Total Synthesis of (-)-Mitragynine and Analogues

Master Thesis

by

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Abstract

Mitragynine, paynantheine and speciogynine belong to the group of corynanthe alkaloids, a large class of biologically active indole alkaloids. Present in the leaves of the Asian plant *Mitragyna speciosa* (Rubiaceae) they have been used by Thai and Malaysian natives as a substitute for opium as well as for their stimulating activity. Besides the use as a drug, the plant has found application in medicine in the treatment of coughing, diarrhea, muscle pain and hypertension. Interestingly, mitragynine has a stronger analgesic effect than morphine, so that it has been suggested as a useful compound in the treatment of opiate addiction in replacement therapy. About the biological activity of paynantheine and speciogynine there are very little studies reported.

Three syntheses of mitragynine have been developed, two starting from enantiopure starting materials and a formal synthesis using organocatalysis. Syntheses of paynantheine and speciogynine have not been reported so far. Our approach to the three alkaloids proceeds via an asymmetric Pictet-Spengler reaction catalyzed by organic bifunctional cinchona alkaloids. This strategy allows fast and highly selective formation of the tetrahydro-β-carboline skeleton. The second key-step in the synthesis is a Tsuji-Trost allylic alkylation precedented in earlier work of our group. Based on achiral starting materials, a fast and enantioselective excess to mitragynine, paynantheine and speciogynine was established. Additionally, our method allows to design new unnatural derivatives which exhibit improved biological properties.

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1. Introduction

1.1. Mitragyna Speciosa

Mitragyna speciosa is a tree growing in the tropical climate of Thailand and Malaysia whereas the leaves and extracts are commercially sold under the name ”Kratom”. The plant is classified as a representative of the family Rubiaceae which is also known as the “coffee family”. With only 10 species worldwide the genus of *Mitragyna* is relatively small.[1] Its popularity is based on its unique biological activity, so that the leaves have been traditionally consumed by natives of Thailand and Malaysia for over hundred years.

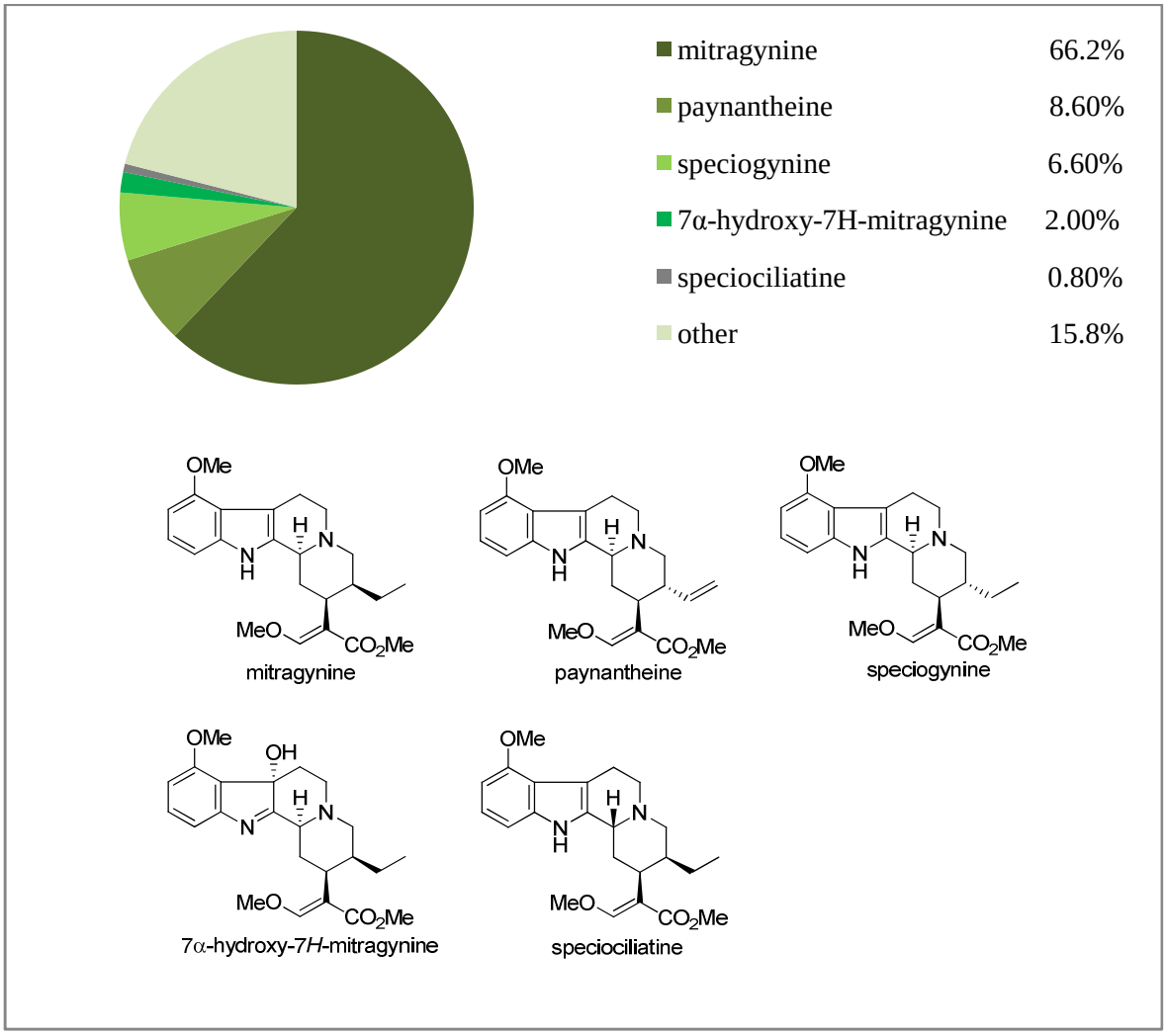
The extract of the plant has dose-dependent effects: a stimulating activity with small doses while higher amounts lead to euphoric and sedative effects.[1] Therefore, it has been applied as a substitute for opium by natives and has as well been considered as a helpful agent for replacement therapy in the western world. The leaves, either fresh or dried, and the resin were consumed mainly orally to release their relaxing or stimulating activity.[2, 3] Despite the use of *Mitragyna speciosa* as a drug, the plant has also found medicinal application in the treatment of coughing, diarrhea, muscle pain and hypertension.[4]

Figure 1: A picture of *Mitragyna speciosa* by the Dutch botanist Pieter Korthals[5]

Studies about chronic use of kratom revealed side effects like anorexia, weight loss, constipation and hyperpigmation of the face.[2, 3][6] Uncontrolled consumption of kratom can

lead quickly to an addictive behavior with abstinence syndromes such as insomnia, lethargy, myalgia, arthralgia, aggression and myonclonus.[6] In Thailand it has therefore already been outlawed in 1939 through the "Kratom Act". Later, countries such as Australia, Malaysia and Myanmar followed.[7] In the Western World however, the distribution over the internet proceeds rather uncontrolled.

Responsible for the biological activity of the tree are the compounds which are present in the leaves or the resin. These compounds (mainly alkaloids) are released during the consumption[a] to exhibit their desired effects. The alkaloid content of the leaves is about 0.5%[8] whereas the isolation of 44 different compounds has been reported over the last 87 years. The exact distribution of alkaloids varies depending on the region and each specific plant but mitragynine is generally obtained as the major constituent. In 2004 Takayama investigated the distribution of alkaloids with a plant growing on the campus of the Chulalongkorn University of Bangkok (Scheme 1).[9]



Scheme 1: Alkaloid distribution

[a] Brewing the leaves in hot water and serving them as a tea, chewing the fresh leaves or smoking the resin.

More than half of the amount of isolated alkaloids turned out to be mitragynine with 66.2%, followed by paynantheine with 8.6% and speciogynine with 6.6%.

1.2. Structure of Mitragynine, Paynantheine and Speciogynine

The naturally occurring indole alkaloid (-)-mitragynine and its analogues (+)-paynantheine and (+)-speciogynine belong the class of corynanthe alkaloids. First isolated in 1965 by the group of Shellard[10] the final structure of mitragynine was confirmed by an X-ray analysis of the group of Zacharias with a mitragynine hydroiodide salt.[11] The isolation of paynantheine and speciogynine followed soon.[12, 13] Structurally, they all consist of an aromatic indole system bearing a methoxy-group at the 4-position. In addition to that, there are two six-membered rings both sharing nitrogen-4 and carbon-3. In total there are three stereocenters. Mitragynine and speciogynine only differ in the configuration of stereocenter C-20, so that both molecules are diastereomers of each other. Paynantheine and speciogynine have the same configuration at C-20 but paynantheine is bearing a vinyl-group at this position instead of an ethyl-group.

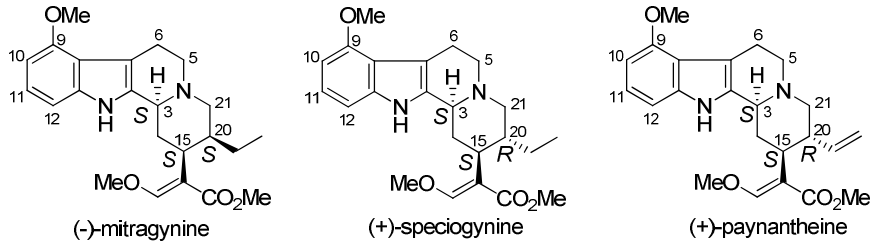
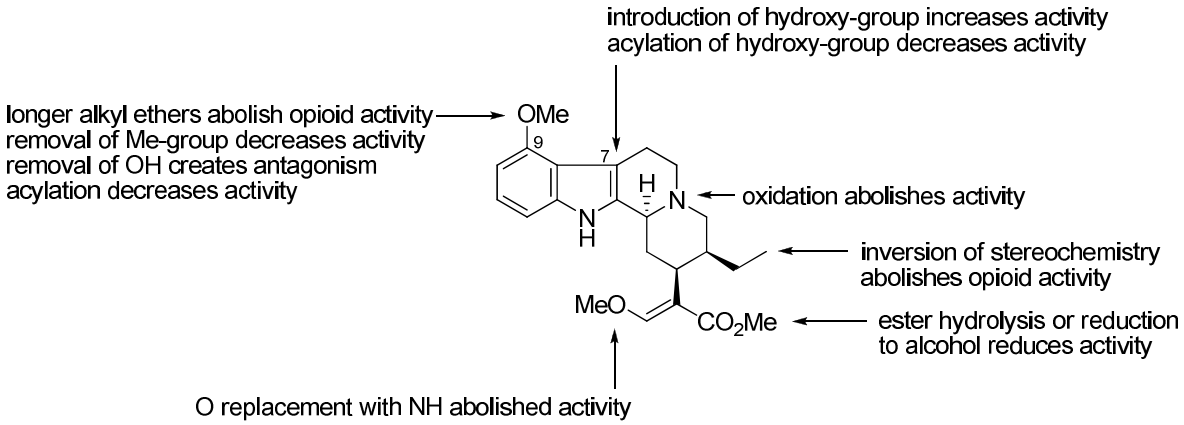


Figure 2: Structures of (-)-mitragynine, (+)-speciogynine and (+)-paynantheine

1.3. Biological Activity of (-)-Mitragynine

Although there are studies which deal with metabolism of paynantheine and speciogynine[14, 15] concrete studies on the biological activity are not reported so far. On the other hand, main alkaloid mitragynine has been investigated in more detail. In vivo and in vitro studies indicated that mitragynine is a central nervous system stimulant[3, 16] and primarily acts on μ-opioid receptors.[17, 18]

Studies about the relationship between structure of the molecule and biological activity are summarized in a review by McCurdy *et al.*[1] and are shown in Scheme 2.



Scheme 2: Structure and activity in (-)-mitragynine

First of all, the methoxy-group on the C-9 is essential for the biological activity. When the methoxy group is replaced by a longer alkoxy-group, the biological activity is abolished. When the group is removed completely to give the natural product corynantheidine an antagonist[b] is produced. This shows that modulation of this functionality can dramatically alter the biological properties of the molecule. Secondly, oxidation and introduction of a hydroxyl-group on the C-7 carbon with phenyliodine bis(trifluoroacetate)[19] give the 46-fold higher active 7α-hydroxy-7*H*-mitragynine (for the structure see Scheme 1).[8] Finally, loss of the basic character of the tertiary amine through oxidation as well as disruption of the *β*-methoxyacrylate moiety abolish the activity.[c]

1.4. Reported Syntheses of (-)-Mitragynine

Since the characterization of (-)-mitragynine through the crystal structure in 1965[11] there have been two syntheses of enantiopure mitragynine and one formal synthesis reported. The first one has been published in 1995 by Takayama *et al.* using chiral starting materials generated by enzymes.[20] Later, Cook *et al.* developed the second synhesis using a chiral

[b] A receptor antagonist is drug that does not provoke a biological response itself upon binding to a receptor, but blocks or dampens agonist-mediated responses. Mitragynine on the contrary, belongs to the class of agonists.
[c] Unfortunately, the origin (references) of the semi-synthesis/SAR-studies are not mentioned in the review.

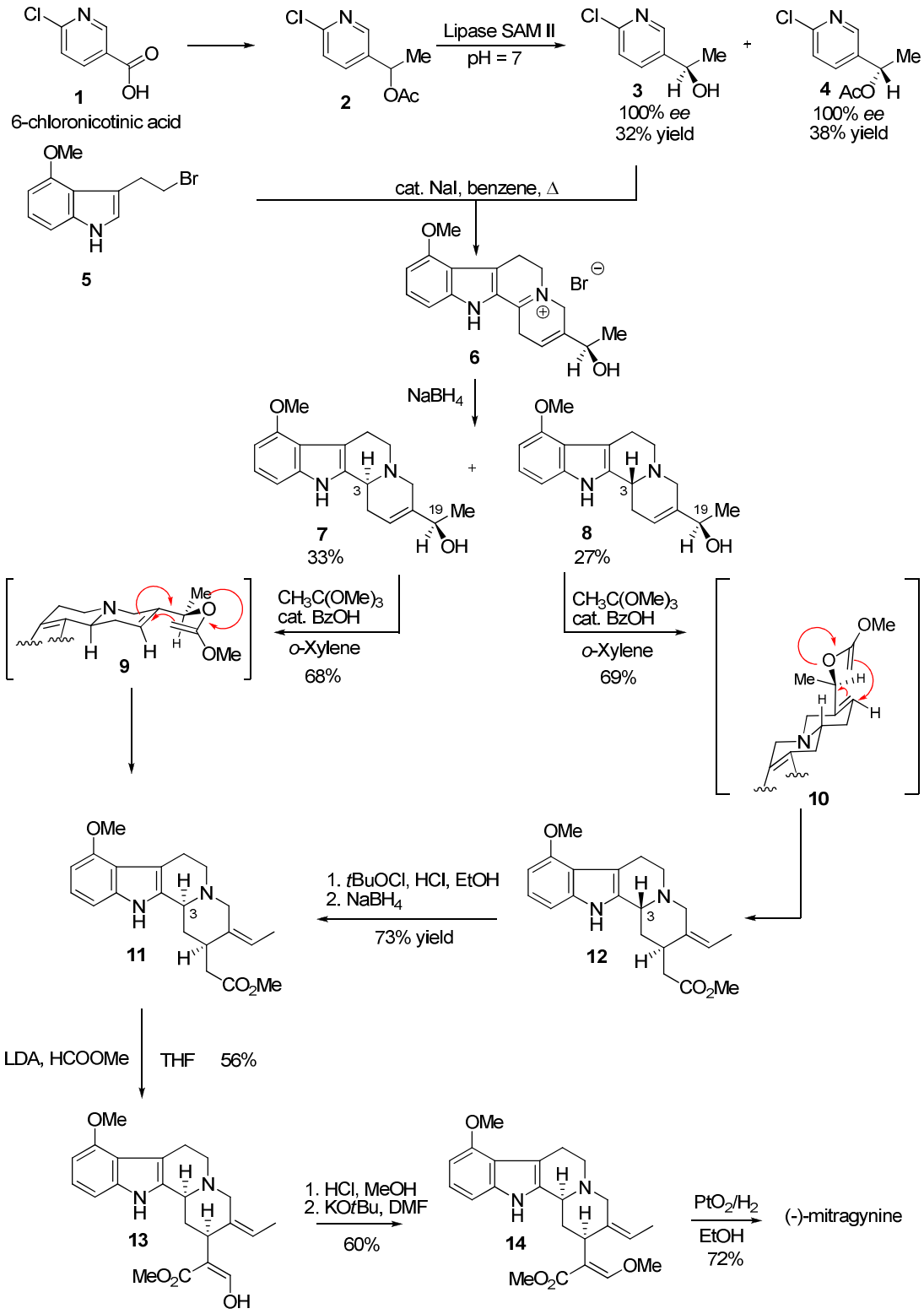
auxiliary.[8] The first organocatalytic approach has been published very recently by Ma *et al*. with a formal synthesis of (-)-mitragynine.[21]

1.4.1. *Synthesis by Takayama et al.*

Takayama's synthesis starts with commercially available 6-chloronicotinic acid which is converted into the racemic acetate **2** and subjected to enzymatic hydrolysis to afford the resulting secondary alcohol **3** and acetate **4** in 100% *ee* (Scheme 3). In the next step the enantiopure alcohol was condensed with bromide **5**[d] in heated benzene and catalytic amount of sodium iodide to give pyridinium salt **6** in 56% yield. Reduction of the salt resulted in an allylic alcohol with two separable diastereomers **7** and **8**. Although two diastereomers have been formed it was assumed that through a Claisen-rearrangement and their corresponding chair-like transition states, the newly formed stereocenter can be controlled by the absolute configuration of C-19. Moreover, it was believed that the undesired configuration of stereocenter C-3 of diastereomer **8** could be converted into the desired one after the Claisen-rearrangement. Both diastereomers **7** and **8** were subjected to the Claisen-rearrangement with trimethyl orthoacetate and catalytic amounts of benzoic acid to give the corresponding acetates **11** and **12**. The configuration of C-3 in acetate **12** was inverted to **11** with an oxidation-reduction sequence via a 3,4-dehydroimmonium salt.

Next, a formyl-group was introduced in **11** at C-16 to give the resulting product **13** in 56% yield.[e] The formyl group was converted into the dimethyl acetal and then treated with KO*t*Bu to generate the corresponding enol ether **14** in the *trans* configuration. Stereoselective hydrogenation with PtO_2 gave (-)-mitragynine in 9 steps.

[d] 5-step synthesis, yields are not mentioned.
[e] The formyl group was obtained in the enol-form with the undesired *cis*-configuration.

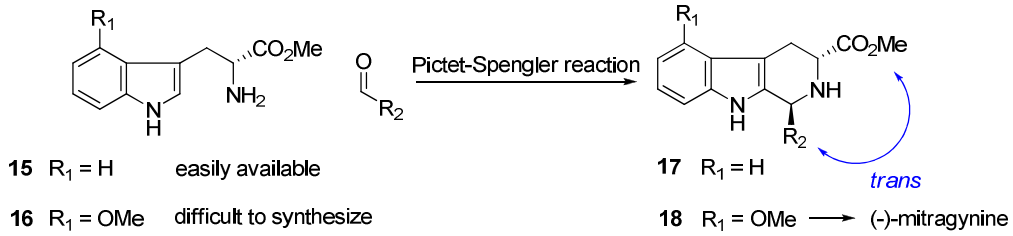


Scheme 3: Total synthesis of (-)-mitragynine published by Takayama *et al.*

1.4.2. *Synthesis by Cook et al.*

James Cook from the University of Wisconsin-Milwaukee spent a lot of research on the chemistry of tryptophanesters. He found out that enantiopure tryptophan esters such as **15**

undergo a Pictet-Spengler reaction with aldehydes to condensation product **17**[f] with the ester-group and the R_2-substituent *trans* to each other.[22, 23] With this *trans*-preference the stereochemistry of C-3 can be controlled in a diastereoselective fashion. Tryptophan esters are easily available from the naturally occurring amino acid tryptophan and the condensation product **17** resembles the core structure of mitragynine to great extend. Therefore, for the synthesis of mitragynine it would be the easiest to start from 4-methoxy-substituted tryptophan esters and to control the stereochemistry of the created stereocenter C-3 in condensation product **18** through the preferred *trans* relationship of the ester group and the R_2-substituent. Unfortunately, methoxy-substituted tryptophans are not available from nature. For the synthesis of (-)-mitragynine, as a consequence, first the methoxy-substituted tryptophan ester had to be synthesized.

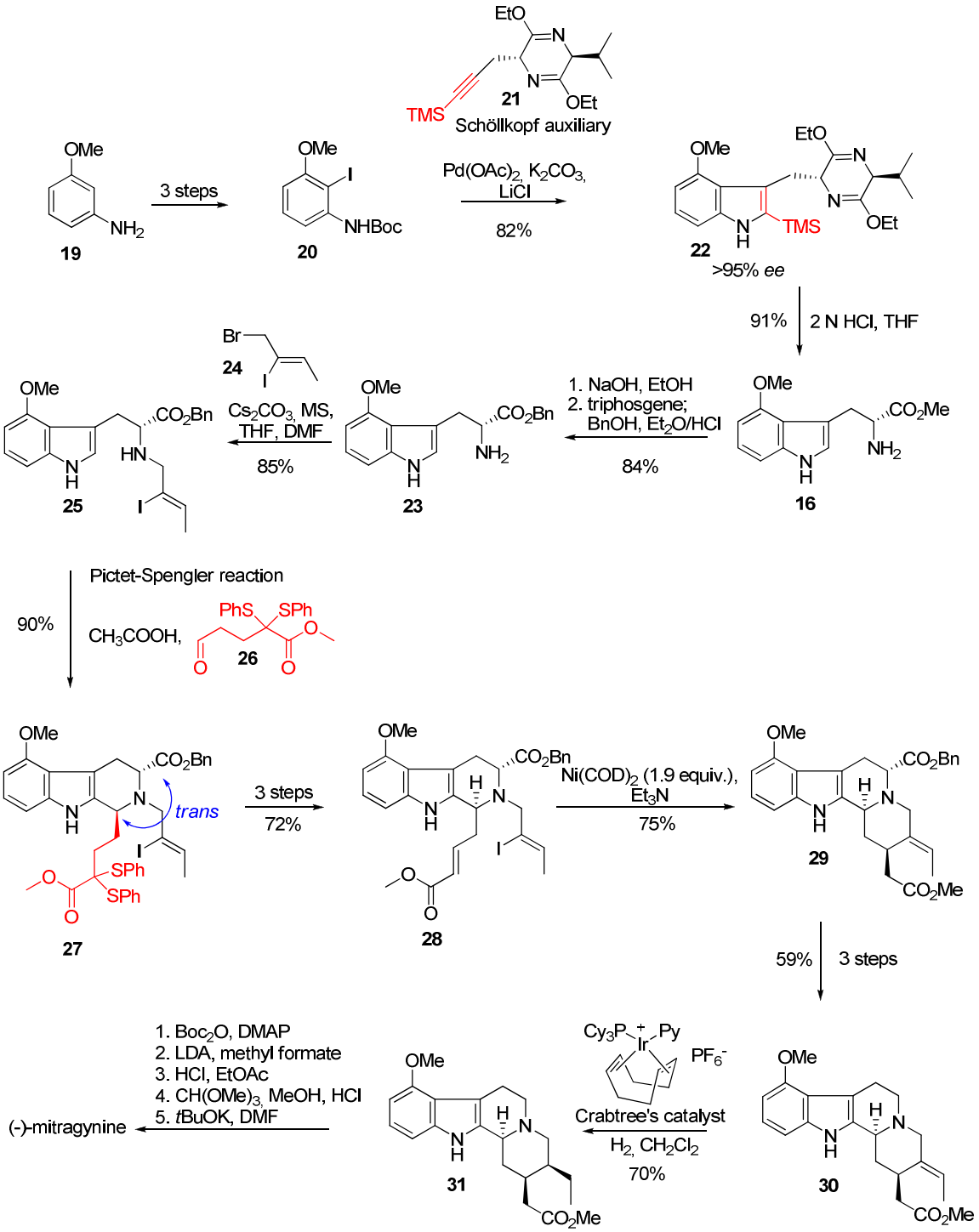


Scheme 4: Tryptophan ester are desired compounds for the Pictet-Spengler reaction

To realize a synthesis of mitragynine, Cook *et al*. envisioned a chiral auxiliary approach for the preparation of enantiopure methoxy substituted tryptophan ester **18** using a modified Schöllkopf auxiliary (a bis-lactim derived from the amino acid valine). The synthesis starts with commercially available 3-methoxy-anilin which is easily converted into iodine **20**.[24] The iodine was coupled via a Larock heteroannulation[25] to a TMS propargyl-substituted Schöllkopf auxiliary.[26] At the same time the Boc-group on the indolic nitrogen was removed and the desired indole derivative **22** was obtained in 82% yield and >95% *ee*. Removal of the auxiliary went nicely in one step through hydrolysis with hydrochloric acid to give the desired methoxy-substituted tryptophanester **16**. Employing a sterically demanding substituent on the amine in three steps, the substrate **25** for the Pictet-Spengler reaction was obtained. With acetic acid and aldehyde **26** the Pictet-Spengler reaction was carried out in a diastereoselective fashion to the *trans* isomer **27**. From *trans*-tetrahydro-*β*-carboline **27** the two thiophenol groups were removed and a $Ni(COD)_2$ mediated cyclization was carried out with intermediate **28** to give **29**. From cyclized product **29** the ester-group was removed in

[f] This reaction will be later discussed extensively, but for now it is only important to know that a tryptamine reacts with an aldehyde to a system as **17**.

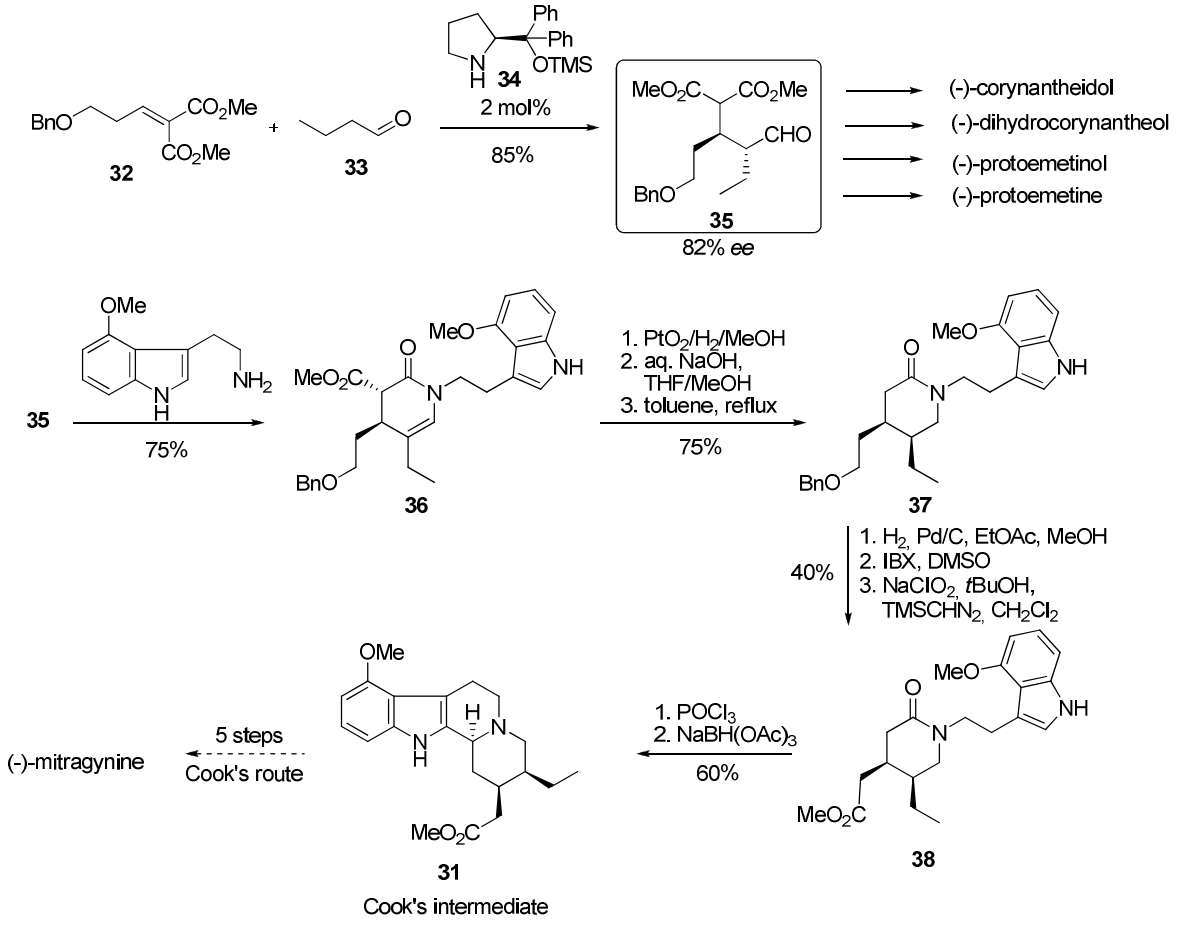
three steps and the double bond of **30** selectively hydrogenated with Crabtree's catalyst. Five more steps from **31** gave (-)-mitragynine in >95% *ee* and an overall number of 22 steps.



Scheme 5: Total synthesis of (-)-mitragynine by Cook *et al.*

1.4.3. *Synthesis by Ma et al.*

In 2011 Ma *et al*. published a formal synthesis of (-)-mitragynine using organocatalysis for the introduction of chirality.[21] The Key feature of their work is a chiral fragment synthesized via an organocatalyzed Michael-addition between **32** and *n*-butanal with *O*-TMS-protected diphenylprolinol **34**. **35** serves as a building block for the synthesis of several natural products as well as for (-)-mitragynine. The organocatalyzed Michael-addition went in good yield, unfortunately the *ee* dropped significantly when the reaction was performed on a 1 mmol scale (from 91% to 82% *ee*). Having fragment **35** at hand, this was coupled to 4-methoxy-substituted tryptamine via a reductive amination. **36** was then selectively hydrogenated and further subjected to saponification and decarboxylation to end up with lactam **37**. After debenzylation through Pd/C-catalyzed hydrogenation to give a primary alcohol, IBX-oxidation to the aldehyde, Pinnick oxidation to an acid and esterification, **37** was converted into **38**. Bischler-Napieralski cyclization followed by reduction afforded intermediate **31**, from which the synthesis could be finalized following Cook's route (see Scheme 5).



Scheme 6: Formal synthesis of (-)-mitragynine published by Ma *et al*.

1.5. Aim and Motivation of the Investigations

Aim of this master project was to develop an efficient asymmetric synthesis of (-)-mitragynine, (+)-paynantheine and (+)-speciogynine.

Due to its unique biological activity (-)-mitragynine promises to be an interesting compound for medicinal applications. In contrast to mitragynine, there are hardly no studies known which deal with the medicinal evaluation of paynantheine and speciogynine. An easy access to these compounds through a chemical synthesis would facilitate the studies of these compounds. No synthesis for these compounds has been reported yet. Moreover, with a flexible synthetic strategy, not only the natural product itself but also derivatives with structural variation can be accessible. These compounds might have an increased or even different biological activity and are therefore interesting to investigate.

In addition to the accessibility of these compounds, chemists always aim for the development of new synthetic methods. Especially, the field of organocatalysis has grown exponentially over the last fifteen years. The use of small organic molecules functionalized as catalysts to perform a diversity of chemical reactions is strongly desired since they bring a number of advantages compared to metal- or biocatalysts.[g] Since the pioneer work in the early 2000s[27-34] many asymmetric organocatalytic methods have been developed. Based on these achievements it is a challenge to apply these methods in the total synthesis of complex natural products.

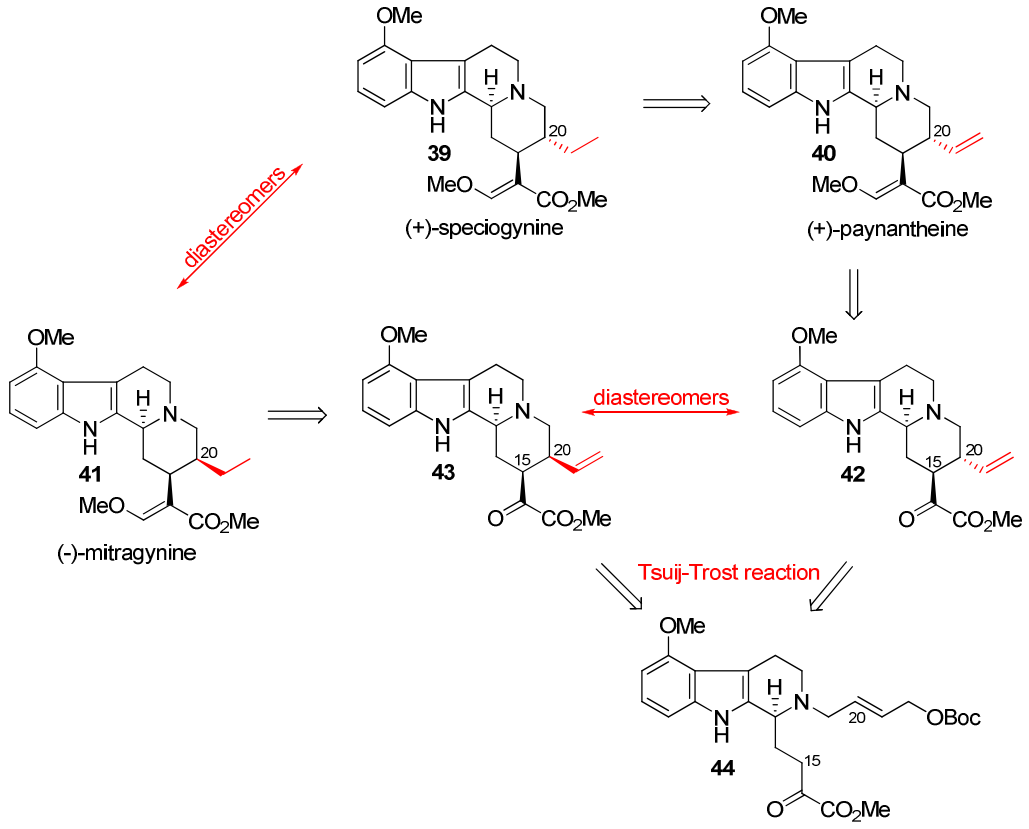
[g] Broad substrate scope, less toxic, easy handling.

2. Synthesis of (-)-Mitragynine, (+)-Paynantheine and (+)-Speciogynine

2.1. Synthetic Strategy and Outline of This Thesis

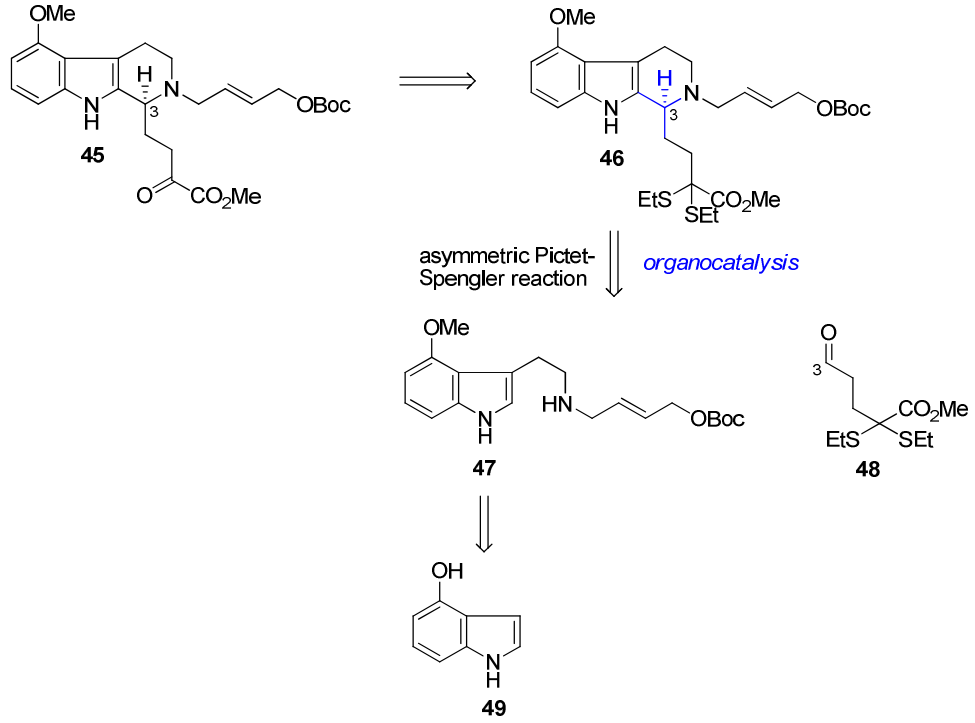
The retrosynthetic analysis of mitragynine, paynantheine and speciogynine is depicted in Scheme 7. Due to their strong structural resemblance it was envisioned that all three molecules can be generated through a common route which splits at a certain point later in the synthesis. This strategy has been applied before by our group in the synthesis of (-)-corynantheidine, (+)-corynantheine and (+)-dihydrocorynantheine.[35]

Starting the retrosynthesis, speciogynine **39** can be obtained from paynantheine **40** with hydrogenation of the vinylic substituent at C-20. Paynantheine **40** and mitragynine **41** both result from the corresponding α-keto-esters **43** and **42**. These two diastereomers are the products of a Tsuji-Trost reaction which functions as an intramolecular ring closing operation of intermediate **44**.



Scheme 7: Retrosynthesis I

α-Keto-ester **45** can be obtained from the corresponding thioacetal **46** which is the product of an asymmetric Pictet-Spengler reaction between tryptamine **47** and aldehyde **48** (Scheme 8). The Pictet-Spengler reaction should be carried out with a chiral organocatalyst. Tryptamine **47** was synthesized from commercially available 4-hydroxy-indole.



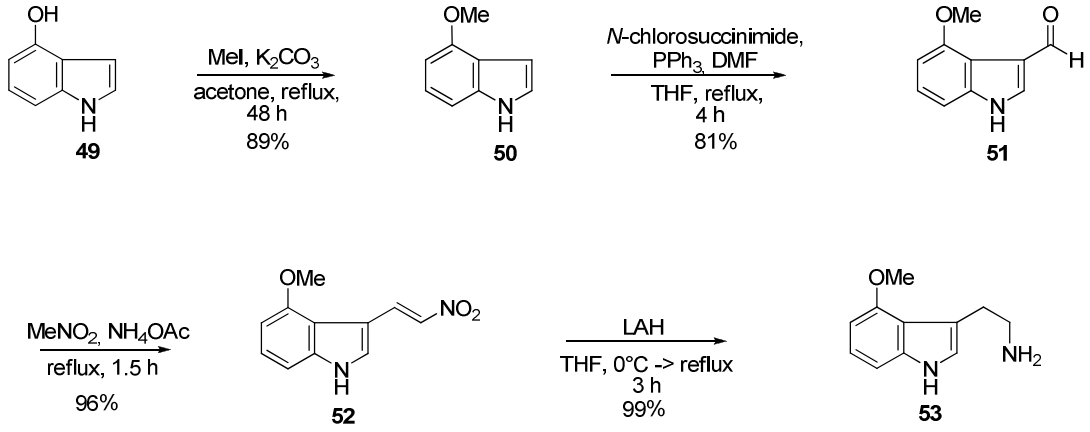
Scheme 8: Retrosynthesis II

The structure of this thesis is oriented along the retrosynthesis starting with the commercially available compounds and ending with the natural products mitragynine, paynantheine and speciogynine. First, the synthesis of tryptamine **35** starting from 4-hydroxy-indole and aldehyde **36** will be described. The next section deals with the key step of the synthesis, the asymmetric Pictet-Spengler reaction. Before the separation of the route in the two diastereomers via a Tsuji-Trost reaction, the transformation of the thioacetal into the ketone will be described. The last section deals with the finalization of the three syntheses.

2.2. Synthesis of the Components for the Pictet-Spengler Reaction

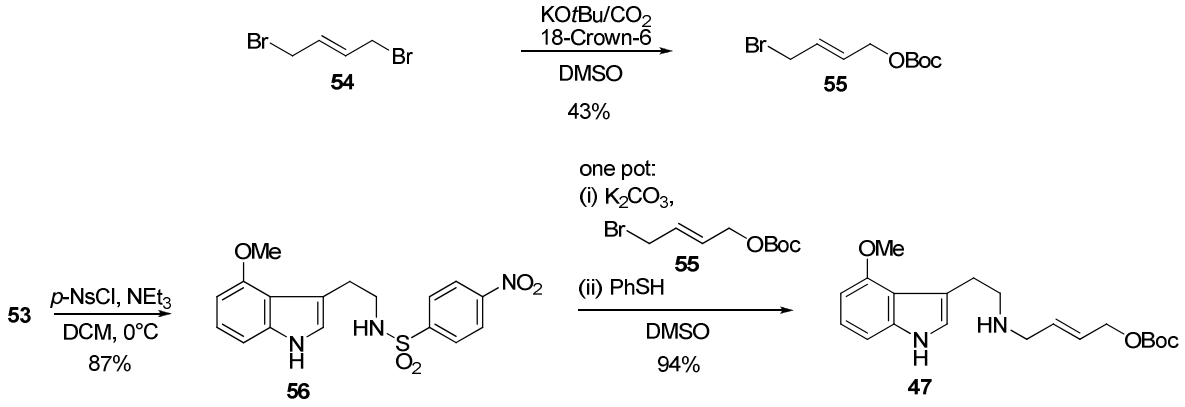
2.2.1. *Synthesis of the Tryptamine*

The synthesis of tryptamine **47** starts with commercially available 4-hydroxy-indole which was first methylated with iodomethane and potassium carbonate.[36] Next, 4-methoxy-indole **50** was formylated at the 3-position of the indole ring through a Vilsmeier-Haack reaction with *N*-chlorosuccinimide, triphenylphosphine and *N*,*N*-dimethylformamide to give aldehyde **51**.[37] Aldehyde **51** was treated with ammonium acetate and nitromethane to form first the Henry-product which immediately eliminates water to give the conjugated and therefore highly stable nitro alkene **52**. This was subsequently reduced to amine **53** with the help of lithium aluminum hydride.[38]



Scheme 9: Synthesis of the 4-methoxy-tryptamine

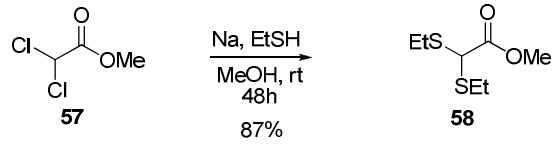
The synthesis of the functionalized amine **47**, was continued with protection of **53** using *p*-nosyl-chloride followed by alkylation with bromide **55** and deprotection after a Fukuyama protocol.[39, 40] The bromide **55** was synthesized in one step from (*E*)-1,4-dibromobut-2-en.[35]



Scheme 10: Synthesis of the functionalized tryptamine with help of a Fukayama protocol

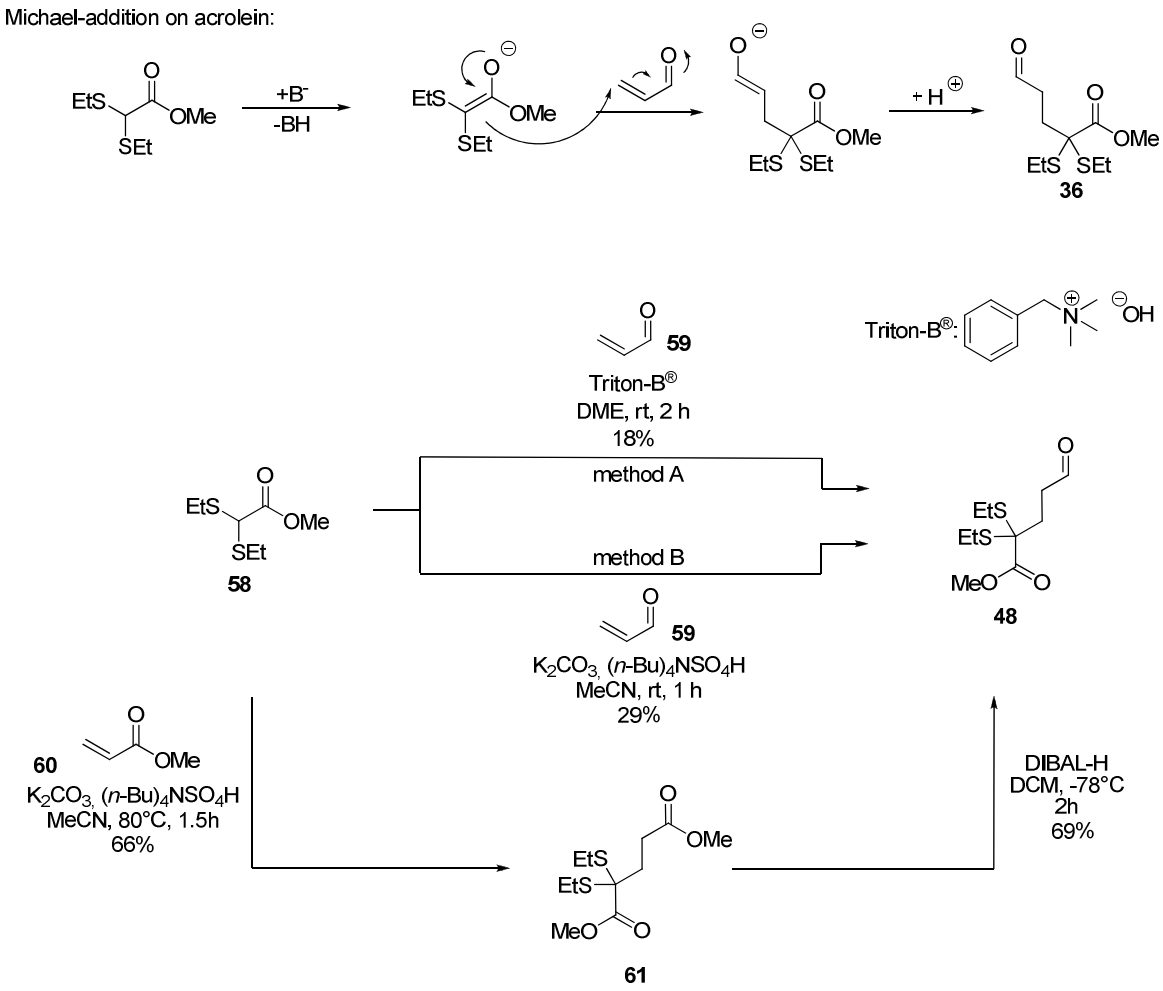
2.2.2. *Synthesis of the Aldehyde*

The synthesis of the aldehyde starts with installation of a thioacetal moiety in α-position to the ester group. This was realized with substitution of both chlorides of dichloroacetate **43** by ethanethiol (Scheme 11).[41]



Scheme 11: Synthesis of methyl bis(ethylthio)acetate

From **58** it was envisioned that after deprotonation a Michael-addition on acrolein would furnish aldehyde **48** (Scheme 12). As a first attempt Triton-B®, a quaternary ammonium hydroxide base, was applied with dimethoxyethane as a solvent for 2 h at room temperature (method A).[42] Unfortunately, the yield of 18% was rather disappointing. Therefore, another method was tried using tetrabutylammonium hydrogen sulfate in combination with potassium carbonate (method B).[43] The high reactivities of acrolein and the formed aldehyde both easily undergoing polymerization reactions are probably responsible for the low yield. In a third attempt to synthesize aldehyde **48** the same bases as for method B were applied in the Michael-addition this time on methyl acrylate instead on acrolein, followed by reduction of the resulting ester **61** with DIBAL-H. Although the overall yield for this method was higher than for method B, finally it was decided to synthesize the aldehyde with direct addition on acrolein due to the simplicity of the procedure and the fact that 20% starting material **58** was recoverable from the reaction.

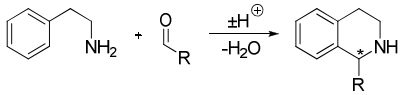


Scheme 12: Different strategies for the synthesis of aldehyde **48**

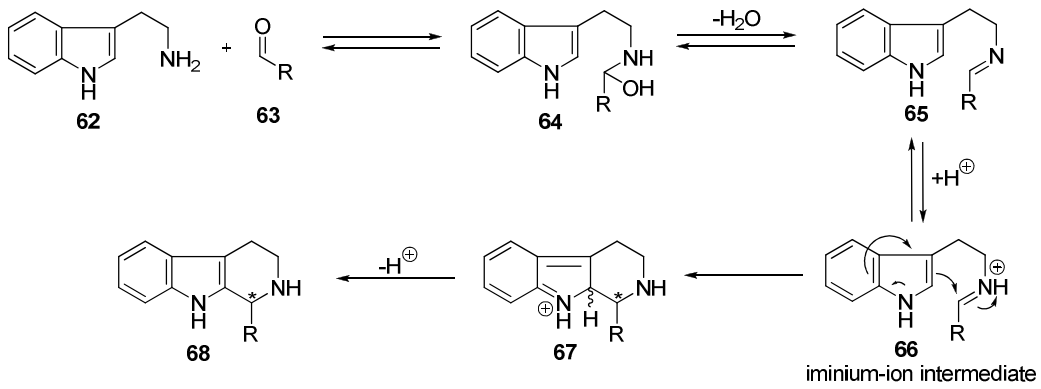
2.3. Asymmetric Pictet-Spengler Reaction

The Pictet-Spengler reaction is an acid catalyzed ring closing reaction between a tryptamine and an aldehyde to form tetrahydro-*β*-carbolines.[a] Discovered in 1911 by Amé Pictet and Theodor Spengler[44] and extended to indole bases by Tatsui in 1928[45] the Pictet-Spengler reaction still remains one of the most important methods for the preparation of these tricyclic systems. The mechanism of the reaction starts with condensation of tryptamine **62** with an aldehyde to form first the corresponding hemi-aminal which looses water to form imine **65**. Protonation of the imine gives the iminium-ion intermediate **66** on which ring-closure occurs

[a] The reaction can also be applied to phenylethylamines to form tetrahydroisoquinolines.

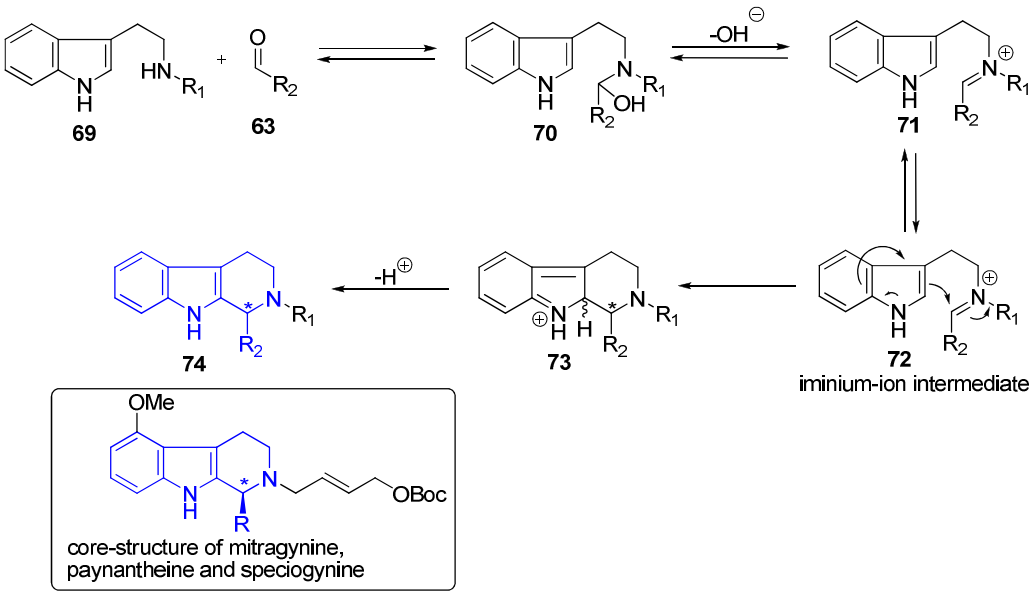


initiated by the electron rich indole system in a Mannich-type fashion. This step is not only enantiodiscriminating but has as well been reported as the rate-determining step.[46] With loss of a proton, **67** re-aromatizes to the tetrahydro-*β*-carboline **68**.



Scheme 13: Mechanism of the Pictet-Spengler reaction with unsubstituted tryptamines

For substituted tryptamines the mechanism is slightly different. Because of the substituent on the N_b-nitrogen the iminium-ion formation does not occur via protonation, but through loss of the hydroxyl-group of the hemi-aminal. Therefore, acid is not necessarily required for this process.



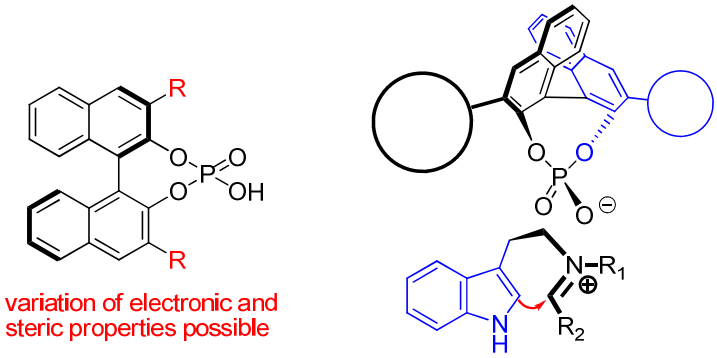
Scheme 14: Mechanism of the Pictet-Spengler reaction with substituted tryptamines

Since the tetrahydro-*β*-carboline core structure is present in many natural products, the Pictet-Spengler reaction became a useful tool for the preparation of these systems.[47, 48] After two decades of research using auxiliaries and chiral starting materials to create enantiopure

tetrahydro-*β*-carbolines the first catalytic and at the same time organocatalyzed approach was published in 2004.[49] The group of Jacobsen used a thiourea as an organocatalyst for the enantioselective synthesis of these compounds. Other publications utilizing organocatalysts with high enantioselectivity in the Pictet-Spengler reaction followed.[50-52] Because of the applicability and usefulness of the method, it was envisioned to use organocatalysis in the synthesis of (-)-mitragynine, (+)-paynantheine and (+)-speciogynine as well.

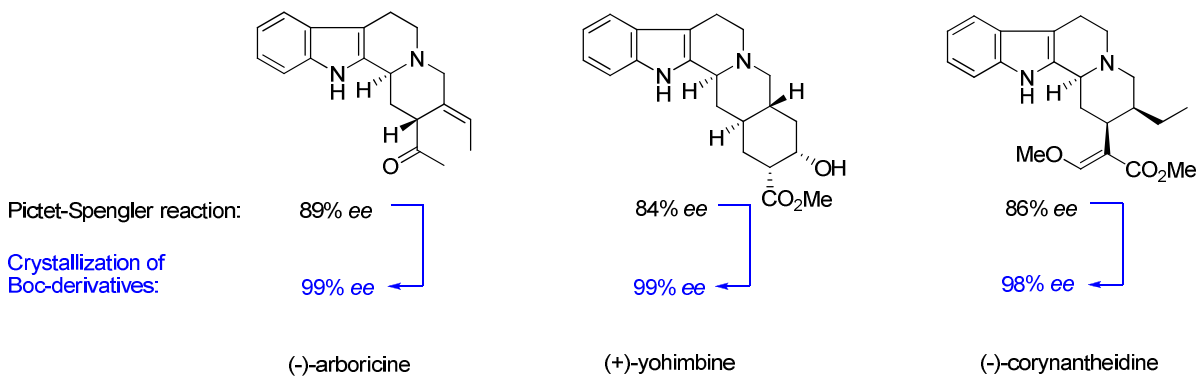
2.3.1. *Use of Binol-Phosphoric Acids as Organocatalysts*

First applied by List in 2006, BINOL-phosphoric acids evolved to widely applicable catalysts for the Pictet-Spengler reaction.[50] The versatile variation of the chiral backbone allows steric and electronic tuning depending on the required properties for the reaction. The interaction of the catalyst with the substrate is depicted in Scheme 15. BINOL phosphoric acids are suitable catalysts for the reaction because the anionic form of the acid is able to coordinate to the iminium ion intermediate via ion attraction. The backbone of the catalyst creates a chiral environment around the substrate in which ring-closure occurs selectively from one side. The interaction of the organocatalyst with the substrate and the resulting stereochemistry are therefore established in the rate-determining step.



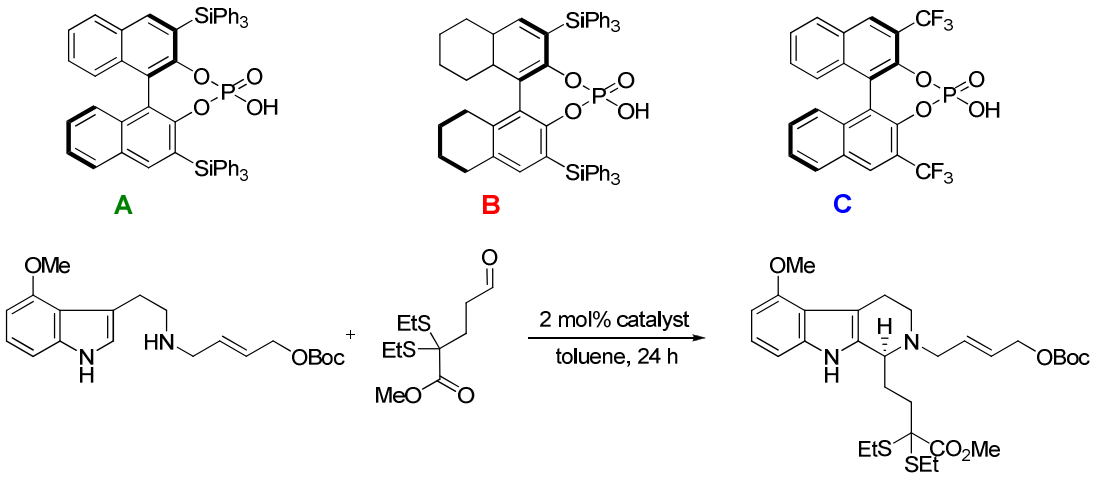
Scheme 15: Interaction of BINOL-phosphoric anion with the iminium-ion intermediate

In our group, BINOL-phosphoric acids have been applied in the synthesis of several natural products (Scheme 16).[53-55] In the synthesis of arboricine, yohimbine as well as corynantheine, the Pictet-Spengler reaction was carried out with very good enantioselectivity. Later in the syntheses, when a Boc-group was installed on the indolic nitrogen, the intermediates were crystallized to higher *ee* to furnish the end-products in high enantiomeric purity.



Scheme 16: Natural products synthesized through an asymmetric Pictet-Spengler reaction

To determine the applicability of BINOL-phosphoric acids in the synthesis of mitragynine, paynantheine and speciogynine three different catalysts (Scheme 17) were screened in the Pictet-Spengler reaction. Catalyst A and B are sterically different since the backbone of catalyst B is hydrogenated, whereas catalyst C differs in the electronegativity of the substituent at the 3-position.



Scheme 17: Pictet-Spengler reaction with BINOL-phosphoric acids

1. Variation of the Catalyst

The reactions were performed with 2 mol% catalyst, 1.2 equivalents of aldehyde and molecular sieves as a drying agent at room temperature for 24 h. The results of the reactions are shown in the table below. Unfortunately, the catalysts seemed to be completely

unsuccessful in introducing chirality to the reaction. The measured *ee*s were very low and although all catalysts had the same chirality, different enantiomers were obtained.

entry	catalyst	drying agent	temperature	*ee* [%]
1	A	MS 4 Å	0 °C	-3
2	B	MS 4 Å	0 °C	7
3	C	MS 4 Å	0 °C	7

Table 1: Variation of the catalyst

2. Variation of the Temperature

Next it was tried to improve the results of the previous experiments by variation of the temperature (Table 2). Again low *ee*s were obtained and the enantiomeric outcome seemed random.

entry	catalyst	drying agent	temperature	*ee* [%]
1	A	MS 4 Å	-10 °C	-2
2	B	MS 4 Å	-10 °C	-6
3	C	MS 4 Å	-10 °C	0
4	A	MS 4 Å	-78 °C	11

Table 2: Variation of the temperature

3. Variation of Drying Agents

During the investigations on the phosphoric acid catalyzed Pictet-Spengler reaction it was noticed that the reaction already proceeds when no chiral acid was used. It was discovered that the molecular sieves were responsible for the fast product formation and obviously had sufficient catalytic activity for our system. Originally, the molecular sieves were intended to work as a drying agent to keep away the water which might interfere in the interaction of the catalyst with the substrate. As a consequence, it was concluded that when no drying agent or other drying agents were used, the BINOL-phosphoric acids were able to catalyze the process. Other drying agents such as $MgSO_4$ and Na_2SO_4 (entries 1 and 2 in Table 3) were expected to lack any catalytic activity. Unfortunately, for $MgSO_4$ hardly no product was formed and for Na_2SO_4 the *ee* was really low. When no drying agent was applied and the reaction was performed with BINOL-phosphoric acids only the *ee* was unsatisfactory as well.[b] At this stage no further attempts were made using phosphoric acids in this reaction.

[b] Even when the catalyst loading was increased by twice the amount, no change in the *ee* was observed.

entry	catalyst	drying agent	temperature	*ee* [%]
1	B	MgSO4	-10 °C	-
2	B	Na_2SO4	-10 °C	-9
3	B	-	0°C	-10

Table 3: Variation of drying agents

2.3.2. *Use of Bifunctional Cinchona Alkaloids as Organocatalysts*

Inspired by the work of Jacobsen who used thiourea catalysts in his Pictet-Spengler reactions,[49, 56, 57] the bifunctional catalyst developed by Takemoto[58] was applied to the reaction. The catalyst contains a thiourea functionality which is able to increase the electrophilicity of carbonyl groups through coordination. Additionally, a tertiary amine is able to abstract hydrogens and thus donate electrons due to its Lewis-basic character.

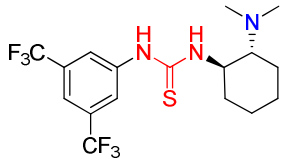
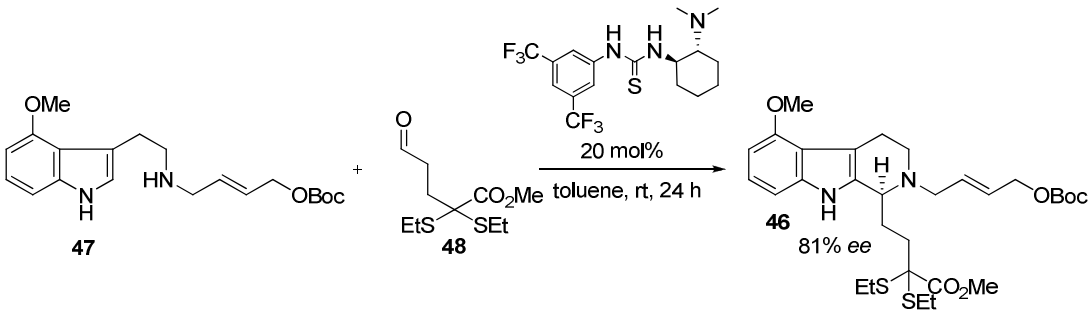


Figure 3: Takemoto catalyst

The catalyst was applied in 20 mol%, a normal catalyst loading for thiourea catalysts. Fortunately, the catalyst was extraordinarily good and gave an *ee* of 81% (Scheme 18).

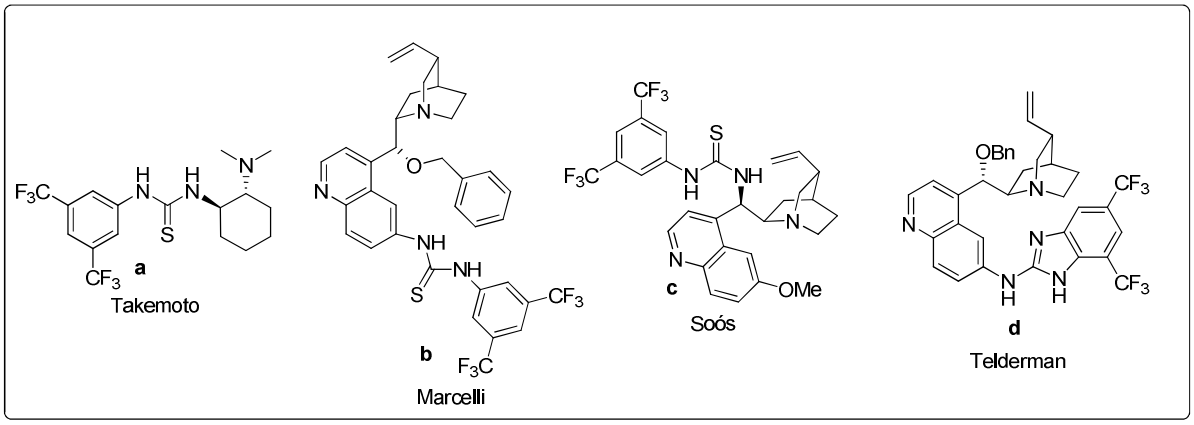


Scheme 18: Takemoto's catalyst in the Pictet-Spengler reaction

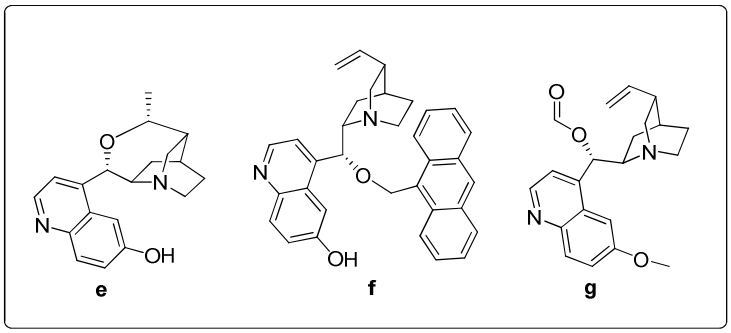
This result encouraged us to investigate the bifunctional catalyzed Pictet-Spengler reaction in more detail (Table 4). When the catalyst loading of Takemoto's catalyst was reduced to 10 mol%, the *ee* dropped by 20% (entry 1). Other catalysts such as **b**,[59] carrying the thiourea at the quinoline part, or **d**,[60] bearing a benzimidazole at this position, were not successful and

gave a very low enantioselectivity as well as an unclean reaction. Catalyst **c** developed by the Soós group gave by far the best result.[61] The observed *ee* of 89% was even higher than the *ee* obtained with the Takemoto catalyst. To find out whether the basic nitrogen or the thiourea group was responsible for the catalysis, catalysts **e-g**[62, 63] and one of Jacobsen's commercially available thiourea catalysts **h** were applied.[57, 64]

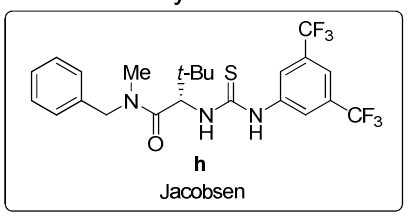
bifunctional catalysts



cinchona catalysts



thiourea catalyst

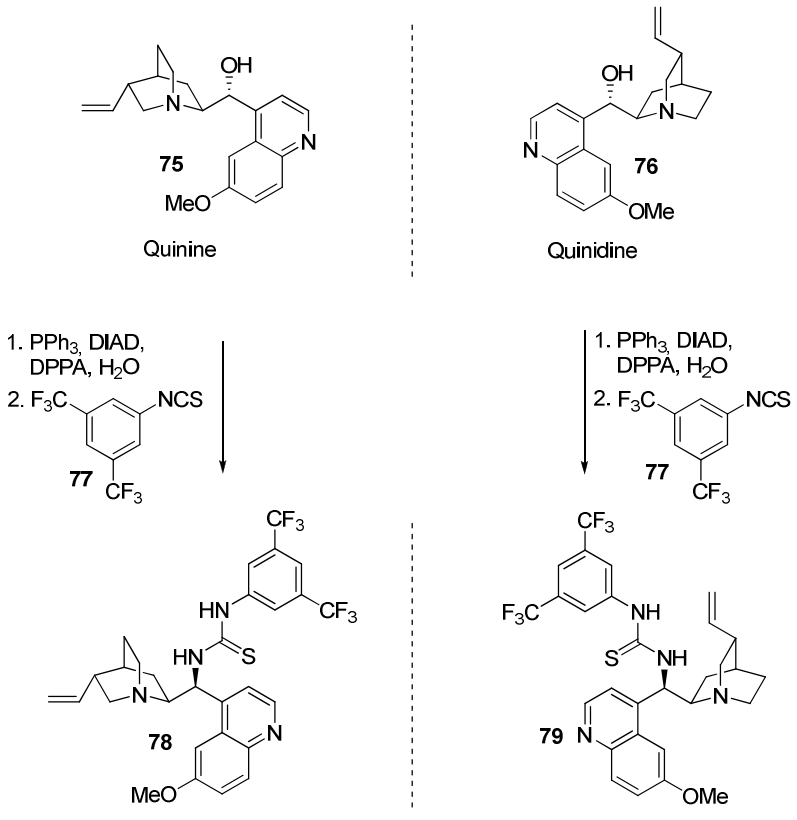


entry	catalyst	cat. loading	solvent	time	temperature	yield[a]	ee [%]
1	a	0.1	toluene	3 d	rt	47	-60
2	a	0.2	toluene	4 d	rt	57	-81
3	b	0.2	toluene	3 d	rt	29	-7
4	c	0.2	toluene	3 d	rt	90	-89
5	d	0.2	toluene	2 d	rt	71	-5
6[b]	e	0.2	toluene	5 d	rt→ 70°C	57	-11
7[c]	f	0.2	toluene/DCM	2 d	rt	58	-2
8[b]	g	0.2	toluene	5 d	rt→ 70°C	63	-6
9	h	0.2	toluene	2 d	rt	68	53
10[d]	h	0.2	toluene	2 d	rt	99	10

[a] determined by weight, [b] after 4 days very little conversion was obtained, the solution was heated to 70°C for 4 h; [c] due to the insolubility of the catalyst in pure toluene 50% DCM were added; [d] BzOH was used as an additive (20 mol%).

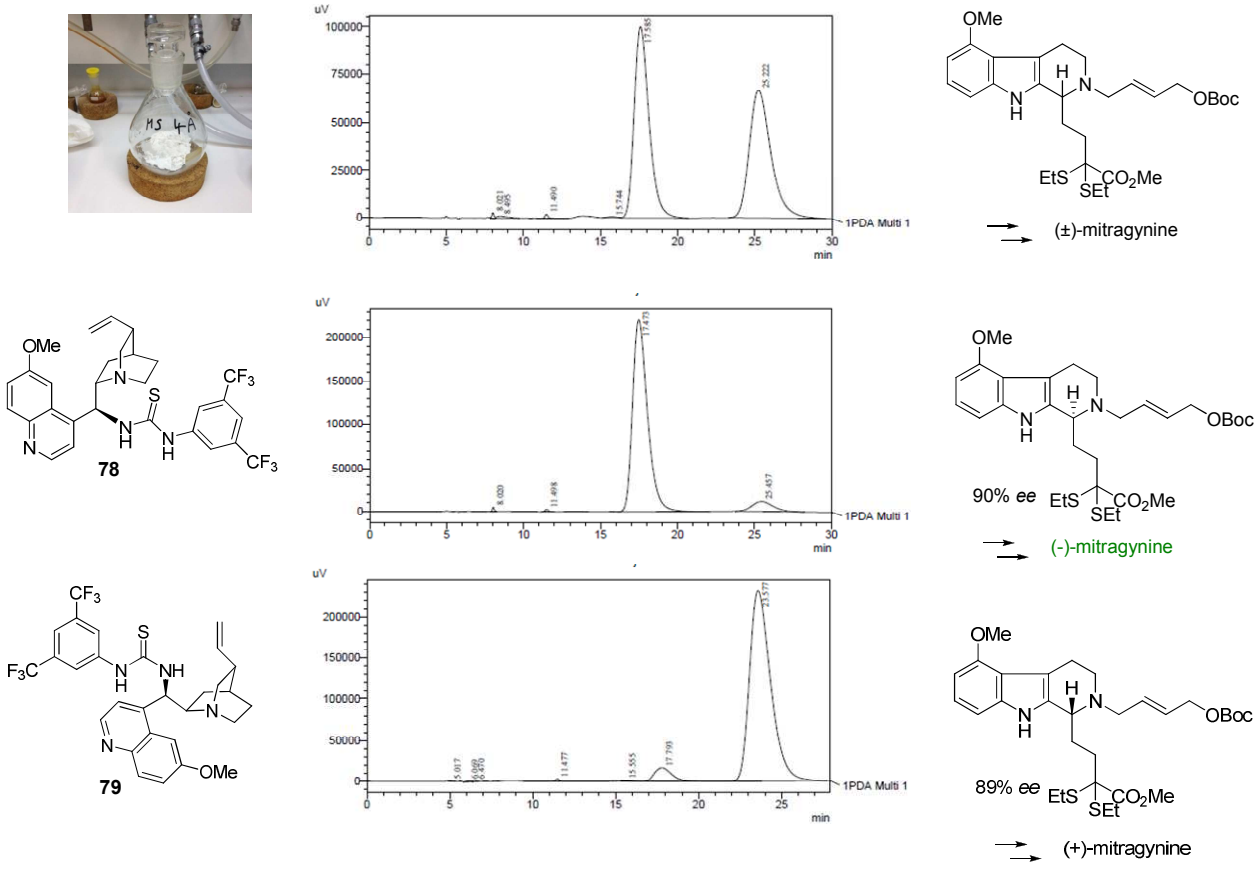
Table 4: Catalyst screening

Basic catalysts **e** and **g** gave low *ee*s and the reactions were slow so that heating was required to get some product formation. In these cases product formation occurs just by addition of enough activation energy but not necessarily catalyzed by the bifunctional catalyst. Catalyst **f** showed a really unclean reaction and low *ee* as well. The Jacobsen catalyst gave an enantiomerically enriched product of 53% *ee* but an unclean mixture was observed (entry 9). When benzoic acid is added as a co-catalyst the *ee* dropped to 10% (entry 10). Obviously, the best results were obtained using bifunctional catalysts like **a** and **c** which carry a thiourea group and a basic tertiary amine. The good stereoinduction and the similar results of both catalysts probably result from the close proximity of the thiourea group to the quinuclidine system. The functional groups are close together and the system allows less flexibility than catalyst **b** or **d**. Catalyst **c** can be synthesized from the natural product quinidine **76**, an alkaloid isolated from the Chinchona bark, a number of small trees native to South America.[65] The pseudoenantiomer of quinidine, quinine **75** is also isolated from the same tree species and only the position of the vinyl group keeps them apart from being exact enantiomers. From both pseudoenantiomers catalysts **78** and **79** can be obtained by a Mitsunobu-Staudinger sequence were the alcohol is converted into an amine followed by addition of the amine to an isothiocyanate to introduce the thiourea functionality.[61] This process is easily scalable, so that several grams of the catalyst were accessible.



Scheme 19: Synthesis of the Soós catalyst

With both pseudoenantiomeric forms of the catalyst at hand we were then able to synthesize both enantiomers in the Pictet-Spengler reaction. From the reaction with molecular sieves 4 Å we had access to the racemic product.[c] In Scheme 20 the chromatograms of the chiral HPLC measurements are depicted. Using catalyst **78** derived from quinine the intermediate leading to natural (-)-mitragynine becomes accessible. With the other catalyst **79**, the route towards (+)-mitragynine can be established, offering the possibility to investigate the difference in biological activity between the two enantiomers.

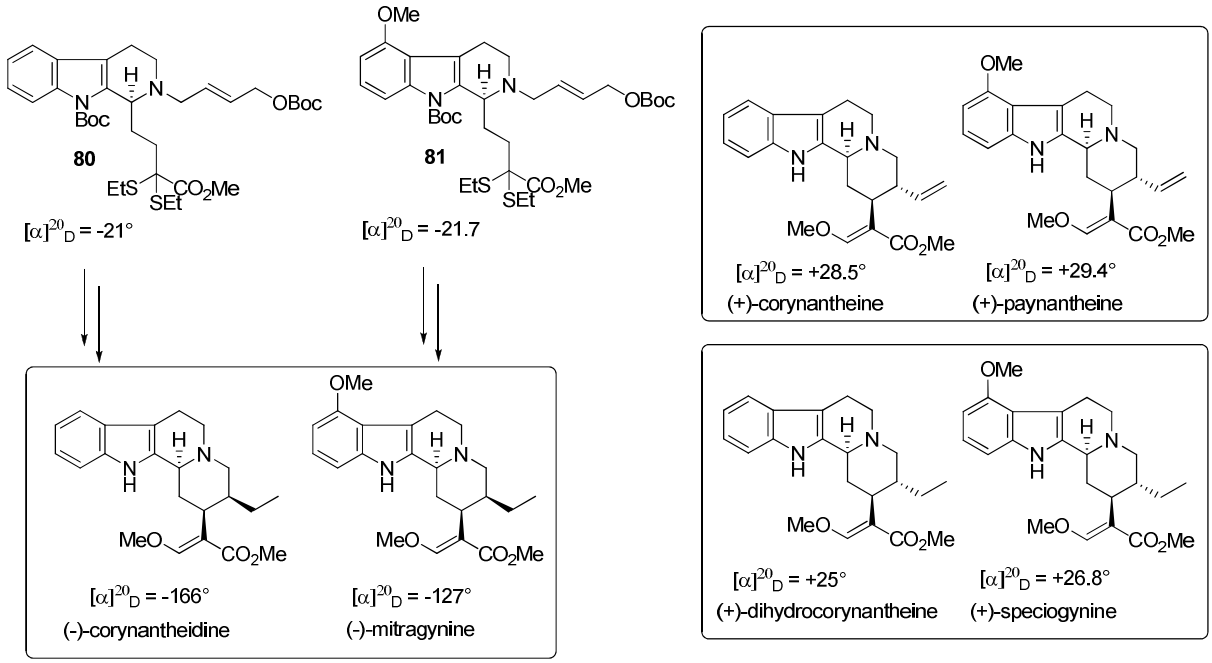


Scheme 20: Enantiomers available from the Pictet-Spengler reaction

[c] The molecular sieves also functioned nicely as a catalyst up to a 6 mmol scale.

2.3.3. *Optimization of the Thiourea-Catalyzed Pictet-Spengler Reaction*

Having obtained good results with the Soós catalyst it was tried to further enhance the *ee* through variation of the conditions. It was measured that with catalyst **79** the order of elution in the chiral HPLC was the same as for the corynanthe alkaloids.[d] Because of that it was assumed that with catalyst **79**, the right enantiomer is obtained. When the optical rotation was determined later, it turned out that an opposite direction was observed than for the intermediate of the (-)-corynantheidine-synthesis.[55] There is a close analogy of optical rotations between the natural products mitragynine and corynantheidine, paynantheine and corynantheine as well as for speciogynine and dihydrocorynantheine (Scheme 21). Therefore, it can be concluded that both Pictet-Spengler products **80** and **81** should have the same optical rotation. Hence, the enantiomers of mitragynine and corynantheidine elute in reversed order in HPLC. To synthesize the enantiomer **81** which leads to (-)-mitragynine catalyst **78** is required instead of **79**. This was found, after the optimization experiments were carried out.



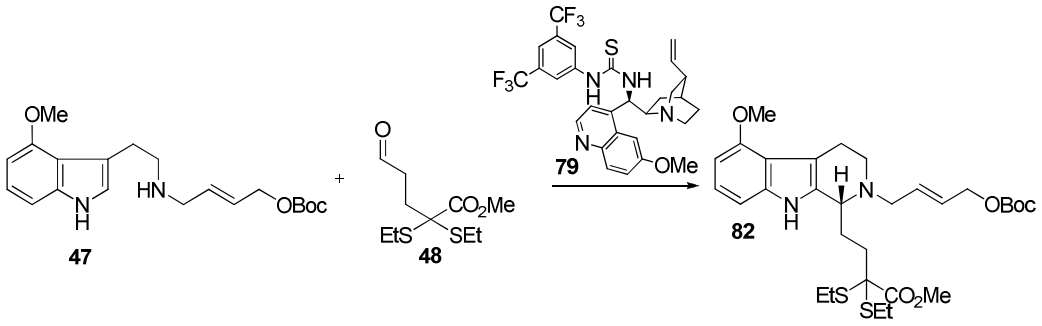
Scheme 21: Resemblance of optical rotation and structure

The optimization experiments were performed with catalyst **79** as shown in Table 5. All reactions were carried out over 24 h and the *ee* was determined by chiral HPLC. Important to mention: in all experiments the same batches of tryptamine, aldehyde and catalyst were used to exclude a deviation of the results depending on the starting materials. Entry 1 of

Table 5 shows the initial experiment carried out in toluene at room temperature for 24 h where an *ee* of 89% was observed. Firstly, the temperature of the reaction was changed

[d] Very similar natural product series, recently synthesized by our group.

(entries 2-4). Surprisingly the *ee* decreased with lower temperatures. When the temperature was increased a slightly lower *ee* was observed which shows that room temperature seems to be the optimal temperature for the reaction. Variation of the solvent (entries 5-8) did not result in an increase of the *ee*. Ethers such as THF and *n*-dibutylether gave the lowest enantioselectivity probably due to disturbance of the catalyst-substrate interaction through the lone-pair bearing oxygens. The addition of drying agents to absorb water which is released from the reaction (entries 9-11) did not result in significant improvement of the enantiomeric excess. Usually, water strongly disturbs the catalysis as was often observed for BINOL-phosphoric acids.[51] In our case, water seems not to have a strong influence on the *ee*. Finally, optimization of the catalyst loading was studied. Although the catalyst is easy to make it would be advantageous to reduce the catalyst loading to less than 20 mol%. With a lower amount of catalyst, the enantioselectivity decreased significantly (entries 12 and 13). Using a higher catalyst loading (entry 14), however, did not improve the *ee* in comparison to the initial experiment with 20 mol%. In addition to the experiments shown in the table, the dependence of the *ee* on the equivalent of aldehyde and the molarity of the reaction were investigated. It was observed, that the amount of aldehyde did not have any influence on the selectivity of the reaction, so did the concentration. Previous reports stated that there is a strong dependence of the enantiomeric excess on the concentration caused by possible complexation of the catalyst.[66] Using solutions of different molarity, however, did not verify this result. Overall, the reaction showed strong reproducibility and robustness.



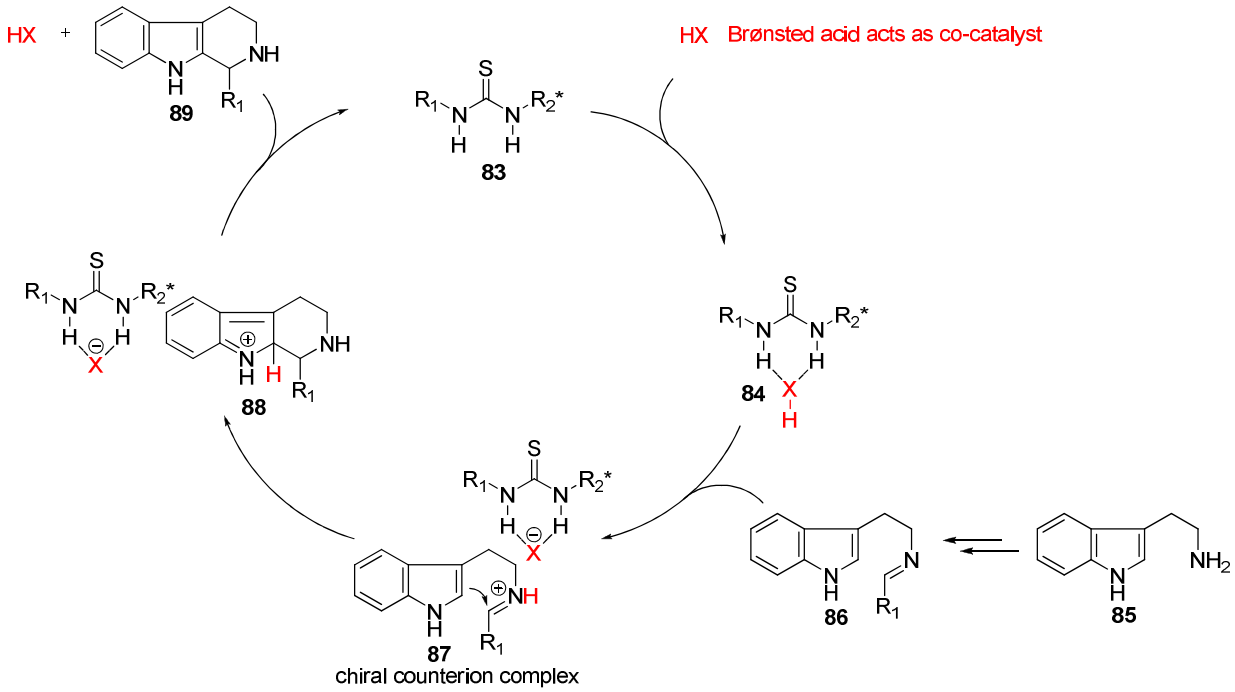
entry	temperature	solvent	drying agents	cat. loading	conversion [%]	*ee* [%]
1	rt	toluene	-	20 mol%	99	89
2	-20°C	toluene	-	20 mol%	99	82
3	0°C	toluene	-	20 mol%	99	80
4	40°C	toluene	-	20 mol%	99	86
5	rt	DCM	-	20 mol%	91	84
6	rt	*n*-dibutylether	-	20 mol%	95	78
7	rt	THF	-	20 mol%	90	63
8	rt	CHCl3	-	20 mol%	90	83
9	rt	toluene	MS 4 Å	20 mol%	99	90
10	rt	toluene	$MgSO_4$	20 mol%	99	92
11	rt	toluene	Na_2SO_4	20 mol%	99	91
12	rt	toluene	-	10 mol%	99	78
13	rt	toluene	-	15 mol%	99	85
14	rt	toluene	-	30 mol%	99	90

Table 5: Optimization of the Pictet-Spengler reaction

2.3.4. *Mechanistic Considerations Towards the Substrate-Catalyst Interaction*

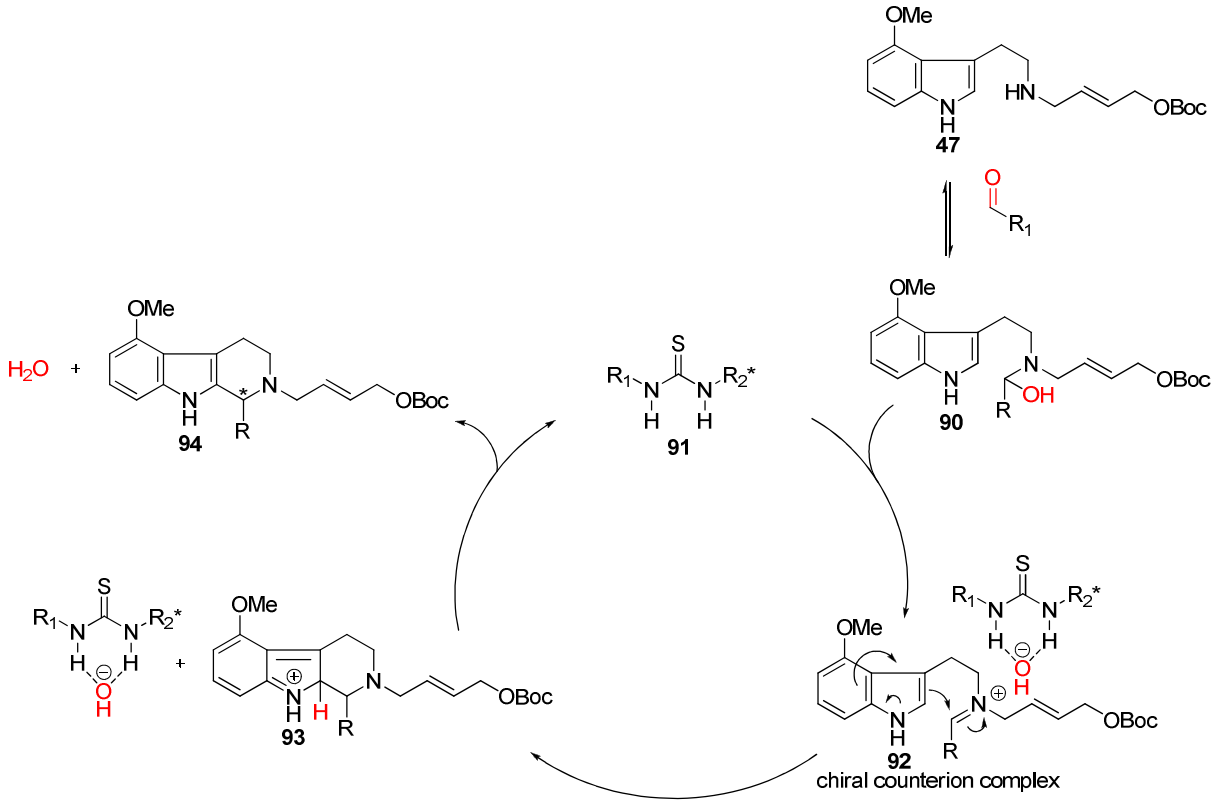
Switching to another catalyst system from BINOL-phosphoric acids to bifunctional *Cinchona* alkaloids carrying a thiourea group implements a completely different interaction between the catalyst and the substrate. While deprotonated phosphoric acids form anion pairs with the iminium ion, this is not possible with a neutral thiourea. In their reports Jacobsen and coworkers formulated a catalytic cycle involving thioureas.[57] In contrast to our substrate Jacobsen used unsubstituted tryptamines which do not carry a substituent on the N_b-nitrogen. Additionally, Jacobsen applied Brønsted acids as co-catalysts which act in combination with the thiourea catalyst. In the first catalytic step, the thiourea is coordinating to the Brønsted acid to form the active species of the catalyst **84** (Scheme 22). When the imine enters the catalytic cycle it is protonated by the catalyst species to from a chiral counter-ion complex **87**. This one consists of the iminium ion and the thiourea carrying the anion of the Brønsted acid via anion-bonding. The thiourea creates a chiral environment in which the ring-closure takes place, similar to the catalysis with phosphoric acids. When the attack occurred, ring-closed

product **88** rearomatizes to the tetrahydro-*β*-carboline **89** with reformation of the Brønsted acid and the thiourea catalyst.



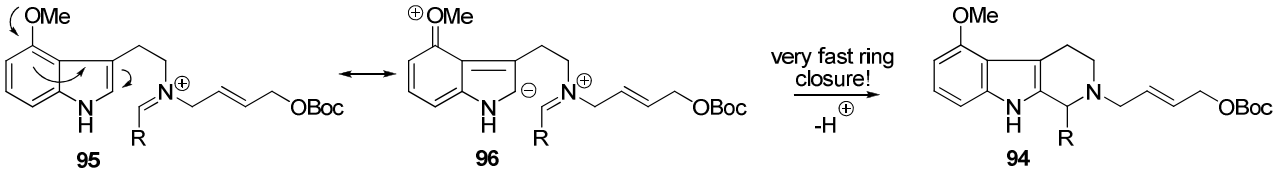
Scheme 22: Proposed catalytic cycle for thiourea catalysts by Jacobsen

Comparing Jacobsen's and our catalytic system, there are certainly differences, but also similarities. The most important difference is the presence of a substituent on the N_b-nitrogen. In contrast to Jacobsen's Pictet-Spengler reaction our substrate does not need to be activated by an acid but by simple secondary iminium ion formation. Our presumption is that the thiourea assists in this imine formation. In our case the imine is formed through abstraction of the hydroxyl anion from hemi-aminal **90**. This abstraction is facilitated by the thiourea via hydrogen-bonding. A chiral counterion-complex is formed resembling the one proposed by Jacobsen. In proximity of the thiourea catalyst ring-closure occurs and after re-aromatization of intermediate **93**, the tetrahydro-*β*-carboline, the thiourea catalyst and water are formed.



Scheme 23: Proposed catalytic cycle

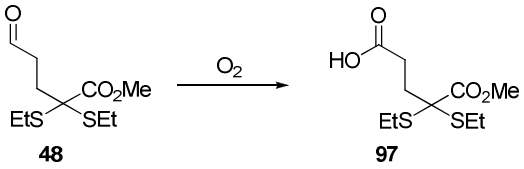
When we deal with the process of thiourea catalysis it is necessary to think about the question why there were such tremendous problems involved with BINOL-phosphoric acid catalysts. Our conjecture is that the explanation could be found if one had a closer look on the rate-determining step of the catalysis. In contrast to the natural products which were successfully synthesized by our group with the help of BINOL-phosphoric acid catalysis (Scheme 16) in this system the indole ring is strongly activated by an electron-donating methoxy group (Scheme 24). Through the strongly nucleophilic indole ring the ring-closure takes place very fast so that it is probably not the ring-closure anymore which is rate-determining, but the formation of the iminium ion. Exactly this formation of the iminium ion is facilitated by a thiourea catalyst (Scheme 23) which gives additional rigidity by two hydrogen bonds. Moreover, the assumption is supported by the fact that molecular sieves catalyzed the reaction as well. This is easy to understand since they support abstraction of the hydroxyl-group from the hemi-aminal through their water-binding properties. To conclude, having the methoxy-group present on the indole ring consequently changes the rate-determining step of the reaction and another catalyst system is required.



Scheme 24: Strong activation through electron-donating methoxy-group

2.3.5. *Necessity of Acid for the Pictet-Spengler Reaction*

During the scale-up of the Pictet-Spengler reaction it was discovered, that a freshly prepared aldehyde resulted in significant lower *ee* and yield as an aldehyde which was made half a year ago and stored in the fridge under argon. The same result was observed when an older batch of aldehyde was columned and used immediately in the reaction. This result was highly surprising since a possible oxidation of the aldehyde over time (Scheme 25) was always considered disadvantageous for the enantioselectivity.[e] In our case however, acid is absolutely required for a good stereoselective reaction.[f]



Scheme 25: Oxidation of the aldehyde

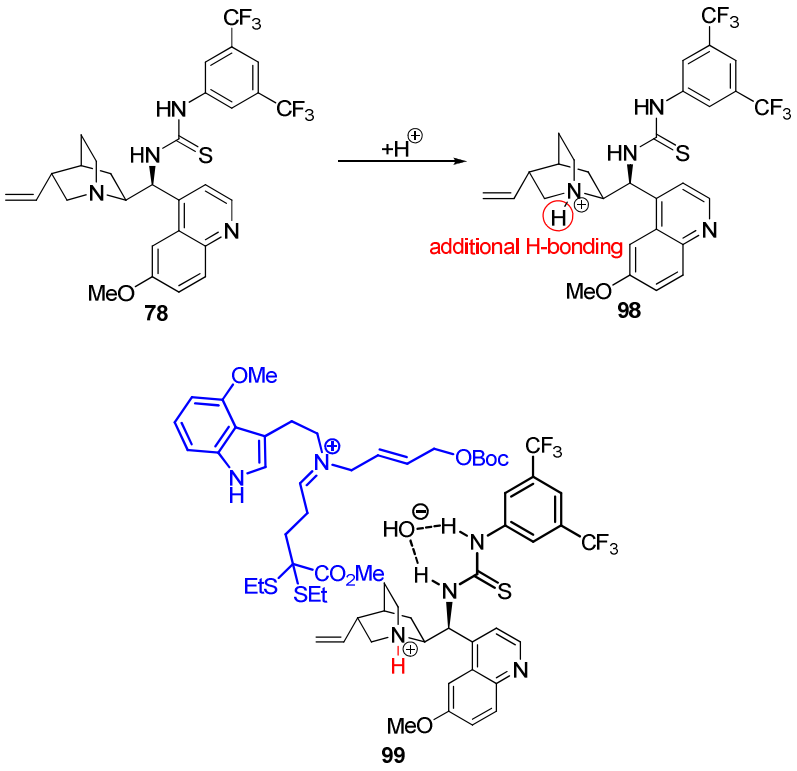
The source of acid can be either partly oxidized aldehyde or added benzoic acid. The results available are of a rather qualitative nature.

An aldehyde batch which was freshly made gave an *ee* of 52% (90% with an old batch) and a yield of 60% (80-90% with and old batch). If the aldehyde was exposed to air for two days at room temperature, the *ee* increased to 66%. Two further days resulted in an *ee* of 81%, when benzoic acid (20 mol%) was added the *ee* was even increased to 88%. Obviously there is a strong dependence between acid and enantioselectivity. A possible reason for this necessity to achieve a selective reaction might be a protonation of the quinuclidine-nitrogen. Through protonation, additional hydrogen is available which can assist in beneficial interaction with

[e] Carboxylic acids are able to catalyze the Pictet-Spengler reaction as well which usually results in a decrease of the *ee*.

[f] Although the aldehyde was stored under argon, the compound surely was exposed to air when the container was opened and closed.

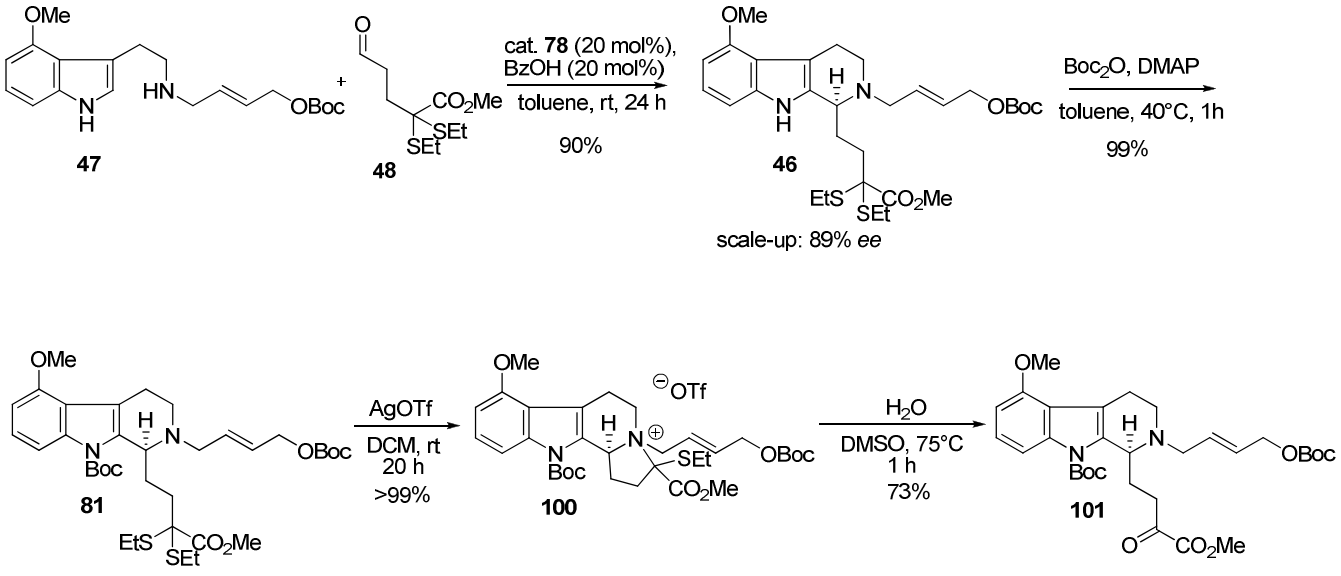
the substrate through hydrogen-bonding (Scheme 26). It is hard to predict with which group the hydrogen-bonding takes place but a possible interaction would be with the abstracted hydroxyl-anion. It is also possible that internal hydrogen binding takes place in the catalyst, forcing the catalyst in a special conformation which is beneficial for the stereoinduction.



Scheme 26: Protonation of the catalyst

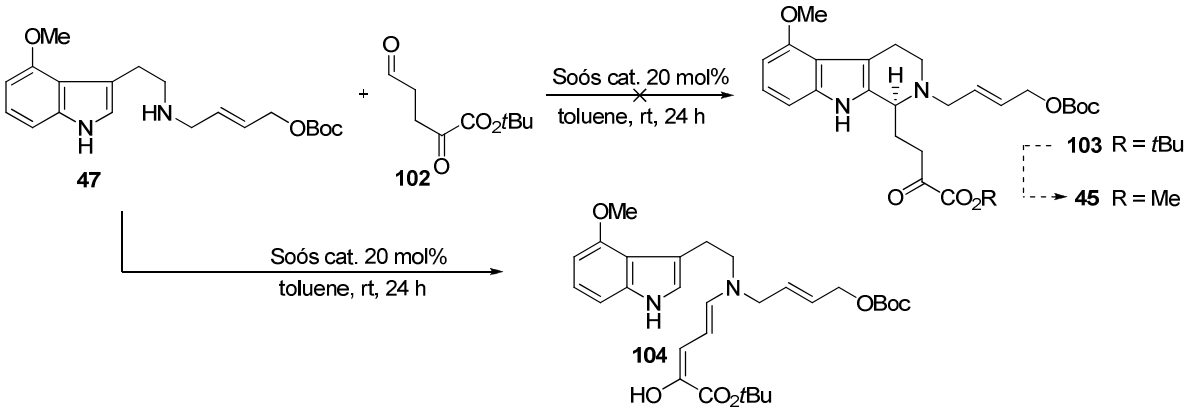
2.4. Synthesis of the α-Keto-Ester

The next step towards the desired corynanthe alkaloids was the deprotection of the thioacetal. At first instance the indole-nitrogen of **46** was protected with a Boc group (Scheme 27). This is necessary since the indole nitrogen is more nucleophilic than the N_b-nitrogen and, unprotected, forms irreversible ring-closure on the α-keto-ester instead the N_b-nitrogen. Additionally, the indole ring is stabilized against oxidation during hydrolysis.[55] Boc-protected tetrahydro-*β*-carboline **81** is transformed to salt **100** with addition of AgOTf. The salt is hydrolyzed in the next step to give the α-keto-ester.



Scheme 27: Synthesis of the α-keto-ester

To shorten the synthesis it was attempted to use an aldehyde containing the keto-functionality already, so that Boc-protection and the two following steps are not necessary anymore. Previous investigations in our group experienced great instability of the corresponding methyl ester. The analogous *t*Butyl-ester however, promised to be more stable to the conditions and could later be transformed to the desired methyl ester **45**. The aldehyde was applied in the Pictet-Spengler reaction with 20 mol% bifunctional catalyst (Scheme 28).

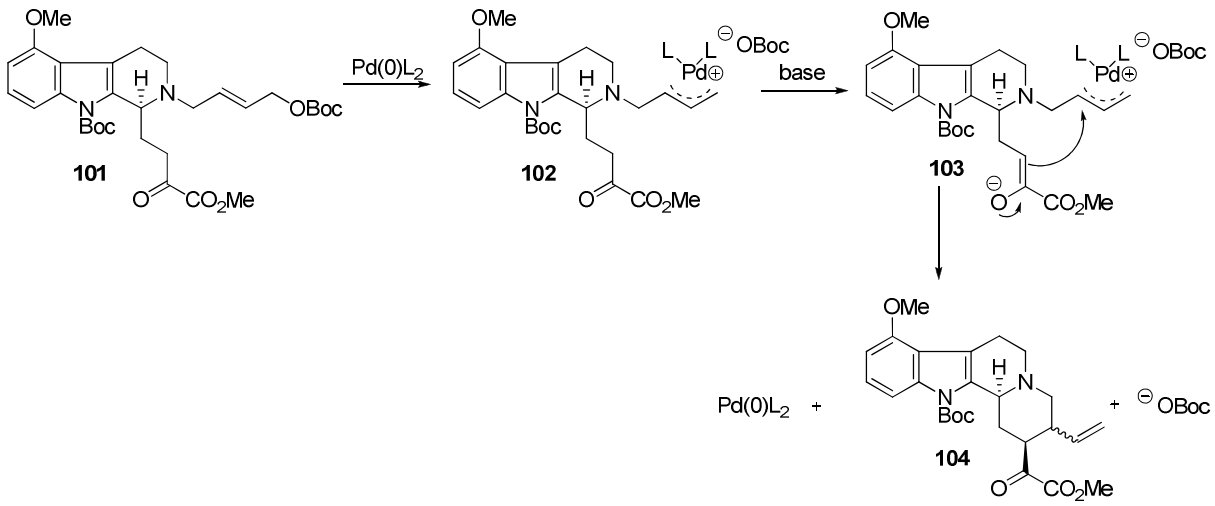


Scheme 28: Pictet-Spengler with α-keto-ester

Unfortunately, instead of the corresponding Pictet-Spengler product **103**, enamine **104** was obtained forming a stable, conjugated and irreversible intermediate. A short cut of the synthesis using aldehydes carrying a keto-group already was therefore not possible.

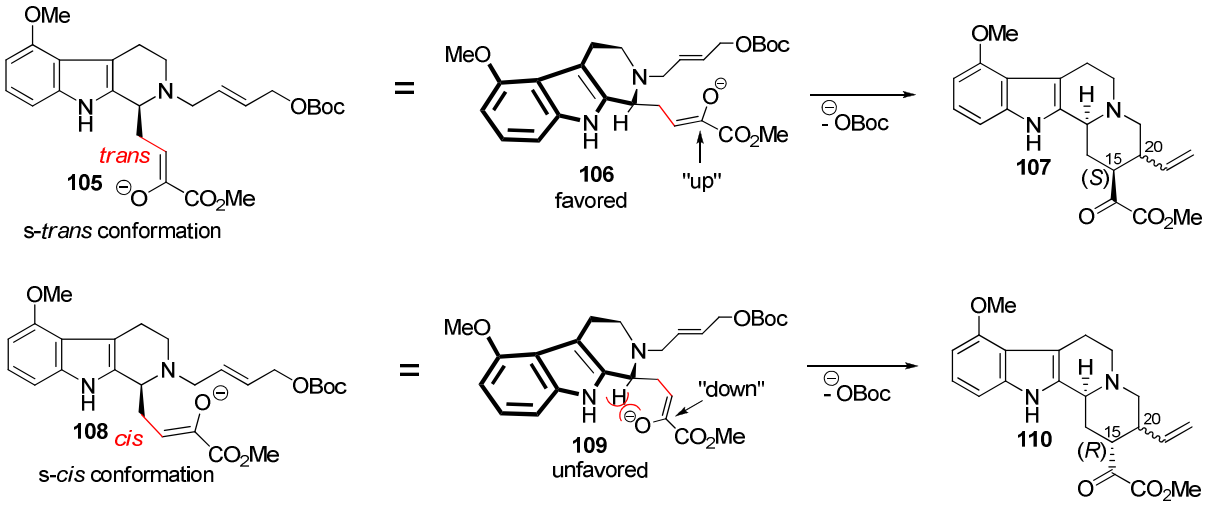
2.5. Tsuji-Trost Allylic Alkylation

The final ring was installed via a Tsuji-Trost allylic alkylation. In general, a palladium complex is added to the alkene which coordinates to the allylic fragment with loss of the OBoc group to from **102** (Scheme 29). A base is added to deprotonate the α-position of the ketone to form the enolate **103** which undergoes nucleophilic attack on the allylic fragment. As a product a six-membered ring bearing a vinyl-substituent is formed.



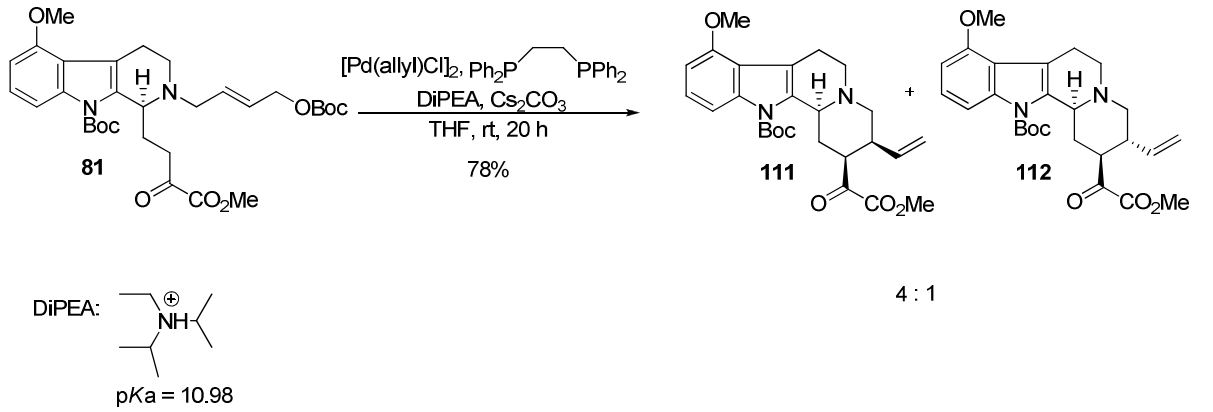
Scheme 29: Mechanism of the Tsuji-Trost allylic alkylation

The stereoselectivity in the reaction is determined by the already existing stereocenter. After formation of enolate **103** there are two conformations possible. The first one having the single bond in a s-*trans* configuration leading to diastereomer **107** and the second one with the single bond in a s-*cis* configuration which results in stereoisomer **110**. In the intermediate with s-*cis* configuration unfavorable steric interactions occur making the formation of isomer **110** rather unlikely. On the other hand, intermediate **106** does not show this unfavorable interaction while having an s-*trans* configuration. Therefore, the formation of isomer **107** is clearly favored and leads to preferred (*S*)-configuration of stereocenter C-15. Influence on stereocenter C-20 is rather difficult since there is no stereoselective induction in close proximity of the substrate available.



Scheme 30: Diastereoselection of stereocenter C-15

In the reaction we used allylpalladium(II) chloride dimer as the catalyst precursor. The precursor was combined with a bidentate phosphine ligand to from the active catalyst species. As a base, *N*,*N*-diisopropylethylamine (Hünig's base) in combination with Cs_2CO_3 was applied. The reaction gave the two desired diastereomers in a ratio of 4:1 with predominance of the *cis*-isomer which leads to (-)-mitragynine.

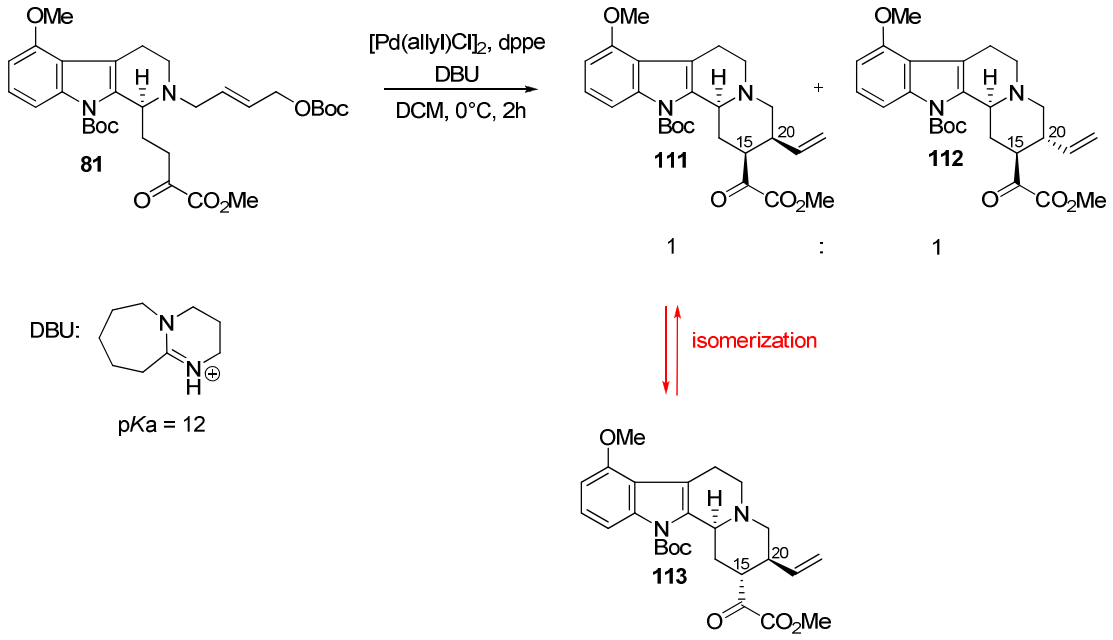


Scheme 31: Tsuji-Trost reaction using DiPEA as a base

As another base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was used since its basicity is slightly higher and it was expected to change the rate of enolate formation. This possibly changes the ratio between the observed isomers as well (Scheme 32). The resulting ratio was about 1:1 which is favorable because an equal amount of material is obtained to finish both routes towards mitragynine, paynantheine and speciogynine. Unfortunately, a third isomer **113** was observed disturbing the separability of the two favored isomers. Exposing the two

isomers **111** and **112** to catalytic amounts of DBU and following the mixtures by NMR revealed that the unfavored isomer was formed from **111** in the basic medium. The *trans*-isomer **112**, however, remained unaffected by addition of base. From that it was concluded that the unwanted isomer is formed through an isomerization process from *cis*-isomer **111** and ends up with inversion of stereocenter C-15. Unfortunately, the structure could not be confirmed analytically, since the isomer was always observed in mixtures with **111** or **112** and never isolated separately.

The attempts to use different ligands with increased bite angles in the reaction with DiPEA did not lead to significant improvement of the *cis*/*trans* ratio. On the contrary, with increased bite angle, the reaction rate decreased significantly and product formation stopped completely at an angle of 111.7° (Xantphos). Dppm with a smaller bite-angle than dppe (72° compared to 85° for dppe) or $P(OMe)_3$ as a monodentated ligand barely resulted in product formation.

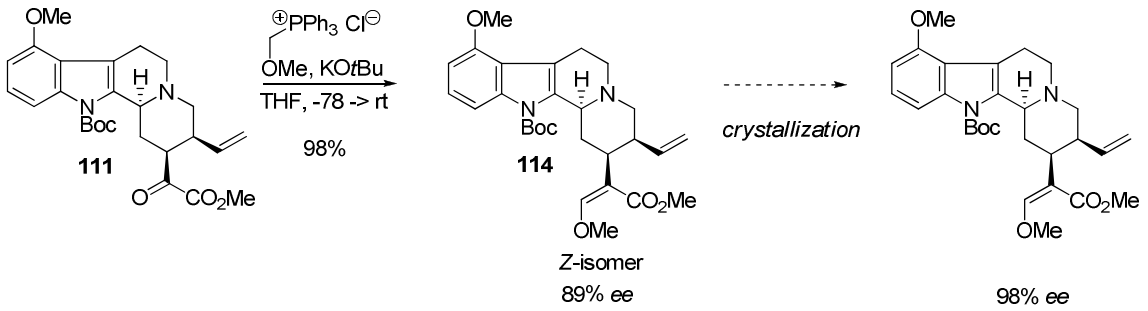


Scheme 32: Tsuji-Trost reaction with DBU as a base

2.6. Final Steps Towards (-)-Mitragynine

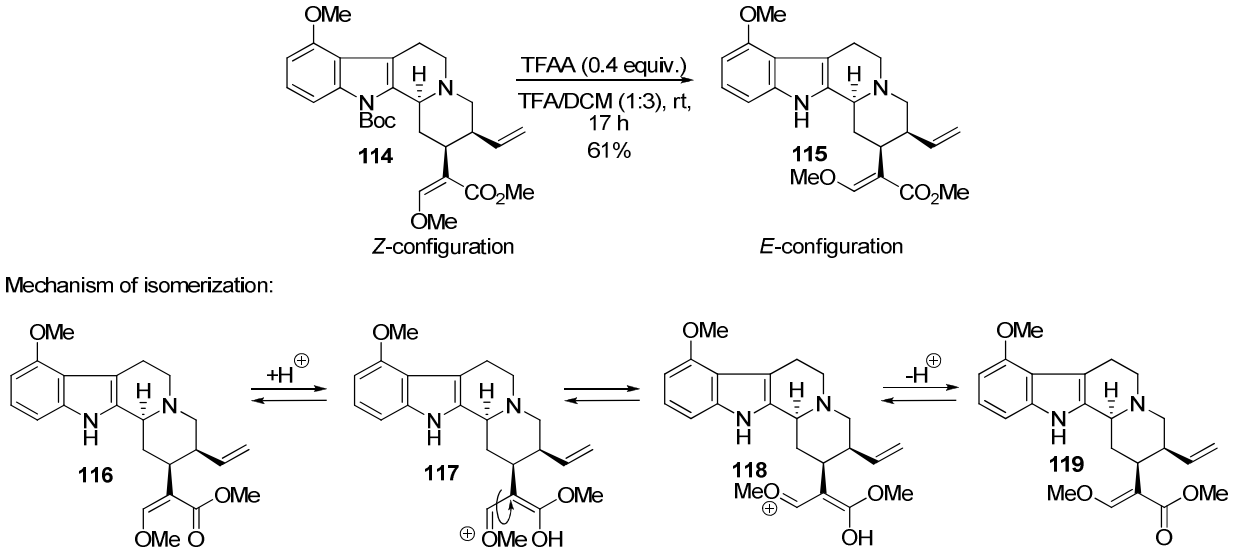
The synthesis towards mitragynine went on with conversion of ketone **111** to enol ether **114**. This was realized with a Wittig reaction using (methoxymethyl)triphenylphosphonium chloride as an ylid-precursor. The reaction was performed in high yield furnishing the *Z*-

isomer as the only product. At this stage partial crystallization of the racemate occurred so that the filtrate was observed with an increased *ee* of 98%.



Scheme 33: Synthesis of enol ether **114** leading to mitragynine

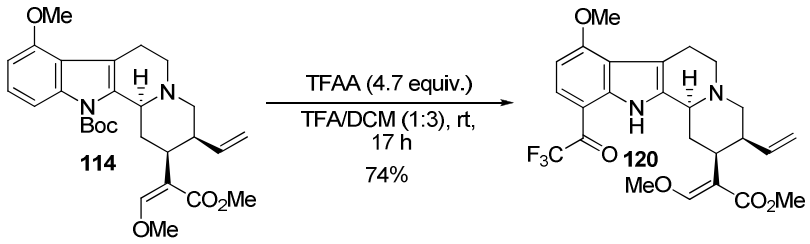
To remove the Boc-protecting group on the indolic nitrogen, enol ether **114** was exposed to a TFA/DCM mixture (Scheme 34). Besides deprotection, isomerization of the enol ether to the right configuration took place. Through protonation of the ester to intermediate **117**, the double bond turns into a single bond allowing free rotation. After loss of a proton the thermodynamically more stable *E*-configuration is obtained.



Scheme 34: Isomerization and deprotection of enol ether **114**

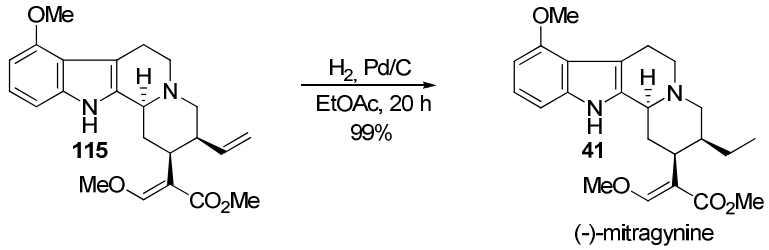
To obtain a good yield in the reaction it is important to work very dry and to use high quality TFA. Due to the hygroscopicity of TFA there are traces of water present which easily hydrolyze the enol ether. An attempt to remove traces of water from the reaction was to add the anhydride of TFA (TFAA) to the reaction mixture so that possible water present reacts with the anhydride to form acid again (Scheme 35). Addition of TFAA prevents the

hydrolysis of the enol ether very well, but the equivalent of TFAA needs to be chosen carefully. Using an excess of TFAA leads to acylation of the indole ring, yielding the very stable but undesired product **120** (Scheme 35). Through the electron donating methoxy group the substrate is obviously strongly activated and undergoes Friedel-Crafts acylation very easily. This process was prevented if the quantity of TFAA was reduced significantly to catalytic amounts.



Scheme 35: Addition of TFAA to the reaction mixture

The last step of the synthesis represented hydrogenation of the vinyl-group which went in quantitative yield to furnish (-)-mitragynine in 14 steps, 98% *ee* and an overall yield of 13% from commercially available 4-hydroxyindole.

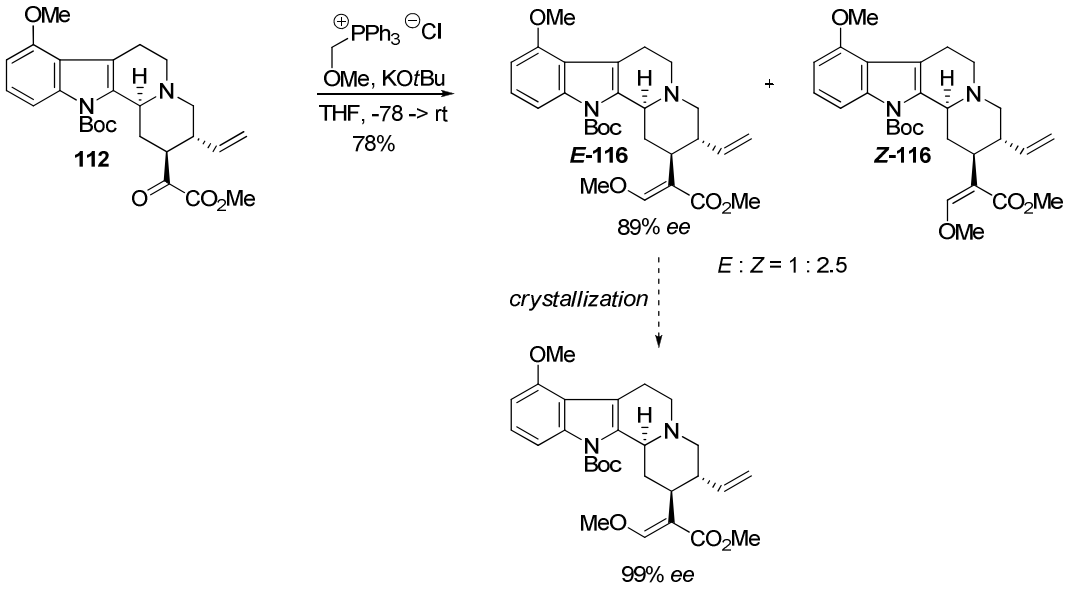


Scheme 36: Hydrogenation of the vinyl-group

2.7. Final Steps Towards (+)-Paynantheine and (+)-Speciogynine

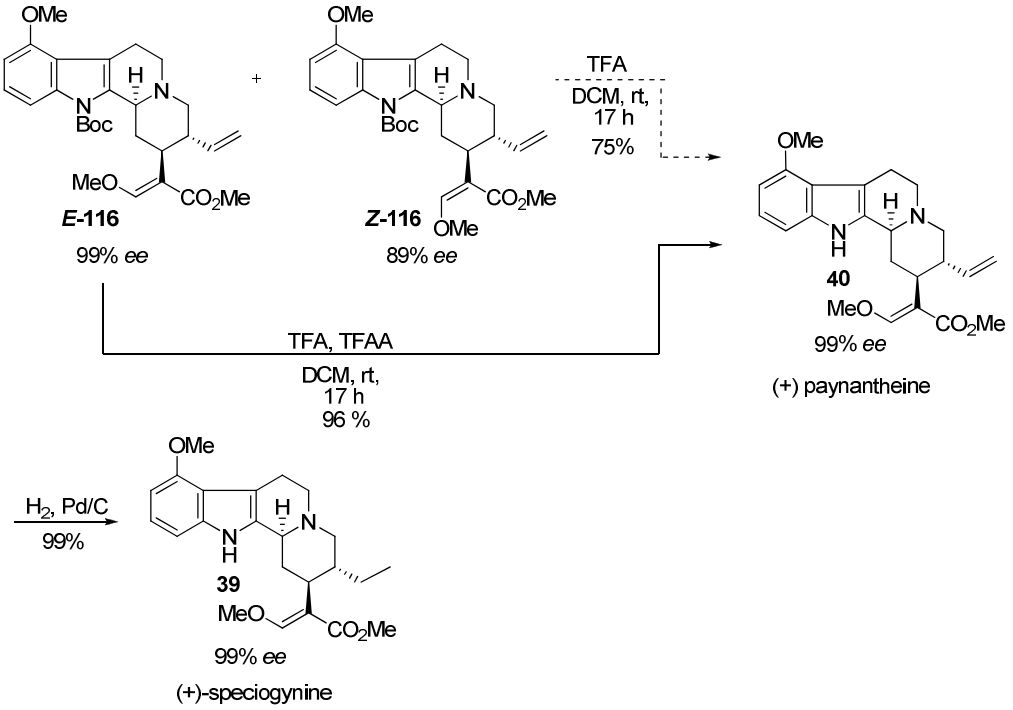
The synthesis of paynantheine and speciogynine proceeded the same way as for mitragynine. From α-keto ester **112** via a Wittig reaction enol ethers ***E*-116** and ***Z*-116** were synthesized (Scheme 37). To obtain two isomers in this step is at first instance not relevant because both can be used in the next deprotection/isomerization step. For crystallization, however, it was indeed important since a strong difference was observed for the two isomers. Unfortunately, only ***E*-116** was crystallizable to 99% *ee* but with ***Z*-116** neither the racemate nor the

enantiomer crystallized. Because of that only the minor isomer observed from the Wittig-reaction was obtained in enantiopure form.



Scheme 37: Wittig reaction of α-keto ester **112**

For the next step both products ***E*-116** and ***Z*-166** can be used synthesize paynantheine which was performed with racemic material in 75% yield. To yield the end-products in high *ee*, the reaction was repeated only with ***E*-116** which was crystallized to 99% *ee*. Using TFA and catalytic amounts of TFAA furnished paynantheine in 13 steps and an overall yield of 4.3%. The last step towards speciogynine was realized through hydrogenation.

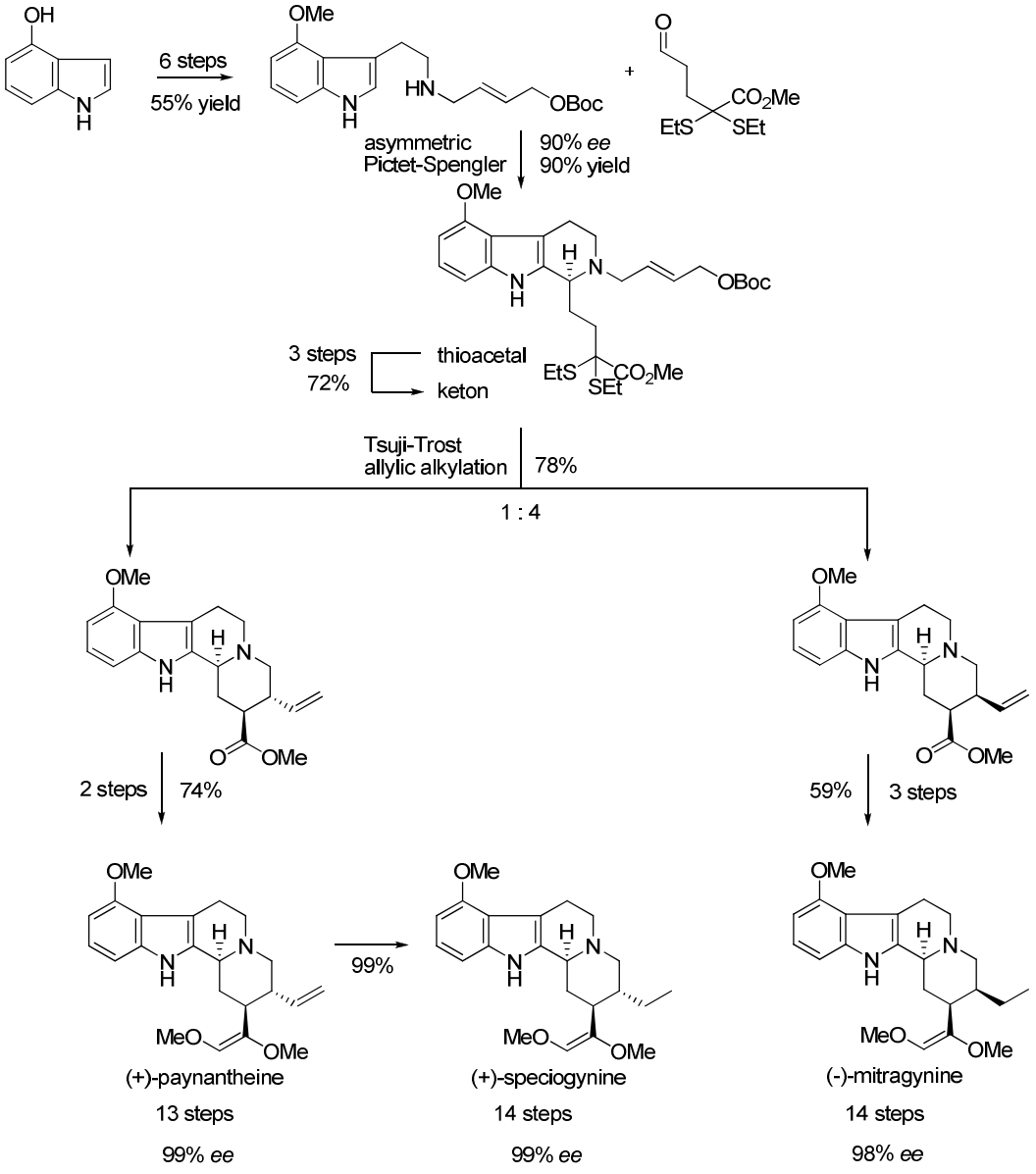


Scheme 38: Deprotection and isomerization towards paynantheine and speciogynine

3. Conclusion

3.1. Summary

Within the scope of this thesis, the enantioselective total synthesis of the three natural products mitragynine, paynantheine and speciogynine was realized. Over an asymmetric Pictet-Spengler reaction an *ee* of 90% (89% scale-up) was introduced in the route which was later increased by crystallization.



Scheme 39: Summary of the synthesis towards mitragynine, paynantheine and speciogynine

After a Tsuji-Trost reaction two diastereomers were obtained each leading to the natural products mitragynine or paynantheine and speciogynine. Mitragynine was made in 14 steps with an *ee* of 98% in the final product. Paynantheine and speciogynine were synthesized with an *ee* of 99%.

3.2. Comparison with Other Syntheses

To formulate a precise comparison of our synthesis of (-)-mitragynine with the already published routes (presented in the introduction: section 1.4) is rather difficult because the overall aim of research has been different in each case. However, I will try to point out some characteristics of each synthesis and ours. When Takayama published the first synthesis, the focus was not to develop the most efficient way but to make the molecule in first instance. Using enzyme-catalyzed hydrolysis of an acetate, an enantiopure alcohol was obtained. The synthesis is relatively short, but the observed yields remain rather low, so that an overall yield of 3% is obtained for 9 steps[a] compared to 13% yield with our synthesis. Although the enantiodetermining step results in higher *ee* than our organocatalyzed Pictet-Spengler reaction, enzymes always feature limited substrate specificity and the question of availability arises. For the biological evaluation of unnatural derivatives, the synthetic use of enzymes might be problematic. Our catalyst on the contrary allows more substrate-flexibility and is based on the *Cinchona* bark, a cheap and renewable resource. The synthesis by Cook published 14 years later envisioned the synthesis of several natural products applying a chiral auxiliary strategy. From an intermediate in the synthesis several natural products including mitragynine were reached. Although the observed enantioselectivity of the asymmetric step was higher than with our Pictet-Spengler reaction (95% *ee* compared to 90% *ee*), we were able to exceed the enantiomeric purity of the final product later by crystallization. Overall, Cooks synthesis is significantly longer than ours (23 steps compared to 14), unfortunately the overall yield could not be determined due to missing information about the yields of single steps. The most recent published formal synthesis by Ma *et al*. uses an organocatalytic approach. A lower *ee* of 81% was achieved in the scale-up and the synthesis was not finished, so that the overall yield could not be determined.

[a] Synthesis of bromine **5** not included.

3.3. Conclusion

The synthesis of (-)-mitragynine, (+)-paynantheine and (+)-speciogynine has been realized using an organocatalytic Pictet-Spengler reaction. It is therefore the first completed synthesis of mitragynine using organocatalysis and the first synthesis of paynantheine and speciogynine in general. With our route, new analogues can be synthesized which might show increased or different biological activity.

Additionally, we developed the first Pictet-Spengler reaction catalyzed by a bifunctional organocatalyst reaching an *ee* of 90%. Strongly activated substrates with electrondonating substituents on the indole system might not be catalyzed by BINOL-phosphoric acids. In these cases, a bifunctional catalyst bearing a thiourea might be a possible solution. This turns the class of bifunctional *Chincona* alkaloids to a new attractive catalyst species for the Pictet-Spengler reaction on which further research is worthwhile.

4. Abbreviations

Ac	acetyl
aq.	aqueous
BINOL	1,1'-bi-2-naphthol
Bn	benzyl
Boc	*tert*-butylcarbonyl
b.p.	boiling point
bs	broad signal (NMR)
Bu	butyl
Bz	benzoyl
cat.	catalyst
d	doublet (NMR)
d	day(s) (reaction)
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DiPEA	*N*,*N*-diisopropylethylamine
DMAP	4-dimethylaminopydridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
DPPA	diphenylphosphoryl azide
dppe	1,2-bis(diphenylphosphino)ethane
dppm	1,2-bis(diphenylphosphino)methane
E	entgegen
ee	enantiomeric excess
equiv.	equivalent(s)
Et	ethyl
h	hours
Hz	Hertz

HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectroscopy
IBX	2-iodoxybenzoic acid
IR	infrared
L	ligand
LAH	lithium aluminium hydride
LDA	lithium diisoproylamine
m	*meta*
m	multiplet (NMR)
Me	methyl
min	minute(s)
MP	melting point
MS	molecular sieves
ND	not determined
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
Ns	nosyl
o	*ortho*
p	*para*
ppm	parts per million
PE	petroleum ether
Ph	phenyl
rt	room temperature
s	singlet (NMR)
t	*tert*
t	triplet (NMR)
Tf	trifluoromethanesulfonate
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Z	zusammen

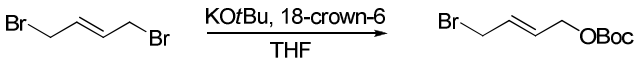
5. Experimental

General remarks:

All ^{1}H-NMR and ^{13}C-NMR (APT) spectra were recorded with a Bruker Avance 400 spectrometer (^{1}H 400 MHz, ^{13}C 100 MHz) at room temperature. IR spectra were obtained using a Bruker IFS 28 FT-spectrophotometer. Optical rotations were measured with a Perkin-Elmer 241 polarimeter. Analytical thin layer chromatography was performed using Merck TLC plastic roll 500 x 20 cm silica gel F_{254}. Flash chromatography was carried out on Biosolve 60 Å (0.032 – 0.063 mm) silica gel. *Ee*s were determined on Chiracel® OD-H (Chiral Technologies Europe, 0.46 cm x 25 cm) columns. Melting points were measured with a Leitz-Wetzlar melting point microscope and are uncorrected. Mass spectra and accurate mass measurements were performed using a JEOL JMS-SX/SX 102 A Tandem Mass Spectrometer.

All reactions were carried out in oven-dried glassware with magnetic stirring under nitrogen atmosphere. Tetrahydrofuran (THF) was freshly distilled from sodium and benzophenone. Toluene was stored under 4 Å molecular sieves. Commercial reagents and solvents were purchased from Biosolve, Sigma-Aldrich, Fluka or Acros and used as received. 4-hydroxy-indole was purchased from AK Scientific Inc. (100g, 215 $). Powdered 4 Å molecular sieves (Fluka) were dried at 200°C and 0.1 mbar.

(E)-4-bromobut-2-enyl *tert*-butyl carbonate



11 g (0.1 mol) KO*t*Bu and 0.5 g 18-crown-6 was dissolved in 250 mL anhydrous DMSO. A CO_2-stream generated from dry ice was directed through the solution with two thick needles and the mixture was stirred with a mechanical stirrer for 1 h. After formation of a thick gel, 21.4 g (0.1 mol) of 1,4-dibromobutene dissolved in 40 mL THF was given to the mixture in one portion. After 2 h of stirring the reaction was quenched with half saturated NH_4Cl solution. The layers were separated and the aqueous phase was extracted with Et_2O (3x). The organic layers were combined and washed with water (2x) and the organic phase was dried

with $MgSO_4$ and the solvents evaporated. A column of thickness: 66 mm and length: 150 mm was packed with EtOAc:PE, 6:94; Eluent EtOAc:PE, 6:94 (1L) and EtOAc:PE, 8:92 (1L). The product was isolated as a colorless oil.

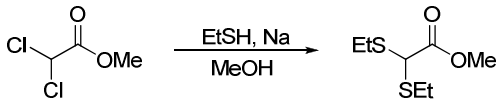
Yield: 43% (10.9 g, 0.043 mol)

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 6.02 (m, 1H), 5.90 (m, 1H), 4.60 (d, 2H, J=5.70 Hz), 3.97 (d, 2H, J=7.40 Hz), 1.51 (s, 9H) ppm.

For the remaining analytical data see:

M. J. Wanner, E. Claveau, J. H. Van Maarseveen, H. Hiemstra, *Eur. J. Org. Chem.* **2011**, *17*, 13680-13683.

methyl 2,2-bis(ethylthio)acetate



58

4.6 g (0.2 mol) sodium was placed in a three-neck flask with a dropping funnel and a condenser under nitrogen-atmosphere. The flask was chilled in an ice-bath and 100 mL of methanol was added slowly. When the sodium dissolved completely, 15 mL (0.2 mmol) ethanethiol was added dropwise. The ice bath was removed and 10.39 mL (0.1 mol) methyl dichloroacetate was slowly given to the mixture and the suspension was stirred for 48 h at room temperature. The mixture was quenched with 75 mL H_2O and 150 mL of diethyl ether. The ether layer was separated and washed with water (50 mL) and saturated NaCl solution (50 mL). The organic phase was dried over $MgSO_4$, the solvent removed and the resulting oil purified by distillation: 60°C ($1.4 \cdot 10^{-1}$ Torr); Lit: 125-127°C (5 Torr).

Yield: 87% (16.87 g, 0.087 mol)

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 4.40 (s, 1H), 3.80 (s, 3H), 2.74 (m, 4H), 1.30 (t, 6H, J=7.43 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 13.9, 24.9, 49.8, 52.5, 169.5 ppm.

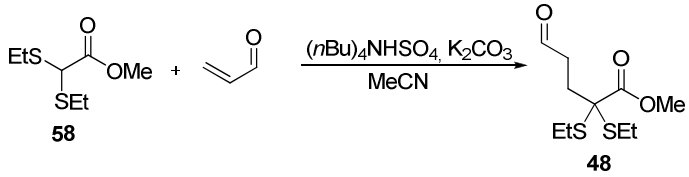
IR: ν = 2967, 2929, 1731, 1434, 1260, 1137 cm^{-1}.

For the remaining analytical data see:

L.M. Lerner, *J. Org Chem.* **1976**, *41*, 2228-2229.

Synthesis of aldehyde 48

Michael-addition



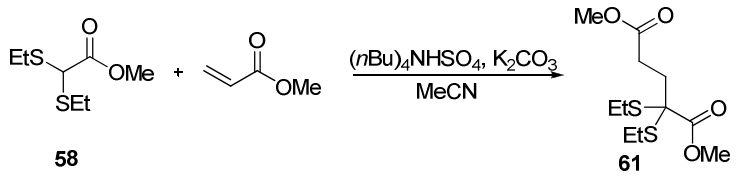
2.91 g (15 mmol) of methyl 2,2-bis(ethylthio)acetate was dissolved in 50 mL of acetonitrile. 8.29 g (60 mmol) finely powdered potassium carbonate and 0.255 g (0.75 mmol) tetrabutylammonium hydrogen sulfate was given to the mixture. Then, freshly distilled acrolein was added in two portions one at the beginning of the reaction (2.5 mL, 38.5 mmol) and one after 30 min (2.5 mL, 38.5 mmol). The suspension was stirred at room temperature for 1 h in total. The inorganic solid was removed by filtration, the solvent evaporated and the mixture purified via column chromatography (EtOAc:PE, 1:4/1:3). The product was obtained as a colorless oil.

Yield: 29% (1.09 g, 4.35 mmol)

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 9.83 (s, 1H), 3.80 (s, 3H), 2.64 (m, 2H), 2.73 (m, 4H), 2.34 (m, 2H), 1.24 (t, 6H, J=7.5 Hz) ppm.

For the remaining analytical data see:

J. Gonzalez, F. Sánchez, T. Torres, *Synthesis*, **1983**, *911-913*.



0.969 g (5 mmol) of methyl 2,2-bis(ethylthio)acetate was dissolved in 16 mL of acetonitrile. 2.76 g (20 mmol) of finely powdered K_2CO_3 salt and 0.085 g (0.25 mmol) of tetrabutylammonium hydrogen sulfate was added. 0.5 mL (5.5 mmol) of methylacrylate was given to the mixture and the suspension was stirred at 80°C for 90 min. The inorganic salts

were filtered and washed with acetonitrile. The solvent was evaporated and the product obtained as a colorless oil via distillation. b.p. 104°C, $8 \cdot 10^{-1}$ Torr.

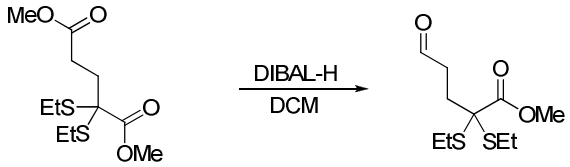
Yield: 66% (0.9538 g, 3.40 mmol)

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 3.80 (s, 3H), 3.70 (s, 3H), 2.65 (m, 4H), 2.57 (m, 1H), 2.34 (m, 1H), 1.24 (t, 6H, J=7.51) ppm.

For the remaining analytical data see:

J. Gonzalez, F. Sánchez, T. Torres, *Synthesis*, **1983**, *911-913*.

DIBAL-H reduction

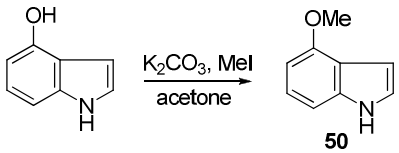


61 **48**

0.954 g (3.40 mmol) **61** was dissolved in 14 mL DCM and the solution was cooled to -78°C. 3.74 mL (3.74 mmol) of DIBAL-H as a 1M solution in hexane was slowly added and the mixture was stirred for 2 h at -78°C. The reaction was quenched with methanol and 16 mL of saturated potassium sodium tartate solution (Rochelle salt). The mixture was stirred vigorously for 30 min. The layers were separated and the aqueous phase was washed with DCM (4x). The organic layers were combined and the solvent removed. Column chromatography with EtOAc:PE 1:4/1:3 furnished the product as a colorless oil.

Yield: 70% (0.5934 g, 2.37 mmol)

4-methoxy-1H-indole



50

44.9 g (325 mmol) K_2CO_3 and 28.4 g (200 mmol) MeI were added to a solution of 13.31 g (100 mmol) 4-methoxy-1H-indole in 200 mL acetone. The suspension was stirred under reflux for 48 h and at room temperature for further 48 h. The mixture was filtered over celite and the solvent evaporated. Due to limited solubility of the mixture in the eluent, the

compound was absorbed on silica gel during evaporation. Purification through flash chromatography using (EtOAc:PE, 1:2) gave the product as white crystals.

Yield: 89% (13.068 g, 89 mmol)

Melting point: 64 – 67 °C

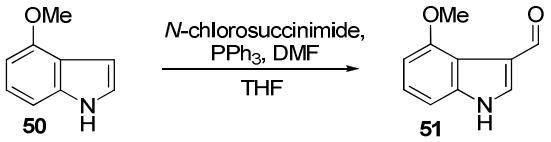
^{1}H-NMR (400 MHz) δ = 8.16 (s, 1H), 7.37 (t, 1H, J=8.0Hz), 7.11 (m, 2H), 6.93 (t, 1H, J=2.6Hz), 6.77 (d, 1H, J=7.8Hz), 4.14 (s, 3H) ppm.

^{13}C-NMR (100 MHz) δ = 153.2, 137.1, 122.6, 122.6, 118.4, 104.4, 99.5, 99.4, 55.2 ppm.

IR: ν = 3408, 1615, 1588, 1502, 1464, 1439, 1361 cm^{-1}.

HRMS (FAB): m/z calcd. for $(M+H)^+$ $C_9H_{10}ON$: 148.0718; found: 148.0770.

4-methoxy-1H-indole-3-carbaldehyde



40.1 g (153 mmol) triphenylphosphine was dissolved in 640 mL dry THF and 20.41 g (153 mmol) *N*-chlorosuccinimide was added in portions. The suspension was stirred vigorously for 30 min at room temperature. Then, 23.5 mL (306 mmol) DMF was added to the reaction and the mixture was stirred under reflux for 1 h. Further, 7.5 g (51 mmol) indole was added and the mixture was stirred under reflux for 1 h. The reaction mixture was cooled down to room temperature and the THF was evaporated. 640 mL H_2O was added to the mixture and it was stirred under reflux for 1 h. The mixture was cooled down and basified with 10% NaOH. The aquaous phase was extracted with 200 mL (4x) EtOAc and the organic layers combined and evaporated. Column chromatography with EtOAc:PE, 1:1 gave the product as orange crystals.

Yield: 81% (7.239 g, 41.3 mmol)

Melting point: 151-154°C

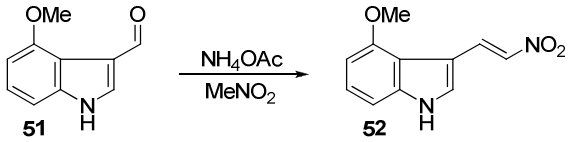
^{1}H-NMR (400 MHz, $CDCl_3$) δ = 10.53 (s, 1H), 8.79 (s, 1H), 7.95 (d, 1H, J=3.07 Hz), 7.24 (t, 1H, J=8.07), 7.10 (d, 1H, J=8.17 Hz), 6.75 (d, 1H, J=7.85 Hz), 4.03 (s, 3H) ppm

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 187.6, 153.7, 137.6, 128.4, 123.1, 118.3, 115.6, 105.3, 101.6, 54.8 ppm.

IR: ν = 3246, 1648, 1463, 1386, 1363, 1328 cm^{-1}.

HRMS (FAB): m/z calcd. for $(M+H)^+$ $C_{10}H_{10}O_2N$:176.0667; found: 176.0712.

(E)-4-methoxy-3-(2-nitrovinyl)-1H-indole



1.76 g (22.8 mmol) NH_4OAc and 2.0 g (11.4 mmol) aldehyde were dissolved in 67 mL nitromethane and the suspension was heated under reflux for 1 h. The mixture was cooled down to room temperature and the solvent evaporated. The solid was dissolved in a small amount of methanol and precipitated slowly with water. The solid was filtrated over celite and dried under vacuum. The product was obtained as a red solid.

Yield: 96% (2.3985 g, 10.99 mmol)

Melting point: 185-188 °C

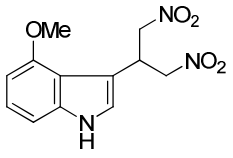
^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.67 (bs, 1H), 8.52 (d, 1H, J=13.38 Hz), 7.98 (d, 1H, J=13.38), 7.61 (d, 1H, J=2.73), 7.25 (d, 1H, J=8.04), 7.07 (d, 1H, J=8.19 Hz), 6.712 (d, 1H, J=7.92 Hz), 4.04 (s, 3H) ppm.

^{13}C-NMR (100 MHz, CDCl3) δ = 152.9, 138.4, 134.5, 131.9, 130.5, 123.5, 114.4, 107.9, 105.1, 101.3, 54.3 ppm.

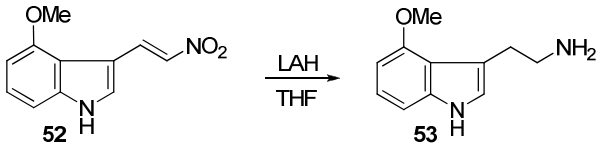
IR: ν = 3285, 2940, 1687, 1612, 1511, 1481, 1440, 1304 cm^{-1}.

HRMS (FAB): m/z calcd. for $(M+H)^+$ $C_{11}H_{11}O_3N_2$: 219.0725, found: 219.0773.

Remark: When the mixture is stirred too long, deprotonated nitromethane adds to the double bond of the product to form the di-nitro-substituted product.



2-(4-methoxy-1H-indol-3-yl)ethanamine



58.53 g (225 mmol) LAH was dissolved in 90 mL of dry THF and cooled to 0°C. 4.456 g (20.4 mmol) (E)-4-methoxy-3-(2-nitrovinyl)-1H-indole was dissolved in 220 mL dry THF and given to the mixture with a dropping funnel. After 3 h of reflux the flask was placed in an ice bath and first water (1.3 g / g $LiAlH_4$), then 15% aqueous NaOH (1.3 g / g $LiAlH_4$) and finally again water (3.25 g / g $LiAlH_4$) was carefully added with a dropping funnel. The mixture was stirred vigorously for 15 min and filtrated. The residue was washed with Et_2O (5x) and the combined organic layers evaporated. The product was obtained as a brown solid.

Yield: 99% (3.848 g, 20.2 mmol)

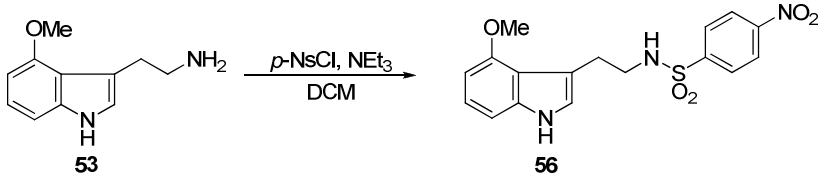
Melting point: 110-105°C

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.06 (bs, 1H), 7.11 (t, 1H, J=7.95 Hz), 6.99 (d, 1H, J=7.70 Hz), 6.91 (d, 1H, J=2.15 Hz), 6.51 (d, 1H, J=7.74 Hz), 3.94 (s, 3H), 3.03 (s, 4H) ppm.

^{13}C-NMR (100 MHz) δ =154.4, 138.1, 122.1, 121.2, 116.9, 112.9, 104.5, 98.7, 54.7, 42.8, 30.6 ppm.

IR: δ = 2932, 1585, 1507, 1463, 1436, 1361 cm^{-1}.

***N*-(2-(4-methoxy-1H-indol-3-yl)ethyl)-4-nitrobenzenesulfonamide**



2.25 mL (16.1 mmol) triethylamine was added to a solution of 2.55 g (13.4 mmol) amine **53** in 50 mL DCM. The mixture was cooled down to 0°C and 3.27 g (14.7 mmol) *p*-nitro-tosylchloride was added in portions. The suspension was stirred for 2 h at 0°C. The mixture was extracted with H_2O (2x) and sat. $NaHCO_3$ (1x) solution. The organic layers were

combined and the compound was absorbed on silica gel. Column chromatography with EtOAc:PE, 1:2/1:1 gave the product as an orange solid.

Yield: 87% (4.37 g, 11.6 mmol)

Melting point: 136-140 °C

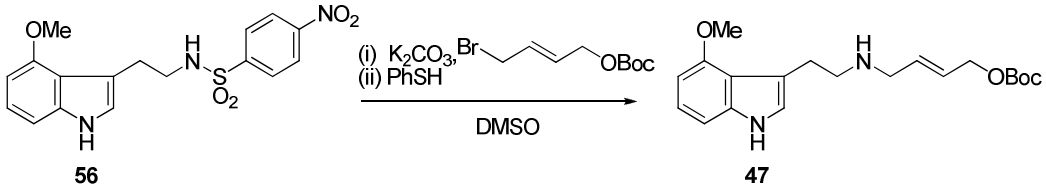
^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.89 (m, 2H), 7.54 (m, 2H), 7.08 (t, 1H, J=7.99 Hz), 6.88 (d, 1H, J=8.18 Hz), 6.76 (d, 1H, J=2.31 Hz), 6.46 (d, 1H, J=7.78 Hz), 3.92 (s, 3H),3.40 (m, 2H), 3.00 (m, 2H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 153.2, 148.2, 145.3, 137.6, 126.7, 122.6, 121.3, 121.5, 116.1, 110.6, 104.5, 98.2, 54.4, 44.1, 26.1 ppm.

IR: ν = 3406, 1528, 1349 cm^{-1}.

HRMS (FAB): m/z calcd. for $(M+H)^+$ $C_{17}H_{18}O_5N_3S$: 376.0922; found: 376.0971.

(E)-*tert*-butyl 4-(2-(4-methoxy-1H-indol-3-yl)ethylamino)but-2-enyl carbonate



56 47

4.10 g (29.7 mmol) of finely powdered K_2CO_3 and 2.73 g (10.9 mmol) bromoalkene were added to a solution of 3.71 g (9.9 mmol) *N*-(2-(4-methoxy-1H-indol-3-yl)ethyl)-4-nitrobenzenesulfonamide in 33 mL DMSO. After stirring for 4 h at room temperature 3.0 mL (29.7 mmol) of thiophenol was given to the mixture. After 2 h the reaction was quenched with water and the aqueous phase was extracted with EtOAc/NH_4Cl. The organic layers were combined and washed with water (3x). After removal of the solvent the mixture was purified by column chromatography (EtOAc:PE, 1:1; EtOAc; MeOH:EtOAc, 1:9; EtOAc with 5% MeOH and 5% NEt_3). The product was obtained as a brown highly viscous oil.

Yield: 94% (3.35 g, 9.3 mmol)

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.64 (bs, 1H), 7.09 (t, 1H, J=7.95 Hz), 6.95 (d, 1H, J=8.14 Hz), 6.87 (s, 1H), 6.49 (d, 1H, J=7.72 Hz), 5.73 (m, 1H), 5.87 (m, 1H), 4.51 (d, 2H, J=6.2Hz),

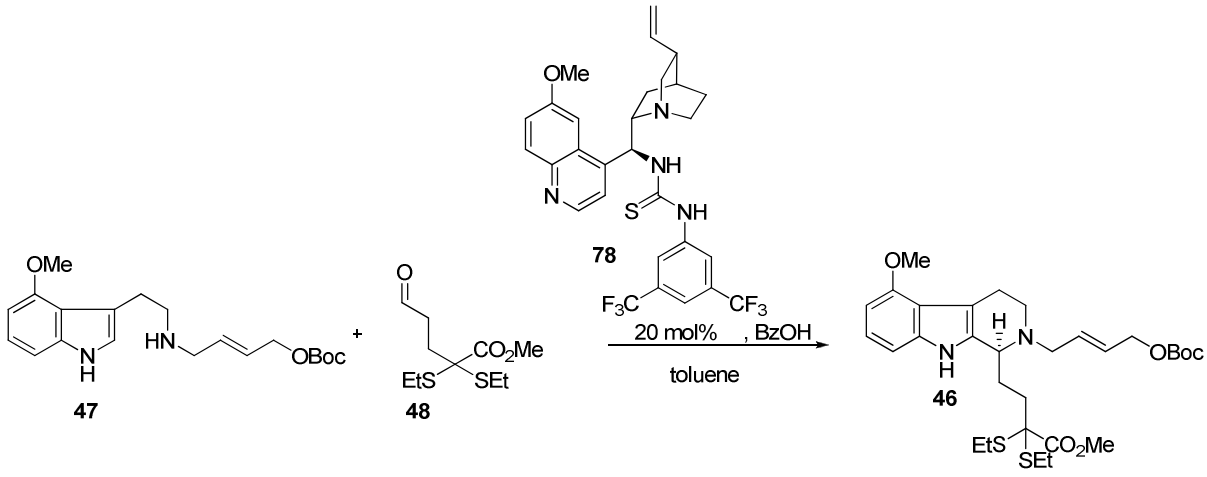
3.92 (s, 3H), 3.30 (d, 2H, J=5.86 Hz), 3.10 (t, 2H, J=6.74 Hz), 2.97 (t, 2H, J=6.74 Hz), 1.50 (s, 9H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 154.6, 153.2, 138.1, 133.5, 125.3, 122.5, 121.1, 117.1, 113.6, 104.5, 99.1, 81.9, 66.9, 54.9, 50.5, 50.1, 27.6, 26.9 ppm.

IR: ν = 2932, 1740, 1368 cm^{-1}.

HRMS (FAB): m/z calcd. for $(M+H)^+$ $C_{20}H_{29}O_4N_2$: 361.2083; found: 361.2122.

Organocatalyzed Pictet-Spengler reaction



0.033 g (0.055 mmol) of catalyst and 0.0067 g (0.055 mmol) benzoic acid was added to a solution of 0.1 g (0.277 mmol) tryptamine **47** in 5 mL of toluene. Next, 0.083 g (0.33 mmol) of aldehyde was given to the mixture and the reaction was stirred for 24 h at room temperature. The solvent was evaporated and the resulting oil purified by column chromatography using EtOAc:DCM:PE, 1:4:4. The product was observed as a colorless oil.

Yield:	90% (0.147 g, 0.25 mmol)
ee:	89%
Optical rotation:	$[\alpha]_D^{20}$ = -19.6° (c = 1.03, $CHCl_3$)
HPLC:	major enantiomer 18.22 min
	minor enantiomer 23.40 min
	(Chiralcel® OD-H, eluent: *n*-heptane:*iso*-propanol = 90:10, flow: 0.6 mL/min)

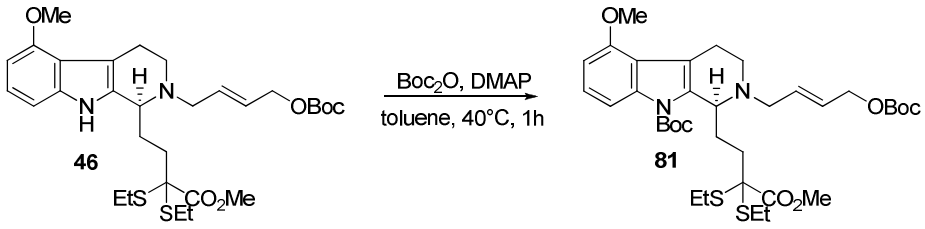
^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.79 (bs, 1H), 7.04 (t, 1H, J=7.9 Hz), 6.94 (d, 1H, J=8.0 Hz), 6.49 (d, 1H, J=7.6 Hz), 5.91 (m, 1H), 5.76 (m, 1H), 4.58 (d, 2H, J=6.1Hz), 3.91 (s, 3H), 3.78 (s, 3H), 3.67 (t, 1H, J=5.5Hz), 3.34 (dd, 1H, J=6.0 Hz, J=14.1Hz), 3.17 (m, 2H), 3.00 (m, 1H), 2.82 (m, 2H), 2.58 (m, 4H), 2.09 (m, 2H), 1.97 (m, 2H), 1.52 (s, 9H), 1.21 (dt, 6H, J=7.5 Hz, J=13.8 Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 171.3, 154.3, 153.3, 137.1, 133.6, 132.3, 126.4, 122.0, 117.2, 108.5, 104.2, 99.6, 82.1, 67.0, 65.0, 56.4, 55.2, 54.6, 53.0, 46.0, 32.0, 29.1, 27.8, 24.0, 23.4, 20.6, 13.6, 13.3 ppm.

IR: ν = 3393, 2931, 1723 cm^{-1}.

HRMS (FAB): m/z calcd. for $(M+H)^+$ $C_{30}H_{45}N_2O_6S_2$: 593.2674; found: 593.2722.

Boc-protection of 46



0.37 g (1.70 mmol) di-*tert*-butyl dicarbonate and 0.035 g (0.28 mmol) DMAP was added to a solution of 0.673 g (1.13 mmol) tetrahydro-*β*-carboline **46** in 20 mL toluene. The mixture was heated to 40°C and stirred for 1 h. Conversion was checked on TLC. The solvent was evaporated and the product isolated via column chromatography using EtOAc:DCM:PE = 1:4:4.

Yield:	99% (0.779 g, 1.12 mmol)
ee:	89%
Optical rotation:	$[\alpha]_D^{20}$ = -21.7° (c = 1.03, $CHCl_3$)
HPLC	major enantiomer 19.52 min
	minor enantiomer 9.90 min
	(Chiralcel® OD-H, eluent: *n*-heptane:*iso*-propanol = 95:5, flow: 0.5 mL/min)

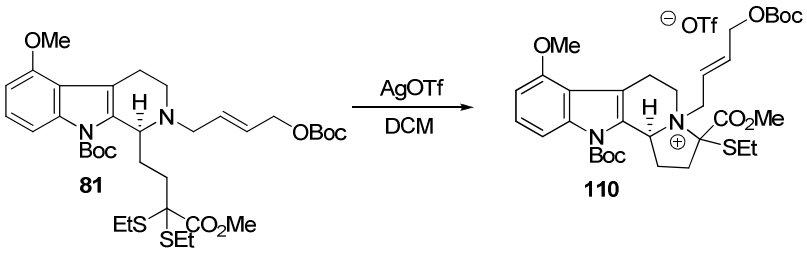
^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.72 (d, 1H, J=8.4Hz), 7.15 (t, 1H, J=8.2Hz), 6.65 (d, 1H, J=8.0Hz), 5.90 (m, 1H), 5.73 (m, 1H), 4.58 (d, 2H, J=6.3Hz), 4.15 (dd, 1H, J=2.3Hz, J=10.6Hz), 3.89 (s, 3H), 3.76 (s, 3H), 3.32 (dd, 1H, J=6.5Hz, J=13.7Hz), 3.22 (dd, 1H, J=6.5Hz, J=13.9Hz), 3.14 (m, 1H), 2.94 (m, 2H), 2.80 (dd, 1H, J=4.7Hz, J=16.4Hz), 2.69 (m, 4H), 2.42 (m, 1H), 2.08 (m, 1H), 1.94 (m, 1H), 1.80 (m, 1H), 1.68 (s, 9H), 1.51 (s, 9H), 1.24 (t, 6H, J=7.5Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 171.2, 153.9, 153.3, 150.2, 137.6, 134.5, 134.4, 125.8, 124.1, 118.8, 114.0, 108.8, 103.3, 83.5, 81.9, 67.0, 65.3, 57.3, 55.2, 54.8, 52.7, 41.4, 33.2, 30.0, 28.1, 27.7, 23.8, 23.7, 19.1, 13.4, 13.3 ppm.

IR: ν = 2974, 2933, 1726, 1438, 1394, 1369, 1325 cm^{-1}.

HRMS (FAB): m/z calcd. for $(M+H)^+$ $C_{35}H_{53}N_2O_8S_2$: 693.3199; found: 693.3248.

Deprotection of thioacetal 81 to salt 110



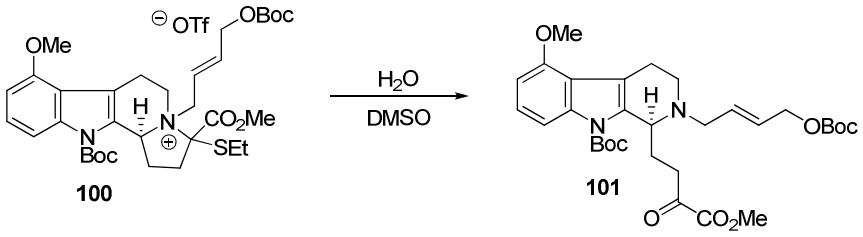
0.5623 g (0.811 mmol) 1,2,3,4-tetrahydro-*β*-carboline was dissolved in 9 mL anhydrous DCM. 0.334 g (1.3 mmol) silver trifluoromethanesulfonate was added in two portions, one at the beginning of the reaction and the second after 60 min of stirring. After 20 h of stirring at room temperature the precipitated AgSEt was removed by filtration over celite and the solvent was evaporated. The pyrrolidinium salt (as a mixture of diastereomers) was obtained as a brown foam in quantitative yield. The salt was hydrolyzed in the next step.

Yield: >99 %

^{1}H-NMR (major diastereomer, 400 MHz, $CDCl_3$) δ = 7.57 (d, 1H, J=8.5Hz), 7.25 (t, 1H, J=8.3Hz), 6.68 (d, 1H, J=8.0Hz), 6.20 (m, 1H), 5.94 (dt, 1H, J=5.3Hz, J=15.5Hz), 5.35 (t, 1H, J=9.0Hz), 4.58 (d, 2H, J=5.2Hz), 4.26 (dd, 1H, J=6.2Hz, J=12.4Hz), 4.05 (d, 2H, J=7.3Hz), 4.00 (s, 3H), 3.89 (s, 3H), 3.82 (m, 1H), 3.72 (dd, 1H, J=5.1Hz, J=18.8Hz), 3.12 (m, 5H), 2.84 (m, 1H), 2.40 (m, 1H), 1.68 (s, 9H), 1.48 (s, 9H), 1.30 (t, 3H, J=7.4Hz) ppm.

IR: ν = 1733 cm^{-1}.

Hydrolysis of salt 100



0.633 g (0.81 mmol) pyrrolidinium salt was dissolved in 10 mL DMSO and 2.4 mL H_2O was added. A stream of nitrogen gas was directed through the solution and it was stirred for 45 min at 75°C. The reaction was quenched with water (100 mL) and aqueous $NaHCO_3$ solution and the aqueous phase was extracted with EtOAc. The organic layers were washed with water, the solvents evaporated and the residue purified by flash chromatography (EtOAc:PE, 1:5/1:4.5/1:4).

Yield:	73% (0.347 g, 0.59 mmol)
ee:	89%
Optical rotation:	$[\alpha]_D^{20}$ = -41.9° (c = 0.95, $CHCl_3$)

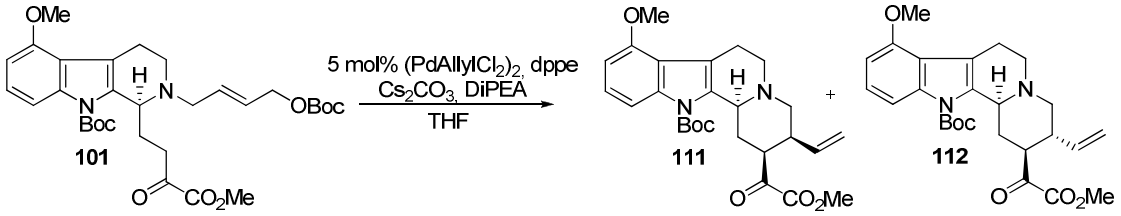
^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.73 (d, 1H, J=8.4Hz), 7.18 (t, 1H, J=8.2Hz), 6.66 (d, 1H, J=8.0Hz), 5.80 (m, 1H), 5.68 (m, 1H), 4.53 (m, 2H), 4.04 (m, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 3.20 (dd, 1H, J=7.9Hz, J=13.4Hz), 3.07 (m, 2H), 2.81 (m, 3H), 2.58 (m, 2H), 2.29 (m, 2H), 1.69 (s, 9H), 1.51 (s, 9H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 188.9, 161.6, 153.8, 153.0, 149.9 137.0, 132.6, 131.5, 127.0, 124.4, 118.4, 113.9, 108.7, 103.2, 83.6, 66.5, 58.1, 55.1, 54.2, 52.3, 38.8, 36.3, 32.5, 28.0, 27.5, 18.8 ppm.

IR: ν = 2977, 1726, 1576, 1495, 1438, 1394, 1369, 1321 cm^{-1}.

HRMS (FAB): m/z calcd. for $(M+H)^+$ $C_{31}H_{43}N_2O_9$: 587.2924; found: 587.2972.

Tsuji-Trost cyclization to 111 and 112



0.017 g (0.042 mmol) bis(diphenyphosphino)ethane was added to a solution of 0.007 g (0.02 mmol) allylpalladium(II) chloride dimer in 2 mL of anhydrous THF under argon. The solution was stirred for 15 min before it was added to a solution of 0.233 g (0.396 mmol) α-keto-ester **101** in 5 mL of dry THF followed by 0.258 g (0.793 mmol) Cs_2CO_3 and 0.135 mL (0.793 mmol) DiPEA. The reaction mixture was stirred for 20 h at room temperature before it was quenched with aqueous NH_4Cl solution and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtrated and the solvent removed. Purification was finalized by column chromatography using EtOAc:PE, 3:1/2:1. The products were obtained in a ratio of *cis*:*trans* = 4 : 1 and an overall yield of 78%.

<u>*cis*-isomer:</u>

yield:	62% (0.114 g, 0.245 mmol)
ee:	89%
optical rotation:	$[\alpha]_D^{20}$ = -145.8° (c = 1.07, $CHCl_3$)

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.63 (d, 1H, J=8.4Hz), 7.15 (t, 1H, J=8.2Hz), 6.63 (d, 1H, J=8.0Hz), 6.10 (td, 1H, J=9.9Hz, J=17.2Hz), 4.99 (m, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 3.56 (dt, 1H, J=3.7Hz, J=12.4Hz), 3.03 (m, 5H), 2.88 (m, 2H), 2.67 (m, 1H), 2.25 (d, 1H, J=13.3Hz), 1.77 (dd, 1H, J=12.7Hz, J=23.8Hz), 1.63 (s, 9H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 194.7, 161.4, 154.0, 150.5, 138.2, 137.6, 134.3, 124.5, 118.7, 117.2, 116.6, 108.5, 103.5, 83.7, 60.9, 59.8, 55.3, 52.7, 50.9, 49.5, 40.8, 28.2, 27.0, 25.1 ppm.

IR: ν = 2978, 2942, 2800, 1724, 1606, 1579, 1495, 1439, 1405, 1394, 1369, 1358, 1323 cm^{-1}.

HRMS (FAB): m/z calcd. for $(M+H)^+$ $C_{26}H_{33}N_2O_6$: 469.2294; found: 469.2340.

trans-isomer:

yield: 16% (0.029 g, 0.063 mmol)

ee: 89%

optical rotation: $[\alpha]_D^{20}$ = -38.9° (c = 0.86, $CHCl_3$)

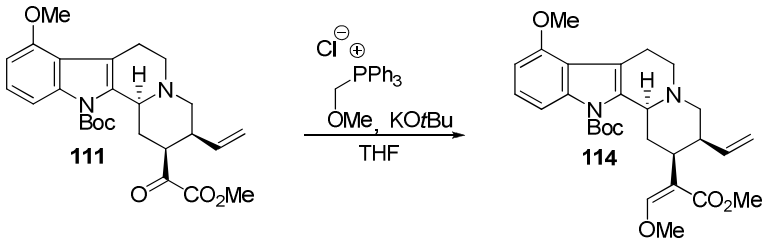
^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.69 (d, 1H, J=8.3Hz), 7.15 (t, 1H, J=8.2Hz), 6.63 (d, 1H, J=7.9Hz), 5.60 (m, 1H), 5.06 (m, 2H), 4.30 (d, 1H, J=10.6Hz), 3.87 (s, 3H), 3.84 (s, 3H), 3.49 (m, 1H), 3.12 (m, 3H), 2.87 (m, 5H), 2.27 (ddd, 1H, J=2.5Hz, J=3.5Hz, J=12.8Hz), 1.68 (s, 9H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 194.7, 161.5, 153.9, 150.1, 137.8, 137.5, 133.7, 124.3, 118.5, 116.9, 115.8, 108.6, 103.4, 83.8, 83.5, 60.2, 59.5, 57.0, 55.2, 52.7, 49.3, 46.3, 37.6, 28.6, 28.0, 24.5 ppm.

IR: ν = 2977, 2940, 2837, 1726, 1606, 1579, 1496, 1440, 1407, 1394, 1369, 1318 cm^{-1}.

HRMS (FAB): m/z calcd. for $(M+H)^+$ $C_{26}H_{32}N_2O_6$: 469.2294, found: 469.2340.

Wittig reaction with *cis*-isomer 111



2.6 mL of a 1M solution of KO*t*Bu in THF was added to a solution of 0.89 g (2.59 mmol) (methoxymethyl)triphenylphosphonium chloride in 6 mL THF at room temperature. The solution was cooled to -78°C and stirred for 15 min before it was added to a solution of 0.405 g (0.864 mmol) keton **111** in 10 mL THF at -78°C. The cooling bath was removed and after 1 hour of stirring at room temperature, the reaction mixture was quenched with NH_4Cl (5 mL) and EtOAc (5 mL). After stirring the quenched mixture vigorously for 12 h the mixture was extracted with EtOAc (3x), the combined organic layers were dried over Na_2SO_4. Removal of the solvent and purification by column chromatography (EtOAc:PE, 1:3, 1:2) furnished the *Z*-isomer as a brown solid.

Yield: 98% (0.419 g, 0.84 mmol)

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.73 (d, 1H, J=8.4Hz), 7.18 (t, 1H, J=8.2Hz), 6.66 (d, 1H, J=8.0Hz), 6.075 (s, 1H), 6.05 (m, 1H), 5.07 (dd, 1H, J=2.1Hz, J=10.4Hz), 4.95 (dd, 1H, J=1.8Hz, J=17.3Hz), 3.89 (s, 3H), 3.78 (s, 3H), 3.75 (s, 3H), 3.02 (m, 4H), 2.88 (m, 2H), 2.65 (m, 2H), 2.00 (d, 1H, J=12.0Hz), 1.64 (s, 9H), 1.50 (m, 1H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 166.8, 156.9, 153.9, 150.4, 138.4, 138.2, 134.4, 124.5, 118.6, 117.0, 116.6, 110.4, 108.2, 103.5, 83.7, 61.9, 61.6, 60.8, 55.3, 51.2, 50.8, 42.6, 39.2, 31.8, 28.1, 25.2 ppm.

IR: ν = 2944, 2838, 2798, 2751, 1727, 1692, 1645, 1579, 1495, 1438, 1360, 1328 cm^{-1}.

HRMS (FAB): m/z calcd. for $(M+H)^+$ $C_{23}H_{29}O_4N_2$: 497.2607; found: 497.2649.

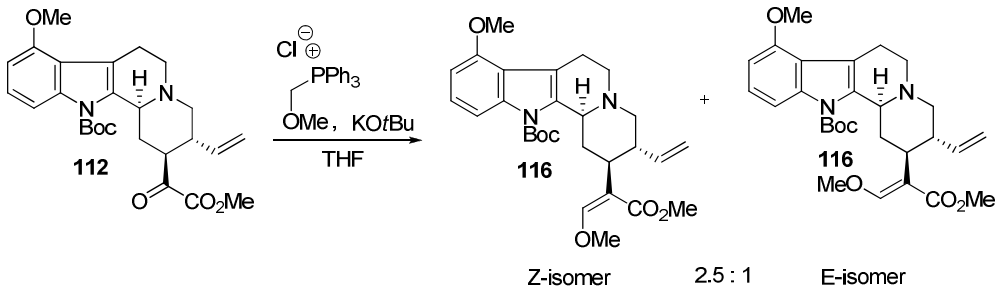
Crystallization:

The product was dissolved in a minimal amount of ethyl acetate and diluted with petroleum ether. After standing for 24 h at room temperature the crystals were removed by filtration.

Crystals: 4% *ee*, 0.0485 g, MP: 151-155°C; Filtrate: 98% *ee*, 0.371 g, 86% yield from **111**.

optical rotation:	$[\alpha]_D^{20}$ = -179.9° (c = 0.97, $CHCl_3$)	
HPLC	major enantiomer	15.22 min
	minor enantiomer	12.73 min
	(Chiralcel® OD-H, eluent: *n*-heptane:*iso*-propanol = 95:5, flow: 0.6 mL/min)	

Wittig reaction with *trans*-isomer 112



The reaction was performed as described for **114** using 0.109 g (0.233 mmol) of ketone **112** and three equivalents of phosphonium ylid. Purification through column chromatography gave both the *Z*-and *E*-isomer in a ratio of 2.5 : 1.

Z-isomer:

Yield: 57% (0.064 g, 0.13 mmol)

ee: 89%

optical rotation: $[\alpha]_D^{20}$ = +2.8° (c = 0.5, $CHCl_3$)

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.70 (d, 1H, J=8.2Hz), 7.13 (t, 1H, J=8.2Hz), 6.62 (d, 1H, J=7.9Hz), 6.37 (s, 1H), 5.54 (m, 1H), 5.02 (m, 2H), 4.14 (d, 1H, J=10.20 Hz), 3.86 (s, 3H), 3.75 (s, 3H), 3.71 (s, 3H), 3.14 (m, 3H), 2.97 (m, 1H), 2.77 (m, 2H), 2.64 (dq, 1H, J=3.8Hz, J=11.4Hz), 2.44 (td, 1H, J=3.6Hz, J=12.0Hz), 2.11 (ddd, 1H, J=2.6Hz, J=3.4Hz, J=12.9Hz), 1.73 (m, 1H), 1.65 (s, 9H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 166.8, 157.1, 154.0, 150.2, 139.2, 138.0, 134.6, 124.4, 118.7, 116.1, 115.4, 110.7, 108.6, 103.5, 83.6, 61.9, 60.8, 60.3, 58.6, 55.3, 51.1, 47.0, 42.4, 42.2, 34.5, 28.1, 24.6, 14.1 ppm.

IR: ν = 2937, 1724, 1320 cm^{-1}.

HRMS (FAB): m/z calcd. for $(M+H)^+$ $C_{28}H_{37}O_6N_2$: 497.2607; found: 497.2652.

E-isomer:

Yield: 21% (0.024 g, 0.047 mmol)

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.78 (d, 1H, J=8.4Hz), 7.28 (s, 1H), 7.13 (t, 1H, J=8.2Hz), 6.62 (d, 1H, J=8.0Hz), 5.53 (m, 1H), 4.96 (m, 2H), 4.20 (d, 1H, J=10.9Hz), 3.87 (s, 3H), 3.78 (s, 3H), 3.65 (s, 3H), 3.25 (m, 1H), 3.05 (m, 4H), 2.80 (m, 3H), 2.12 (q, 1H, J=12.4Hz), 1.84 (d, 1H, J=12.8Hz), 1.64 (s, 9H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 159.4, 154.0, 150.2, 139.9, 138.1, 134.7, 124.4, 118.7, 115.3, 115.1, 112.2, 108.6, 103.5, 83.6, 61.3, 60.9, 58.1, 55.4, 51.0, 46.3, 38.5, 30.8, 28.0, 24.6 ppm.

IR: ν = 1726, 1703, 1637, 1438, 1359, 1327 cm^{-1}.

HRMS (FAB): m/z calcd. for $(M+H)^+$ $C_{28}H_{37}O_6N_2$: 497.2607; found: 497.2652.

Crystallization of **116**:

116 was dissolved in a minimal amount of ethyl acetate and diluted with petroleum ether. After standing for 24 h at room temperature the crystals were removed by filtration.

Crystals: 73% *ee*, 0.0109 g, MP: 184-187°C; filtrate: 97% *ee*, 0.0051 g.

The filtrate resulting from the first crystallization was evaporated and the remaining grass dissolved and the crystallization procedure repeated.

Crystals: 99% *ee*, 0.005 g, MP: 183-187°C; filtrate: 0.0001 g.

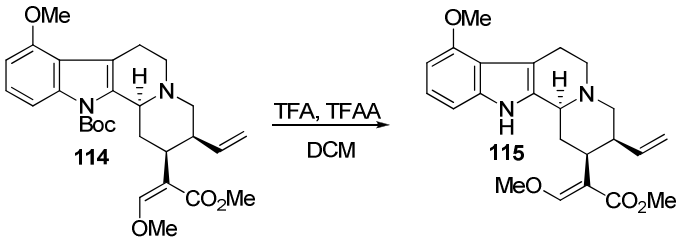
optical rotation: $[\alpha]_D^{20}$= +53.7° (c = 1.08, $CHCl_3$)

HPLC major enantiomer 18.69 min

minor enantiomer 16.39 min

(Chiralcel® OD-H, eluent: *n*-heptane:*iso*-propanol = 95:5, flow: 0.6 mL/min)

Synthesis of (-)-dehydro-mitragynine 115



0.4 equiv. trifluoroacetic anhydride was added to 5 mL good quality TFA under anhydrous conditions. The acid-solution was given to a solution of enolether (0.0336 g, 0.068 mmol) **114** in 15 mL DCM under argon. The reaction was stirred for 17 h at room temperature before it was quenched with Et_2O and neutralized with aqueous $NaHCO_3$. The aqueous phase was extracted with Et_2O, the organic layers combined and dried over Na_2SO_4. Purification by column chromatography using EtOAc:PE, 1:2/1:1 gave the product as a yellow solid.

Yield: 61% (0.0164 g, 0.041 mmol)

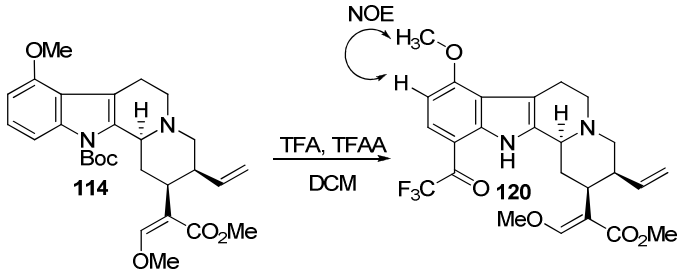
MP: 84-87°C

Optical rotation: $[\alpha]_D^{20}$= -104° (c = 0.93, $CHCl_3$)

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.70 (bs, 1H), 7.35 (s, 1H), 7.00 (t, 1H, J=7.9Hz), 6.90 (d, 1H, J=8.0Hz), 6.46 (d, 1H, J=7.7Hz), 6.32 (dt, 1H, J=9.9Hz, J=17.1Hz), 4.91 (m, 2H), 3.88 (s,

3H), 3.69 (s, 3H), 3.68 (s, 3H), 3.23 (bd, 1H, J=11.2Hz), 3.07 (m, 2H), 2.94 (m, 3H), 2.72 (dd, 1H, J=2.9Hz, J=11.2Hz), 2.55 (m, 2H), 2.42 (bd, 1H, J=7.6Hz), 1.86 (bd, 1H, J=12.8Hz) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$) δ = 169.0, 160.2, 154.4, 139.4, 137.1, 133.3, 121.8, 117.4, 114.2, 111.0, 107.8, 104.1, 99.6, 61.4, 61.2, 60.9, 60.3, 55.2, 53.5, 51.1, 44.5, 39.0, 30.2, 23.7 ppm.
IR: ν = 3364, 2936, 2838, 2791, 2752, 1698, 1643, 1597, 1570, 1507, 1460, 1435, 1350, 1309, cm^{-1}.
HRMS (FAB): m/z calcd. for $(M+H)^+$ $C_{23}H_{29}O_4N_2$: 397.2083; found: 397.2122.

Friedel-Crafts acylation of 114



1.3 mL TFAA was added to 13 mL TFA under anhydrous conditions. The TFA/TFAA-solution was given to a solution of enol ether (0.665 g, 1.339 mmol) **114** in 40 mL DCM and stirred for 20 h at room temperature. The reaction was quenched with Et_2O and neutralized with $NaHCO_3$ under strong stirring. The aqueous layer was extracted with Et_2O (3x), the organic layers combined and dried over Na_2SO_4. Column chromatography using EtOAc:PE 1:2/1:1 furnished product **120** as an orange foam.

Yield: 74% (0.489 g, 0.99 mmol)

Optical rotation: $[\alpha]_D^{20}$= -187.6° (c = 1.18, $CHCl_3$)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.95 (s, 1H), 7.84 (m, 1H), 7.39 (s, 1H), 6.59 (d, 1H, J=8.8Hz), 6.32 (dt, 1H, J=10.0Hz, J=17.0Hz), 4.95 (m, 2H), 4.02 (s, 3H), 3.72 (s, 3H), 3.71 (s, 3H), 3.28 (d, 1H, J=11.1Hz), 3.12 (m, 2H), 2.97 (m, 3H), 2.76 (dd, 1H, J=3.1Hz, J=11.2Hz), 2.57 (m, 2H), 2.47 (dd, 1H, J=2.8Hz, J=6.5Hz), 1.99 (dt, 1H, J=2.4Hz, J=12.9Hz) ppm.

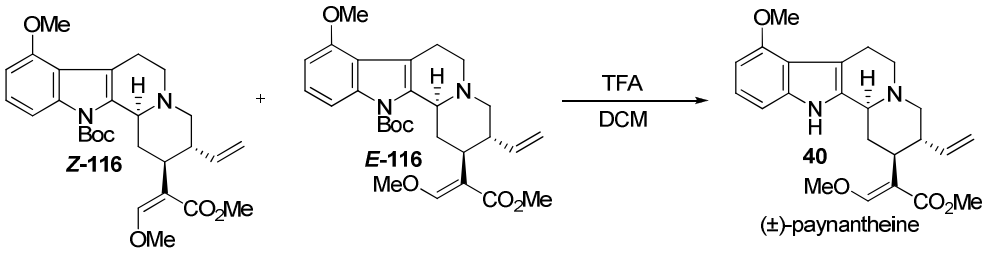
^{13}C-NMR (100 MHz, $CDCl_3$): 168.8, 161.4, 160.2, 139.2, 137.8, 135.1, 128.9, 128.9, 118.5, 117.6, 115.7, 114.4, 110.6, 108.7, 107.8, 100.7, 61.3, 61.2, 60.7, 55.6, 53.1, 51.1, 44.3, 38.9, 30.0, 23.4 ppm.

IR: ν = 2940, 2846, 2791, 2747, 1700, 1646, 1600, 1561, 1510, 1461, 1436, 1391, 1363, 1310 cm^{-1}.

HRMS (FAB): m/z calcd. for $(M+H)^+$ $C_{25}H_{28}O_5N_2F_3$: 493.1906; found: 493.1949.

Deprotection and isomerization to furnish paynantheine

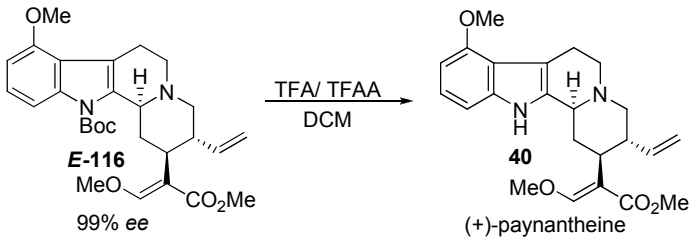
Isomerization with racemic material:



1.6 mL TFA was added to a mixture of racemic ***Z*-116** and ***E*-116** (0.162 mmol) in 4.8 mL anhydrous DCM and was stirred for 12 h at room temperature. The reaction was quenched with Et_2O and aqueous $NaHCO_3$. The aqueous phase was extracted with EtOAc, the organic layers combined and dried over Na_2SO_4. Purification by column chromatography using EtOAc:PE, 1:2/1:1 gave (±)-paynantheine as a brown solid.

Yield: 75% (0.035 g, 0.089 mmol)

Isomerization with enantioenriched (99% *ee*) material:



1.9 µL TFAA was added to 1.7 mL TFA under anhydrous conditions. The TFA/TFAA solution was given to a solution of 0.023 g (0.048 mmol) ***E*-116** in 5.2 mL dry DCM. The solution was stirred for 17 h at room temperature. The reaction was quenched with Et_2O and aqueous $NaHCO_3$. The aqueous phase was extracted with EtOAc, the organic layers

combined and dried over Na_2SO_4. Purification by column chromatography using EtOAc:PE, 1:2/1:1 gave (+)-paynantheine as a brown solid.

Yield: 96% (0.0181 g, 0.046 mmol)

ee: 99%

optical rotation: $[\alpha]_D^{20}$ = +20.2° (c = 0.91, $CHCl_3$)

Lit.: $[\alpha]_D^{25}$ = +29.4° (c = 1.2, $CHCl_3$)[67]

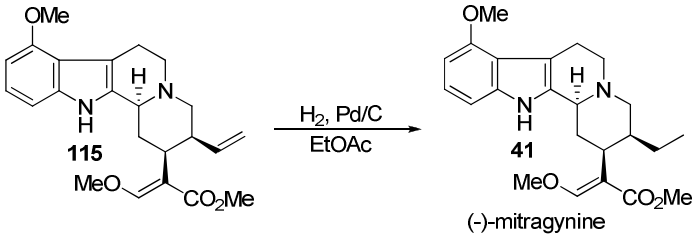
1H-NMR (400 MHz, $CDCl_3$) δ = 7.73 (bs, 1H), 7.33 (s, 1H), 7.00 (t, 1H, J=7.9Hz), 6.87 (d, 1H, J=8.1Hz), 6.46 (d, 1H, J=7.8Hz), 5.58 (m, 1H), 4.98 (m, 2H), 3.87 (s, 3H), 3.77 (s, 3H), 3.69 (s, 3H), 3.26 (bd, 1H, J=11.6Hz), 3.17 (m, 1H), 3.02 (m, 4H), 2.75 (td, 1H, J=3.5Hz, J=11.7Hz), 2.58 (td, 1H, J=4.2Hz, J=11.2Hz), 2.27 (t, 1H, J=11.4Hz), 2.14 (dd, 1H, J=12.0Hz, J=24.2Hz), 1.95 (d, 1H, J=12.5Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 159.8, 154.4, 139.4, 137.4, 133.0, 121.8, 117.5, 115.4, 107.8, 104.3, 99.7, 61.5, 61.3, 60.0, 55.3, 53.2, 51.3, 42.8, 33.4, 23.7 ppm.

IR: ν = 3370, 2940, 2847, 2799, 2751, 1703, 1637, 1596, 1569, 1509, 1461, 1436, 1353, 1336, 1317 cm^{-1}.

HRMS (FAB): m/z calcd. for $(M+H)^+$ $C_{23}H_{29}O_4N_2$: 397.2083; found: 397.2122.

Hydrogenation towards mitragynine



0.011 g (0.028 mmol) of enol ether was dissolved in 2 mL of EtOAc. 2 mg of Pd/C-catalyst was added and the suspension was stirred under H_2 atmosphere (1 atm.) for 12 h. Filtration over celite furnished (-)-mitragynine as a brown solid.

Yield: 99% (0.011 g, 0.028 mmol)

optical rotation: $[\alpha]_D^{20}$= -112° (c = 0.66, $CHCl_3$)

Lit.: $[\alpha]_D^{20}$ = -126 (c = 1.2, $CHCl_3$)[10]

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.73 (bs, 1H), 7.46 (s, 1H), 7.02 (t, 1H, J=7.9Hz), 6.92 (d, 1H, J=8.0Hz), 6.48 (d, 1H, J=7.7Hz), 3.90 (s, 3H), 3.75 (s, 3H), 3.73 (s, 3H), 3.13 (m, 2H),

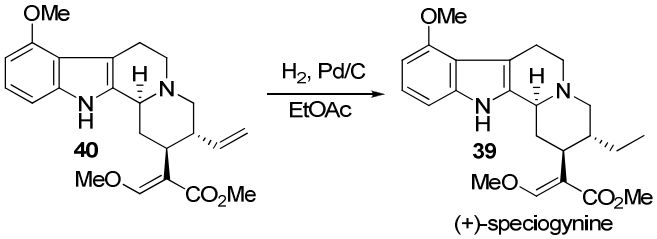
3.05 (m, 3H), 2.94 (m, 1H), 2.53 (m, 3H), 1.79 (m, 2H), 1.66 (m, 2H), 0.89 (t, 3H, J=7.3Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ =169.2, 160.5, 154.5, 137.2, 133.7, 121.8, 117.6, 111.5, 107.8, 104.2, 99.7, 61.5, 61.2, 57.7, 55.3, 53.8, 51.3, 40.7, 39.9, 29.9, 23.9, 19.1, 12.8 ppm.

IR: ν = 3367, 2933, 2849, 2796, 2747, 1703, 1643, 1624, 1597, 1569, 1508, 1461, 1435, 1373, 1350, 1310 cm^{-1}.

HRMS (FAB): m/z calcd. for $(M+H)^+$ $C_{23}H_{30}O_4N_2$: 399.2239; found: 399.2291.

(E)-methyl-2-((2S,3R)-3-ethyl-8-methoxy-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizin-2-yl)-3-methoxyacrylate



0.0342 g (0.086 mmol) of (+)-paynantheine was dissolved in 6 mL of EtOAc and 6 mg of Pd/C-catalyst was added and the suspension was stirred for 12 under H_2 atmosphere for 12 h. Filtration over celite furnished (+)-speciogynine as a brown solid.

Yield: 99%

optical rotation: $[\alpha]_D^{20}$ = +22.8 (c = 0.89, $CHCl_3$)

Lit.: $[\alpha]_D^{24}$ = +26.8°(c = 0.85, $CHCl_3$)[67]

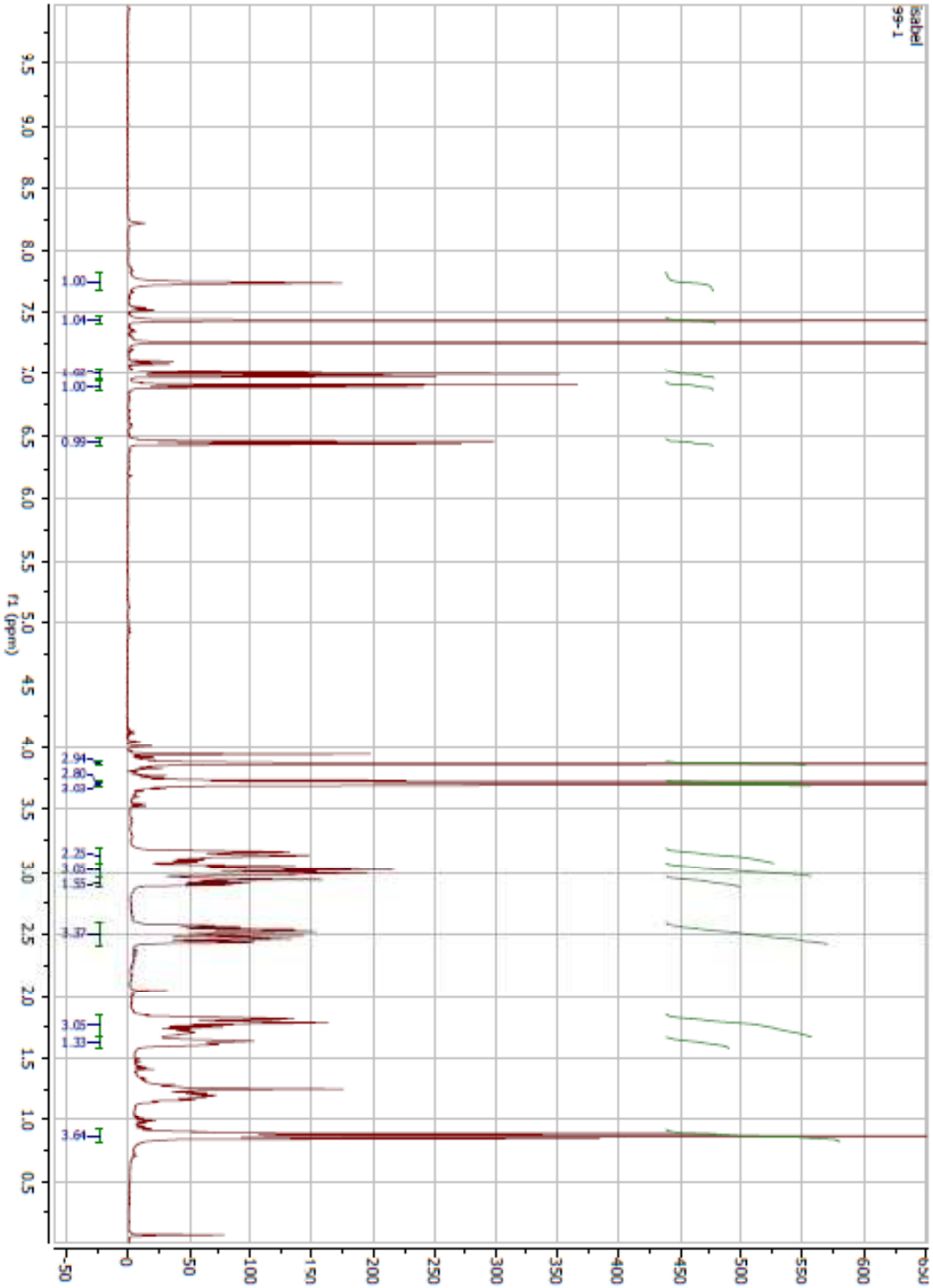
^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.81 (bs, 1H), 7.36 (bs, 1H), 6.99 (t, 1H, J=7.9Hz), 6.86 (d, 1H, J=8.1Hz), 6.45 (d, 1H, J=7.7Hz), 3.87 (s, 3H), 3.58-3.81 (bs, 6H), 3.28-2.93 (m, 5H), 2.78-2.5 (m, 2H), 2.35-2.20 (m, 1H), 2.15-1.82 (m, 3H), 1.50-1.36 (m, 1H), 1.12-0.97 (m, 1H), 0.87 (t, 3H, J=7.4Hz) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$) δ = 159.9, 154.4, 137.4, 133.1, 121.8, 117.5, 107.7, 104.3, 99.7, 61.7, 60.9, 60.3, 55.3, 53.5, 51.5, 39.9, 38.7, 33.7, 30.6, 29.7, 24.4, 23.7, 11.3 ppm.

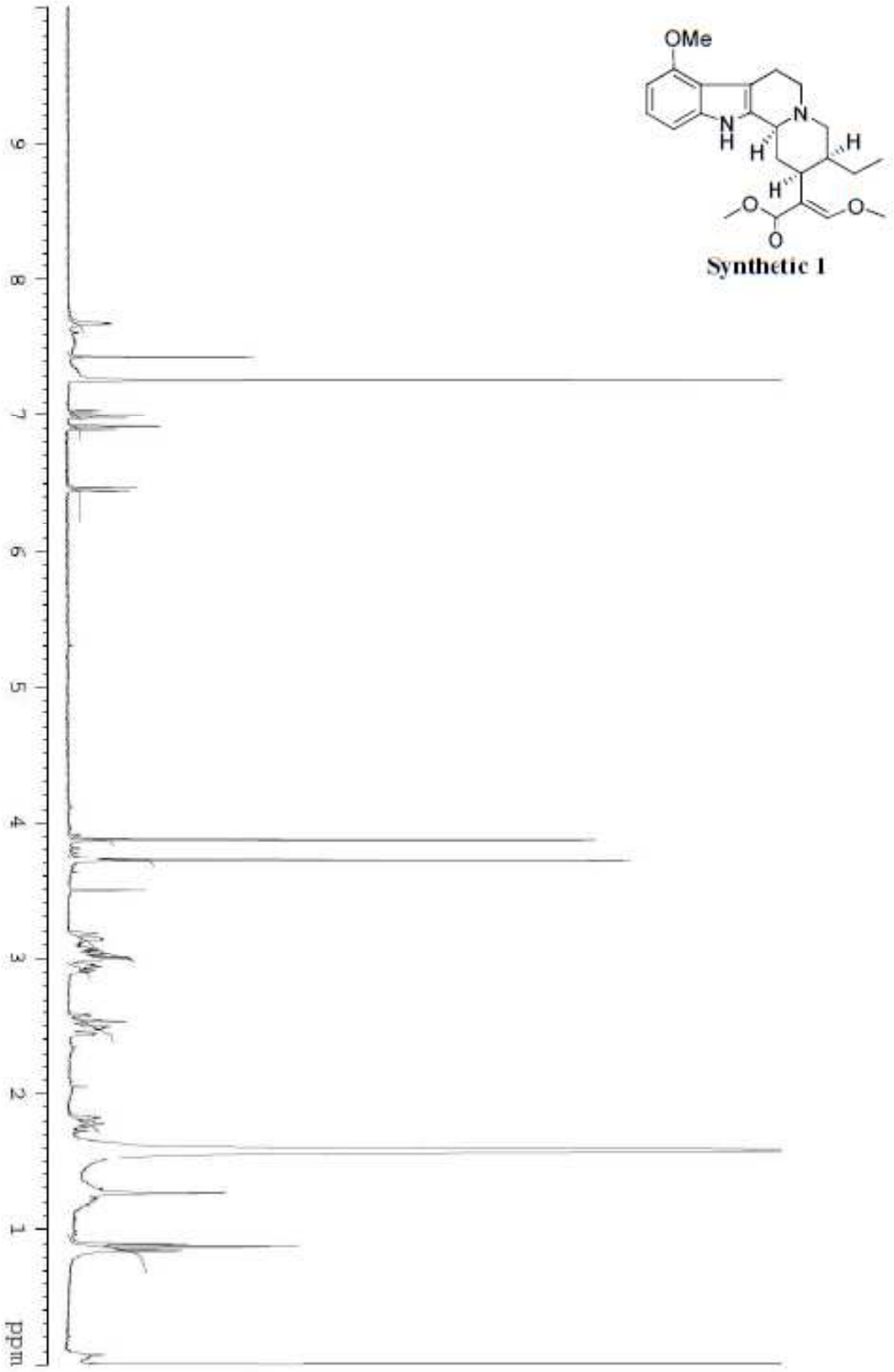
IR: ν = 2936, 2851, 2802, 2750, 1698, 1635, 1597, 1569, 1509, 1461, 1435, 1356, 1336, 1320, cm^{-1}.

HRMS (FAB): m/z calcd. for $(M+H)^+$ $C_{23}H_{31}O_4N_2$: 399.2239; found: 399.2289.

Recorded spectrum of (-)-mitragynine ($CDCl_3$, 400 MHz):

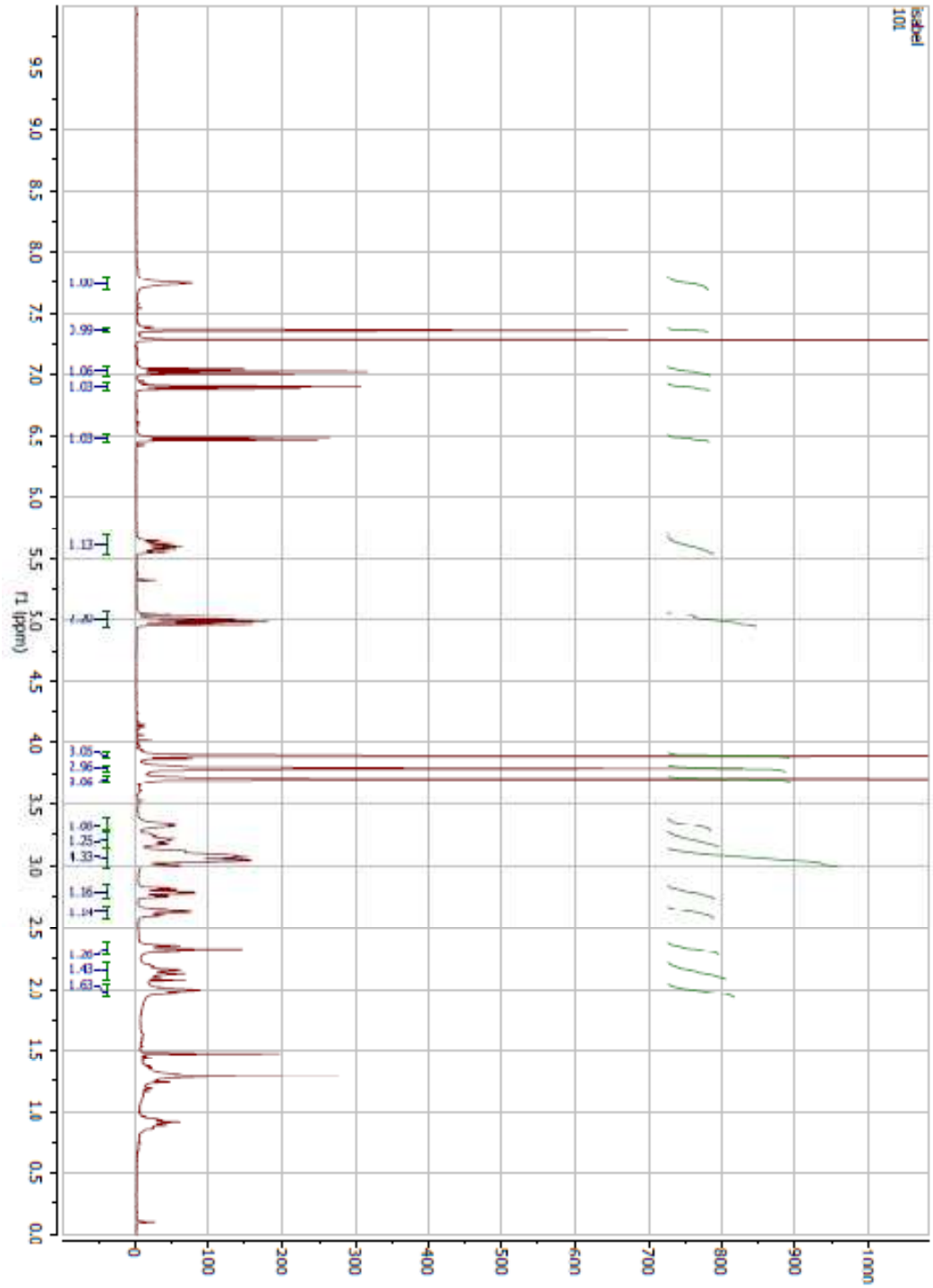


Copy of ^{1}H-NMR spectrum ($CDCl_3$, 300MHz) of (-)-mitragynine published by Cook et al.[8]

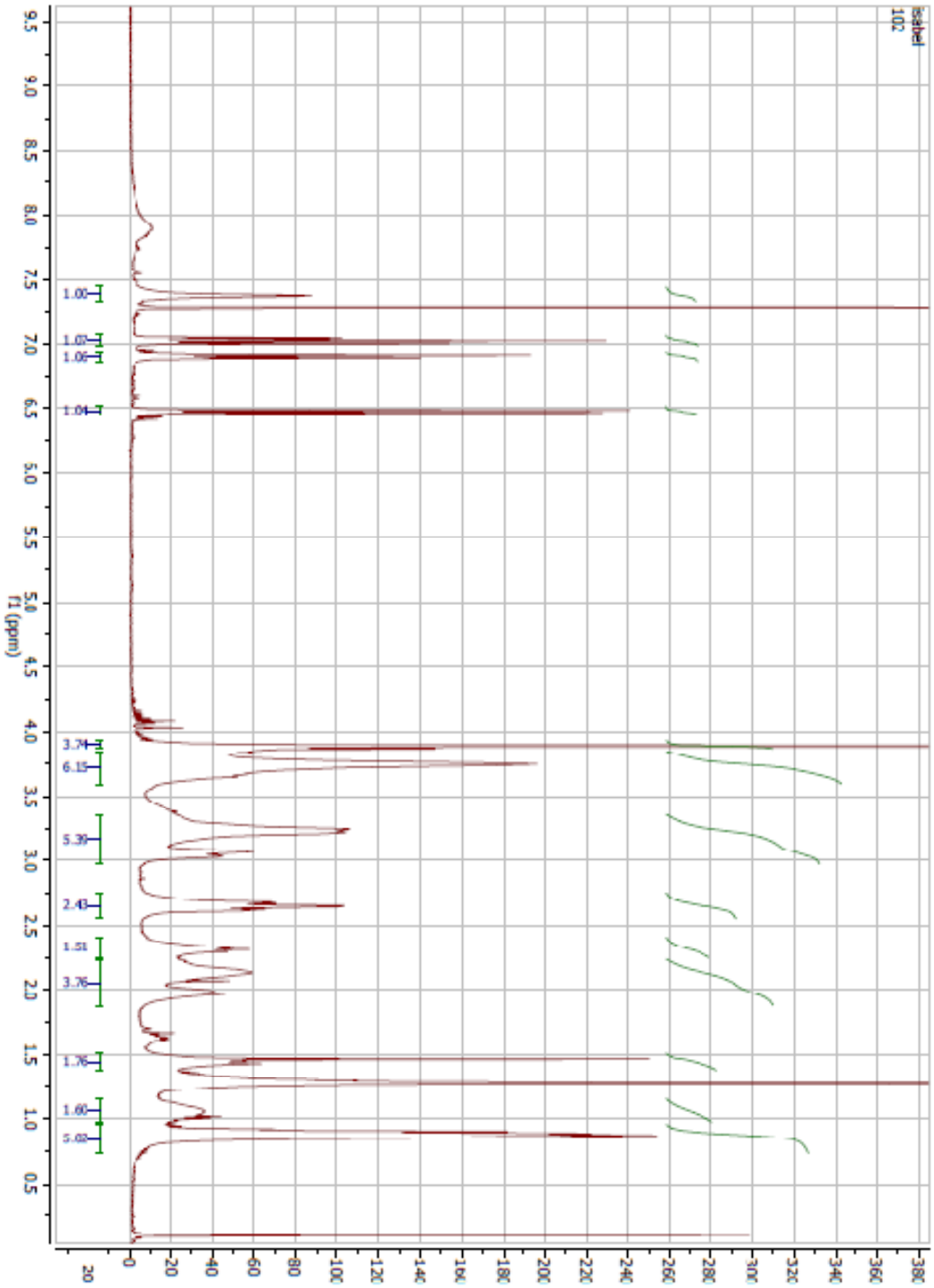


SI-62

Recorded spectrum of (+)-paynantheine ($CDCl_3$, 400 MHz):



Recorded spectrum of (+)-speciogynine ($CDCl_3$, 400 MHz):

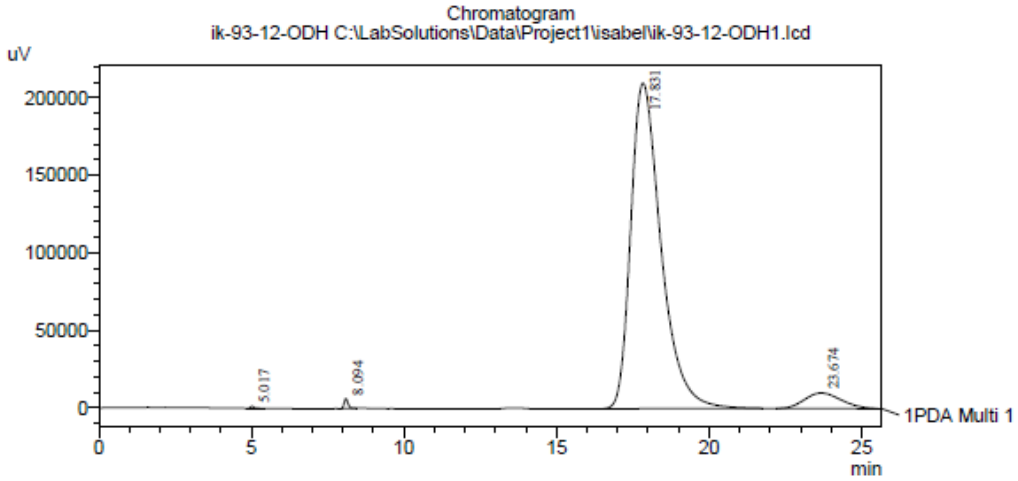


Chiral HPLC chromatogram of the Pictet-Spengler product **46** in the scale-up

Biomolecular Synthesis Shimadzu HPLC Analysis Report

		Method	
Acquired by	: Admin	[Pump A Mobile Phase A]	
Sample Name	: ik-93-12-ODH	Heptane	
Sample ID	: ik-93-12-ODH	Pump A: Heptane, B: 2-Propanol	
Vail #	:	Pump A	:LC-20AD
Injection Volume	: 20 uL	Total Flow	:0.6000 mL/min
Data File Name	: ik-93-12-ODH1.lcd	B.Conc	:10.0 %
Method File Name	: Remko1.lcm	C.Conc	:0.0 %
Batch File Name	:	D.Conc	:0.0 %
Report File Name	: remko-report.lcr	PressMax	:100 bar
Data Acquired	: 4/4/2012 11:58:41 AM	PressMin	:0 bar
Data Processed	: 4/4/2012 12:24:22 PM		

Chromatogram



1 PDA Multi 1 / 254nm 4nm

Results

PeakTable

PDA Ch1 254nm 4nm

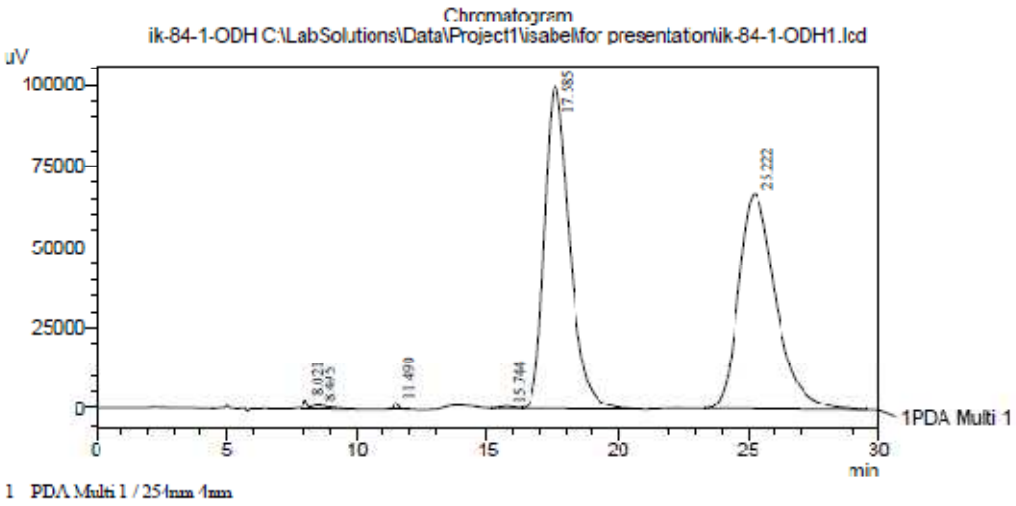
Peak#	Ret. Time	Area	Height	Area %	Height %
1	5.017	13262	1368	0.086	0.600
2	8.094	57850	6433	0.375	2.824
3	17.831	14487048	209874	93.981	92.124
4	23.674	856647	10143	5.557	4.452
Total		15414806	227818	100.000	100.000

Chiral HPLC chromatogram of racemic **46**.

Biomolecular Synthesis Shimadzu HPLC Analysis Report

		Method	
Acquired by	: Admin	[Pump A Mobile Phase A]	
Sample Name	: ik-84-1-ODH	Heptane	
Sample ID	: ik-84-1-ODH	Pump A: Heptane, B: 2-Propanol	
Vail #	:	Pump A	: LC-20AD
Injection Volume	: 20 uL	Total Flow	:0.6000 mL/min
Data File Name	: ik-84-1-ODH1.lcd	B.Conc	:10.0 %
Method File Name	: Remko1.lcm	C.Conc	:0.0 %
Batch File Name	:	D.Conc	:0.0 %
Report File Name	: remko-report.lcr	PressMax	:100 bar
Data Acquired	: 3/15/2012 4:01:46 PM	PressMin	:0 bar
Data Processed	: 3/15/2012 4:31:46 PM		

Chromatogram



1 PDA Multi 1 / 254nm 4nm

Results

PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	8.021	28656	2874	0.214	1.656
2	8.495	51895	1125	0.387	0.648
3	11.490	31363	2145	0.234	1.236
4	15.744	23991	597	0.179	0.344
5	17.585	6724851	100186	50.186	57.714
6	25.222	6530050	69050	48.700	39.402
Total		13399113	173559	100.000	100.000

6. Acknowledgements

Finishing the final stages towards my master degree, I have to thank some people. Thank you, Henk Hiemstra, for giving me the opportunity to work in this group and the trust in me to finish this wonderful project. I always felt in very good hands and never regretted coming to Amsterdam for my master studies. You have provided me with opportunities to experience the work of a scientist and I am convinced that I grew a lot on that. Thank you as well for helping me finding a good place for my future.

Martin, thank you so much for being such a good supervisor! I learned incredibly much from you and hope that during my future research, I am able to apply your way of thinking. Not only chemically but also personally we came along with each other very well and it was always a pleasure to work next to you.

Thanks also got to Jan van Maarseveen and Steen Ingemann for accepting me in this group and for a chat every now and then in the lab. Ron Wever is kindly acknowledged for being my second reviewer. Suze, Guido, Sjoerd, Luuk, Berend and Brian, thank you for the nice study atmosphere, not only during this project but also in the courses last year. I would like to thank the whole group for their kindness and for helping me with daily problems.

Jan Geenevasen, Jan Meine Ernsting and Han Peters are kindly acknowledged for the help with the NMR-machines and the performance of mass analysis.

Ich möchte meinen Eltern danken, die mich während meines Studiums immer unterstützt haben. Ohne Euch wäre ich heute nicht an diesem Punkt. Danke, Philipp, dafür dass du mit mir die letzten zwei Jahre geteilt hast!

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