheme 21

Entry	Solvent	T1 [°C]	t1 [h]	T2 [°C]	t2 [h]	Elimination	Yield [%]
1	PhMe, MeOH	-15	4	-10	1	yes	24
2	DCM	-10	5	-10	1	yes	-
3	DCM	-25	18	-78	2	yes	21
4	DCM	-78	1	-40	1	yes	14
5	DCM	-78	6	-36	1	yes	18
6	Et_2O	-25	18	-25	2	yes	41
7	Et_2O	-38	18	-78	2	no	72

Table 3: Condition screening for reductive amination

2.4. Tsuji-Trost reaction to obtain the isoquinuclidine ring system

The Tsuji-Trost reaction represents a palladium assisted attack of nucleophiles on olefinic compounds bearing a leaving group and was discovered in 1972 by Trost *et al.*[51] For the reaction a leaving group is required in an allylic position together with a base (e. g. NEt_3) and a Pd^0-catalyst. For the target molecule the Tsuji-Trost reaction is a very elegant way to form the C-N bridge in the isoquinuclidine ring system. Initially, the original Trost conditions were applied (Trost obtained a yield of 45 % using acetylated substrate instead of benzoylated).[29] In a reaction vial 50 mg substrate and $Pd(PPh_3)_4$ were dissolved in dry MeCN, NEt_3 was added

and the heterogeneous mixture was stirred at 75 °C bath temperature for 3 h (**Scheme 22**). Compund **7** was obtained after work up and column chromatography in 50 % yield.

Scheme 22

Using this initial result, a lot of screening work was done. The screenings were carried out in 8 mL reaction vials, using 25 mg of substrate and heating with a thermo block. At first different catalyst-ligand systems were tested (**Table 4**, entries 1-9). The best result was obtained with the initially used $Pd(PPh_3)_4$ catalyst. The second screening round was done to determine in which solvent the best yield can be obtained (**Table 4**, entries 10-15). Differences in yield using various solvents were small, but the best yield was obtained using toluene as solvent (65 %).

Entry	Cat. (Mol%)	Ligand	T [°C]	Amount [mg]	Conc. [M]	Solvent	Yield
1	$Pd(OAc)_2$ (10)	PPh_3	75	50	0.24	MeCN	53
2	$Pd(OAc)_2$ (10)	$P(Cy)_3$	75	50	0.24	MeCN	0
3	$Pd(OAc)_2$ (10)	dppp	75	50	0.24	MeCN	13
4	$Pd(OAc)_2$ (10)	tBuMePhos	75	50	0.24	MeCN	26
5	$Pd(OAc)_2$ (10)	PPh_3	75	25	0.12	MeCN	50-59
6	$Pd(PPh_3)_4$ (10)	-	75	25	0.12	MeCN	54
7	$Pd(dba)_2$ (10)	-	75	25	0.12	MeCN	0
8	$Pd(OAc)_2$ (10)	dppf	75	25	0.12	MeCN	4
9	$Pd(OAc)_2$ (10)	SPhos	75	25	0.12	MeCN	3
10	$Pd(PPh_3)_4$ (10)	-	75	25	0.12	MeCN	54
11	$Pd(PPh_3)_4$ (10)	-	75	25	0.12	DMF	50
12	$Pd(PPh_3)_4$ (10)	-	75	25	0.12	THF	55
13	$Pd(PPh_3)_4$ (10)	-	75	25	0.12	DMAc	52
14	$Pd(PPh_3)_4$ (10)	-	75	25	0.12	PhMe	**65**
15	$Pd(PPh_3)_4$ (10)	-	75	25	0.12	DMSO	60

Table 4: Catalyst and solvent screening

Next different bases, catalyst loadings and temperatures were investigated (**Table 5**, entries 16-21). NEt_3 and 10 mol% of catalyst at 75 °C showed the best yield. The optimized conditions were applied to scale up the reaction. However the yield of product was already cut in half, when the substrate was doubled from 25 mg to 50 mg and decreased further using higher amounts of substrate (**Table 5**, entries 22-24). Elongation of reaction time even decreased the yield. Considering that the very first reaction was carried out in dry MeCN with 50 mg and 50 % yield, scale up in MeCN and with 300 mg substrate was attempted, still providing a yield of 41 % which was acceptable (**Table 5**, entries 25-27). Changing the reaction flask from 8 mL vial to a septum covered round bottom flask, using a bigger stirring bar reduced the reaction time to 1.5 h and increased the yield to 76 % (**Table 5**, entry 28). A possible explanation for this can be, that in the thin small reaction vials the heterogeneous mixture is not stirred sufficiently.

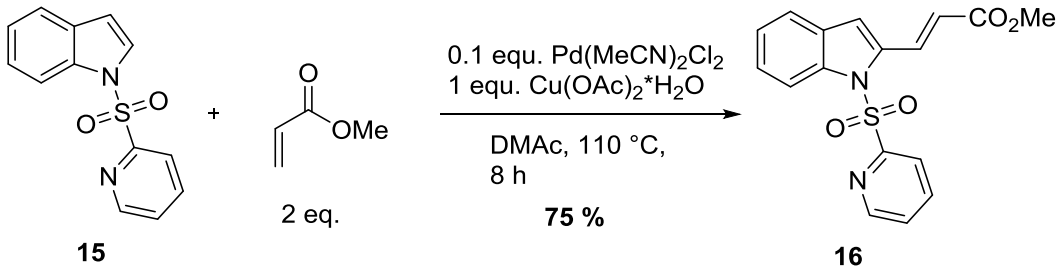
entry	cat. (Mol%)	T [°C]	amount [mg]	solvent	base	yield
16	$Pd(PPh_3)_4$ (10)	75	25	PhMe	DBU	32
17	$Pd(PPh_3)_4$ (10)	75	25	PhMe	K_2CO_3	21
18	$Pd(PPh_3)_4$ (10)	75	25	PhMe	KOtBu	30
19	$Pd(PPh_3)_4$ (5)	75	25	PhMe	NEt_3	55
20	$Pd(PPh_3)_4$ (20)	75	25	PhMe	NEt_3	67
21	$Pd(PPh_3)_4$ (10)	110	25	PhMe	NEt_3	58
22	$Pd(PPh_3)_4$ (10)	75	25	PhMe	NEt_3	65
23	$Pd(PPh_3)_4$ (10)	75	50	PhMe	NEt_3	32
24	$Pd(PPh_3)_4$ (10)	75	100	PhMe	NEt_3	20
25	$Pd(PPh_3)_4$ (10)	75	25	MeCN	NEt_3	54
26	$Pd(PPh_3)_4$ (10)	75	50	MeCN	NEt_3	42
27	$Pd(PPh_3)_4$ (10)	75	300	MeCN	NEt_3	41
28	$Pd(PPh_3)_4$ (10)	75	422	MeCN	NEt_3	76

Table 5: Base-, catalyst- and scale up-screening

3. C2-Alkenylation using N-2-pyridinesulfonyl protected indoles

3.1. Screening of the optimized conditions using a model reaction

For the envisioned synthesis the C2-alkenylation published by Garcia-Rubia and coworkers was planned (see introduction).[45,48] Before working on the actual target system, model reactions were conducted to reproduce the literature and to obtain similar yields like it was published. The reaction shown in **Scheme 23** was published with 75 % yield and full conversion after 8 h.



Scheme 23

Applying the literature conditions gave just 38 % yield in this laboratory and incomplete conversion after 8 h. Different conditions were tried to increase the yield, but changing the amounts of additives had no major influence. A significantly higher yield (64 %) was obtained after degassing the solvent using the freeze-pump-thaw method, although it was not mentioned in the literature, that degassed solvent is necessary (**Table 6**).

Entry	Co-oxidant	Oxidant [eq.]	Pd-cat. [eq.]	Substrate [eq.]	time [h]	T [°C]	Yield [%]
1	$Cu(OAc)_2 \times H_2O$	1	0.1	2	8	110	38
2	$Cu(OAc)_2 \times H_2O$	1	0.1	2	8	110	38
3	$Cu(OAc)_2$	1	0.1	2	8	110	41
4	$Cu(OAc)_2 \times H_2O$	2	0.1	2	8	110	44
5	$Cu(OAc)_2 \times H_2O$	2	0.1	2	8	110	64*
6	$Cu(OAc)_2 \times H_2O$	2	0.2	2	8	110	41*
7	$Cu(OAc)_2 \times H_2O$	2	0.05	2	8	110	38*

* solvent degassed

Table 6 ***Condition screening of 15 with methacrylate***

It was additionally surprising to also obtain a side product which was never mentioned in the literature. After NMR-analysis and TLC-MS measurements, the by-product was identified as compound **71** which was formed after double alkenylation **(Scheme 24)**. A similar product formation was reported after C2- and C3-substitution of benzofurans or indoles using acrylates.[58,59] To further study the alkenylation, it was investigated if full conversion could be reached after more than 8 h and how much product **71** can be formed by performing a time scale experiment. Therefore, C-H activation was started using optimized conditions (**Table 6**, entry 5) at 110 °C and also at 150 °C, to figure out the temperature and time dependence of product/sideproduct formation. Samples of the reaction mixtures were taken after 2, 18, 24 and 42 h and after adding an internal standard (naphthalene), samples were analyzed using HPLC (method: water/methanol=30/70, 1.5 mL/min, 40 °C, 7 min). After 42 h a last sample was taken the reaction mixture was worked-up and the product and side products were isolated to determine the yields after this time. **Figure 11** shows the results of these measurements. At 110 °C the measured yield of the main product was best at 2 h reaction time and was already lower after 18 h. The yield of the side product was above 10 % after 2 h and rose to 19 % at 42 h. At 42 h there was still substrate visible on the TLC but the HPLC chromatogram showed that the amount was below 5 %. Surprisingly the yields at 150 °C were lower compared to 110 °C (Main product and also side product), showing in the HPLC chromatograms also a lot of other side products which weren't analyzed further.

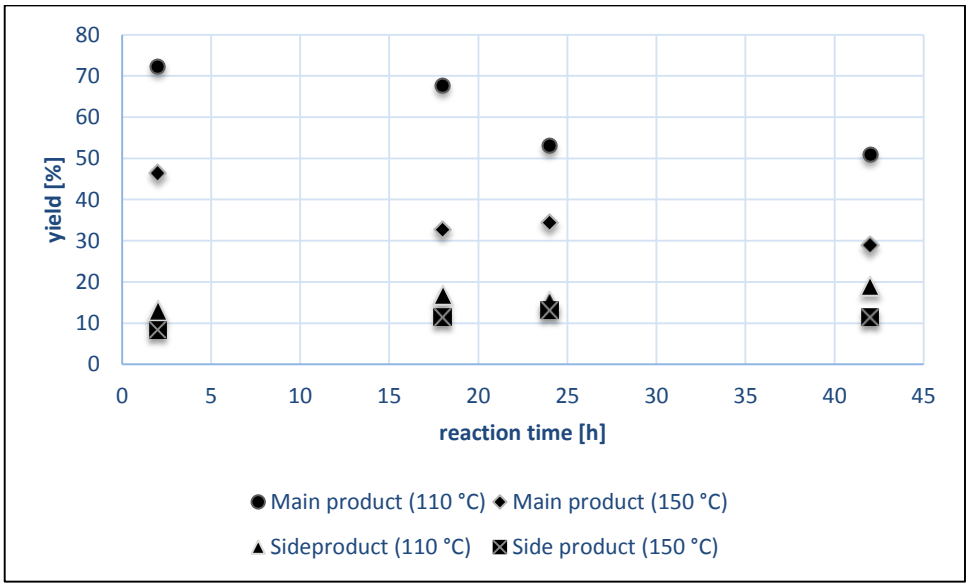


Figure 11: Timescale of the product and side product formation

To get a full picture of the time course, a second run was performed using same conditions at 110 °C, taking a HPLC sample every 30 min (**Figure 12**). It was recognized that the amount

of product reached a maximum at around 4 h and then slightly decreased. Therfore optimized conditions were defined using 2 equ. $Cu(OAc)_2 \times 2H_2O$, in degassed dry DMA for 4 h at 110 °C.

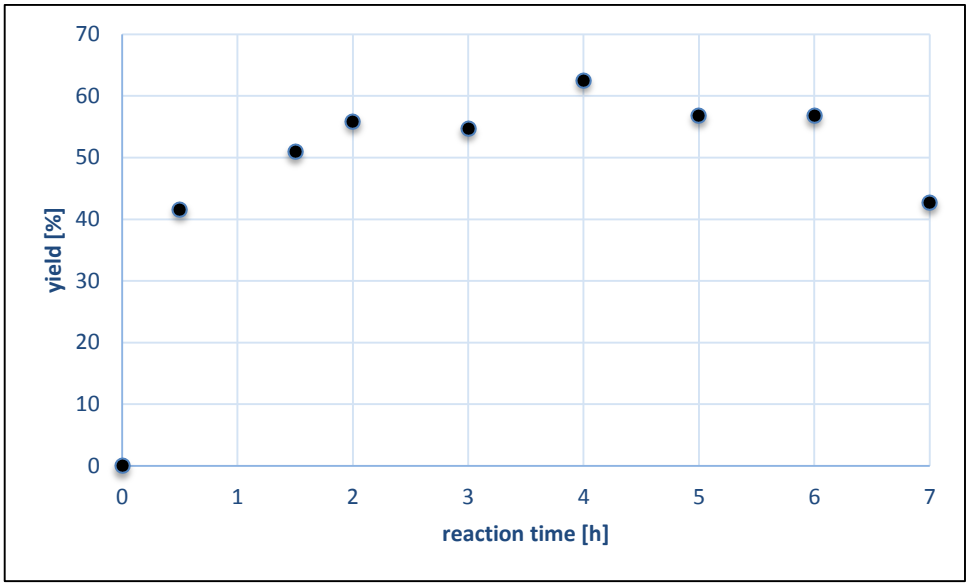
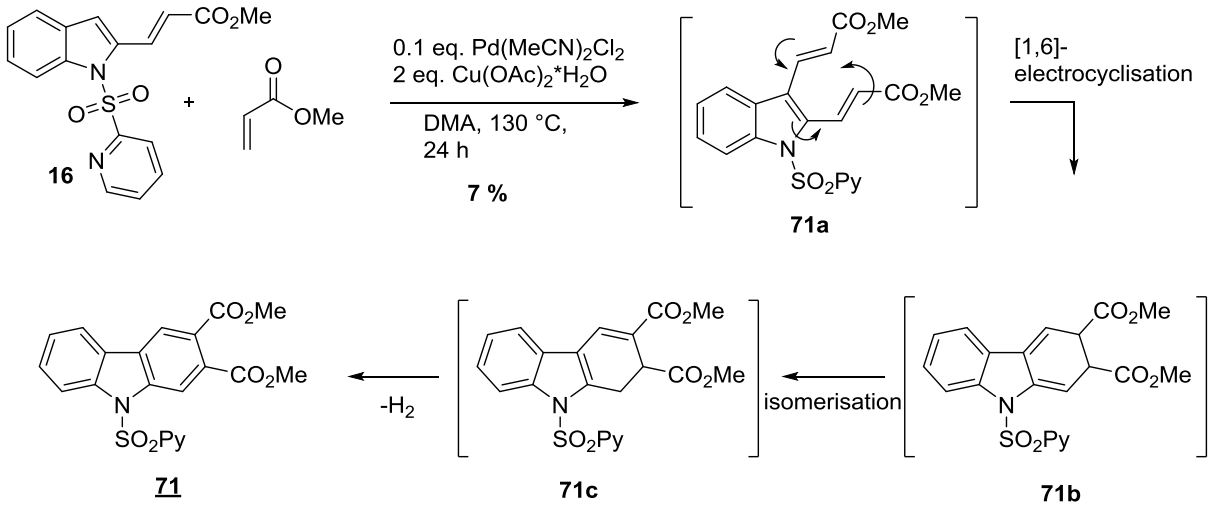


Figure 12: Timescale of the reaction (0-7 h)

The side product formation remained puzzeling and clarification on a possible equilibrium shift was pending, pushing the reaction to the side of the double alkenylated product which then undergoes a [1,6] electrocyclisation followed by oxidation. Therefore the reaction was performed as shown in **Scheme 24**, expecting that product **71** is formed in considerable amount. Unfortunately, after 24 h just 7 % of product **71** could be isolated. Some other side products were formed but due to their small amounts they were not investigated further. This experiment showed that the carbazole formation can be also obtained using already C2-alkenylated indoles. The lower yield compared to the reaction with not alkenylated indole (7 % compared to 19 % which were isolated after the HPLC-experiment) may indicate that intermediates which are present during the alkenylation of free indole could play a role in the formation of **71**



Scheme 24

3.2. Scope of the alkenylation

Having optimized conditions for the model reaction in hand, exploration of the scope of the alkenylation was further investigated. In the literature the alkenylation was performed using different indole and alkene sources. It was published that the reaction is working using electron poor- (acrylates), conjugated- (styrene) and even branched- (methyl methacrylate) alkenes. To further test scope and limitations of the protocol, reactions summarized in Fehler! Verweisquelle konnte nicht gefunden werden. were conducted**.**

The first three examples were already published and carried out to reproduce the literature. With styrene and methacylate nearly literature yields (styrene 72 %, literature = 85 %; methacrylate 64 %, literature = 75 %)[48] were obtained and using methyl methacrylate the identical yield was achieved (both 72 %). In order to test structural effects resembling more closely the actual target compound (ethyl indol isoquinuclidine), the alkenylation was attempted using relatively inactivated 1-hexene. The reaction gave one product on TLC which was isolated in 71 % yield. Unfortunately, the ^{1}H-NMR showed a mixture of at least 5 isomers (Containing most likely 1-*(E)*-hexene-,1-*(Z)*-hexene, 2-*(E)*-hexene-,2-*(Z)*-hexene- isomeres) . This was interpreted because Pd undergoes interactions with double bonds easily and can therefore isomerise them. The isomers could not be separated on preparative scale, but knowing that the alkenylation is working using 1-hexene with a good yield, the same reaction using cyclic alkenes such as cyclohexene and cyclopentene was conducted. In both cases, C2-alkenylation was observed but with cyclopentene the yields were much better. In both cases again isomerisation was encountered leading to inseparable mixtures of double bond isomers. The bridged alkene norbornene was also used in the CH-activation, but no reaction

occurred. Ethyl-vinyl-ether, allylbromide, acrylonitrile and isopropenylacetate represent further alkenes not giving the attempted transformation.

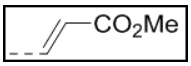
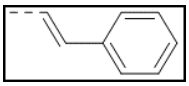
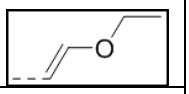
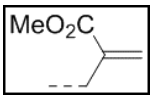
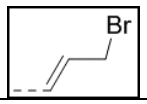
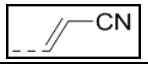
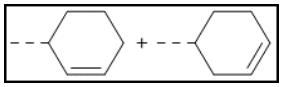
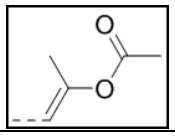
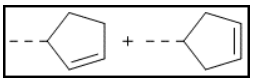
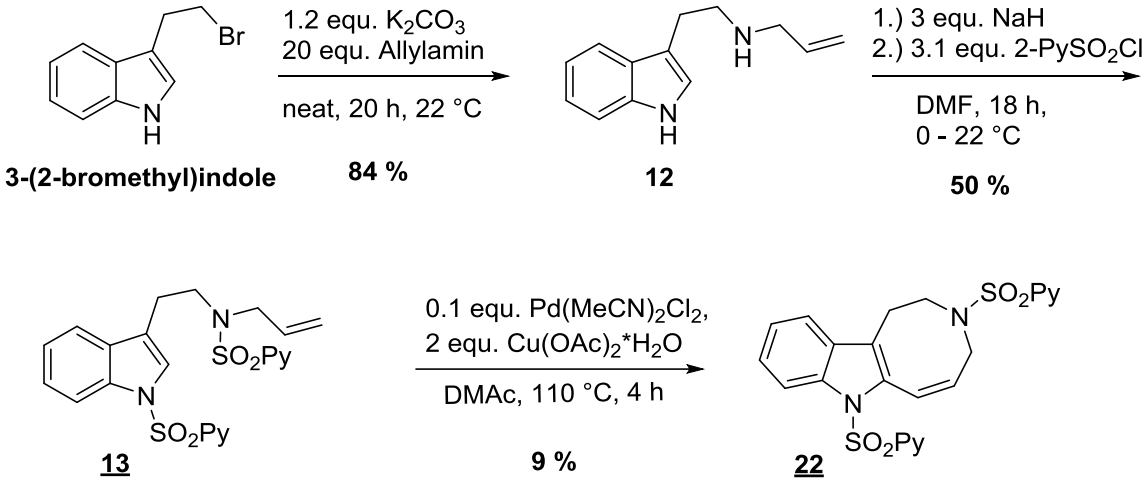
Compound	Yield [%] (product distribution)	R	Compound	Yield [%]	R
16	64		**29**	no reaction	
24	72		**30**	no reaction	
25	72		**31**	no reaction	
26	71		**32**	no reaction	
27a + **27b**	16 (4:1)		**33**	no reaction	
28a + **28b**	53 (9:1)				

Table 7: Scope of the alkenylation

The alkenylation was also attempted in an intramolecular fashion. Therefore substrate **13** was prepared over two steps (**Scheme 25**). In the first entry 3-(2-bromethyl)indole was treated with NaH at 0 °C following by the addition of 2-$PySO_2Cl$ to provide substitution on the nitrogen of the indole moiety. Unfortunately this lead to a mixture of two inseparable compounds which were not possible to identify, but due to the ^{1}H-NMR spectra the formation of desired product was excluded. In the second entry 3-(2-bromethyl)indole was treated with K_2CO_3 in allylamine obtaining product **12** in 84 % yield. Treating amine **12** with 1 equ. NaH at 0 °C and afterwards

adding 1 equ. 2-$PySO_2Cl$, yielded product only substituted on the amine moiety in 83 %. Knowing that application of only ~1 equ. of additives lead to undesired substitution only, the reaction was performed using 3 equ. of base and 3.1 equ. 2-$PySO_2Cl$ to obtain double substituted product **13** in 50 % yield.

Afterwards alkenylation was performed. The reaction progress was monitored *via* TLC. After 2 h no product spot was visible on TLC so it was stirred more time. After 16 h there was a new spot which indicated that product formation occurred, but there was still a large amount of substrate left. After 48 h there was still no full conversion and TLC showed no significant further progress compared to the TLC after 16 h. The reaction mixture was then worked up, purified using column chromatography and product **22** was obtained with 9 % yield. A possible explanation for the lower yield is, that the second directing group located at the amine coordinates the catalyst making it less available to the alkenylation. This experiment gave new information about the scope of the alkenylation: At first the alkenylation was demonstrated to work intramolecular and can be used for the synthesis of annulated indoles. It can further be concluded after this experiment, that groups which are coordinating to the catalyst are lowering the yield, significantly.

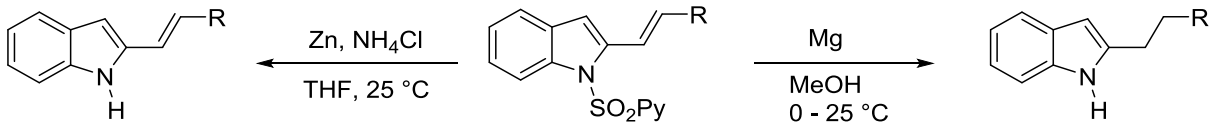


Scheme 25

3.3. Deprotection of the 2-pyridinesulfonyl protected indoles

For C2-alkenylation of indoles the method reported using 2-pyridinesulfonyl protected indoles worked with good yields in most cases. It was of further interest how easily removable the

applied protecting group is, as the literature outlined a facile cleavage using Zn as well as removal with concomitant reduction of the double bond applying Mg (**Scheme 26**).[45,48]



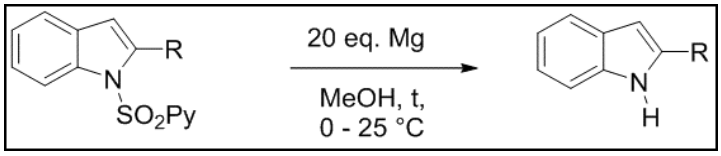
Scheme 26

For application in the target synthesis, the method including Mg would be more interesting, because in the final product ibogamine no olefinic double bond is present. To reproduce literature alkenylated indoles were treated with 20 equ. Mg in dry MeOH.

Table 8 shows the results of these reactions. In cases of methacrylate, methyl methacrylate and styrene derivatives, reactions were complete after 16 h getting the corresponding products with reduced double bonds in yields above 50 %.

For hexene, cyclohexene and cyclopentene derivatives the reaction was already complete after 2 h. After isolation it was surprising to find only the deprotected derivatives in hand where the double bonds were not reduced at all. Conducting the same deprotection with 1-hexene but extending reaction time to 24 h did not lead to reduction of the double bond and isomeric mixtures were again obtained.

It could be proven in all cases that the directing group is easy removable with Mg. In certain cases the double bond can be reduced in the same step using Mg. For the reduction of the double bond of less activated alkenes like 1-hexene attached to the indole, an additional hydrogenation step using for instance H_2, Pd/C would be necessary.



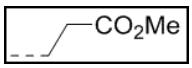
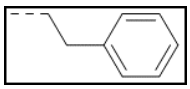
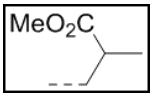
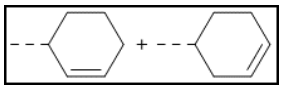
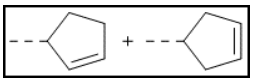
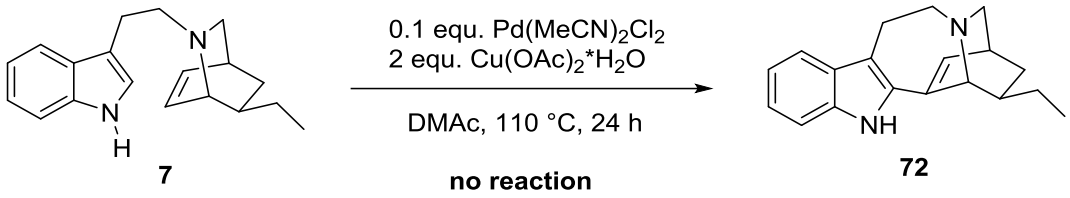
Compound	Yield [%]	R
23	57	
24	52	
25	57	
26	87	
27a +**27b**	88	
28a + **28b**	80	

Table 8: Deprotection oft he alkenes

4. Dehydroazepane formation *via* C-H activation

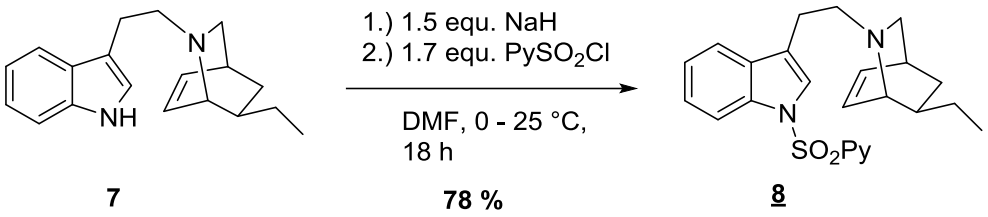
4.1. 2-Pyridinesulfonyl assisted ring formation

After investigating C2-alkenylation of indoles carrying the 2-pyridinesulfonyl directing group, transfer of the C-H activation was attempted towards synthesis of ibogamine. As a control experiment C-H activation including C-C bond formation was attempted without directing group (**Scheme 27**); as expected, this experiment was not successful (after 24 h at 110 °C there was no product visible according to TLC and GC-MS).



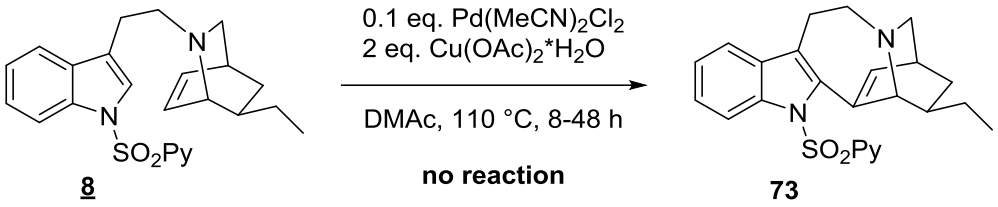
Scheme 27

Consequently, the directing group was installed to give isoquinuclidine **8** (**Scheme 28**) as alternative starting material. Using dry THF as solvent yielded in only 30 % product, while using dry DMF as solvent gave satisfying 78 % yield.



Scheme 28

Product **8** was then treated under conditions discussed in the previous chapter (**Scheme 29**). After 8 hours there was still no new spot visible on TLC. Assuming that substrate and product might have the same Rf-value the mixture was worked up and crude ^{1}H-NMR was measured. The NMR showed very broad signals giving no exact integrals but no new signals were visible, also indicating unsuccessful conversion. After column chromatography only substrate was isolated. The reaction was carried out a second time using 48 h reaction time, but TLC analysis showed the whole time no new spot. ^{1}H-NMR after work-up showed again broad signals, no new signals and after chromatography only substrate was recovered.



8 73

Scheme 29

At first it was puzzling why the method worked for intermolecular reactions using cyclohexene, but not in the intramolecular case with isoquinuclidine. After re-investigating the tentative mechanism of the reaction again in detail (**Figure 13**), a possible explanation was found why here alkenylation cannot work.

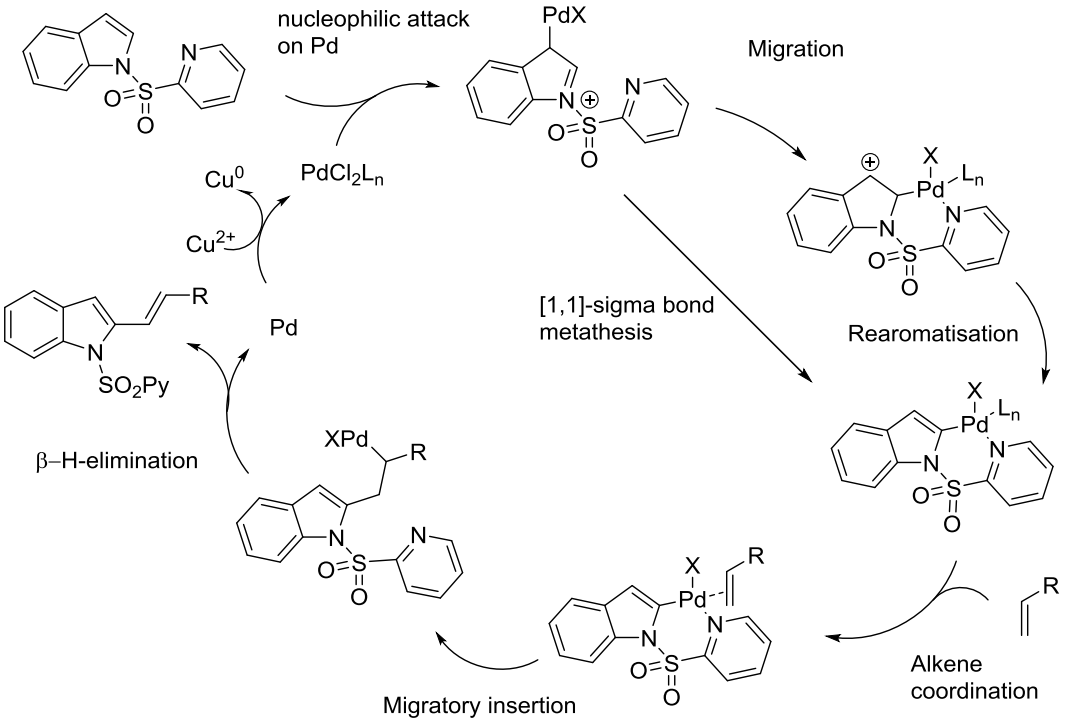
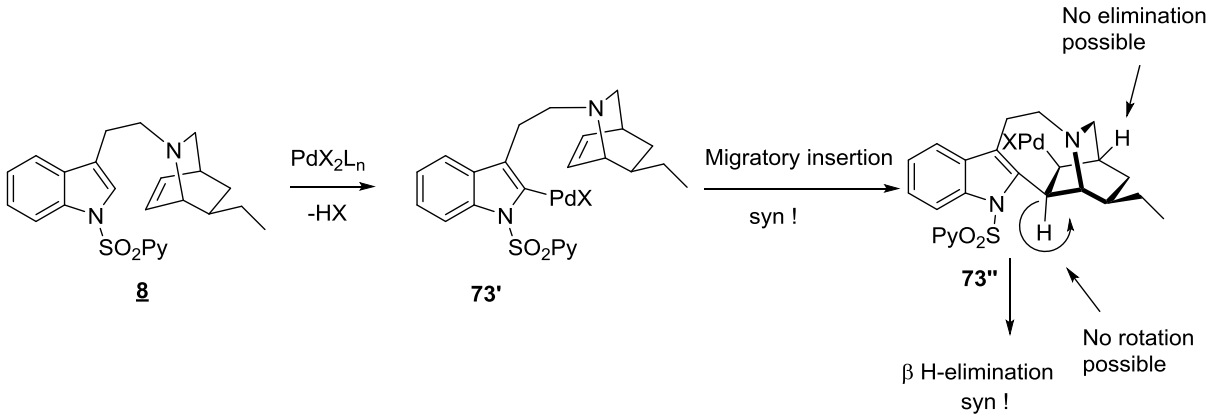


Figure 13

The palladation of indole can proceed either by direct [1,1] sigma-bond metathesis or by electrophilic substitution, whereas the latter route is more plausible according to some

mechanistic studies.[45] In the next steps, the alkene coordinates at first at the Pd catalyst and then inserts into the Pd-C bond. For this process Pd-C and the alkene have to be *syn-coplanar*.[60] A consequence of that is that migratory insertion leads always to intermediates where the newly formed Pd-C and the new formed C-C bond are *syn* to each other. After that, β-hydride elimination occurs releasing the product. Also for this step, the hydride to be eliminated and Pd-X have to be syn-coplanar.



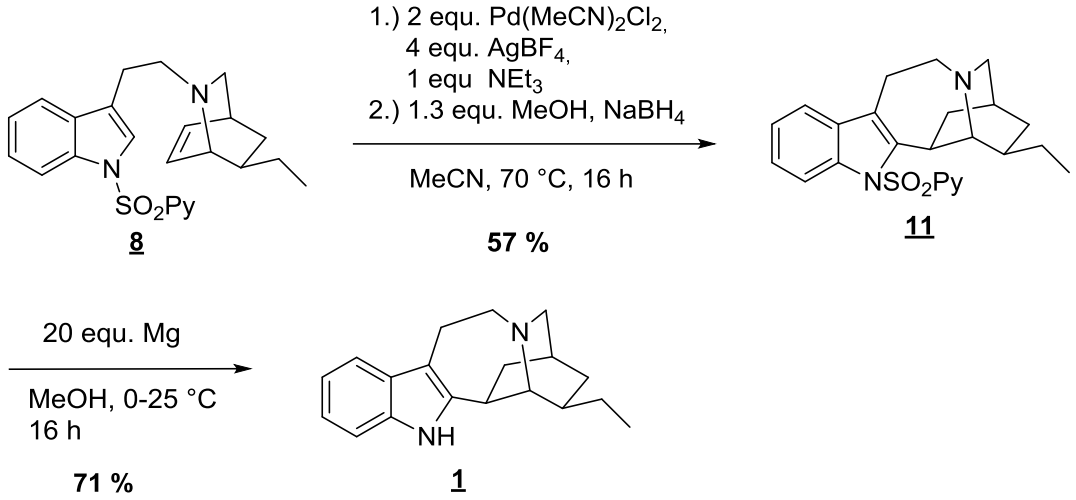
Scheme 30

Scheme 30 presents the detailed mechanistic rationale showing the alkenylation of target compound **8**. At first palladation occurs. Then the olefinic part inserts into the C-Pd bond, this proceeds in syn-conformation. In the next step, the β-hydride would get eliminated, also this has to be syn. However, in this particular case PdX and the β-hydride are anti to each other. Normally the bond would rotate, so PdX and the β-hydride are syn again so β-hydride elimination is possible. Since the isoquinuclidine ring system is rigid, rotation is not possible. In principle, β-hydride elimination can also occur from the other side. Unfortunately, bridged ring systems like here, containing one double bond at the bridgehead carbon are not stable according to the Bredt's rule.[61] Therefore, also at the other side there is no β-hydride elimination possible. Without β-hydride elimination the product cannot be released and so the reaction cannot occur.

4.2. Trosts CH-activation

Based on the findings that according to the proposed mechanisms the cyclization is highly improbable, different routes were required and some possible methods were found in the literature. Most of them were already explained in chapter **I.3**. At first, Trost conditions were applied to the 2-sulfonylpyridine protected substrate,[29] shown in **Scheme 31**. The protected indole was employed preferably, because reactions with unprotected indole were performed already a few times and the yields were normally just around 20-40 % yield[31] and it was

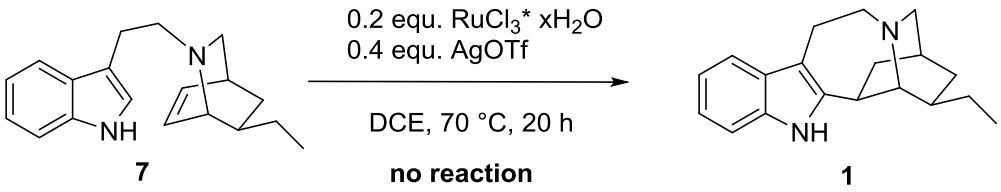
hypnotized that using the directing group will lead to a more activated C2 position on the indole and therefore improve the yield. Luckily this was the case and **11** was received in 57 % yield. Also the cleavage of sulfonylpyridine protected ibogamine was working without problems giving 71 % yield of **1**. Comparing NMR-spectra (including 2-D-NMR-spectra) of the obtained product to literature reports confirmed formation of ibogamine.[33]



Scheme 31

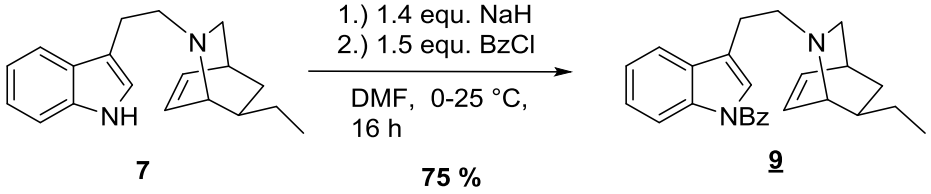
4.3. Indole alkylation using alkenes

Although one possible route to ibogamine was found, the identification of other methods for the last C-C bond forming reaction remained as prime interest, due to the environmentally questionable and expensive Trost C-H activation conditions. At first a method published by Sames and coworkers was investigated.[41] Isoquinuclidine derivative **7** was treated with 0.2 equ. of $RuCl_3 \times xH_2O$ and 0.4 equ. AgOTf in dry DCE at 70 °C but after 20 h no conversion to any product was detected (Monitored by GC-MS and TLC) (**Scheme 32**).



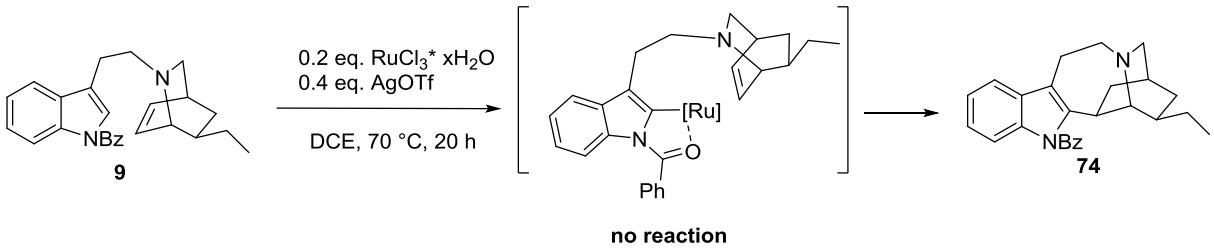
Scheme 32

In other methods it was shown, that a benzoyl protecting group on the indole nitrogen can act as a directing group for metals like Ru^{3+} in C2-alkenylations of indoles.[42,49] A possible explanation for that is that the Ru-species coordinates to the carbonyl of the benzoyl group resulting in a five membered transition state (**Scheme 34**). Consequently, the indole nitrogen was protected accordingly using benzoyl chloride in DMF with 75 % yield (**Scheme 33**).



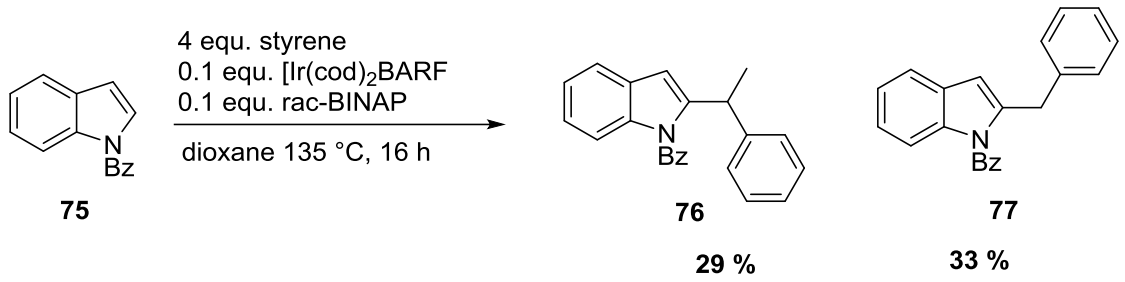
Scheme 33

With this substrate the method published by Sames and coworkers was attempted, again. Unfortunately, this did not give the expected reaction and this method did not yield in any product formation.

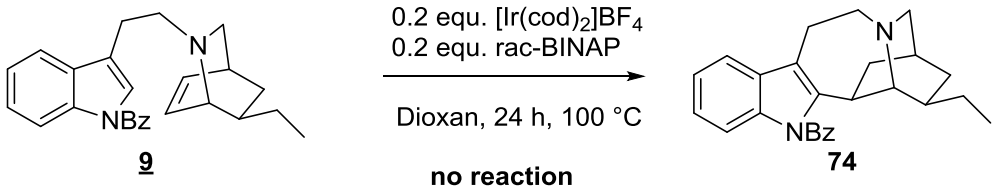


Scheme 34

Another interesting method recently published was the alkylation on C2 of indoles using $[Ir(cod)_2]BF_4$ as a catalyst.[42] After repeating an example from the literature successfully (**Scheme 35**), compound **9** was treated with 0.2 equ. $[Ir(cod)_2]BF_4$ and 0.2 equ. rac-BINAP in dry degassed dioxane at 135 °C. After 48 h there was still no product detectable and after work-up predominatly decomposition of starting material was observed. A second try, stirring at 100 °C for 12 h showed also no product formation (**Scheme 36**)



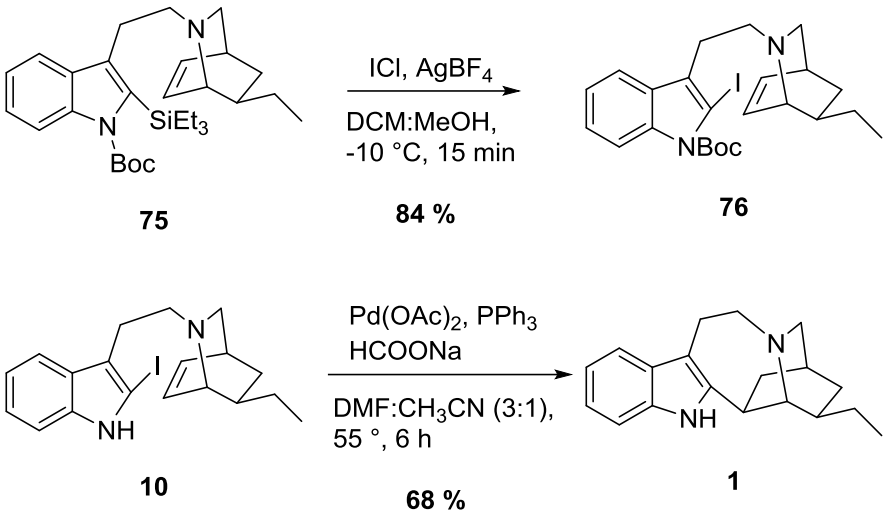
Scheme 35



Scheme 36

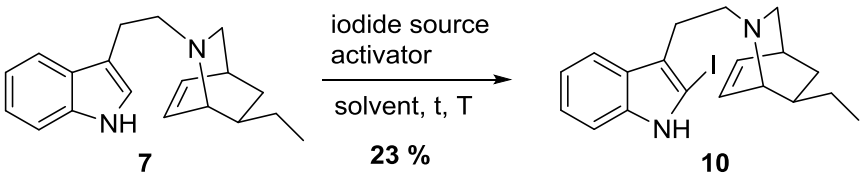
4.4. Reductive Heck coupling

Sinha and coworkers published a possible ring closing procedure, using a reductive Heck approach (**Scheme 37**).[33] They reported a yield of 68 % after treating iodide **10** with a Pd-catalyst and subsequent mild reduction using sodium formiate. In order to check this reference, synthetic access to compound **10** was required. In the literature precursor **10** was prepared treating the silyl group of ***75*** with iodochloride and $AgBF_4$ (**Scheme 37**). In the present isoquinuclidine system a C-H bond had to be broken in order to obtain **10** instead of the weaker C-Si like in the literature. Several iodination protocols were attempted.



Scheme 37

The applied iodination conditions are summarized in (**Table 9**). The first protocol for the iodination (**Scheme 38**) was adapted from a corresponding transformation using tryptamine succinimide.[62] The reported iodination was performed at -78 °C and after 15 min 96 % yield were obtained using elemental iodine as iodine source and AgOTf as activator. In the present case the reaction occurred neither at the original temperature of -78 °C nor at -25 °C and 3 hours stirring (TLC). Enhancing the temperature to room temperature led to product formation together with also side products. Increasing the amount of iodine or activator did not have a positive effect on yield and another solvent like DCM gave no product at all. Complementary alternative protocols from the literature were attempted,[34,63] including iodine sources like NIS or ICl, but the best yield was in the end 23 % using iodine and AgOTf (**Table 9**, Entry 3+9)



Scheme 38

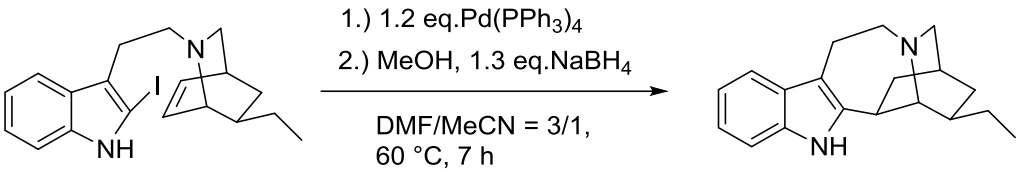
Entry	Solvent	Iodine source ; equ.	Activator; equ.	Time [h]	Temperature [°C]	yield [%]
1	THF	I_2 ; 1.1	AgOTf; 1.1	6	-78 - -25	-
2	THF	I_2 ; 1.1	AgOTf; 1.1 +1	20	0 - 25	11
3	THF	I_2 ; 1.1	AgOTf; 1.1	20	25	23
5	THF	I_2; 1.3	AgOTf; 1.5	20	25	21
4	THF	I_2; 1.1	AgOTf; 1.1	2	25	23
5	DCM	I_2; 1.3	AgOTf; 1.5	20	25	-
6	DCM	ICl; 1.1	Celite	20	25	6
7	THF	ICl; 1.1	AgOTf; 1.1	4	0 - 25	12
8	THF	NIS; 1.1	AgOTf; 1.1	4	0 - 25	-
9	THF	I_2; 1.1	AgOTf; 1.1	2	25	23

Table 9: Different iodination protocols

With iodide **10** in hand, the literature conditions (solvent was dried and degassed before the reaction) were applied for the reductive Heck reaction (**Scheme 37**); however, no conversion of any substrate was observed even after 20 h. Catalyst was changed to $Pd(PPh_3)_4$ instead of $Pd(OAc)_2/PPh_3$ to exclude the possibility that the catalyst employed is inactive, but still no substrate conversion was observed. Consequently, literature conditions could not be reproduced for this transformation.

As a last experiment the same reaction conditions were applied but with stoichiometric amounts of $Pd(PPh_3)_4$ (1.2 equ. instead of 0.1 equ.) and no HCOONa. After 6 h the reaction mixture was quenched by the addition of 1.5 equ. $NaBH_4$. We obtained desired ibogamine with a yield of 31 % (**Scheme 39**).

We were able to find a second approach to ibogamine where less of the expensive metals compared to Trost's method is required (1.2 equ. Pd-cat. instead of 2.2 equ. Pd-cat. + 4.4 equ. silver salt).



31 %

Scheme 39

5. Conclusion

It was the aim of this thesis to design a route based on catalytic metal-assisted bond formation for the synthesis of *iboga*-alkaloids. To get access to different derivatives a short synthesis bearing good yields was desirable. The original approach reported by Trost et al[29] served as guideline and improvements in yield and simplicity were attempted. For each reaction, condition screening was performed to obtain a maximum of yield. Over 9 steps racemic ibogamine was obtained in 5 % yield, so the yield published by Trost (3 %) was nearly doubled. The bottleneck of the synthesis was the metal assisted C-C bond formation. Some methods for the C2-alkenylation and -alkylation of indoles were published and served as alternative routes for the critical C-C bond formation. Therefore different catalyst systems containing Ir or Ru were investigated. Although the usage of stoichiometric amounts of Pd in this step could not be avoided, two different methods leading to product formation, were successfully performed.

The C2-alkenylation of indoles published by Garcia-Rubia and Carretero was investigated in matters of yield and scope. We observed a wide scope and also relatively inactivated alkenes like 1-hexene undergo this reaction smoothly. A drawback of these substrates is the isomerisation of the alkene double bond.

The synthesis was designed in a way that it is also suitable for enantioselective product formation. For that two different strategies can be applied. Reacting 3-hexen-1-one with a chiral acid chloride (e.g. methyl-mandeloyl chloride) leads to a diene attached by a chiral ester moiety.[29] This chiral ester performs in the Diels-Alder cycloaddition as a chiral auxiliar. An even more elegant way to obtain enantioenriched or enantiopure products would include a chiral catalyst in the Diels Alder reaction (e.g. Mikami catalyst, Keck catalyst).[64-66] After the chiral version of this approach is developed, the improved synthesis can be used to build a substance library for the biological interesting *iboga* alkaloids.

III. Experimental

1. General Notes

1.1. Chemicals

Chemicals were purchased from commercial suppliers and used without further purification unless otherwise noted.

1.2. Dry solvents

Dry THF was obtained by distilling pre-dried THF freshly from Na/benzophenone ketyl radical.

Dry NEt_3 was distilled from NaH and was stored under argon and molecular sieves.

Dry DMAc and dry MeCN were distilled from molecular sieves and were stored under argon and molecular sieves.

Dry DMF was purchased from Acros and stored over molecular sieves.

Dry dioxane, dry DCM, dry Et_2O and dry MeOH, were obtained by passing pre-dried material through a cartridge containing activated alumina *via* a solvent dispensing system and stored under nitrogen and over molecular sieve.

1.3. Degassed solvents

Solvents were degassed using the method “Freeze-Pump-Thaw” and three iterations.

Freeze-Pump-Thaw method: A septum covered round bottom flask is charged with the desired solvent under argon atmosphere. Then the solvent is frozen using liquid nitrogen. The atmosphere in the flask is pumped off on a Schlenk line for 5 min. The Schlenk line is closed (neither vaccum nor argon nor air) and the solvent is then thawn using a water bath. The procedure has to be repeated 2 times in the end the vial is backfilled with argon

1.4. Cryostat

For low reaction temperatures that required cooling overnight a Cryostat RKT20 Lauda was used.

1.5. Chromatography (TLC, MPLC)

TLC was performed on aluminum coated silica gel 60 F_{254} from Merck and spots were visualized with UV light and/or staining with various dip reagents. In general, the majority of

compounds are UV active in some cases cerium-ammonium-molybdate/ phosphomolybdic acid dip reagent was used (10 g phosphomolybdic acid, 1 g Ce(IV)-ammoniumnitrate, 20 g conc. sulfuric acid, 300 mL EtOH). Deactivated silica plates were obtained by dipping the silica plates in a mixture of DCM/NEt_3=9/1and drying them in air.

Flash column chromatography was performed on a Büchi Sepacore™ MPLC system, using silica gel 60 (40-63 µm) from Merck. Deactivated silica was obtained with the following procedure: Silica was suspended in a mixture of DCM/NEt_3=9/1 for a few minutes. Then the solvent was removed with a suction filter. The silica was washed two times with DCM and was then dried *in vacuo*.

1.6. Melting points

Melting points were determined using a Stanford Research Systems MPA100 OptiMelt Automatic Melting Point System. Data is given in 0.5 °C intervals.

1.7. GC-MS

A Thermo Finnigan Focus GC / DSQ II using a standard capillary column BGB 5 (30 m x 0.25 mm ID) or a Thermo Trace 1300 / ISQ LT using a standard capillary column BGB 5 (30 m x 0.25 mm ID) were used for GC-MS runs. The following settings were used as standard:

Ionization method: Electron ionization (70 eV)

Injection: 1 µL (hot needle-technique), split-injection (ratio 1:8)

Flow: 2 mL/min helium

Injectorblock temperature: 250 °C

MS-transferline temperature: 280 °C

Method 1: 100 °C for 2 min, 100-280 °C in 10 min, 280 °C for 3 min

Reported are:

all fragment signals at/over mass (m/z) 100 and at/over 10 % relative intensity

all molecular peaks (regardless the relative intensity)

all peaks with 100 % intensity (regardless the mass)

1.8. HR-MS

HR-MS was carried out by Prof. E. Rosenberg at Vienna University of Technology, Institute for Chemical Technologies and Analytics.

Analytical method: All samples were analyzed by LC-IT-TOF-MS with electrospray-ionization (ESI) and atmospheric pressure chemical ionization (APCI) in only positive ion detection mode upon recording of MS spectra. For the evaluation in the following, only positive ionization spectra were used (where the quasi-molecular ion is the one of $[M+H]^+$ or $[M+Na]^+$), and further data or information were not taken into consideration.

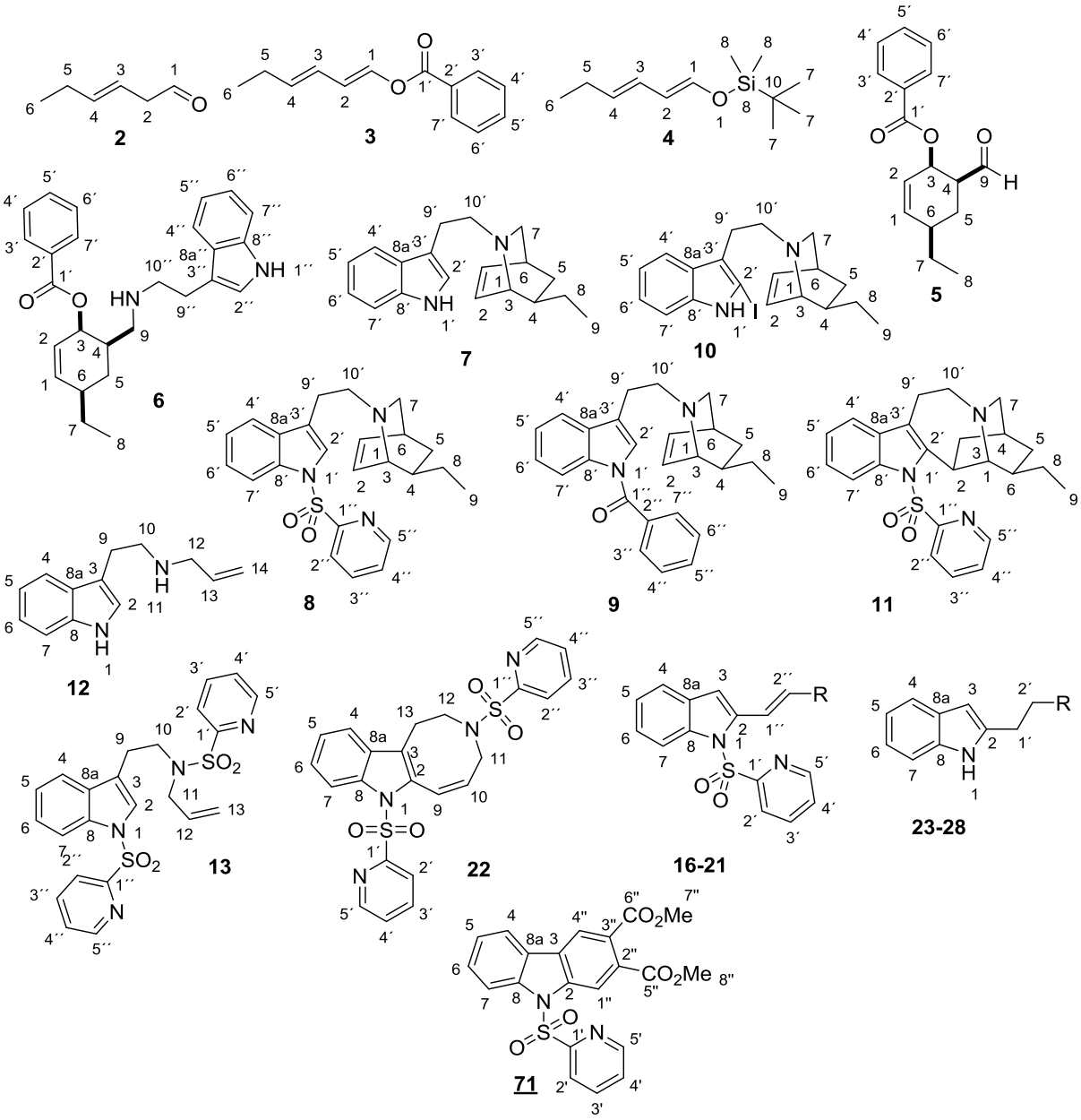
Instrumental parameters: Shimadzu Prominence HPLC, consisting of: solvent degassing unit (DGU-20 A3), binary gradient pump (2 x LC-20AD), auto-injector (SIL-20A), column oven (CTO-20AC), control module (CBM-20A), and diode array detector (SPD-M20A)

MS-system: Shimadzu IT-TOF-MS with ESI and APCI interface.

Chromatography (parameters: Short_Col_PI_NI_MS2): column: Phenomenex ODS(3), 4 mm x 4.6 mm, 5 µm particles, operated at 40 °C; column flow: 0.5 ml/min; injection volume: 2 µl; gradient: A: H_2O + 0.1 % formic acid, B: MeOH; MS parameters as in autotune. Data recorded with detector voltage at autotune value. Scan range: 100 - 1000 amu for both, MS (PI and NI)-detection. ES ionization. Cycle time <0.6 s. CDL-temperature 200 °C, Heating block temperature: 200 °C, scan range 200-400 nm

1.9. NMR-Spectroscopy

^1H- and ^{13}C-NMR spectra were recorded from $CDCl_3$ solutions on a Bruker AC 200 (200 MHz) or on a Bruker Avance UltraShield 400 (400 MHz) spectrometer. Chemical shifts are reported in ppm relative to the nominal residual solvent signal of $CDCl_3$: ^1H: 7.26 ppm, ^{13}C: 77.16 ppm. Allocations of the structures were carried out as follows.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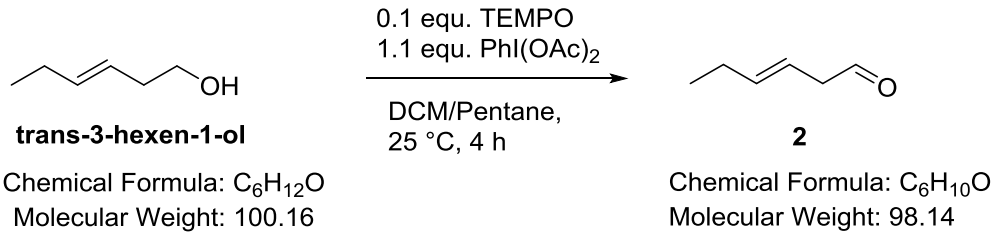
2. Synthesis of Ibogamine

2.1. (E)-Hex-2-enal (2)



trans-3-hexen-1-ol

Chemical Formula: $C_6H_{12}O$
Molecular Weight: 100.16

2

Chemical Formula: $C_6H_{10}O$
Molecular Weight: 98.14

The target compound **2** was obtained, according to a modified literature protocol.[54] In a 250 mL round bottom flask TEMPO (0.468 g; 3 mmol; 0.1 equ.) and $PhI(OAc)_2$ (10.629 g; 33 mmol; 1.1 equ.) were suspended in pentane (84 mL) and dry DCM (10 mL) under an argon atmosphere. Then trans-3-hexen-1-ol (3.66 mL; 30 mmol; 1 equ.) was added with a syringe and the mixture was stirred at room temperature for 6 h until the solution became clear and no more substrate was consumed (monitored by TLC). The reaction mixture was washed with satd. aqu. $NaHCO_3$ solution (100 mL), dried over Na_2SO_4 and the solvent was removed *in vacuo*. ^{1}H-NMR analysis showed a mixture of desired product **2**, iodobenzene and DCM. The crude product was used in the next step without further purification.

Yield: 12.795 g crude mixture containing 2.431 g of **2** (83 %), 6.922 g iodobenzene and 3.502 g DCM)

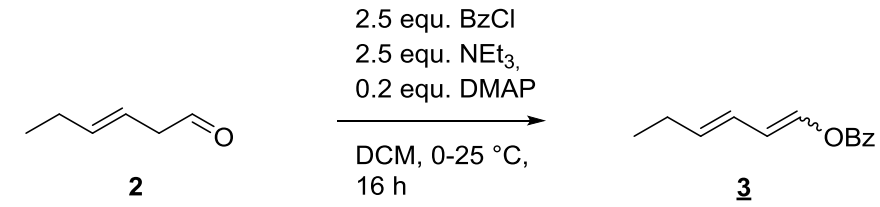
Appearance: slighty yellow liquid

TLC: Rf(PE/EtOAc = 20/1) = 0.62

Product: ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.00 (t, J=7.40 Hz, 3H, H6), 1.99-2.17 (m, 2H, H5), 3.10 (dd, J=6.63, 2.09, 2H, H2), 5.38-5.75 (m, 2H, H3 & H4), 9.66 (t, J=2.09, 1H, H1)

^{13}C-NMR (50 MHz, $CDCl_3$): δ 13.6 (q, C6), 25.7 (t, C5), 47.3 (t, C2), 118.3 (d, C3), 138.4 (d, C4), 200.5 (d, C1)

2.2. (1*E*, 3*E*)-Hexa-1,3-dien-1-yl benzoate, (1*Z*, 3*E*)-hexa-1,3-dien-1-yl benzoate (3)



2

Chemical Formula: $C_6H_{10}O$
Molecular Weight: 98.14

3

Chemical Formula: $C_{13}H_{14}O_2$
Molecular Weight: 202.25

In a 250 mL three necked round bottom flask crude product **2** (2.431 g of **2**; 24.8 mmol; 1 equ.) was dissolved in dry DCM (70 mL) under argon atmosphere and DMAP (0.611 g; 5 mmol, 0.2 equ.) was added. The suspension was cooled to 0 °C before BzCl (7.19 mL, 61.9 mmol; 2.5 equ.) and dry NEt_3 were added dropwise with a syringe. After complete addition the brownish reaction mixture was allowed to warm to room temperature and was stirred for 16 h until complete conversion (monitored by GC-MS). The suspension was washed with satd. aqu. $NaHCO_3$ solution, H_2O, satd. aqu. NH_4Cl solution and brine (50 mL each). The organic phase was dried over Na_2SO_4 and the solvent was removed *in vacuo.* The product was purified *via* column chromatography (MPLC, 90 g silica, 40 mL/min, 100 % PE for 20 min, then 0-5 % EtOAc in 40 min).

Yield: 4.281 g (Isomeric mixture (1*E*,3*E*)/(1*Z*/3*E*) = 1/1, 85 %)

Appearance: colorless liquid

TLC: Rf(PE/EtOAc = 20/1) = 0.67

Underlined C`s correspond to the (1*E*,3*E*) isomere

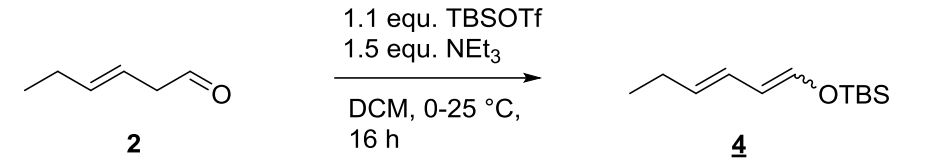
^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.96-1.13 (m, 6H, H6 & H6), 2.05-2.28 (m, 4H, H5 & H5), 5.60 (dd, J=10.89 Hz, 6.55 Hz, 1H, H2) 5.69-6.29 (m, 4H, H4 & H2 & H3 & H4,), 6.45-6.64 (m, 1H, H3), 7.22 (d, J=6.32 Hz, 1H, H1), 7.40-7.67 (m, 7H, H1 & H4´ & H5´ & H6´ & H4´ & H5´ & H6´), 8.12 (m, 4H, H3´ & H7´& H3´ & H7´)

^{13}C-NMR (50 MHz, $CDCl_3$): δ 13.6 (q, C6), 13.7 (q, C6), 26.0 (t, C5), 26.2 (t, C5), 114.0 (d, C2), 116.6 (d, C2), 121.4 (d, C3), 123.7 (d, C3), 128.6 (d, C4´ & C6´), 128.7 (d, C4´ & C6´), 129.2 (s, C2´), 129.3 (s, C2´), 129.7 (d, C3´ & C7´), 130.1 (d, C3´ & C7´), 132.6 (d, C1), 133.6 (d, C4), 133.7 (d, C4), 136.9 (d, C5´ & C5´), 137.6 (C1), 163.3 (s, C1´), 163.7 (s, C1´)

GC-MS (EI, 70 eV): Method 1; Retention time: 7.18 (1Z, 3E); 7.49 (1E, 3E); Main fragments (relative intensity): 202 (M^+, 3), 106 (7), 105 (100), 77 (37), 51 (11),

HR-MS: $[M+H]^+$ m/z (predicted) = 203.1067 , m/z (measured) = 203.1065, difference = 1 ppm

2.3. tert-Butyl(((1E,3E)-hexa-1,3-dien-1-yl)oxy)dimethylsilane, tert-Butyl(((1Z,3E)-hexa-1,3-dien-1-yl)oxy)dimethylsilane (4)



2

Chemical Formula: $C_6H_{10}O$
Molecular Weight: 98.14

4

Chemical Formula: $C_{12}H_{24}OSi$
Molecular Weight: 212.41

A 8 mL reaction vial was charged with crude product **2** (0.2 g of **2**; 2 mmol; 1eq) under argon atmosphere and dry DCM (2 mL) was added. The solution was cooled to -10 °C followed by the dropwise addition of TBSOTf (0.506 mL; 2.2 mmol; 1.1 equ.) and dry NEt_3 (0.416 mL; 2.2 mmol; 1.1 equ.) by syringe. The resulting mixture was allowed to warm to room temperature and was stirred for 16 h until complete conversion (monitored by TLC). Then the organic phase was washed with aqu. satd. NH_4Cl solution (2 mL), H_2O (2 mL), aqu. satd. $NaHCO_3$ solution (2 mL), brine (2 mL). Subsequently it was dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified *via* column chromatography (MPLC, 5 g silica, 10 mL/min, 100 % PE) ^{1}H-NMR analysis showed an inseparable mixture of isomers **4** and iodobenzene.

Yield: 0.761 g mixture containing 0.380 g Isomers of **4** (1*E*,3*E*)/(1*Z*/3*E*)=1/1 (85 %) and 0.381 g iodobenzene

Appearance: colorless liquid

TLC: Rf(PE/EtOAc = 20/1) = 0.93

Underlined C`s correspond to the (1*E*,3*E*) isomere. Signals of iodobenzene are omitted.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.17 (2×s, 6H, H8 & H8), 0.90-1.07 (m, 24H, H7 & H6 & H7 & H6), 1.98-2.23 (m, 4H, H5 & H5), 5.17 (dd, J=11.3 Hz, 5.8 Hz, 1H, C2), 5.42-6.11 (m, 4H, H2

& H3 & H4 & H3), 6.12 (d, J=6.2 Hz, 1H, H2), 6.45 (dd, J=15.7 Hz, 10.7 Hz, 1H, H1), 6.49 (d, J=12.2 Hz, 1H, H1)

^{13}C-NMR (50 MHz, $CDCl_3$): δ -2.8 (q, C8 & C8), 13.9 (q, C6 or C6), 14.0 (q, C6 or C6), 18.4 (t, C5 or C5), 18.5 (t, C5 or C5), 25.7 (q, C7 & C7), 111.0 (d, C2 or C2), 113.7 (d, C2 or C2), 122.1 (d, C3 or C3), 125.0 (d, C3 or C3), 131.2 (d, C4 or C4), 132.5 (d, C4 or C4), 138.5 (d, C1 or C1), 143.0 (d, C1 or C1)

GC-MS (EI, 70 eV): Method 1; Retention time: 4.70 (1Z, 3E); 5.08 (1E, 3E); Main fragments (relative intensity): 212 (M^+, 32), 155 (35), 112 (49), 111 (10), 99 (38), 75 (100), 73 (50), 59 (16)

HR-MS: $[M+H]^+$ m/z (predicted) = 213.1669 , m/z (measured) = 213.1664, difference = 2.4 ppm

2.4. (±)-rel-(-1R,4R,6S)-4-Ethyl-6-formylcyclohex-2-en-1-yl benzoate (5)

3

Chemical Formula: $C_{13}H_{14}O_2$
Molecular Weight: 202.25

5

Chemical Formula: $C_{16}H_{18}O_3$
Molecular Weight: 258.32

The target compound was obtained according to a modified literature protocol.[29] A round bottom flask was charged with the isomeric mixture of **3** (4.281 g mixture; 10.6 mmol (1*E*,3*E*)-isomere; 1 equ.) under argon atmosphere and was dissolved in dry DCM (60 mL). The solution was cooled to -60 °C, then freshly distilled acrolein (1.41 mL; 21.2 mmol; 2 equ.) and BF_3×Et_2O (1.33 mL; 10.6 mmol; 1 equ.) were added dropwise by syringe. The reaction mixture was stirred for 3 h at -60 °C until complete conversion of the (1*E*,3*E*)-isomere (monitored by GC-MS). The cold solution was quenched by addition of H_2O (30 mL) and satd. aqu. $NaHCO_3$ solution (30 mL). The phases were separated, the organic phase was dried over Na_2SO_4 and the solvent was removed *in vacuo*. ^{1}H-NMR analysis showed a mixture of desired product **5** and unreacted (1Z, 3E)-diene. The crude product was used in the following reaction without further purification.

Yield: 4.541 g crude mixture containing ~2.211 g product (81 %) and ~2.330 g (1Z, 3E)-diene

Appearance: light-yellow liquid

TLC: Rf(PE/EtOAc = 20/1) = 0.67

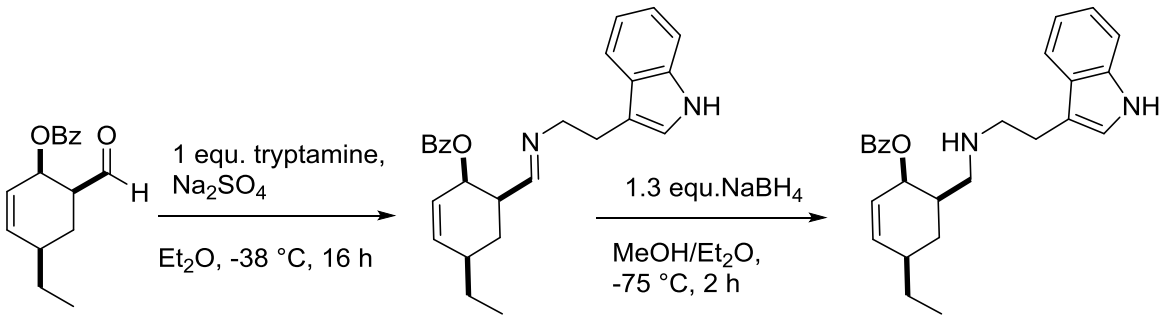
^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.00 (t, J=7.41 Hz, 3H, H8), 1.20-1.70 (m, 2H, H5), 1.98-2.28 (m, 2H, H7), 2.66-2.80 (m, 1H, H6), 6.85-6.06 (m, 3H, H1 & H2 & H4), 7.36-7.74 (m, 4H, H4´ & H5´ & H6´ & H3), 7.90-7.99 (m, 2H, H7´ & H3´), 9.81 (s, 1H, H9)

^{13}C-NMR (50 MHz, $CDCl_3$): δ 10.9 (q, C8), 23.2 (t, C5), 28.1 (t, C7), 37.1 (d, C6), 50.6 (d, C4), 65.9 (d, C3), 122.7 (d, C2), 128.2 (d, C4´&C6´), 129.5 (d, C3´&C7´), 133.0 (d, C5´), 139.3 (d, C1), 165.7 (s, C1´), 201.0 (d, C9)

GC-MS (EI, 70 eV): Method 1; Retention time: 9.57; Main fragments (relative intensity): 153 (13), 123 (11), 108 (36), 107 (22), 105 (77), 79 (100)

HR-MS: $[M+Na]^+$ m/z (predicted) = 281.1148 , m/z (measured) = 281.1137, difference = 3.9 ppm

2.5. (±)-rel-(1R,4R,6R)-6-(((2-(1H-Indol-3-yl)ethyl)amino)methyl)-4-ethylcyclohex-2-en-1-yl benzoate (6)



5 **5a** **6**

Chemical Formula: $C_{16}H_{18}O_3$
Molecular Weight: 258.32

Chemical Formula: $C_{26}H_{30}N_2O_2$
Molecular Weight: 402.53

A 8 mL reaction vial was charged with the crude mixture of **5** (0.303 g containing 0.100 g of substrate **5**; 0.39 mmol; 1 equ.) under argon atmosphere and dry Et_2O (2 mL) and Na_2SO_4 (0.600 g) were added. The suspension was cooled to -38 °C and tryptamine (0.062 g; 0.39

mmol; 1 equ.) was added all at once. The resulting reaction mixture was stirred at -38 °C for 16 h then dry MeOH (2 mL) was added. It was cooled to -75 °C and $NaBH_4$ (0.019 g; 0.50 mmol; 1.3 equ.) was added in three portions. The suspension was stirred for 2 h more at – 75 °C until it was quenched with H_2O (2 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3×2 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The product was purified *via* column chromatography (MPLC, 9 g deactivated silica, 20 mL/min, DCM with 0-10 % MeOH in 30 min).

Yield: 0.113 g (72 %)

Appearance: colorless solid

Melting point: 103 – 105 °C

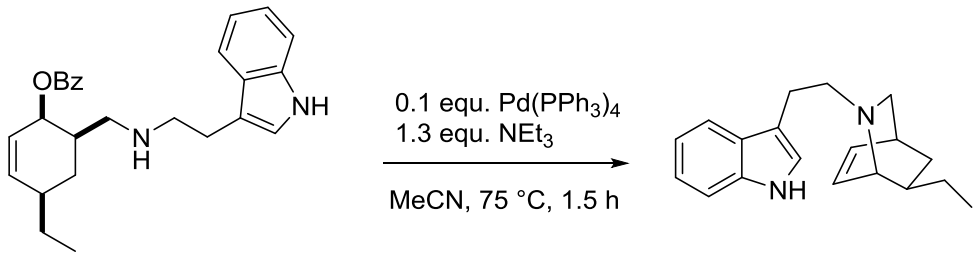
TLC: Rf(DCM/MeOH = 95/5) = 0.44; stationary phase: deactivated silica

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.93 (t, J=7.39 Hz, 2H, H8), 1.18-1.52 (m, 4H, H7 & H5), 1.72 (broad d, J = 12.23 Hz, 1H, NH), 1.86-2.14 (m, 2H, H4 & H6), 2.57-2.83 (m, 2H, H9), 2.84-2.98 (m, 4H, H9´´ & H10´´), 5.46 (t, J = 3.74, 1H, H3), 5.83-6.01 (m, 2H, H1 & H2), 6.93 (s, 1H, H2´´), 7.00-7.09 (m, 1H, H6´´), 7.7.09-7.19 (m, 1H, H6´´) 7.22-2.32 (m, 1H, H5´), 7.34-7.45 (m, 2H, H4´´ & H7´´), 7.45-7.58 (m, H4´ & H6´), 7.80 (d, J = 7.81 Hz, 2H, H7´ & H3´), 8.33 (broad s, 1 H, NH-indole)

^{13}C-NMR (50 MHz, $CDCl_3$): δ 11.2 (q, C8), 25.8 (t, C9´´), 28.5 (t, C5), 28.6 (t, C7), 38.4 (d, C6), 38.7 (d, C4), 50.2 (t, C9), 51.6 (t, C10´´), 68.3 (d, C3), 111.2 (d, C7´´), 114.0 (s, C3´´), 118.9 (d, C4´´), 119.3 (d, C5´´), 122.0 (d, C6´´), 124.0 (d, C1), 127.5 (s, C8a´´) 128.5 (d, C4´ & C6´), 129.7 (d, C3´ & C7´), 130.7 (s, C2´), 133.0 (d, C5´), 136.5 (s, C8´´), 138.9 (d, C1), 166.4 (s, C1´)

HR-MS: $[M+H]^+$ m/z (predicted) = 403.2380 , m/z (measured) = 403.2392, difference = 3.0 ppm

2.6. (±)-rel-(1R,4S,7R)-2-(2-(1H-Indol-3-yl)ethyl)-7-ethyl-2-azabicyclo[2.2.2]oct-5-ene (7)



6

Chemical Formula: $C_{26}H_{30}N_2O_2$
Molecular Weight: 402.53

7

Chemical Formula: $C_{19}H_{24}N_2$
Molecular Weight: 280.42

The target compound **6** was obtained according to a modified literature protocol.[29] A 25 mL three necked round bottom flask was charged with **6** (0.422 g; 1.05 mmol; 1 equ.), $Pd(PPh_3)_4$ (0.117; 0.1 mmol; 0.1 equ.) and dry MeCN (8 mL) under argon atmosphere. Then dry NEt_3 (0.197 mL; 1.36 mmol; 1.3 equ.) was added. The resulting orange suspension was heated to 75 °C and was stirred at this temperature for 1.5 h until complete conversion (monitored by TLC). Then satd. aqu. $NaHCO_3$ solution (10 mL) was added and the aqueous phase was extracted with EtOAc (5×10 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified *via* column chromatography (MPLC, 18 g deactivated silica, 20 mL/min, PE with 20-50 EtOAc in 30 min). Analytical data matched with reported data from literature.[29]

Yield: 0.223 g (76 %)

Appearance: orange oil

TLC: Rf(PE/EtOAc= 1/1) = 0.69; stationary phase: deactivated silica

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.93 (t, J = 7.34 Hz, 3H, H9), 0.94-1.02 (m, 1 H, H4), 1.23-1.74 (m, 4H, H8 & H5), 2.00 (dt, J = 9.08 Hz, 2.54 Hz, 1H, H6), 2.39-2.64 (m, 2H, H9´), 2.73-3.00 (m, 3H, H10´ & H3), 3.14 (dd, J = 9.21 Hz, 2.30 Hz, 1H, H9´), 3.36-3.34 (m, 1H, H9´), 6.26-6.42 (m, 2H, H1 & H2), 7.03 (d, J = 2.24, 1H, H2´), 7.07-7.24 (m, 2H, H5´ & H6´), 7.35 (d, J = 8.01, 1H, H7´), 7.62 (d, J = 7.30 Hz, 1H, H4´), 7.93 (broad s, 1H, NH)

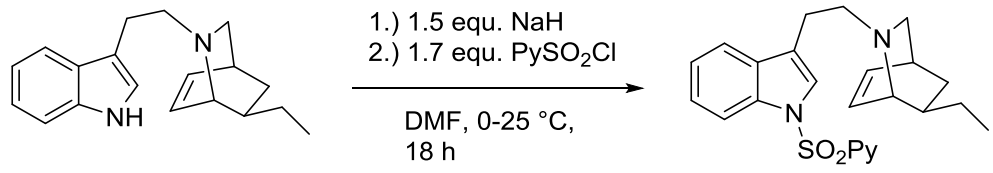
^{13}C-NMR (50 MHz, $CDCl_3$): δ 12.7 (q, C9), 24.5 (t, C8), 27.35 (t, C9´), 29.4 (t, C5), 31.8 (d, C6), 41.3 (d, C4), 56.0 (d, C3), 56.4 (t, C7), 59.1 (t, C10´), 111.1 (d, C7´), 115.2 (s, C3´), 119.0

(d, C5´), 119.2 (d, C4´), 121.6 (d, C6´), 121.9 (d, C2´), 127.8 (s, C8a´), 132.9 (d, C1 & C2), 136.3 (s, C8´),

GC-MS (EI, 70 eV): Method 1; Retention time: 11.96; Main fragments (relative intensity): 280 (M^+, 3), 151 (12), 150 (100), 130 (25),

HR-MS: $[M+H]^+$ m/z (predicted) = 281.2012 , m/z (measured) = 281.2011, difference = 0.4 ppm

2.7. (±)-rel-(1R,4S,7R)-7-Ethyl-2-(2-(1-(pyridin-2-ylsulfonyl)-1H-indol-3-yl)ethyl)-2-azabicyclo[2.2.2]oct-5-ene (8)



7

Chemical Formula: $C_{19}H_{24}N_2$
Molecular Weight: 280.41

8

Chemical Formula: $C_{24}H_{27}N_3O_2S$
Molecular Weight: 421.56

A 10 mL round bottom flask was charged with **7** (0.075 g; 0.37 mmol; 1 equ.) which was dissolved in dry DMF (2mL) under argon atmosphere. The solution was cooled to 0 °C and NaH (0.016 g 55-65 % suspension in mineral oil; 0.38 mmol; 1.5 equ.) was added all at once. The suspension was stirred at 0 °C for 45 min until a solution of 2-$PySO_2Cl$ (0.41 mL 1M in THF; 0.41 mmol; 1.7 equ.) was added slowly at this temperature. Then the cooling bath was removed and the reaction mixture was stirred at room temperature for 16 h until complete conversion (monitored by TLC). The mixture was quenched with satd. aqu. NH_4Cl solution (2 mL), the phases were separated and the aqueous phase was extracted with EtOAc (3×2 mL). The combined organic phases where dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified *via* column chromatography (MPLC, 5 g deactivated silica, 10 mL/min, PE with 10-50 EtOAc in 20 min).

Yield: 0.082 g (78 %)

Appearance: light yellow oil

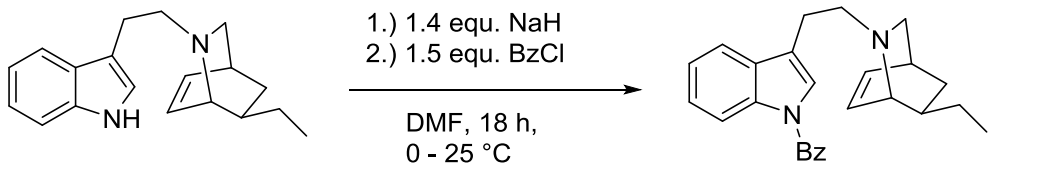
TLC: Rf(PE/EtOAc= 2/1) = 0.60; stationary phase: deactivated silica

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.85 (t, J = 7.39 Hz, 3H, H9), 0.78-0.96 (m, 1H, H4), 1.27-1.67 (m, 4H, H5 & H8), 1.93 (dt, J = 9.2 Hz, 2.6 Hz, 1H, H6), 2.36-2.59 (m, 2H, H9´), 2.65-2.91 (m, 3H, H3 & H10´), 3.07 (d, J = 9.06, 1H, H7), 3.00-3.26 (m, 1H, H7), 6.23-6.39 (m, 2H, H1 & H2), 7.15-7.33 (m, 2H, H5´ & H6´), 7.38-7.52 (m, 3H, H4´ & H7´ & H2´), 7.85 (t, J = 7.53 Hz, 1H, H4´´), 7.94-8.10 (m, 2H, H3´´ & H2´´), 8.59 (d, J = 4.49 Hz, 1H, H5´´)

^{13}C-NMR (50 MHz, $CDCl_3$): δ 12.6 (q, C9), 24.2 (t, C8), 27.3 (t, C9´), 29.8 (t, C5), 31.7 (d, C6), 41.2 (d, C4), 56.1 (t, C7), 56.2 (d, C3), 57.7 (t, C10´), 113.9 (d, C5´), 119.5 (d, C2´´), 121.6 (s, C3´), 122.3 (d, C4´), 123.1 (d, C7´), 123.8 (d, C6´), 124.5 (d, C4´´), 127.5 (d, C2), 131.5 (s, C8a´), 132.7 (d, C2), 133.0 (d, C1), 135.3 (s, C8´), 138.1 (d, C3´´), 150.5 (d, C5´´), 155.6 (s, C1´´)

HR-MS: $[M+H]^+$ m/z (predicted) = 422.1897 , m/z (measured) = 422.1887, difference = 2.4 ppm

2.8. (±)-rel-(3-(2-((1R,4S,7R)-7-Ethyl-2-azabicyclo[2.2.2]oct-5-en-2-yl)ethyl)-1H-indol-1-yl)(phenyl)methanone (9)



7

Chemical Formula: $C_{19}H_{24}N_2$
Molecular Weight: 280.41

9

Chemical Formula: $C_{26}H_{28}N_2O$
Molecular Weight: 384.52

A round bottom flask was charged with **7** (0.055 g; 0.20 mmol; 1 equ.) which was dissolved in dry DMF (2mL) under argon atmosphere. The solution was cooled to 0 °C and NaH (0.012 g 55-65 % suspension in mineral oil; 0.28 mmol; 1.4 equ.) was added all at once. The suspension was stirred at 0 °C for 45 min until a solution of BzCl (0.29 mL 1M in THF; 0.29 mmol; 1.5 equ.) was added slowly with a syringe. Then the cooling bath was removed and the reaction mixture was stirred at room temperature for 16 h until complete conversion (monitored by TLC). The mixture was quenched with satd. aqu. NH_4Cl solution (2 mL), the phases were separated and the aqueous phase was extracted with EtOAc (3×2 mL). The combined organic phases where dried over Na_2SO_4 and the solvent was removed *in vacuo*.

The crude product was purified *via* column chromatography (MPLC, 5 g deactivated silica, 10 mL/min, PE with 5-20 EtOAc in 20 min).

Yield: 0.058 g (75 %)

Appearance: light yellow oil

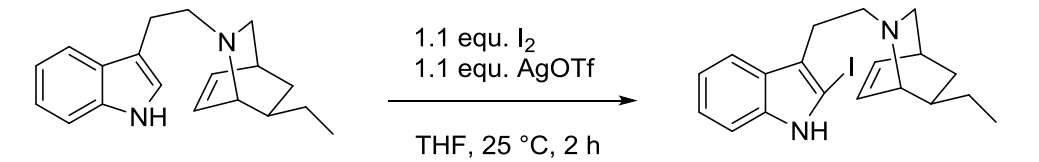
TLC: Rf(PE/EtOAc= 2/1) = 0.73; stationary phase: deactivated silica

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.78 (t, J = 7.08 Hz, 3H, H9), 0.80-0.92 (m, 1H, H4), 1.19-1.64 (m, 4H, H5 & H8), 1.91 (dt, J = 9.0 Hz, 2.6 Hz, 1H, H6), 2.35-2.56 (m, 2H, H9´), 2.55-2.86 (m, 3H, H3 & H10´), 3.02 (d, J = 8.91, 1H, H7), 3.12-3.21 (m, 1H, H7), 6.22-6.37 (m, 2H, H & H2), 7.17 (s, 1H, H2´), 7.27-7.42 (m, 2H, H5´ & H6´), 7.47-7.61 (m, 4H, H4´ & H7´ & H4´´ & H6´´), 7.85 (d, J = 7.10 Hz, 2H, H3´´ & H7´´), 8.34-8.42 (m, 1H, H5´´)

^{13}C-NMR (50 MHz, $CDCl_3$): δ 12.6 (q, C9), 24.0 (t, C8), 27.4 (t, C9´), 29.7 (t, C5), 31.6 (d, C6), 41.2 (d, C4), 56.2 (t, C7), 56.4 (d, C3), 57.9 (t, C10´), 116.7 (d, C5´´), 119.1 (d, C4´´), 121.2 (s, C3´), 123.8 (d, C5´), 124.7 (d, C6´), 125.1 (d, C2´), 128.7 (d, C5´), 129.2 (d, C7´), 131.5 (s, C8a´), 131.8 (d, C5´´), 132.7 (d, C2), 133.2 (d, C1), 135.2 (s, C2´´), 136.4 (s, C8´) 168.7 (s, C1´´)

HR-MS: $[M+H]^+$ m/z (predicted) = 385.2274 , m/z (measured) = 385.2291, difference = 4.4 ppm

2.9. (±)-rel-(1R,4S,7R)-7-Ethyl-2-(2-(2-iodo-1H-indol-3-yl)ethyl)-2-azabicyclo[2.2.2]oct-5-ene (10)



7

Chemical Formula: $C_{19}H_{24}N_2$
Molecular Weight: 280.41

10

Chemical Formula: $C_{19}H_{23}IN_2$
Molecular Weight: 406.31

A 8 mL reaction vial was charged with **7** (0.055 g; 0.20 mmol; 1 equ.) which was dissolved in dry THF under argon atmosphere. Then AgOTf (0.057 g; 0.22 mmol; 1.1 equ.) and I_2 (0.055 g; 0.22 mmol; 1.1 equ.) were added and the suspension was stirred at room temperature for 2 h.

Then satd. aqu. $NaHCO_3$ solution (2 mL) and satd. aqu. $Na_2S_2O_3$ solution were added to the reaction mixture and it was stirred for 5 min. The suspension was extracted with EtOAc (3 × 2 mL) and the combined organic phases where dried over Na_2SO_4. The solvent was removed *in vacuo* and the crude product was purified *via* column chromatography (MPLC, 5 g deactivated silica, 10 mL/min, PE with 15 EtOAc in 20 min).

Yield: 0.019 g (23 %)

Appearance: light yellow oil

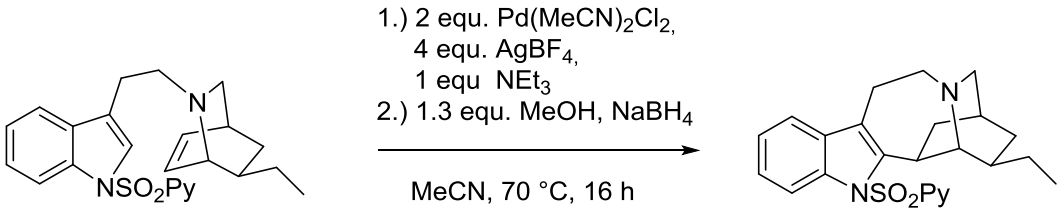
TLC: Rf(PE/EtOAc= 5/1) = 0.75; stationary phase: deactivated silica

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.87 (t, J = 7.40 Hz, 3H, H9), 0.88-1.00 (m, 1H, H4), 1.20-1.64 (m, 4H, H5 & H8), 2.00 (dt, J = 9.2 Hz, 2.4 Hz, 1H, H6), 2.27-2.51 (m, 2H, H9´), 2.60-2.90 (m, 3H, H3 & H10´), 3.10-3.33 (m, 1H, H7), 6.24-6.38 (m, 2H, H1 & H2), 7.01-7.16 (m, 2H, H5´ & H6´), 7.22-7.32 (m, 1H, H7´), 7.48-7.59 (m, 1H, H4´) 7.96 (broad s, 1H, NH)

^{13}C-NMR (50 MHz, $CDCl_3$): δ 12.6 (q, C9), 26.4 (t, C8), 27.2 (t, C9´), 29.8 (t, C5), 31.7 (d,C6), 41.1 (d, C4), 56.2 (t, C10´), 56.5 (d, C3), 58.7 (t, C7), 110.4 (d, C7´), 118.4 (s, C3´), 119.8 (d, C4´), 121.0 (d, C5´), 122.3 (d, C6´), 127.6 (s, C8a´), 132.9 (d, C1), 133.0 (d, C2), 139.0 (s, C2´)

HR-MS: $[M+H]^+$ m/z (predicted) = 407.0979 , m/z (measured) = 407.0987, difference = 2.0 ppm

2.10. (±)-rel-[6R-(6α,6aβ,7β,9α)]-7-Ethyl-5-(pyridin-2-ylsulfonyl)-6,6a,7,8,9,10,12,13-octahydro-5H-6,9-methanopyrido[1',2':1,2]azepino[4,5-b]indole (11)



8

Chemical Formula: $C_{24}H_{27}N_3O_2S$
Molecular Weight: 421.56

11

Chemical Formula: $C_{24}H_{27}N_3O_2S$
Molecular Weight: 421.56

The target compound was obtained according to a modified literature protocol.[29] A 10 mL round bottom flask was charged with $Pd(MeCN)_2Cl_2$ (0.101 g; 0.39 mmol; 2 equ.), $AgBF_4$ (0.152 g;

0.78 mmol; 4 equ.), degassed dry MeCN (1 mL) and dry NEt_3 (0.027 mL; 0.19 mmol; 1 equ.) under argon atmosphere. The resulting suspension was stirred at room temperature for 15 min. Then **8** (0.082 g; 1.19 mmol; 1 equ.) dissolved in degassed dry MeCN (1 mL) was added and it was stirred at room temperature for 1 h. After that it was heated to 70 °C and stirred at this temperature for 16 h. The reaction mixture was cooled to 0 °C, dry MeOH (2 mL) was added followed by the addition of $NaBH_4$ (0.009 g; 0.23 mmol; 1.2 equ.) and it was stirred for 1 h more at 0 °C. The suspension was quenched by the addition of H_2O (2 mL), the phases were separated and the aqueous phase was extracted with EtOAc (3×2 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified *via* column chromatography (MPLC, 9 g deactivated silica, 15 mL/min, PE with 20-50 EtOAc in 20 min).

Yield: 0.047 g (57 %)

Appearance: light orange oil

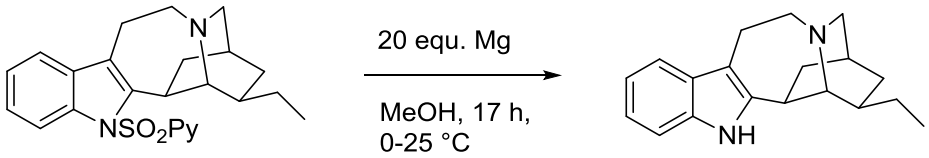
TLC: Rf(PE/EtOAc= 2/1) = 0.35; stationary phase: deactivated silica

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.79 (t, J = 7.4 Hz, 3H, HC9), 1.00-1.66 (m, 5 H, H5 & H8 & H6), 1.67-1.85 (m, 2H, H3), 2.02-2.12 (m, 1H, H4), 2.48 (dt, J = 15.8, 2.7 Hz, 1H, H7), 2.57-2.65 (m, 1H, H7), 2.83-3.32 (m, 5H, H10´ & H9´ & H1), 3.89 (dd, J = 11.8 Hz, 5.8 Hz, 1H, H2), 7.08-7.19 (m, 2H, H5´ & H6´), 7.22-7.38 (m, 2H, H4´ & H7´), 7.74 (td, J = 7.8 Hz, 1.1 Hz, 1H, H4´´), 7.88 (d, J = 7.8 Hz, 1H, H5´´), 7.98-8.09 (m, 1H, H3´´), 8.47 (d, J = 4.6 Hz, 1H, H2´´)

^{13}C-NMR (50 MHz, $CDCl_3$): δ 12.2 (q, C9), 20.8 (t, C9´), 26.8 (d, C4), 28.3 (t, C8), 31.7 (t,C5), 34.4 (t, C3), 39.0 (d, C2), 42.8 (d, C2), 51.2 (t, C 7), 53.8 (t, C10´), 57.1 (d, C1), 115.2 (d, C7´), 118.0 (d, C4´), 119.0 (s, C3´), 121.9 (d, C5´), 123.3 (d, C2´´), 127.4 (d, C4´´), 131.2 (s, C2´), 136.0 (s, C8a´), 138.1 (d, C3´´), 144.8 (s, C8), 150.2 (d, C5´´), 156.5 (s, C1´´)

HR-MS: $[M+H]^+$ m/z (predicted) = 422.1897 , m/z (measured) = 422.1889, difference = 1.9 ppm

2.11. (±)-rel-[6R-(6α,6aβ,7β,9α)]-7-ethyl-6,6a,7,8,9,10,12,13-Octahydro-5H-6,9-methanopyrido[1',2':1,2]azepino[4,5-b]indole = ibogamine (1)



11

Chemical Formula: $C_{24}H_{27}N_3O_2S$
Molecular Weight: 421.56

1

Chemical Formula: $C_{19}H_{24}N_2$
Molecular Weight: 280.41

A 8 mL reaction vial was charged with **11** (0.047 g; 0.11 mmol; 1 equ.) which was dissolved in dry MeOH (5 mL) under argon atmosphere. The solution was cooled to 0 °C and powdered Magnesium (0.053 g; 2.2 mmol; 20 equ.) was added all at once. The suspension was stirred at this temperature for 1 h, then warmed to room temperature and was stirred for 16 h until complete conversion (monitored by TLC). The reaction mixture was filtered through a pad of Celite, was washed with satd. aqu. $NaHCO_3$ solution (5 mL) and it was extracted with EtOAc (3×5 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified *via* column chromatography (flash chromatography, 5 g deactivated silica, PE/EtOAc = 10/1).Analytical data matched with reported data from literature.[33]

Yield: 0.022 g (71 %)

Appearance: colorless oil

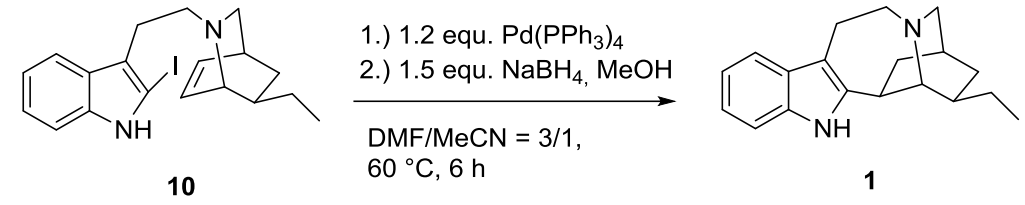
TLC: Rf(PE/EtOAc= 5/1) = 0.47; stationary phase: deactivated silica

^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.92 (t, J=7.3 Hz, 3H, C9), 1.22-1.30 (m, 1H, H5), 1.45-1.62 (m, 3H, H8 & H6), 1.66 (ddd, J=12.7 Hz, 3.1 Hz, 3.1 Hz, 1H, H3), 1.80-1.85 (m, 1H, H5), 1.85-1.90 (m, 1H, H4), 2.06 (t, J=12.7 Hz, 1H, H3), 2.71 (d, J=15.3 Hz, 1H, H9´), 2.90 (s, 1H, H1), 2.96 (d, J=11.3 Hz, 1H, H2), 2.99-3-11 (m, 2H, H7), 3.18 (dd, J=14.0, Hz, 15.3 Hz, H10´), 3.31-3.39 (m 1H, H9´), 3.42 (d, J=14.7 Hz, H10´), 7.06-7.16 (m, 2H, H5´& H6´), 7.27 (d, J=6.3 Hz, 1H, H7´), 7.49 (d, J=7.9 Hz, 1H, H4´), 7.69 (broad s, 1H, NH)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 12.1 (q, C9), 20.6 (t, C9´), 26.5 (d, C4), 28.0 (t, C8), 32.2 (t, C5), 34.3 (t, C3), 41.5 (d, C2), 42.1 (d, C6), 50.1 (t, C7), 54.4 (t, C10´), 57.9 (d, C1), 109.3 (s, C3´), 110.3 (d, C7´), 118.1 (d, C4´), 119.3 (C5´), 121.1 (d, C6´), 129.8 (s, C8a´), 134.8 (s, C8´), 141.9 (s, C2´)

HR-MS: $[M+H]^+$ m/z (predicted) = 281.2012 , m/z (measured) = 281.2010, difference = 0.7 ppm

2.12. (±)-rel-[6R-(6α,6aβ,7β,9α)]-7-Ethyl-6,6a,7,8,9,10,12,13-octahydro-5H-6,9-methanopyrido[1',2':1,2]azepino[4,5-b]indole = ibogamine (1)



10

Chemical Formula: $C_{19}H_{23}IN_2$
Molecular Weight: 406.31

1

Chemical Formula: $C_{19}H_{24}N_2$
Molecular Weight: 280.41

In a 8 mL reaction vial **10** (0.017 g; 0.04 mmol; 1 equ.) was dissolved in dry DMF (0.15 mL) and dry MeCN (0.05 mL) under argon atmosphere. The solvent was degassed, then $Pd(PPh_3)_4$ (0.054 g; 0.048 mmol; 1.2 equ.) was added and the resulting suspension was stirred at 60 °C for 6 h. The mixture was cooled to 0 °C then dry MeOH (0.2 mL) and $NaBH_4$ (2 mg; 0.06 mmol; 1.5 equ.) were added and it was stirred for 2 h more at 0 °C. After that, it was quenched with H_2O (0.2 mL), extracted with EtOAc (3×0.2 mL) and the combined organic phases where dried over Na_2SO_4. The solvent was removed *in vacuo* and the crude product was purified *via* column chromatography (MPLC, 4 g deactivated silica, 10 mL/min, PE with 5-30 % EtOAc in 20 min). Analytical data matched with reported data from literature.[33]

Yield: 0.004 g (31 %)

Appearance: colorless oil

TLC: Rf(PE/EtOAc= 5/1) = 0.47; stationary phase: deactivated silica

^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.92 (t, J=7.3 Hz, 3H, C9), 1.22-1.30 (m, 1H, H5), 1.45-1.62 (m, 3H, H8 & H6), 1.66 (ddd, J=12.7 Hz, 3.1 Hz, 3.1 Hz, 1H, H3), 1.80-1.85 (m, 1H, H5), 1.85-1.90 (m, 1H, H4), 2.06 (t, J=12.7 Hz, 1H, H3), 2.71 (d, J=15.3 Hz, 1H, H9´), 2.90 (s, 1H, H1), 2.96 (d, J=11.3 Hz, 1H, H2), 2.99-3-11 (m, 2H, H7), 3.18 (dd, J=14.0, Hz, 15.3 Hz, H10´), 3.31-3.39

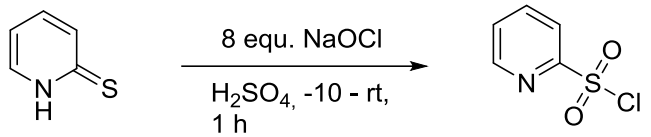
(m 1H, H9´), 3.42 (d, J=14.7 Hz, H10´), 7.06-7.16 (m, 2H, H5´& H6´), 7.27 (d, J=6.3 Hz, 1H, H7´), 7.49 (d, J=7.9 Hz, 1H, H4´), 7.69 (broad s, 1H, NH)

^{13}C-NMR (50 MHz, $CDCl_3$): δ 12.1 (q, C9), 20.6 (t, c9´), 26.5 (d, C4), 28.0 (t, C8), 32.2 (t, C5), 34.3 (t, C3), 41.5 (d, C2), 42.1 (d, C6), 50.1 (t, C7), 54.4 (t, C10´), 57.9 (d, C1), 109.3 (s, C3´), 110.3 (d, C7´), 118.1 (d, C4´), 119.3 (C5´), 121.1 (d, C6´), 129.8 (s, C8a´), 134.8 (s, C8´), 141.9 (s, C2´)

HR-MS: $[M+H]^+$ m/z (predicted) = 281.2012 , m/z (measured) = 281.2010, difference = 0.7 ppm

3. Synthesis precursor for C2-alkenylation of indoles

3.1. Pyridine-2-sulfonyl chloride (14)



2-Mercaptopyridine

Chemical Formula: C_5H_5NS
Molecular Weight: 111.16

14

Chemical Formula: $C_5H_4ClNO_2S$
Molecular Weight: 177.60

The target compound was obtained according to a modified literature protocol.[67] A three necked round bottom flask was charged with 2-mercaptopyridine (1 g; 9 mmol; 1 equ. equ.) and conc. H_2SO_4 (32 mL) was added. The solution was cooled to -10 °C and under stirring (mechanical stirrer) a solution of NaOCl (45 mL of a 10 w% NaOCl solution in H_2O; 72 mmol; 8 equ.) was added *via* a dropping funnel. During the addition the solution temperature was kept below 5 °C. After complete addition the cooling bath was removed and it was stirred 1 h more at room temperature until no starting material was left (monitored by TLC). The solution was extracted with Et_2O (3×50 mL), the combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. NMR analysis showed no significant impurities so the crude product was used in following reactions without further purification

Yield: 1.198 g (75 %)

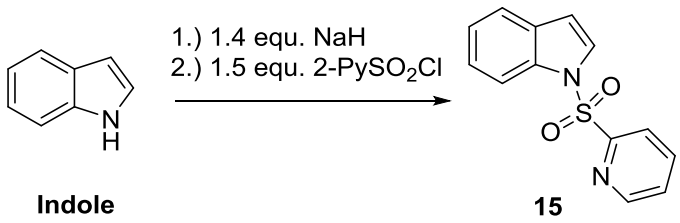
Appearance: colorless liquid

TLC: Rf(PE/EtOAc= 5/1) = 0.76

^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.70 (ddd, J=7.2 Hz, 4.6 Hz, 1.8 Hz, 1H, H2), 8.08 (ddd, J=7.2 Hz, 4.8 Hz, 1.9 Hz, 1H, H3), 8.10 (d, J=1.9 Hz, 1H, H4), 8.84 (d, J=4.8 Hz, 1H, H1)

^{13}C-NMR (50 MHz, $CDCl_3$): δ 121.9 (d, C2), 129.1 (d, C4), 139.0 (d, C3), 150.7 (d, C5), C1 not visible

3.2. 1-(Pyridin-2-ylsulfonyl)-1H-indole (15)



Indole **15**

Chemical Formula: C_8H_7N
Molecular Weight: 117,15

Chemical Formula: $C_{13}H_{10}N_2O_2S$
Molecular Weight: 258,30

The target compound was obtained according to a modified literature protocol.[48] Indole (0.82 g; 7 mmol; 1 equ.) was dissolved in a 100 mL three necked round bottom flask in dry THF (30 mL) under Argon atmosphere. The solution was cooled to 0 °C and NaH (0.235 g; 10.5 mmol; 1.5 equ.) was added all at once. The resulting suspension was stirred at 0 °C for 30 min and then a solution of 2-$PySO_2Cl$ (10.5 mL of a 1M solution in dry THF; 10.5 mmol; 1.5 equ.) was added dropwise *via* syringe. The reaction mixture was allowed to warm to room temperature and was stirred for 16 h until complete conversion (monitored by TLC). Then satd. aqu. NH_4Cl solution (30 mL) was added and it was extracted with EtOAc (3×30 mL). The combined organic phases were dried over Na_2SO_4 the solvent was removed *in vacuo* and the crude product was purified *via* column chromatography (MPLC, 30 g deactivated silica, 20 mL/min, PE/EtOAc = 85/15).

Yield: 1.688 g (93 %)

Appearance: slightly pink solid

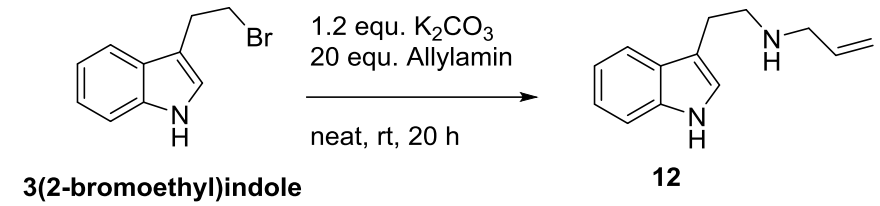
Melting point: 63.5 – 65.5 °C (Literature: 60-62 °C)

TLC: Rf(PE/EtOAc = 5/1) = 0.20

^{1}H-NMR (200 MHz, $CDCl_3$): δ 6.68 (d, J=3.8 Hz, 1H, H3), 7.26 (m, 2H, H5 & H6), 7.42 (ddd, J=7.8 Hz, 4.7 Hz, 1.2 Hz, 1H, H4´), 7.54 (dd, J=6.2 Hz, 1.7 Hz, 1H, H2´), 7.67 (d, J=3.8 Hz, H2), 7.86 (dt, J=7.8 Hz, 1.7 Hz, 1H, H3´), 8.00 (d, J=8.2 Hz, 1H, H7), 8.11 (d, J=7.9 Hz, 1H, H4), 8.58 (d, J=4.7 Hz, 1H, H5´)

^{13}C-NMR (50 MHz, $CDCl_3$): δ 109.0 (d, C3), 113.8 (d, C2), 121.5 (d, C7), 122.4 (d, C5), 123.6 (d, C2´), 124.6 (d, C4)127.5 (d, C6), 127.7 (d, C4´), 130.9 (s, C8a´), 135.1 (s, C8´), 138.2 (d, C3´), 150.6 (d, C5´),155.5 (s, C1´)

3.3. N-(2-(1H-Indol-3-yl)ethyl)prop-2-en-1-amine (12)



3(2-bromoethyl)indole

Chemical Formula: $C_{10}H_{10}BrN$
Molecular Weight: 224.10

12

Chemical Formula: $C_{13}H_{16}N_2$
Molecular Weight: 200.29

The target compound was obtained according to a modified literature protocol.[68] In a 10 mL round bottom flask K_2CO_3 (0.222g; 1.62 mmol; 1.2 equ.) was suspended in allylamine (2.01 mL; 26.77 mmol; 20 equ.) under argon atmosphere and 3-(2-bromoethyl)indole (0.300 g; 1.34 mmol; 1 equ.) was added in portions over 20 min. After complete addition, the suspension was stirred at room temperature for 20 h until complete conversion (monitored by TLC). Then H_2O (10 mL) was added and the aqueous phase was extracted with DCM (2x10 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified *via* column chromatography (MPLC, 9 g deactivated silica, 20 mL/min, DCM with 0-5 % MeOH in 40 min).

Yield: 0.226 g (84 %)

Appearance: light yellow oil

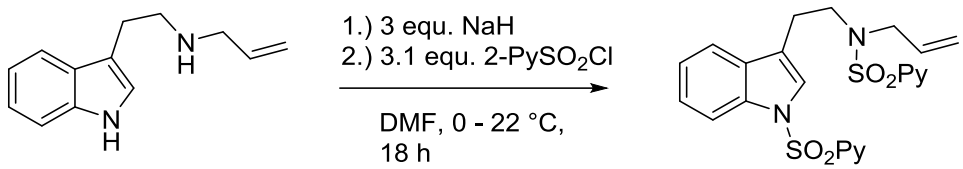
TLC: Rf(DCM/MeOH= 9/1) = 0.29; stationary phase: deactivated silica

^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.85 (broad s, 1H, N11), 3.94-3.06 (m, 4H, H9 & H10), 3.30 (d, J=6.01 Hz, 2H, H12), 5.08 (dd, J=9.94 Hz, 1.64 Hz, 1H, H14 (syn H)), 5.16 (dd, J=17.07 Hz, 1.57 Hz, 1H, H14 (anti H)), 5.79-6.02 (m, 1H, H13), 7.03 (s, 1H, C2), 7.08-7.26 (m, 2H, H5 & H6) 7.36 (d, J=7.86 Hz, 1H, H7) 7.65 (d, J=7.58 Hz, 1H, H4), 8.37 (broad s, 1H, NH).

^{13}C-NMR (50 MHz, $CDCl_3$): δ 25.8 (t, C9), 49.4 (t, C10), 52.4 (t, C12), 111.3 (d, C7), 113.8 (s, C3), 116.2 (t, C14), 119.0 (d, C4), 119.3 (d, C5), 122.1 (d, C2 & C6), 127.5 (s, C8a), 136.6 (s & d, C8 & C13).

HR-MS: $[M+H]^+$ m/z (predicted) = 201.1386 , m/z (measured) = 201.1387, difference = 0.5 ppm

3.4. N-Allyl-N-(2-(1-(pyridin-2-ylsulfonyl)-1H-indol-3-yl)ethyl)pyridine-2-sulfonamide (13)



12

Chemical Formula: $C_{13}H_{16}N_2$
Molecular Weight: 200.29

13

Chemical Formula: $C_{23}H_{22}N_4O_4S_2$
Molecular Weight: 482.57

In a 8 mL reaction vial **12** (0.040 g; 0.2 mmol; 1 equ.) was dissolved in dry DMF (2 mL) under argon atmosphere and this solution was cooled to 0 °C. NaH (0.026 g 55-65% suspension in mineral oil; ~0.6 mmol; 3 equ.) was added and the resulting suspension was stirred at 0 °C for 40 min. Then a solution of 2-PySO_2Cl (0.8 mL of a 1 M solution in dry THF; 0.8 mmol; 4 equ.) was added dropwise at 0 °C, the cooling bath was removed and the reaction mixture was stirred at room temperature for 18 h until complete conversion (monitored by TLC). Satd. aqu. NH_4Cl solution (2 mL) was added and the aqueous phase was extracted with EtOAc (3×2 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified *via* column chromatography (MPLC, 5 g deactivated silica, 10 mL/min PE/EtOAc= 1/1).

Yield: 0.048 g (50 %)

Appearance: light yellow solid

Melting point: 80-82 °C

TLC: Rf(PE/EtOAc = 1/1) = 0.48; stationary phase: deactivated silica

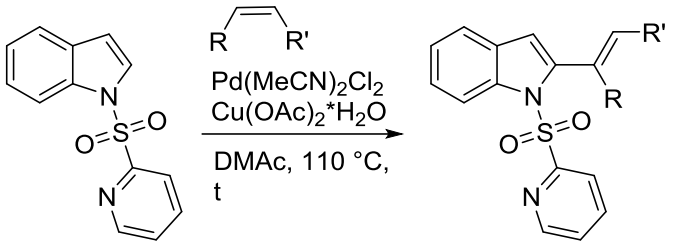
^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.92-3.05 (m, 2H, H10), 3.53-3.67 (m, 2H, H9), 3.99 (d, J=6.4 Hz, H11), 5.11 (s, 1H, H13), 5.17 (d, J=8.5 Hz, H13), 5.61-5.85 (m, 1H, H12), 7.18-7.34 (m, 2H, H5 & H6), 7.42 (s, 1H, H2), 7.38-7.58 (m, 3H, H7 & H2´´ & H2´), 7.80-8.08 (m, 4H, H3´ & H3´´ & H4´& H4´´), 8.10 (d, J=7.27 Hz, 1H, H4), 8.57 (d, J=4.4 Hz, 1H, H1´), 8.67 (d, J=4.7 Hz, 1H, H1´´)

^{13}C-NMR (50 MHz, $CDCl_3$): δ 25.2 (t, C9), 47.5 (t, C10), 52.0 (t, C11), 113.9 (d, C2), 119.0 (d, C5), 119.5 (d, C4), 122.3 (d, C2´), 122.4 (d, C2´´), 123.4 (d, C6), 124.3 (d, C4´´) 124.8 (d, C4´´), 126.6 (t, C13), 127.7 (d, C7), 130.7 (s, C8a), 133.5 (d, C12), 135.3 (s, C8), 138.0 (d, C3´), 138.3 (d, C3´´), 150.1 (d, C5´), 150.5 (d, C5´´), 155.3 (s, C1´), 158.2 (s, C1´´)

HR-MS: $[M+H]^+$ m/z (predicted) = 483.1155 , m/z (measured) = 483.1174, difference = 3.9 ppm

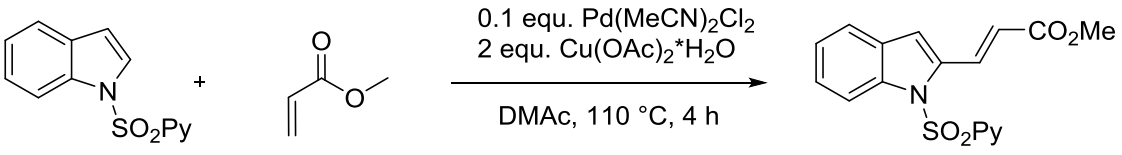
4. C2-Alkenylation of indole derivatives

4.1. General procedure A



The target compounds **16-22** were obtained according to a modified literature protocol.[48]
A 8 mL reaction vial was charged with **15** (1 equ.), $Pd(MeCN)_2Cl_2$ (0.1 equ.) and $Cu(OAc)_2 \times H_2O$ (2 equ.) under argon atmosphere, the degassed dry DMAc and the alkene (2-5 equ. specified in each case) were added. The mixture was heated to 110 °C and was stirred at this temperature for the indicated period of time. Then it was cooled to room temperature, H_2O was added and the mixture was extracted three times with EtOAc. The combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified *via* MPLC (parameters specified in each case)

4.2. Methyl (E)-3-(1-(pyridin-2-ylsulfonyl)-1H-indol-2-yl)acrylate (16)



15 Chemical Formula: $C_{13}H_{10}N_2O_2S$
Molecular Weight: 258.30

Chemical Formula: $C_4H_6O_2$
Molecular Weight: 86.09

16 Chemical Formula: $C_{17}H_{14}N_2O_4S$
Molecular Weight: 342.37

Product **16** was synthesized according to general procedure A using following amounts: **15** (0.15 g; 0.58 mmol; 1 equ.), $Cu(OAc)_2 \times H_2O$ (0.232 g; 1.16 mmol; 2 equ.) $Pd(MeCN)_2Cl_2$ (0.016 g; 0.06 mmol; 0.1 equ.), freshly distilled methacrylate (0.105 mL; 1.16 mmol; 2 equ.) and dry

degassed DMAc (4 mL). It was stirred at 110 °C for 4 h. The crude product was purified *via* column chromatography (MPLC, 9 g, 20 mL/min, PE with 5-20 EtOAc in 20 min then 20 % EtOAc (5 min)). Analytical data matched with reported data from literature.[45]

Yield: 0.107 g (53 %)

Appearance: light yellow solid

Melting point: 196 – 198 °C (Literature: 197-199 °C)

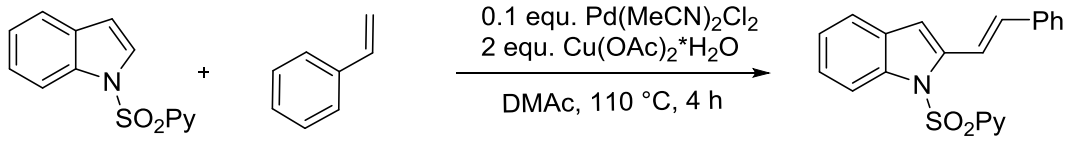
TLC: Rf(PE/EtOAc= 2/1) = 0.26

^{1}H-NMR (200 MHz, $CDCl_3$): δ 3.83 (s, 3H, H4´´), 6.41 (d, J=16.4 Hz, 1H, H1´´), 7.02 (s, 1H, H3), 7.18-7.56 (m, 4H, H4 & H5 & H6 & H4´), 7.80-7.92 (m, 1H, H7), 8.07 (d, J=8.0 Hz, H2´), 8.14 (d, J=8.0 Hz, H2´´), 8.54 (d, J=4.7 Hz, 1H, H5´)

^{13}C-NMR (50 MHz, $CDCl_3$): δ 52.0 (q, C4´´), 111.6 (d, C3), 115.2 (d, C7), 120.6 (d, C2´´), 121.5 (d, C5), 122.2 (d, C2´), 124.4 (d, C4), 126.1 (d, C6), 127.8 (d, C4´), 129.2 (s, C2), 134.6 (d, C1´´), 137.3 (s, C8a´), 138.1 (s, C8´), 138.2 (d, C3´), 150.6 (d, C5´), 155.7 (s, C1´), 166.8 (s, C3´´)

HR-MS: $[M+H]^+$ m/z (predicted) = 343.0747 , m/z (measured) = 343.0760, difference = 3.8 ppm

4.3. (*E*)-1-(Pyridin-2-ylsulfonyl)-2-styryl-1H-indole (17)



15 Chemical Formula: $C_{13}H_{10}N_2O_2S$
Molecular Weight: 258.30

Chemical Formula: C_8H_8
Molecular Weight: 104.15

17 Chemical Formula: $C_{21}H_{16}N_2O_2S$
Molecular Weight: 360.43

Product **17** was synthesized according to general procedure A using following amounts: **15** (0.1 g; 0.39 mmol; 1 equ.), $Cu(OAc)_2 \times H_2O$ (0.155 g; 0.77 mmol; 2 equ.) $Pd(MeCN)_2Cl_2$ (0.01 g; 0.04 mmol; 0.1 equ.), styrene (0.229 mL; 2 mmol; 5 equ.) and dry degassed DMAc (4 mL). It was stirred at 110 °C for 4 h. The crude product was purified *via* column chromatography

(MPLC, 9 g, 20 mL/min, PE with 5-20 EtOAc in 20 min then 20 % EtOAc (10 min)). Analytical data matched with reported data from literature.[45]

Yield: 0.101 g (72 %)

Appearance: light yellow oil

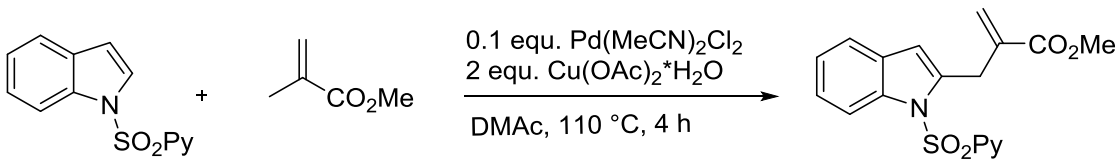
TLC: Rf(PE/EtOAc= 2/1) = 0.55

^{1}H-NMR (200 MHz, $CDCl_3$): δ 6.91 (s, 1H, H3), 7.07 (d, J=15.9 Hz, 1H, H2´´), 7.22-7.61 (m, 9H, H4 & H5 & H6 & H4´ & H4´´ & H5´´ H6´´& H7´´ & H8´´), 7.74-7.84 (m, 1H, H7), 7.91 (d, J=15.9 Hz, 1H, H1´´), 8.00 (d, J=8.2 Hz, 1H, H2´), 8.21 (d, J=8.2 Hz, 1H, H3´), 8.53 (d, J=4.6 Hz, H5´)

^{13}C-NMR (50 MHz, $CDCl_3$): δ 107.9 (d, C3), 115.1 (d, C7), 118.7 (d, C5), 120.7 (d, C2´), 122.1 (d, C1´´), 124.1 (d, C4), 124.7 (d, C6), 127.0 (d, C8´´ & C4´´), 127.6 (d, C6´´), 128.3 (d, C4´) 128.8 (d, C7´´ & C5´´), 129.9 (s, C2), 132.3 (d, C2´´), 136.9 (s, C8a), 137.6 (s, C8), 138.1 (d, C3´), 140.3 (s, C3´´), 150.3 (d, C5´), 155.9 (s, C1´)

HR-MS: $[M+H]^+$ m/z (predicted) = 361.1005 , m/z (measured) = 361.1013, difference = 2.2 ppm

4.4. Methyl 2-((1-(pyridin-2-ylsulfonyl)-1H-indol-2-yl)methyl)acrylate (18)



15

Chemical Formula: $C_5H_8O_2$
Molecular Weight: 100.12

18

Chemical Formula: $C_{13}H_{10}N_2O_2S$
Molecular Weight: 258.30

Chemical Formula: $C_{18}H_{16}N_2O_4S$
Molecular Weight: 356.40

Product **18** was synthesized according to general procedure A using following amounts: **15** (0.1 g; 0.39 mmol; 1 equ.), $Cu(OAc)_2 \times H_2O$ (0.155 g; 0.77 mmol; 2 equ.), $Pd(MeCN)_2Cl_2$ (0.01 g; 0.04 mmol; 0.1 equ.), methyl metacrylate (0.213 mL; 2 mmol; 5 equ.) and dry degassed DMAc (4 mL). It was stirred at 110 °C for 4 h. The crude product was purified *via* column

chromatography (MPLC, 9 g, 20 mL/min, PE with 5-20 EtOAc in 20 min then 20 % EtOAc (10 min)). Analytical data matched with reported data from literature.[45]

Yield: 0.101 g (72 %)

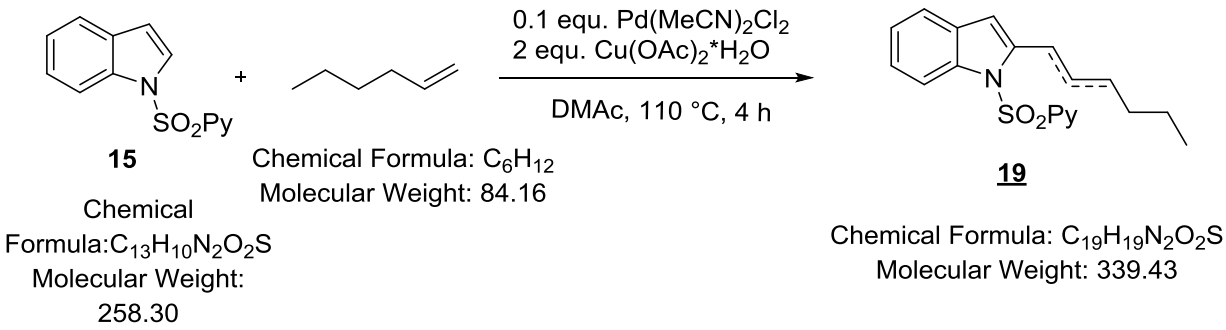
Appearance: light yellow oil

TLC: Rf(PE/EtOAc= 2/1) = 0.26

^{1}H-NMR (200 MHz, $CDCl_3$): δ 3.75 (s, 3H, H5´´), 4.25 (s, 2H, H1´´), 5.64 (s, 1H, H3), 6.36 (d, J=8.4 Hz, 2H, H4´´), 7.21 (m, 2H, H5 & H6), 7.38-7.45 (m, 2H, H4 & H7), 7.83 (m, 1H, H4´), 7.95-8.14 (m, 2H, H2´ & H3´), 8.56 (d, J=4.0 Hz, H5´)

^{13}C-NMR (50 MHz, $CDCl_3$): δ 31.6 (t, C1´´), 52.2 (q, C5´´), 110.3 (d, C3), 114.8 (d, C7), 120.4 (d, C5), 122.1 (d, C2´), 123.7 (d, C4), 124.2 (t, C4´´), 127.6 (s, C8a), 127.7 (d, C6), 129.7 (d, C4´), 137.2 (s, C2), 137.8 (s, C8), 138.1 (d, C3´), 140.1 (s, C2´´), 150.5 (d, C5´), 155.9 (d, C1´), 167.3 (s, C3´´)

4.5. 2-(Hexen-1-yl)-1-(pyridin-2-ylsulfonyl)-1H-indole (<u>19</u>)



Product **19** was synthesized according to general procedure A using following amounts: **15** (0.1 g; 0.39 mmol; 1 equ.), $Cu(OAc)_2 \times H_2O$ (0.155 g; 0.77 mmol; 2 equ.) $Pd(MeCN)_2Cl_2$ (0.01 g; 0.04 mmol; 0.1 equ.), 1-hexene (0.251 mL; 2 mmol; 5 equ.) and dry degassed DMAc (4 mL). It was stirred at 110 °C for 4 h. The crude product was purified *via* column chromatography (MPLC, 9 g, 20 mL/min, PE with 5-20 EtOAc in 20 min then 20 % EtOAc (10 min)).

Yield: 0.094 g isomeric mixture (71 %). The product is an inseparable mixture of at least 5 different double bond isomers.

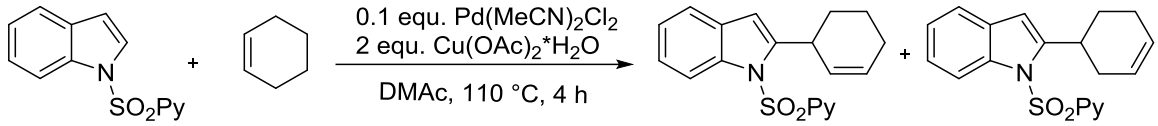
Appearance: light yellow oil

TLC: Rf(PE/EtOAc= 2/1) = 0.51

NMR-shifts were measured but not allocated due to the complexity of the isomeric mixture

HR-MS: $[M+H]^+$ m/z (predicted) = 341.1318 , m/z (measured) = 341.1322, difference = 1.2 ppm

4.6. (rac)-2-(Cyclohexen-1-yl)-1-(pyridin-2-ylsulfonyl)-1H-indole (20)



15 Chemical Formula: C_6H_{10}
Molecular Weight: 82.15

Chemical Formula:$C_{13}H_{10}N_2O_2S$
Molecular Weight: 258.30

20a **20b**

Chemical Formula: $C_{19}H_{18}N_2O_2S$
Molecular Weight: 338.42

Products **20a/b** were synthesized according to general procedure A using following amounts: **15** (0.1 g; 0.39 mmol; 1 equ.), $Cu(OAc)_2 \times H_2O$ (0.155 g; 0.77 mmol; 2 equ.) $Pd(MeCN)_2Cl_2$ (0.01 g; 0.04 mmol; 0.1 equ.), cyclohexene (0.203 mL; 2 mmol; 5 equ.) and dry degassed DMAc (4 mL). It was stirred at 110 °C for 4 h. The crude product was purified *via* column chromatography (MPLC, 9 g, 20 mL/min, PE with 5-20 EtOAc in 20 min then 20 % EtOAc (10 min)).The product is an inseparable mixture of 2 double bond isomers. The distribution of the isomers is 0.40/0.52 = **20a**/**20b**

Yield: 0.021 g isomeric mixture (16 %)

Appearance: light yellow oil

TLC: Rf(PE/EtOAc= 2/1) = 0.51

^{1}H-NMR (200 MHz, $CDCl_3$)(20a): δ 1.57-1.95 (m, 2H, H5´), 2.00-2.30 (m, 4H, H6´& H4´), 4.38-4.57 (m, 1H, H1´), 5.68-5.98 (m, 2H, H2´& H3´), 6.45 (s, 1H, H3), 7.11-7.24 (m, 2H, H5 & H6), 7.33-7.44 (m, 2H, H4 & H7), 7.74-7.85 (m, 1H, H4´´), 7.91-7.99 (m, 1H, H2´´), 8.03-8.12 (m, 1H, H3´´), 8.48-8.55 (m, 1H, H5´´)

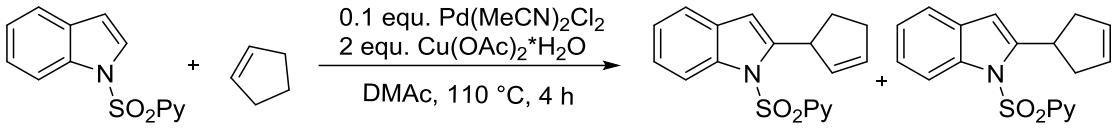
^{1}H-NMR (200 MHz, $CDCl_3$)(3-cyclohexene isomer): δ 1.57-1.95 (m, 2H, H6´), 2.00-2.30 (m, 3H, H6´& H4´),2.58 (d, J=17.0 Hz, 1H, H2) 3.76-393 (m, 1H, H1´), 5.68-5.98 (m, 2H, H2´&

H3´), 6.46 (s, 1H, H3), 7.11-7.24 (m, 2H, H5 & H6), 7.33-7.44 (m, 2H, H4 & H7), 7.74-7.85 (m, 1H, H4´´), 7.91-7.99 (m, 1H, H2´´), 8.03-8.12 (m, 1H, H3´´), 8.48-8.55 (m, 1H, H5´´)

^{13}C-shifts are not allocated due to the isomeric mixture

HR-MS: $[M+H]^+$ m/z (predicted) = 339.1162 , m/z (measured) = 339.1159, difference = 0.9 ppm

4.7. (rac)-2-(Cyclopent-2-en-1-yl)-1-(pyridin-2-ylsulfonyl)-1H-indole (21)



15 Chemical Formula: C_5H_8
Molecular Weight: 68.12

Chemical Formula:$C_{13}H_{10}N_2O_2S$
Molecular Weight: 258.30

21a **21b**

Chemical Formula: $C_{18}H_{16}N_2O_2S$
Molecular Weight: 324.40

Products **21a/b** were synthesized according to general procedure A using following amounts: **15** (0.15 g; 0.58 mmol; 1 equ.), $Cu(OAc)_2 \times H_2O$ (0.232 g; 1.16 mmol; 2 equ.) $Pd(MeCN)_2Cl_2$ (0.016 g; 0.06 mmol; 0.1 equ.), cyclopentene (0.256 mL; 2.9 mmol; 2 equ.) and dry degassed DMAc (4 mL). It was stirred at 110 °C for 4 h. The crude product was purified *via* column chromatography (MPLC, 9 g, 20 mL/min, PE with 5-20 EtOAc in 20 min then 20 % EtOAc (5 min)). The product is an inseparable mixture of 2 double bond isomers. The distribution of the isomers is 0.10/0.90 = **21b/21a**

Yield: 0.099 g (53 %)

Appearance: light yellow oil

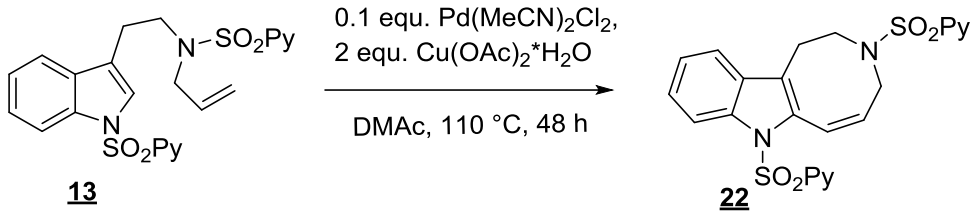
TLC: Rf(PE/EtOAc= 2/1) = 0.51

^{1}H-NMR (200 MHz, $CDCl_3$) (Main isomere): δ 1.83-2.07 (m, 1H, H5´´), 2.27-2.69 (m, 3H, H4´´ & H5´´), 4.69-6.86 (m, 1H, H1´´), 5.79-5.92 (m, 1H, H2´´), 5.92-6.04 (m, 1H, H3´´), 6.37 (s, 1H, H3), 7.08-7.27 (m, 2H, H5 & H6), 7.29-7.46 (m, 2H, H4 & H7), 7.80 (dt, J=7.7 Hz, 1.7 Hz, 1H, H3´), 7.93-8.03 (m, 1H, H2´), 8.03-8.15 (m, 1H, H4´), 8.53 (d, J=4.5 Hz, 1H, H5´)

^{13}C-NMR (50 MHz, $CDCl_3$) (Main isomere): δ 31.8 (t, C5´´), 32.5 (t, C4´´), 44.2 (d, C1´), 107.3 (d, C7), 114.7 (d, C7), 120.2 (s, C2), 121.9 (d, C4), 123.7 (d, C4´), 127.4 (d, C3´´), 132.1 (d, C2´), 132.8 (d, C2´´), 138.0 (d, C3´), 147.6 (s, C1´), 150.3 (d, C5´), C8 and C8a not visible.

HR-MS: $[M+H]^+$ m/z (predicted) = 325.1005 , m/z (measured) = 325.1004, difference = 0.3 ppm

4.8. (Z)-3,7-bis(Pyridin-2-ylsulfonyl)-2,3,4,7-tetrahydro-1H-azocino[5,4-b]indole (22)



Chemical Formula: $C_{23}H_{22}N_4O_4S_2$
Molecular Weight: 482.57

Chemical Formula: $C_{23}H_{20}N_4O_4S_2$
Molecular Weight: 480.56

Product was synthesized according to general procedure A using following amounts: **13** (0.10 g; 0.21 mmol; 1 equ.), $Cu(OAc)_2 \times H_2O$ (0.0.082 g; 0.41 mmol; 2 equ.) $Pd(MeCN)_2Cl_2$ (0.005 g; 0.02 mmol; 0.1 equ.), and dry degassed DMAc (2 mL). It was stirred at 110 °C for 48 h

The crude product was purified *via* column chromatography (MPLC, 5 g deactivated silica, 10 mL/min, PE with 20-50 EtOAc in 20 min then 50 % EtOAc (10 min)).

Yield: 0.009 g (9 %)

Appearance: colorless oil

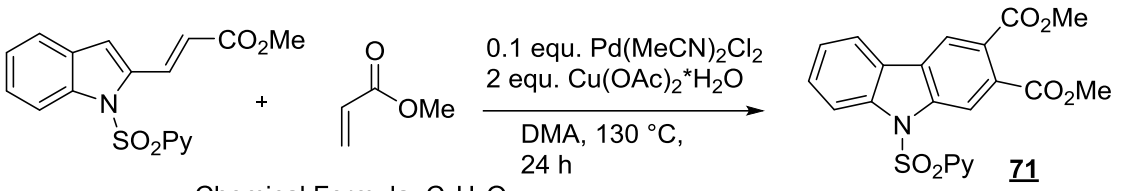
TLC: Rf(PE/EtOAc= 2/1) = 0.20; stationary phase: deactivated silica

^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.83-2.97 (m, 2H, H13), 3.40-3.56 (m, 2H, H12), 3.76-3.88 (m, 2H, H11), 6.08 (dt, J=11.2 Hz, 7.1 Hz, 1H, H10), 7.06 (d, J=11.2 Hz, H9), 7.20-7.48 (m, 4H, H4 & H5 & H6 & H7), 7.58-8.17 (m, 6H, H2´& H3´& H4´& H2´´ & H3´´ & H4´´), 8.47 (d, J=4.4 Hz, 1H, H5´), 8.57 (d, J=4.8 Hz, 1H, H5´´)

^{13}C-NMR (50 MHz, $CDCl_3$): δ 25.2 (t, C13), 45.3 (t, C12), 47.1 (t, C11), 115.0 (d, C7), 118.6 (d, C4), 120.7 (s, C3), 122.3 (d, C5), 122.4 (d, C9), 123.1 (d, C2´), 123.9 (d, C2´´), 125.4 (d, C6), 126.6 (d, C4´), 127.6 (d, C4´´), 129.1 (d, C10), 130.0 (s, C2), 134.5 (s, C8a), 136.9 (s, C8), 138.1 (d, C3´´), 138.3 (C3´), 150.02 (d, C5´), 150.3 (s, C5´´), 155.7 (s, C1´´), 158.1 (s, C1´)

HR-MS: $[M+H]^+$ m/z (predicted) = 481.10999 , m/z (measured) = 481.1007, difference = 1.7 ppm

4.9. Dimethyl 9-(pyridin-2-ylsulfonyl)-9H-carbazole-2,3-dicarboxylate



16

Chemical Formula: $C_{17}H_{14}N_2O_4S$
Molecular Weight: 342.37

Chemical Formula: $C_4H_6O_2$
Molecular Weight: 86.09

Chemical Formula: $C_{21}H_{16}N_2O_6S$
Molecular Weight: 424.43

Product **71** was synthesized according to general procedure A using following amounts: **16** (0.1 g; 0.29 mmol; 1 equ.), $Cu(OAc)_2 \times H_2O$ (0.116 g; 0.58 mmol; 2 equ.) $Pd(MeCN)_2Cl_2$ (0.008 g; 0.03 mmol; 0.1 equ.) and dry degassed DMAc (2 mL). It was stirred at 130 °C for 24 h. The crude product was purified *via* column chromatography (MPLC, 9 g, 10 mL/min, PE with 10-30 % EtOAc in 10 min then 30 % EtOAc (10 min)

Yield: 0.009 g (7 %)

Appearance: light yellow oil

TLC: Rf(PE/EtOAc= 2/1) = 0.18

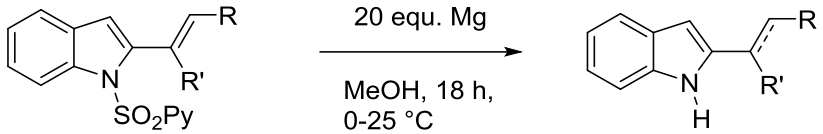
^{1}H-NMR (200 MHz, $CDCl_3$)(20a): δ 3.96 (s, 3H, H7''), 3.98 (s, 3H, H8''), 7.37-7.47 (m, 2H, H5 & H6), 7.50-7.60 (m, 1H, H7), 7.87 (dt, J=7.8 Hz, 1.9 Hz, 1H, H3'), 7.98 (d, J=7.8 Hz, 1H, H2'), 8.12 (d, J=8.1 Hz, 1H, H4), 8.28-8.35 (m, 2H, H4' & H1''), 8.44 (d, J=4.3 Hz, 1H, H5'), 8.66 (s, 1H, H4''),

^{13}C-NMR (50 MHz, $CDCl_3$): δ 52.8 (q, C7''), 52.9 (q, C8''), 115.3 (d, C1''), 115.9 (d, C7), 120.6 (d, C5), 121.2 (d, C4), 122.2, (d, C2') 124.5 (C4''), 124.7 (s, C3), 127.3 (s, C2), 127.7 (s, C8a), 127.9 (d, C6), 128.8 (d, C4'), 131.2 (s, C8), 138.2 (d, C3'), 139.7 (s, C2'') 139.8 (s, C3'' 150.5 (s, C5'), 155.2 (s, C1'), 167.9 (s, C2''), 168.2 (s, C3'')

HR-MS: $[M+H]^+$ m/z (predicted) = 425.0802 , m/z (measured) = 425.0813, difference = 2.6 ppm

5. Deprotection of alkenylated indoles

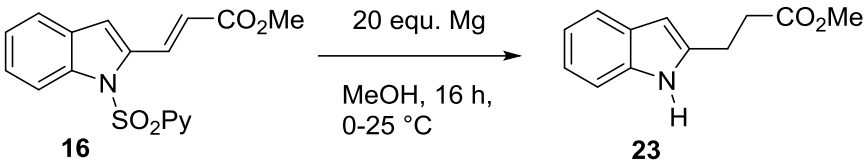
5.1. General procedure B



16-21 **23-28**

The target compounds **23-28** were obtained according to a literature protocol.[48] An 8 mL reaction vial was charged with the substrate **16-21**, dry MeOH was added under argon atmosphere and the solution was cooled to 0 °C. Powdered magnesium (20 equ.) was added all at once and the suspension was stirred at 0 °C for 1-2 h and at room temperature (time specified in each case) until complete conversion (Monitored by TLC). Then aqu. satd. $NaHCO_3$ solution was added and the resulting reaction solution was extracted three times with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4, the solvent was removed *in vacuo* and the crude product was purified using MPLC (Parameters specified in each case).

5.2. Methyl 3-(1H-indol-2-yl)propanoate (23)



16 **23**

Chemical Formula: $C_{17}H_{14}N_2O_4S$
Molecular Weight: 342.37

Chemical Formula: $C_{12}H_{13}NO_2$
Molecular Weight: 203.24

Product **23** was synthesized according to general procedure B using following amounts: **16** (0.061 g; 0.18 mmol; 1 equ.), powdered magnesium (0.085 g; 3.56 mmol; 20 equ.) in dry MeOH (5 mL), stirred at 0 °C for 2 h and at room temperature for 16 h. The crude product was purified *via* column chromatography (MPLC, 5 g, 10 mL/min, PE with 5-15 EtOAc in 20 min then 15 % EtOAc (5 min)). Analytical data matched with reported data from literature.[45]

Yield: 0.021 g (57 %)

Appearance: white solid

Melting point: 115-117 °C (Literature: 115-117 °C)

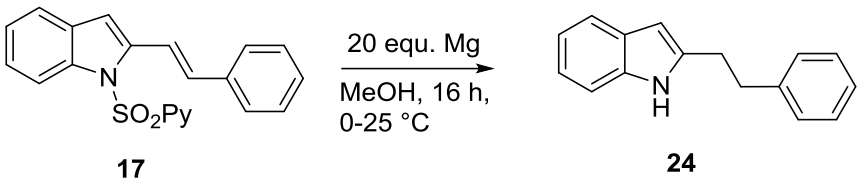
TLC: Rf(PE/EtOAc= 5/1) = 0.24

^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.75 (t, J=6.8 Hz, 2H, H1´), 3.09 (t, 6.8 Hz, 1H, H2´), 3.73 (s, 3H, H4´), 6.25 (s, 1H, H3), 7.02-7.19 (m, 2H, H3 & H2), 7.32 (d, J=8.3 Hz, H7), 7.54 (d, J=7.4 Hz, H4), 8.48 (broad s, 1H, NH)

^{13}C-NMR (50 MHz, $CDCl_3$): δ 22.2 (t, C1´), 33.0 (t, C3´), 51.1 (q, C4´), 99.0 (d, C3), 109.7 (d, C7), 118.7 (d, C5), 119.0 (d, C4), 120.4 (d, C6), 127.6 (s, C8a), 135.1 (d, C2), 137.32 (s, C8), 173.5 (s, C3´)

HR-MS: $[M+H]^+$ m/z (predicted) = 204.1019 , m/z (measured) = 204.1017, difference = 1.0 ppm

5.3. 2-Phenethyl-1H-indole (24)



17

Chemical Formula: $C_{21}H_{16}N_2O_2S$
Molecular Weight: 360.43

24

Chemical Formula: $C_{16}H_{15}N$
Molecular Weight: 221.30

Product **24** was synthesized according to general procedure B using following amounts: **17** (0.076 g; 0.21 mmol; 1 equ.), powdered magnesium (0.102 g; 4.20 mmol; 20 equ.) in dry MeOH (5 mL) stirred at 0 °C for 2 h and at room temperature for 16 h. The crude product was purified *via* column chromatography (MPLC, 10 g, 15 mL/min, PE with 5-20 EtOAc in 20 min then 20 % EtOAc (5 min)). Analytical data matched with reported data from literature.[45]

Yield: 0.024 g (52 % o. th.)

Appearance: colorless oil

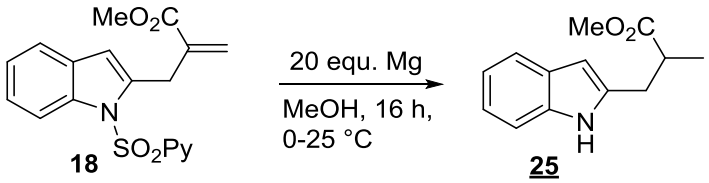
TLC: Rf(PE/EtOAc= 10/1) = 0.44

^{1}H-NMR (200 MHz, $CDCl_3$): δ 3.03-3.10 (m, 4H, H1´ & H2´), 6.29 (s, 1H, H3), 7.03-7.19 (m, 2H, H5 & H6), 7.19-7.39 (m, 6H, H7 & H4´ & H5´ & H6´ & H7´ & H8´) 7.56 (d, J=7.3 Hz, 1H, H4), 7.71 (broad s, 1H, NH)

^{13}C-NMR (50 MHz, $CDCl_3$): δ 30.2 (t, C1´), 35.7 (t, C2´), 99.9 (d, C3), 110.5 (d, C7), 119.8 (d, C5), 120.0 (d, C6), 121.2 (d, C4), 126.4 (d, C6´), 128.5 (d, C4´ & C5´ & C7´ & C8´), 128.8 (s, 8a), 135.9 (s, C2), 139.1 (s, C8), 141.3 (s, C3´)

HR-MS: $[M+H]^+$ m/z (predicted) = 222.1277 , m/z (measured) = 222.1272, difference = 2.3 ppm

5.4. Methyl 3-(1H-indol-2-yl)-2-methylpropanoate (*25*)



Chemical Formula: $C_{18}H_{16}N_2O_4S$
Molecular Weight: 356.40

Chemical Formula: $C_{13}H_{15}NO_2$
Molecular Weight: 217.27

Product **25** was synthesized according to general procedure B using following amounts: **18** (0.062 g; 0.17 mmol; 1 equ.), powdered magnesium (0.083 g; 3.40 mmol; 20 equ.) in dry MeOH (5 mL) stirred at 0 °C for 2 h and at room temperature for 16 h. The crude product was purified *via* column chromatography (MPLC, 10 g, 15 mL/min, PE with 5-20 EtOAc in 20 min then 20 % EtOAc (5 min)). Analytical data matched with reported data from literature.[45]

Yield: 0.021 g (57 %)

Appearance: light yellow oil

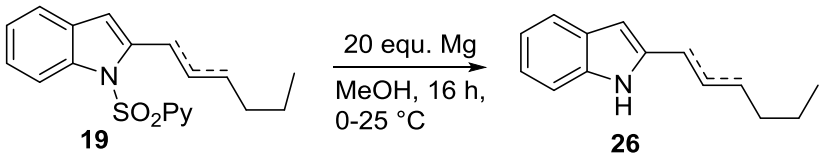
TLC: Rf(PE/EtOAc= 10/1) = 0.21

^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.25 (d, J=7.0 Hz, H4´), 2.89 (m, 1H, H1´), 2.75-2.92 (d, J=4.8 Hz, 1H, H1´), 3.1(dd, J=8.2 Hz, 14.5 Hz, 1H, H2´), 3.71 (s, 3H, H3´), 6.26 (s, 1H, H3), 7.00-7.19 (m, 2H, H5 & H6), 7.31 (d, J=8.1 Hz, 1H, H7), 7.54 (d, J=7.7 Hz, 1H, H4), 8.37 (broad s, 1H, NH)

^{13}C-NMR (50 MHz, $CDCl_3$): δ 17.5 (q, C4´), 31.8 (t, C1´), 40.1 (d, C2´), 52.2 (q, C5´), 101.2 (d, C3), 110.7 (d, C7), 119.7 (d, C5), 120.0 (q, C4), 121.4 (d, C6), 128.6 (s, C8a), 136.1 (s, C2), 136.8 (s, C8), 177.4 (s, C3´)

HR-MS: $[M+H]^+$ m/z (predicted) = 218.1176 , m/z (measured) = 218.1185, difference = 4.1 ppm

5.5. 2-(Hexen-1-yl)-1H-indole (26)



Chemical Formula: $C_{19}H_{19}N_2O_2S$
Molecular Weight: 339.43

Chemical Formula: $C_{14}H_{16}N$
Molecular Weight: 198.29

Product **26** was synthesized according to general procedure B using following amounts: **19** (0.066 g; 0.19 mmol; 1 equ.), powdered magnesium (0.094 g; 3.88 mmol; 20 equ.) in dry MeOH (5 mL) stirred at 0 °C for 1 h and at room temperature for 3 h. The crude product was purified *via* column chromatography (MPLC, 5 g, 10 mL/min, PE with 5-20 EtOAc in 20 min then 20 % EtOAc (5 min)). The product is an inseparable mixture of at least 5 different double bond isomers

Yield: 0.033 g isomeric mixture (87 %) The product is an inseparable mixture of several isomers. GC-MS analysis shows, that 5 major isomers are present.

Appearance: light yellow oil

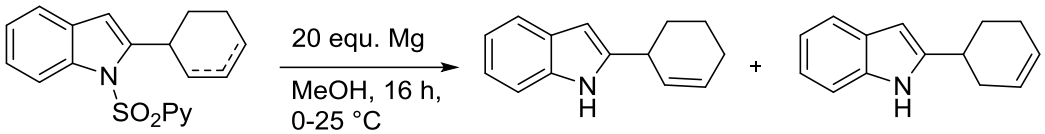
TLC: Rf(PE/EtOAc= 10/1) = 0.59

NMR-shifts were measured but not allocated due to the complexity of the isomeric mixture

GC-MS (EI, 70 eV): Method 1; Retention times: 9.36, 9.78, 9.84 (Main isomere), 10.01, 10.35; Main fragments (Main isomere) (relative intensity): 199 ($[M-H]^-$, 31), 170 (38), 156 (39), 131 (29), 130 (100), 129 (48), 128 (38), 117 (69), 115 (27), 103 (29), 89 (32), 77 (49),

HR-MS: $[M+H]^+$ m/z (predicted) = 200.1434 , m/z (measured) = 200.1443, difference = 4.5 ppm

5.6. (rac)-2-(cyclohexen-1-yl)-1H-indole (27)



20a+20b

Chemical Formula: $C_{19}H_{17}N_2O_2S$
Molecular Weight: 337.41

27a

27b

Chemical Formula: $C_{14}H_{15}N$
Exact Mass: 197.12

Products **27a/b** were synthesized according to general procedure B using following amounts: **20** (0.033 g; 0.10 mmol; 1 equ.), powdered magnesium (0.047 g; 1.95 mmol; 20 equ.) in dry MeOH (5 mL) stirred at 0 °C for 1 h and at room temperature for 3 h.. The crude product was purified *via* column chromatography (MPLC, 5 g, 10 mL/min, PE with 5-20 EtOAc in 20 min then 20 % EtOAc (5 min)). The product is an inseparable mixture of 2 double bond isomers. The distribution of the isomers is 0.43/0.56 = **27a/27b**

Yield: 0.017 g isomeric mixture (88 %)

Appearance: light yellow oil

TLC: Rf(PE/EtOAc= 10/1) = 0.51

^{1}H-NMR (200 MHz, $CDCl_3$)(27a): δ 1.58-1.90 (m, 2H, H5´), 1.98-2.60 (m, 4H, H6´& H4´), 3.56-3.70 (m, 1H, H1´), 5.74-6.03 (m, 2H, H2´& H3´), 6.30 (s, 1H, H3), 7.02-7.20 (m, 2H, H5 & H6), 7.32 (d, J=7.4 Hz, 1H, H7), 7.56 (d, J=7.4 Hz, 1H, H4), 7.96 (broad s, 1H, NH)

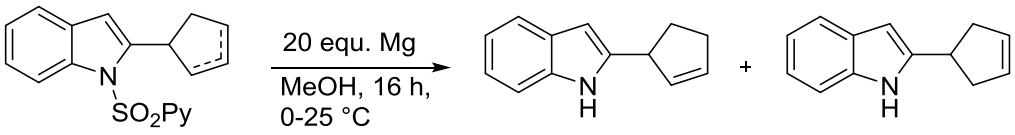
^{1}H-NMR (200 MHz, $CDCl_3$)(27b): δ 1.58-1.90 (m, 2H, H6´), 1.98-2.60 (m, 4H, H5´& H2´), 2.97-3.15 (m, 1H, H1´), 5.74-6.03 (m, 2H, H2´& H3´), 6.30 (s, 1H, H3), 7.02-7.20 (m, 2H, H5 & H6), 7.32 (d, J=7.4 Hz, 1H, H7), 7.56 (d, J=7.4 Hz, 1H, H4), 7.96 (broad s, 1H, NH)

^{13}C-NMR (50 MHz, $CDCl_3$) (27a+27b)(Shifts are not allocated due to the isomeric mixture**):** δ 20.8, 25.1, 28.9, 30.6, 31.4, 33.3, 35.1, 98.1, 99.3, 110.5, 110.6, 119.8, 120.1, 121.2, 126.1, 127.4, 127.8, 128.7, 128.8, 129.7, 135.8, 143.3, 144.4

GC-MS (EI, 70 eV): Method 1; Retention times: 9.42 (2-cyclohexene isomere), 9.56 (3-cyclohexene isomere); Main fragments (2-cyclohexene isomere) (relative intensity): 197 (52), 196 (13), 169 (34), 168 (92), 167 (33), 154 (16), 130 (24), 117 (100); Main fragments (3-cyclohexene isomere) (relative intensity): 197 (M^-, 14), 144 (11), 143 (100), 117 (20), 115 (18), 89 (12), 77 (10)

HR-MS: $[M+H]^+$ m/z (predicted) = 198.1277 , m/z (measured) = 198.1282, difference = 2.52 ppm

5.7. (rac)-2-(Cyclopent-2-en-1-yl)-1H-indole (28)



21a+21b

Chemical Formula: $C_{18}H_{15}N_2O_2S$
Molecular Weight: 323,3900

28a **28b**

Chemical Formula: $C_{13}H_{13}N$
Exact Mass: 183,1048

Product was synthesized according to general procedure B using following amounts: **21** (0.078 g; 0.24 mmol; 1 equ.), powdered magnesium (0.117 g; 4.81 mmol; 20 equ.) in dry MeOH (5 mL) stirred at 0 °C for 1 h and at room temperature for 3 h.

The crude product was purified *via* column chromatography (MPLC, 5 g, 10 mL/min, PE with 5-20 EtOAc in 20 min then 20 % EtOAc (5 min)). The product is an inseparable mixture of 2 double bond isomers. The distribution of the isomers is 0.10/0.90 = **28b**/**28a**

Yield: 0.035 g isomeric mixture (80 %)

Appearance: light yellow oil

TLC: Rf(PE/EtOAc= 10/1) = 0.46

^{1}H-NMR (200 MHz, $CDCl_3$) (Main isomer): δ 1.83-2.03 (m, 1H, H5´), 2.30-2.69 (m, 3H, H4´& H5´), 4.04-1.14 (m, 1H, H1´), 5.82-8.08 (m, 2H, H2´ & H3´), 6.28 (s, 1H, H3), 7.03-7.21 (m, 2H, H5 & H6), 7.31 (d, J=7.3 Hz, 1H, H7), 7.56 (d, J=7.8 Hz, 1H, H4), 7.87 (broad s, 1H, NH)

^{13}C-NMR (50 MHz, $CDCl_3$) (Main isomer): δ 31.9 (t, C5´), 32.4 (t, C4´), 44.6 (d, C1´), 98.7 (d, C7), 119.8 (d, C5), 120.1 (d, C4), 121.2 (d, C6), 128.9 (s, C8a), 132.1 (d, C3´), 133.2 (d, C2´), 136.0 (s, C8), 143,2 (s, C2)

GC-MS (EI, 70 eV) (Main isomere) Method 1; Retention time: 9.46; Main fragments (relative intensity): 183 (M^-, 69), 182 (59), 168 (43), 166 (41), 117 (100), 90 (46), 89 (43), 77 (38), 63 (40)

HR-MS: $[M+H]^+$ m/z (predicted) = 184.1121 , m/z (measured) = 184.1118, difference = 1.6 ppm

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Curriculum Vitae

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