Universität Hamburg
DER FORSCHUNG | DER LEHRE | DER BILDUNG

Prenylation of Tryptophan Derivatives for the Synthesis of Biologically Active Indole Alkaloid Natural Products

Conducted at the
Faculty of Mathematics, Informatics and Natural Sciences,
Department of Chemistry, Institute of Organic Chemistry
at the University of Hamburg

INAUGURAL-DISSERTATION

to obtain the academic degree

DOCTORUM RERUM NATURALIUM

(*Dr. rer. nat.*)

submitted by

M.Sc. Carina Susanne Michaelis
born the 22.05.1991 in Mönchengladbach

Hamburg 2020

1. Evaluator: Prof. Dr. Christian B. W. Stark

2. Evaluator: Prof. Dr. Joachim Thiem

Date of the oral defense: 25.09.2020

The experimental work for this thesis was conducted in the period between August 2016 and December 2019 at the Institute of Organic Chemistry at the University of Hamburg under the supervision of Prof. Dr. Christian B. W. Stark.

“Although nature commences with reason and ends in experience it is necessary for us to do the opposite, that is to commence with experience and from this to proceed to investigate the reason.”

- Leonardo Da Vinci

Acknowledgements

First of all, I would like to thank Prof. Dr. Christian B. W. Stark for enabling me to do this thesis in his research group, for giving me this interesting assignment and for his guidance during this whole time.

Furthermore, I would like to thank Prof. Dr. Thiem for taking the time to evaluate this thesis as well.

My special thanks go to Dr. Gunnar Ehrlich, Charlotte O`Donnell, Thorsten von Drathen, Katharina Hirte and Lara Simon for the meticulous proofreading of this thesis.

To my lab partners, especially Katharina Hirte and Denise Oetzmann, thank you for all the fun hours, the long nights, the constructive, inspiring and mood-lightening times that we spent together.

I would also like to thank all the previous and current members of the research group, Katharina, Denise, Lara, Charlotte, Sarah, Gunnar, Lilia, Kirsten, Thorsten, Mauricio, Philipp, André, Christian, Leon, Daniel, Jelena, Berk, Johann, Karin, Lena, Matthias and Jonas, for the very nice time we spent together. Thank you for your support and for making our labs a place I really enjoyed coming to every day.

In addition to this, I want to thank all the students, especially Daniel Schmelzer, who have done an internship or their bachelor thesis under my supervision, for their help and the good times we have had together.

Thank you to the staff of the departments of the NMR-spectroscopy and Mass-spectrometry under the supervision of Dr. Thomas Hackl and Dr. Maria Riedner for the recording of spectra and the conscientious handling of my samples.

I owe a very special thanks to all my friends and family for supporting me during this, sometimes stressful, time. Thank you so much for your support, for lending me your ear when I needed it and for staying with me over such a long time and distance.

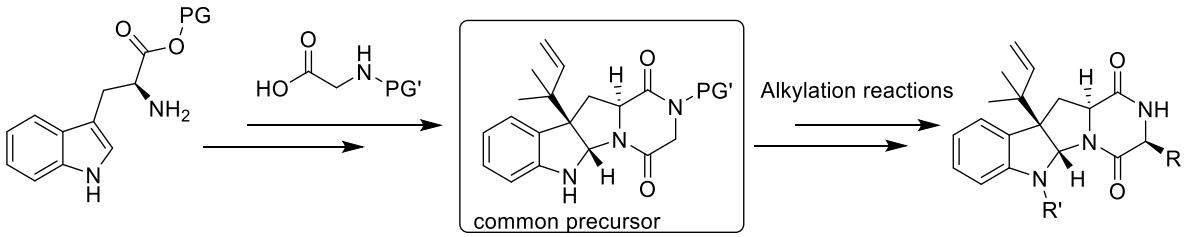
Lastly, I want to thank Yannick Wencke, without whom I would not have ended up here, would not have met all these very nice people and would not have made a lot of experiences that I am proud of today. Thank you for your endless support and your love.

Thank you all very much!

Abstract

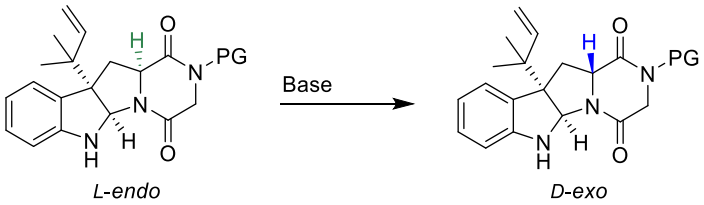
Reverse prenylated indole alkaloid natural products are an interesting class of substances due to their variety of biological activities, such as cytotoxicity, mycotoxicity or plant growing inhibitory activity. Their synthesis has been of interest for many years now; however, the need for a diastereoselective introduction of a reverse prenyl group and further conversion of these complex molecules often presents a challenging task.[1–3]

In the first part of this thesis, the iridium catalysed reverse prenylation reaction developed by Stark *et al.* was employed to establish a new and uniform pathway for the synthesis of derivatives of reverse prenylated hexahydropyrrolo[2,3-*b*]indole natural products.[4] Studies of a *C*-alkylation reaction on the common precursor of these natural products gave eight single alkylated derivatives in moderate to good yields. Due to issues with the deprotection of the PMB- and, later, the DMB-protecting groups the target natural products fructigenine A (**4a**) and brevicompanine E (**5**) were only produced in their *N*-protected form. However, the general applicability of this reaction sequence, which allows a more biomimetic access to this class of natural products, was demonstrated starting from *L*-tryptophan (**75a**).[5]



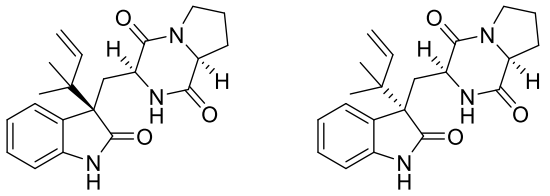
Short scheme of the unified pathway towards reverse prenylated hexahydropyrrolo[2,3-*b*]indole natural products *via* a common precursor.

During the study of the alkylation reactions on reverse prenylated hexahydropyrrolo[2,3-*b*]indole compounds, the reverse prenylated compounds containing the *endo*-structures unexpectedly inverted during the alkylation reaction. This was due to the deprotonation under basic conditions and the conversion of the molecule to the thermodynamically more favoured *exo*-isomer taking place faster than the deprotonation and subsequent alkylation of the methylene group of the DKP-ring. In further studies, this was shown to occur with both the *L*- and *D*-amino acid derivatives, as well as with substoichiometric quantities of base.



Example of the inversion of the *endo*-structure of the reverse prenylated natural product precursor derived from L-tryptophan (**75a**).

In the second part of this thesis, the synthesis of two notoamide derivatives was achieved by the prevention of an *N*-nucleophilic attack of the nitrogen atom of the amino group during the prenylation reaction. This was followed by the use of an external *O*-nucleophile in a one-pot prenylation and subsequent oxidation reaction on a protected L-tryptophan (**75a**) derivative. This synthesis was performed with good yields of up to 15% over six steps and demonstrates the potentially broad use of the established iridium catalysed reverse prenylation reaction for the synthesis of prenylated indole alkaloid natural products.



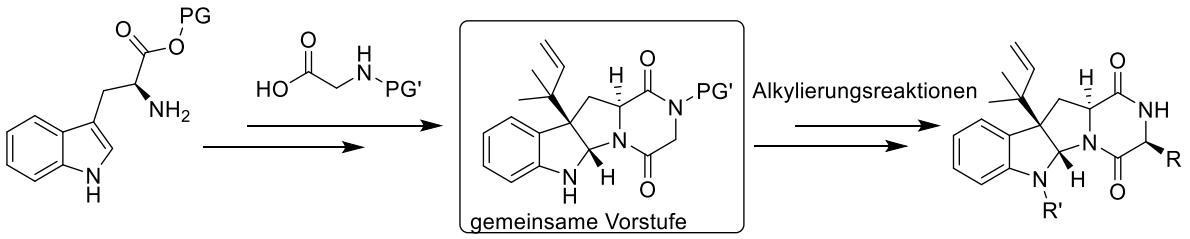
128a **128b**

Two successfully synthesised notoamide derivatives.

Kurzzusammenfassung

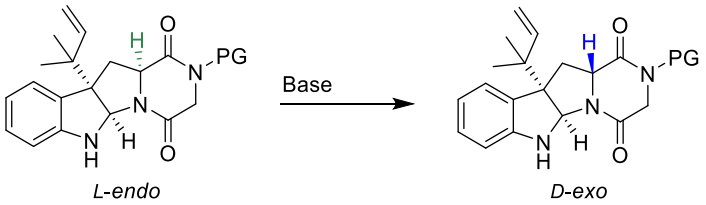
Die Naturstoffe der Klasse der invers prenylierten Indolalkaloide sind sehr interessant, da sie eine Reihe von biologischen Aktivitäten aufweisen, wie Zytotoxizität, Mykotoxizität oder wachstumshemmende Eigenschaften bei Pflanzen. Ihre Synthese ist deshalb schon seit einigen Jahren von großem Interesse, aber die Notwendigkeit einer diastereoselektiven Einführung der inversen Prenyl-Gruppe und die weitere Modifizierung dieser komplexen Moleküle stellt sich oft als eine herausfordernde Aufgabe heraus.[1–3]

In dem ersten Teil dieser Arbeit wird die von Stark *et al.* entwickelte Iridium-katalysierte inverse Prenylierungsreaktion angewendet, um einen neuen und einheitlichen Syntheseweg für die Darstellung von invers prenylierten Hexahydropyrrolo[2,3-*b*]indol-Naturstoff-Derivaten zu entwickeln.[4] Untersuchungen der *C*-Alkylierungsreaktion der gemeinsamen Vorstufe dieser Naturstoffe hat zu acht einfach alkylierten Substraten in moderaten bis guten Ausbeuten geführt. Aufgrund von Schwierigkeiten bei der Entschützung der PMB- und später auch der DMB-Schutzgruppen konnten die Naturstoffe Fructigenin A (**4a**) und Brevicompanin E (**5**) jeweils nur in ihrer *N*-geschützten Form erhalten werden. Nichtsdestotrotz konnte die generelle Anwendbarkeit dieser Synthesestrategie, ausgehend von *L*-Tryptophan (**75a**), gezeigt werden, was einen Zugang zu diesen Naturstoffen eröffnet, der Nahe dem der Biosynthese liegt.[5]



Kurzes Schema des allgemeinen Syntheseweges zu invers prenylierten Hexahydropyrrolo[2,3-*b*]indol Naturstoffen über eine gemeinsame Vorstufe.

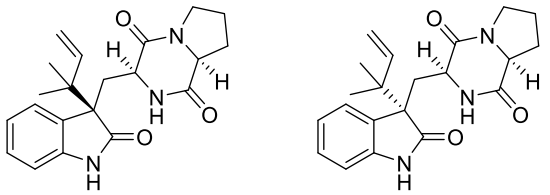
Während der Untersuchung der Alkylierungsreaktionen an invers prenylierten Hexahydropyrrolo[2,3-*b*]indol-Substraten wurde eine interessante Entdeckung gemacht. Die invers prenylierten Verbindungen, die eine *endo*-Struktur aufwiesen, sind während der Alkylierungsreaktion invertiert. Die Deprotonierung durch die Base und die Umwandlung des Moleküls in die begünstigte *exo*-Struktur verlief schneller als die Deprotonierung und anschließende Alkylierung der Methylengruppe des Diketopiperazinrings. Weitere Studien konnten zeigen, dass dies sowohl bei Derivaten der jeweiligen *L*- und *D*-Aminosäure sowie bei der Zugabe von katalytischen Mengen der Base stattfand.



L-endo *D-exo*

Beispiel der Invertierung einer *endo*-Struktur des invers prenylierten Naturstoffvorläufers, ausgehend von *L*-Tryptophan (**75a**).

Im zweiten Teil dieser Arbeit wurden zwei Derivate der Notoamide, durch das Verhindern des *N*-nucleophilen Angriffs des Stickstoffs der Aminogruppe während der Prenylierungsreaktion und der anschließenden Verwendung eines externen *O*-Nucleophils, in einer Ein-Topf Prenylierungs- und nachfolgenden Oxidationsreaktion an einem geschützten Derivat des *L*-Tryptophans (**75a**), dargestellt. Dies konnte mit guten Ausbeuten von bis zu 15% über sechs Schritte erzielt werden und zeigt die potentiell breite Anwendbarkeit der zuvor etablierten Iridium-katalysierten inversen Prenylierungsreaktion in der Synthese von Indolalkaloid-Naturstoffen.



128a **128b**

Die beiden erfolgreich synthetisierten Notoamid-Derivate.

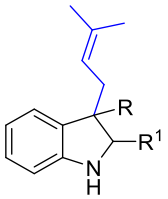
Table of Contents

1 General Introduction

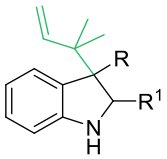
1.1 Reverse prenylated indole alkaloid natural products

1.1.1 Structures and properties of reverse prenylated indole alkaloids

Within the class of indole alkaloid natural products, the so-called “reverse prenylated” indole alkaloids represent a structurally unique group with a high density of biologically active compounds. Among them are members of the fructigenine-, roquefortine-, amauromine- and notoamide-families (Figure 1.1.2). Many of those substances are antibacterial, antifungal, anti-inflammatory, antioxidative or show cytotoxic or antitumoral effects.[6,7] The decisive structural motifs of reverse prenylated indole alkaloids are a tryptophan- or a tryptamine-based indoline core and a reverse prenyl unit. The term “reverse prenyl group” was coined by Danishefsky to distinguish between a 1,1-dimethylallyl substituent, containing two adjoining quaternary centres, and the more common “linear prenyl group”, which contains the 3,3-dimethylallyl motif (Figure 1.1.1).[8,9] In addition to indole derivatives, prenylated natural products can also contain other electron-rich aromatic systems, such as pyrroles and phenols.[10–12]



linear prenylated indole derivative



revers penylated indole derivative

Figure 1.1.1: C3-linear prenylated and C3-reverse prenylated indole structures.

C3-prenylated natural products are often isolated from fungi but have also been found in other plants and sea sponges.[13]

In Figure 1.1.2 a selection of well-known biologically active reverse prenylated indole alkaloids, with their reverse prenyl moiety in green, are shown. Among them are roquefortine D (**2**), from the substance class of mycotoxins, the dimer amauromine (**1a**) and notoamide A (**6**), which contains an intramolecularly integrated reverse prenyl group.[1,14–16]

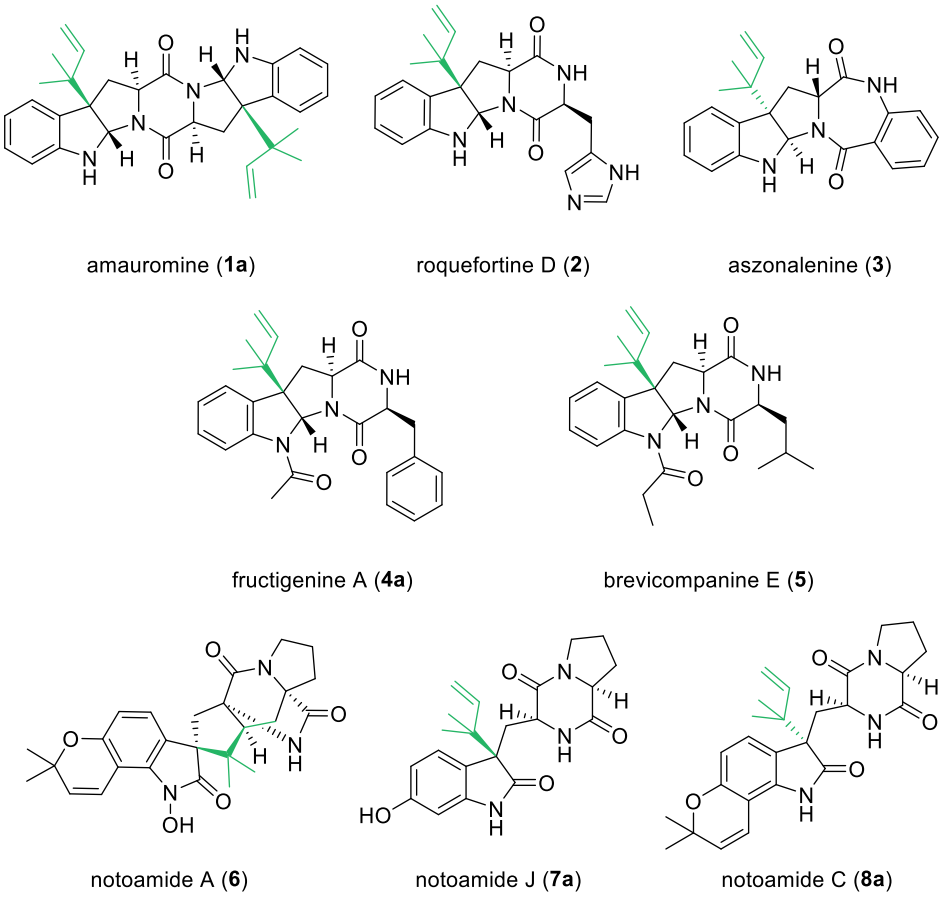
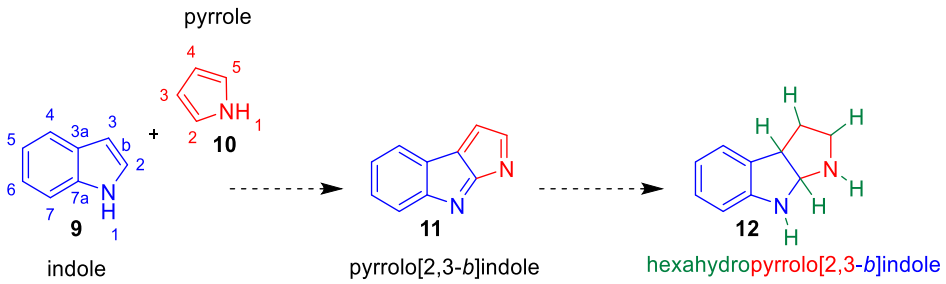


Figure 1.1.2: A selection of natural products containing reverse prenylated indole units, shown in green.[1,3,15,17–20]

There are several structural similarities between the compounds shown in Figure 1.1.2. Many of these compounds contain a hexahydropyrrolo[2,3-*b*]indole moiety and/or a diketopiperazine (DKP) moiety, which is built by condensation of two natural amino acids or their derivatives.[17,21,22] Interestingly, aszonalenine (**3**) is one of the few structures that appears to be derived from *D*-tryptophan (**75b**), rather than the more common *L*-tryptophan (**75a**).

Hexahydropyrrolo[2,3-*b*]indoles have long been studied due to their interesting bioactivities. Notably, their prenylated derivatives only represent one of the many subclasses of these natural products. The term hexahydropyrrolo[2,3-*b*]indole is based on the IUPAC nomenclature rules and its composition is shown in Scheme 1.1.1. The core structure contains a six times (hexa) hydrogenated (hydro) ring-system, which is built from an indole unit (**9**) and a pyrrole (**10**) unit.[11,23–26]



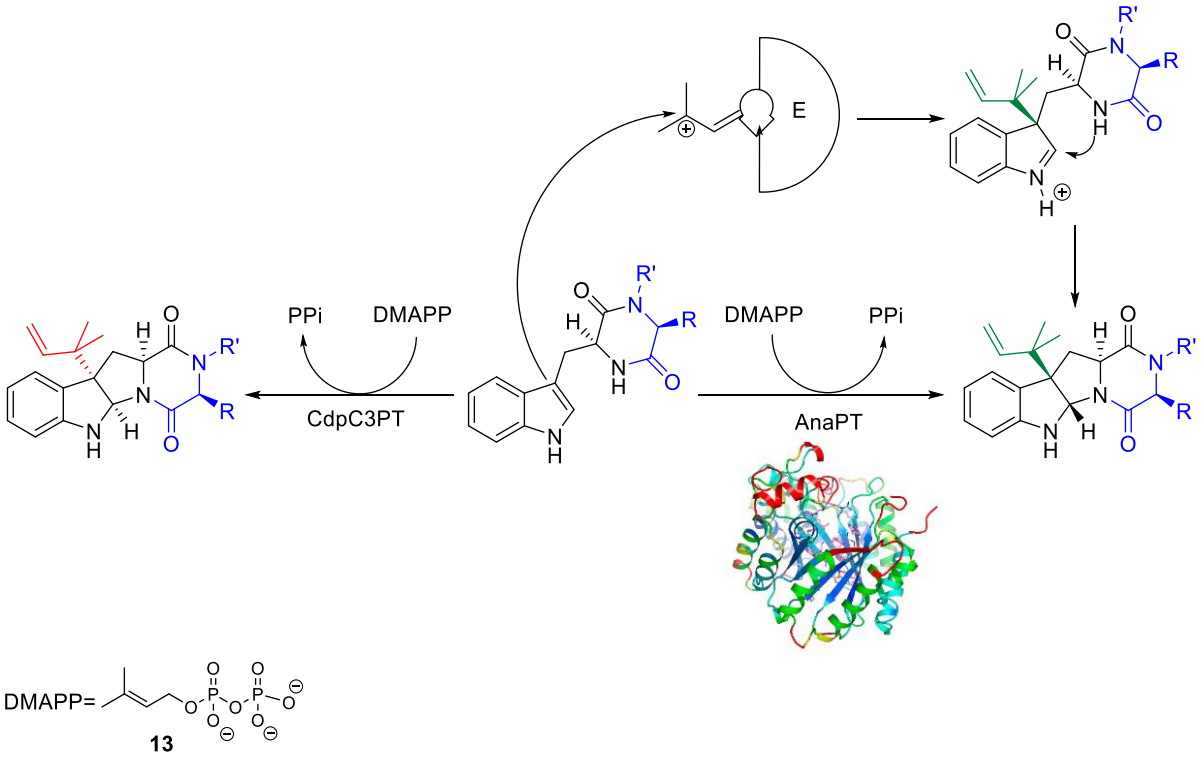
Scheme 1.1.1: Nomenclature of hexahydropyrrolo[2,3-*b*]indoles.

1.1.2 Biosynthetic pathways of reverse prenylated indole alkaloids

As far as it is known, the key step in the biogenetic synthesis of reverse prenylated indole alkaloids is believed to be the transmission of a prenyl group, as an electrophile, to an indole system through a prenyltransferase enzyme.[10]

There are a variety of prenyltransferases, for example (e.g.) dimethylallyl transferase (DMAT), which has been isolated from fungi and activates the first step in the biosynthesis of ergot alkaloids.[27–29] Prenyltransferase enzymes catalyse the introduction of the prenyl group, usually from dimethylallyl diphosphate (DMAPP) (**13**) to different positions on the indole core, depending on the prenyltransferase.[30–33] This prenyl group transfer occurs *via* an electrophilic aromatic substitution reaction. Nucleophilic attack from the indole to the primary position of the dimethylallyl carbocation results in a linear prenyl unit in the product, whereas attack to the tertiary position of the carbocation results in a reverse prenyl unit in the product.[34]

Studies on the biosynthetic prenylation of tryptophan derivatives were already reported in the 1970s.[35,36] Even though the C2- and C3-positions of the indole core are more nucleophilic, the enzyme DMAT catalyses the prenylation at the C4-position.[37,38] Wenkert *et al.* gave a possible explanation for this finding.[36] They proposed that the initial prenylation takes place at the C3-position of the indole unit followed by rearomatisation *via* a Cope rearrangement, giving a C4-linear prenylated product. However, this hypothesis was later dismissed as it could not be experimentally supported *in vitro*. An alternative biosynthetic Cope rearrangement was then proposed by Gaich *et al.* They suggested that the enzyme pre-orients the substrate into a reactive conformation. To support their hypothesis they designed a highly rigid, bio-inspired test substrate. Thus showing that the stereochemistry of the substrate is responsible for the overlap of the orbitals, which turned out to be crucial for the feasibility of the reaction.[39]



Scheme 1.1.2: Proposed biosynthetic, stereospecific C3-reverse prenylation with prenyltransferase CdpC3PT giving the *endo*-product and prenyltransferase AnAPT giving the *exo*-product.[5]

In 2013, Li *et al.* reported a mechanism for the stereospecific prenylation of tryptophan-containing cyclic dipeptides (DP) to give pyrroloindole diketopiperazines (Scheme 1.1.2). The stereoselectivities of the three prenyltransferases AnaPT, CdpC3PT and CdpNPT were studied.[5] These enzymes belong to the family of the DMAT synthases and were isolated from the fungi *Neosartorya fischeri* and *Aspergillus fumigatus*.[40–42] As well as catalysing the introduction of a prenyl group, they also ensure the formation of a five-membered ring between the indole- and the DKP-unit of the substrate. Furthermore, Li *et al.* discovered a new indole binding mode by comparison of the crystal structures of AnaPT and CdpNPT. They found that the substitution of the DKP-unit is crucial for the stereoselective outcome of the reaction, as the enzymes usually introduce the prenyl group from the opposite side. As a result, the configuration of the binding prenyltransferase determines the stereochemical outcome of the reaction.[5]

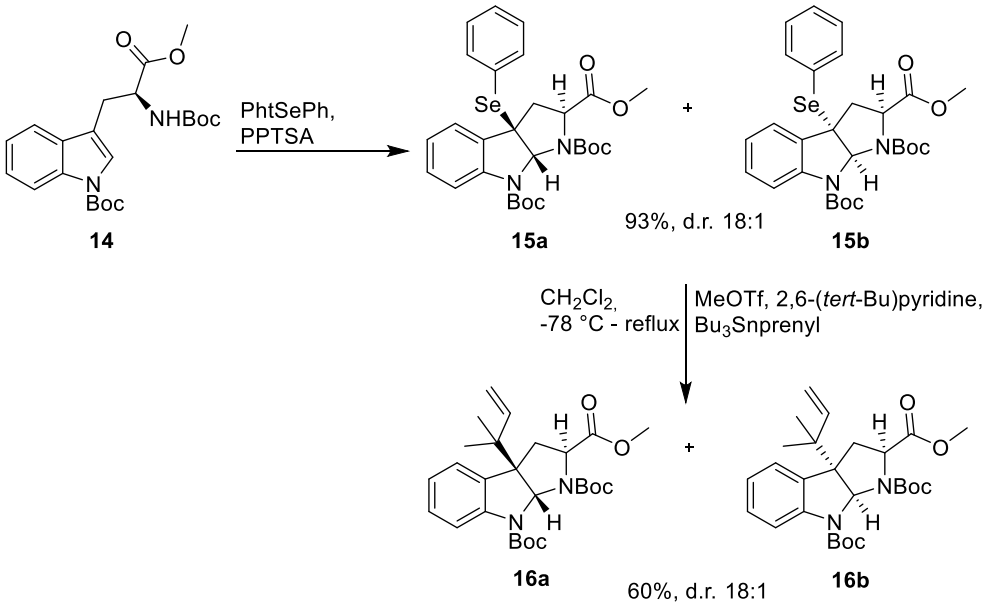
1.1.3 Reverse prenylation reactions and their application in natural product synthesis

In recent years, the insight into the biogenesis of reverse prenylated substances has increased significantly. However, the stereoselective synthetic access was, until recently, hardly possible or only manageable through indirect routes. Therefore, the development of a biomimetic asymmetric prenylation reaction would be extremely attractive as it would start from easily accessible starting materials and would also open a pathway to quickly and efficiently synthesise complex natural products and their derivatives. This would be of significant importance for application in the fields of medicinal and biological chemistry.[13]

1.1.1.1 Development of the synthetic introduction of a reverse prenyl group

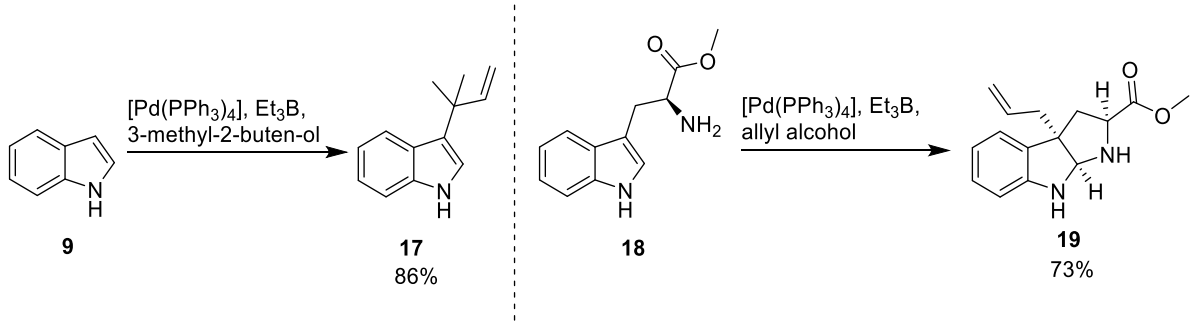
The synthetic introduction of isoprene units, mostly at the C3-position of indole derivatives, has long been challenging. This is mostly due to the need to control the regioselectivity regarding the electrophile, as well as the control of the relative and absolute configuration of the newly formed stereogenic centres. Previously reported total syntheses could only master these problems through indirect synthetic routes and rearrangements.[14,43]

In 1999, Danishefsky *et al.* reported one of the first synthetic introductions of a reverse prenyl group at the C3-position of an indole unit in their total synthesis of 5-*N*-acetyladeemin and amauromine (**1a**).[16] They achieved this transformation by oxidative cyclisation of the protected *L*-tryptophan derivative **14** into selenides **15a** and **15b** followed by alkylation to give products **16a** or **16b** respectively (Scheme 1.1.3). Interestingly, they found that compound **15a** was obtained in high excess which led them to believe that it is the kinetically more favoured configuration. This opened a new pathway for the direct synthesis of *exo*-pyrroloindoles as the diastereomeric ratio remained unchanged during the following alkylation reaction.[16]



Scheme 1.1.3: Reverse prenylation at the C3-position as reported by Danishefsky *et al.* in 1999.[16]

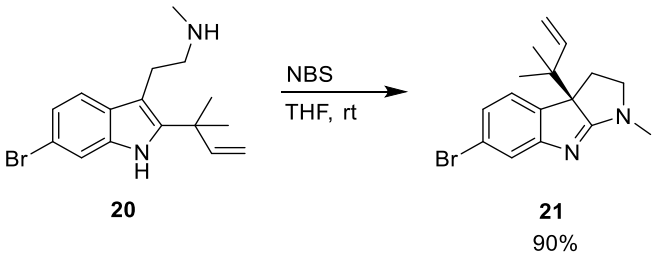
Tamaru *et al.* reported a palladium catalysed reverse allylation on 1*H*-indole (**9**) and its derivatives in 2005.[44] They were the first to use triethylborane as additive to promote the reaction. When they used 3-methyl-2-buten-1-ol (**41**) as the allyl source on 1*H*-indole (**9**) they obtained the prenylated derivative **17**. Interestingly, when they used allyl alcohol as the allyl source on *L*-tryptophan methyl ester (**18**) they exclusively obtained the *endo*-isomer of the product **19** (Scheme 1.1.4).



Scheme 1.1.4: Palladium catalysed allylation on indole units as reported by Tamaru *et al.* in 2005.[44]

Interestingly, this method never provided the *N*-alkylated substrates as previous investigations on palladium catalysed allylic alkylation reactions had suggested.[45,46] The specific role of the borane as additive could not be fully determined. However, it was believed to be the reason for the selectivity and crucial for the reaction to occur. The broad scope of the reaction could be demonstrated by using allyl alcohol substrates with a wide structural diversity. The reported yields were all above 80% but the regioselectivity, in reference to a reverse or linear product, and the resulting, though good, diastereoselectivities could not be fully explained.[44]

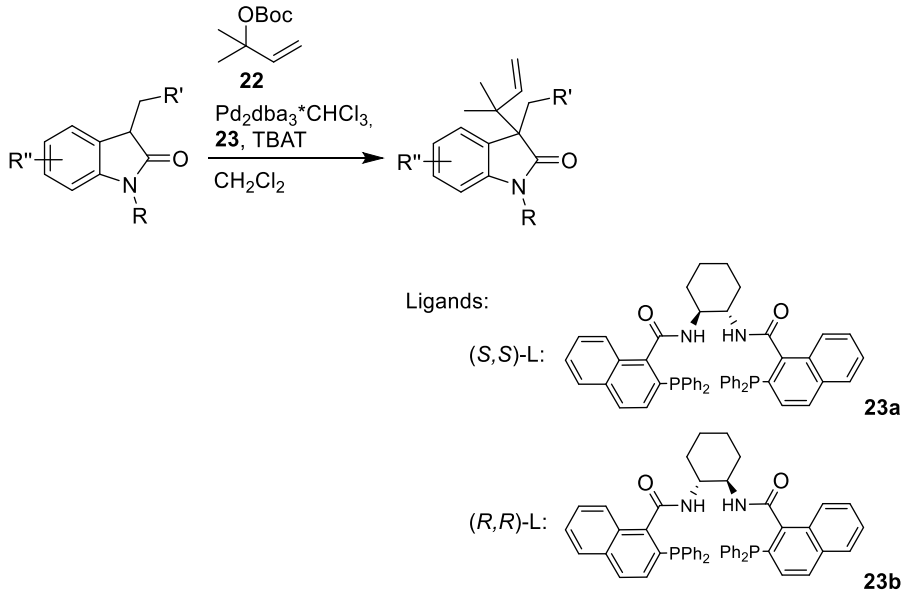
In their total synthesis of flustramine C (**21**), Lindel *et al.* reported an alternative approach in 2007.[47] The introduction of a reverse prenyl group at the C3-atom of the indole unit was achieved *via* a dimethylallyl rearrangement (Scheme 1.1.5).[47] The prenyl group is initially introduced at the C2-position and is moved to the C3-position *via* oxidation with *N*-bromosuccinimide (NBS), which entails selective 1,2-rearrangement. They demonstrated the applicability of their method through the synthesis of the natural product flustramine C (**21**).[47]



20 **21** 90%

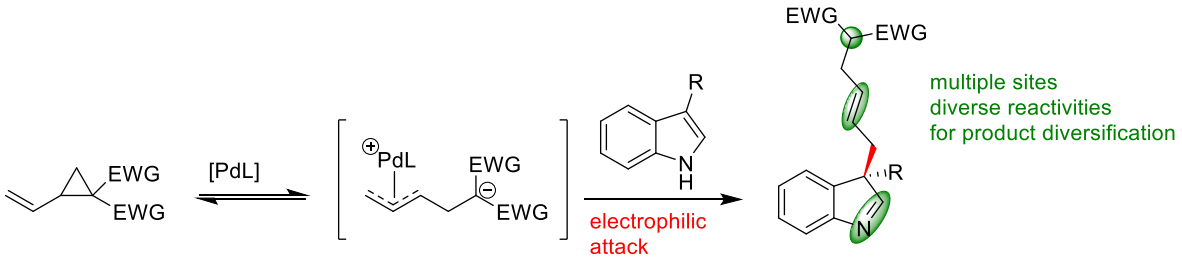
Scheme 1.1.5: Introduction of a reverse prenyl group at the C3-position *via* dimethylallyl rearrangement as reported by Lindel *et al*.[47]

Trost *et al.* were able to report a regioselective palladium catalysed asymmetric prenylation reaction in 2011.[43] Scheme 1.1.6 illustrates the general reaction conditions for this asymmetric reverse prenylation reaction. Carbonate **22** serves as prenyl donor and the choice of the ligand is critical to the regioselectivity of the reaction. Different substitution at the former indole nitrogen atom did not prevent C3-prenylation; however, unsubstituted 2-oxindoles were also formed as *N*-alkylated side products. The introduction of a linear prenyl and a geranyl group using these conditions could also be performed successfully. This opened up a new pathway towards the synthesis of a variety of indole alkaloid natural products.[43]



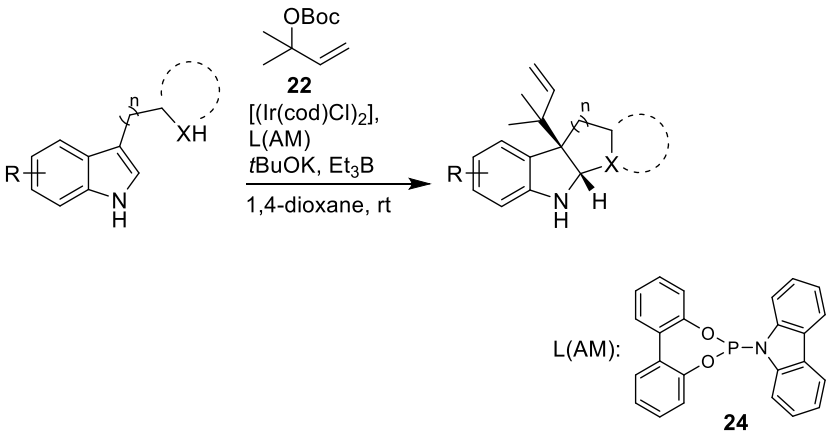
Scheme 1.1.6: Palladium catalysed asymmetric reverse prenylation reaction as reported by Trost *et al.* in 2011.[43]

More recently, Trost *et al.* reported an allylic alkylation at C3-substituted indoles and tryptophan derivatives using vinylcyclopropanes (Scheme 1.1.7).[48] The automatically occurring tandem allylation/cyclisation reaction is highly selective through the use of ligands and boranes. This leads to compounds containing an imine, an internal olefin and a malonate moiety, which makes them excellent substrates for the target-oriented synthesis of many natural products and other interesting biologically active compounds. Although this method is suitable for constructing the core structures of many hexahydropyrrolo[2,3-*b*]indole natural products, the introduction of a reverse prenyl group was not realised.[48]



Scheme 1.1.7: Pd-catalysed asymmetric allylic alkylation reaction with vinylcyclopropanes on C3-substituted indoles.[48]

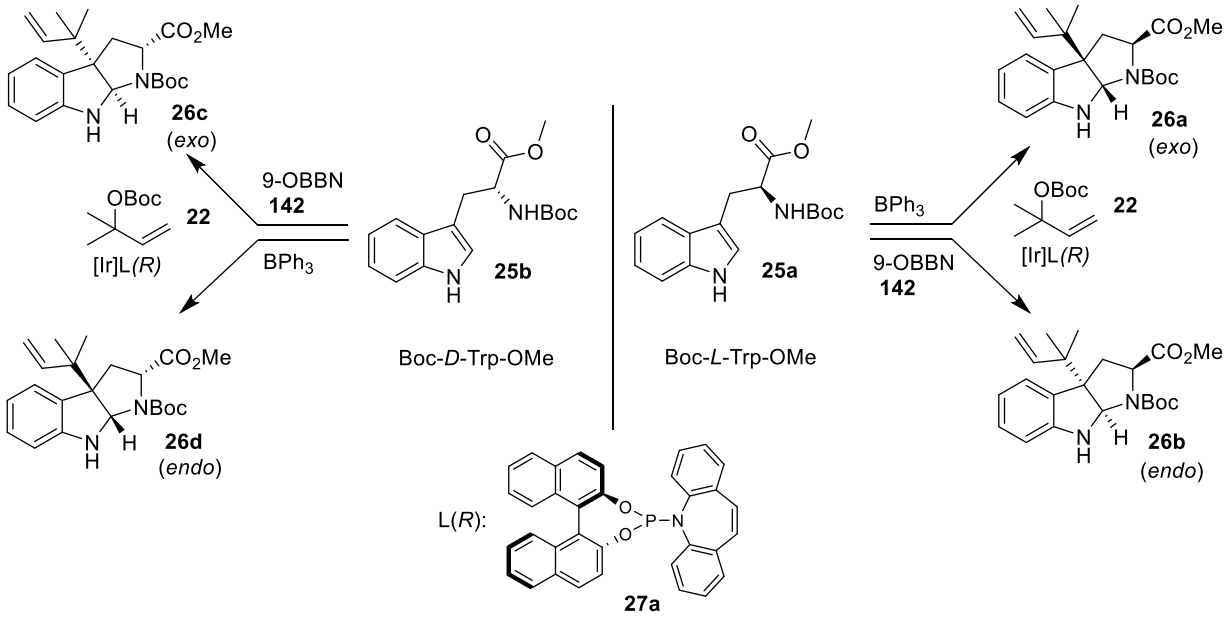
One of the first iridium catalysed reverse prenylation reactions was published by Carreira *et al.* in 2014.[49] They used the phosphoramidite ligand **24** and were able to achieve a high regioselectivity (>20:1) of reverse to linear prenylated products (Scheme 1.1.8). Similar to Tamaru *et al.*[44], they also reported the use of triethylborane as an additive in their reaction. The applicability of this method was demonstrated on a series of C3-substituted indoles, including the successful stereoselective reverse prenylation of L-tryptophan methyl ester (**18**), which subsequently led to the synthesis of the natural product aszonalenine (**3**).[49]



Scheme 1.1.8: Iridium catalysed reverse prenylation reaction as reported by Carreira *et al.* in 2014.[49]

In 2014 and subsequently in 2015, You *et al.* went one step further with this method.[50,51] They reported highly diastereoselective and enantioselective allylic alkylation reactions when using different chiral phosphoramidite ligands. They obtained a broad product scope of C3-alkylated indoline derivatives using the same iridium catalyst as reported by Carreira *et al*.[49] Their asymmetric alkylation reaction sequence was performed on C3-substituted indole substrates; with an initial allylation followed by an intramolecular alkylation. During this reaction up to three contiguous stereocentres are built.[51] The use of allylic alcohols as nucleophiles, in the presence of a Lewis acid, led to the formation of prenylated indoles *via* a similar method and in good enantioselectivities. However, the introduction of a reverse prenyl group was not reported in either case.[50,51]

In the Stark group a novel regio- and stereoselective reverse prenylation reaction on indole- and tryptophan-derivatives was reported in 2016 (Scheme 1.1.9). This method combines and refines many of the previously reported prenylation reactions and its applicability was demonstrated in the successful synthesis of all known isomers of the amauromines (Chapter 1.1.3.2).[4,44,49,50]



Scheme 1.1.9: Diastereodivergent reverse prenylation reaction of protected *L*- and *D*-tryptophan derivatives **25a** and **25b** using one enantiomer of a chiral ligand **27a** as developed by Stark *et al*.[4]

In this iridium catalysed reverse prenylation reaction yields of up to 95% and diastereoselectivities of >20:1 were obtained. It was also shown that the use of a specific borane additive is important for the stereoselectivity. For a given substrate, switching between 9-octyl-9-borabicyclo[3.3.1]nonane (9-OBBN) (**142**) or triphenylborane as the borane additive, gave enantiomerically pure mirror images of the products. Starting from the protected *L*-tryptophan derivative **25a** the use of 9-OBBN (**142**) coupled with the (*R*)-configured ligand **27a** led to the formation of the *endo*-product **26b**. Switching of either the (*R*)-ligand **27a** to the (*S*)-ligand **27b** or from 9-OBBN (**142**) to triphenylborane led to the formation of the *exo*-product **26a**. Both borane reagents gave the products in good yields and opposing selectivities. Thus, all four stereoisomers of the reverse prenylation reaction could be formed through targeted use of the two achiral borane additives as well as only one isomer of the chiral ligands.[4,52]

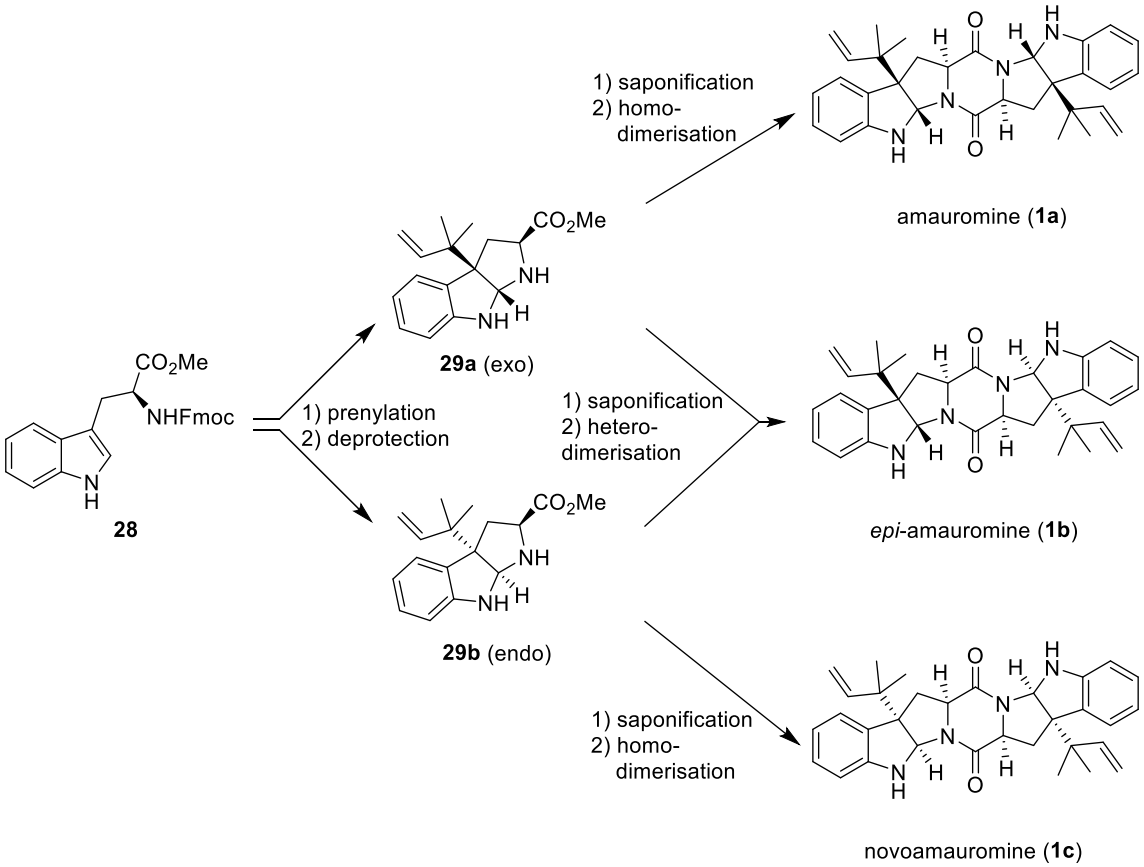
Figure 1.1.3 illustrates the terminology of *exo* and *endo* in connection with the prenylated substrates. In the *exo*-substrate both the ring system and the amino acid ester point in the same direction, whereas in the *endo*-substrate the prenyl group and the carboxylic group point in different directions. This terminology will be applied to a variety of prenylated substrates throughout this thesis.[4]

26a (*exo*) **26b** (*endo*)

Figure 1.1.3: Illustration of the *exo*/*endo*-configuration on the protected *L*-tryptophan derivatives **26a** and **26b** as examples of reverse prenylated indole alkaloids.[4]

1.1.1.2 Total synthesis of the amauromines

Stark *et al.* have applied their method in the total synthesis of amauromine (**1**) and both its natural diastereomers novoamauromine (**1c**) and *epi*-amauromine (**1b**) (Scheme 1.1.10). The amauromines are a class of natural products that were first isolated by Takase *et al.* in 1984 from the culture broth of *Amauroascus* sp. The amauromines displayed potent vasodilating activity.[4,15,16,53]



Scheme 1.1.10: Total synthesis of amauromine (**1**), novoamauromine (**1c**) and *epi*-amauromine (**1b**).[4]

These natural products were synthesised in only four reaction steps. The first step for the total synthesis of amauromine (**1a**) was a one-pot reverse prenylation and following fluorenylmethoxycarbonyl- (Fmoc) deprotection of protected tryptophan **28** to the *exo*-product **29a**. The resulting *exo*-compound **29a** was then submitted to methyl ester hydrolysis using CsOH and subsequent double amide coupling with an excess of *O*-(1*H*-benzotriazol-1-1yl),*N,N,N',N'*-tetramethyluronium-hexafluorophosphate (HBTU). Thus, homodimerisation directly gave the desired C_2-symmetric natural product amauromine (**1a**) in a yield of 35% for the coupling step.

The synthesis of novoamauromine (**1c**) was performed accordingly. It also started from substrate **28** and was completed with a homodimerisation. However, in this case the conditions for the iridium catalysed reverse prenylation reaction were chosen with regard to the synthesis of the *endo*-product **29b**, which was then submitted to the dimerisation reaction conditions. The synthesis of novoamauromine (**1c**) was achieved with a yield of 57% for the homodimerisation step.

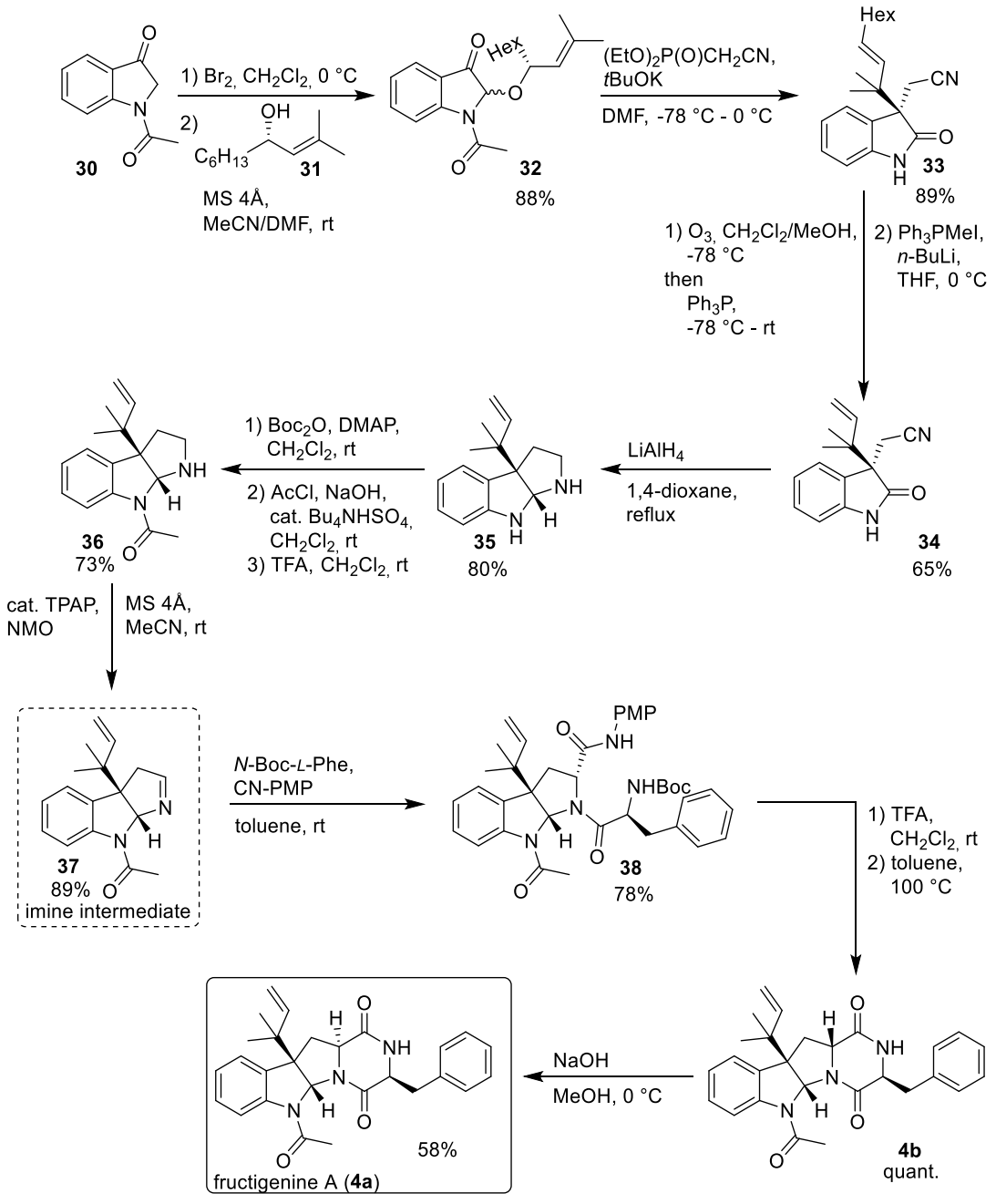
The total synthesis of *epi*-amauromine (**1b**) could be achieved by submitting equimolar quantities of the *exo*- and the *endo*- substrates **29a** and **29b** to the dimerisation reaction conditions. Gratifyingly, this resulted in a heterodimerisation reaction giving *epi*-amauromine (**1b**) with a yield of 47%, with only traces of the other isomers detectable.[4]

1.1.1.3 Total synthesis of fructigenine A (4a)

Fructigenine A (**4a**) is a member of compounds of the fructigenine family, which are a class of prenylated hexahydropyrrolo[2,3-*b*]indole natural products with a variety of biological activities, such as growth-inhibitory activity against *Avena coleoptile* and leukemia L-5178Y cells.[3] Additionally, Moon *et al.* reported anti-inflammatory activities of many fructigenine A (**4a**) derivatives.[54] Fructigenine A (**4a**) was first isolated and characterised by Kunizo *et al.* in 1989 from the fungus *Penicillium fructigenum*.[3]

In 2009 Kawasaki *et al.* reported the first total synthesis of fructigenine A (**4a**) (Scheme 1.1.11).[55] In this synthesis they prepared a common imine intermediate **37**, which was also a precursor for their synthesis of (–)-5-*N*-acetylardeemin, starting from 1-acetylindoline-3-one (**30**). The first step was the bromination of compound **30** at the C2-position followed by substitution with alcohol **31** to afford ether **32** in a good yield of 88% over two steps. The ether **32** was then converted *via* a Horner-Wadsworth-Emmons reaction with a domino olefination/isomerization/Claisen rearrangement into enantiomerically pure oxindole **33** with a good yield of 89%. Then an ozonolysis followed by a Wittig reaction converted the alkene moiety of compound **33** into the reverse prenyl group in 3-prenylindoline-2-one (**34**) with a yield of 65% over two steps.

The following reductive cyclisation on 3-prenylindoline-2-one (**34**) afforded compound **35** with a yield of 80%. Subsequent *tert*-butyloxycarbonyl (Boc) protection, *N*-acetylation and Boc-deprotection gave compound **36** with a yield of 73% over three steps. A final oxidation of N^8-acetylpyrroloindole (**36**) with tetrapropylammonium perruthenate (TPAP) and *N*-methylmorpholine *N*-oxide (NMO) gave the desired imine intermediate **37** with a yield of 27% over ten steps and an enantiomeric excess (ee) of over 99%.[55]

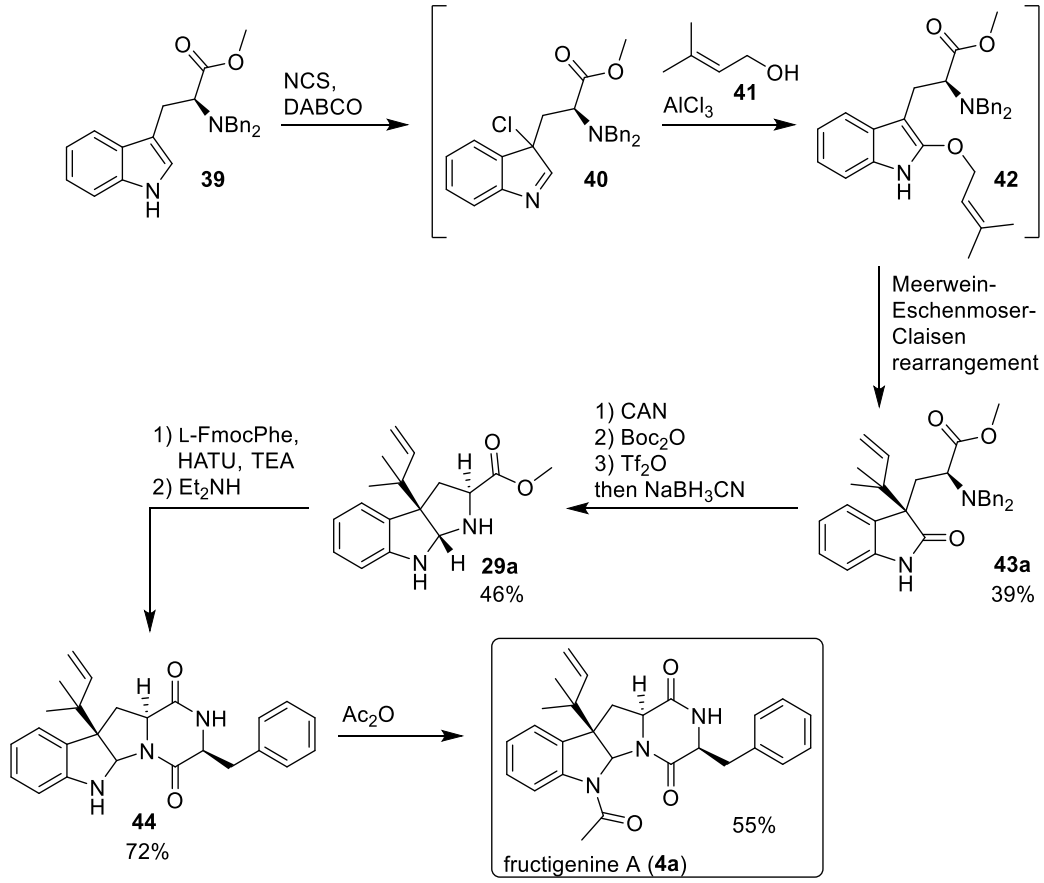


Scheme 1.1.11: First reported total synthesis of fructigenine A (**4a**) by Kawasaki *et al*.[55]

With imine **37** in hand, Kawasaki *et al*. proceeded to complete the total synthesis of fructigenine A (**4a**). They first formed the dipeptide **38** through a stereoselective Ugi three-component reaction of imine **37**, with a yield of 78%.[56]

The diketopiperazine **4b** was quantitatively formed by deprotection of the Boc-group and subsequent cyclisation through heating the reaction mixture, after addition of toluene, to 100 °C. The stereochemistry of product **4b** was established by nuclear overhauser enhancement and exchange spectroscopy (NOESY) experiments and was found to be the C11-epimer of fructigenine A (**4a**). Interestingly, the desired natural product **4a** was finally formed through epimerisation of compound **4b** by heating in methanol in the presence of sodium hydroxide, with an overall yield of 45% over four steps from imine **37**.[55] This behaviour is in accordance to similar findings discussed in the course of this thesis (Section 3.2).

Recently, another total synthesis of fructigenine A (**4a**) was reported by Xu *et al.* (Scheme 1.1.12).[57] They synthesised fructigenine A (**4a**) as a key intermediate in their total synthesis of (–)-penicimutanin A.



Scheme 1.1.12: Total synthesis of fructigenine A (**4a**) by Xu *et al.*[57]

The key step of their synthesis was a one-pot diastereoselective Meerwein-Eschenmoser-Claisen rearrangement, which they developed to form C3-reverse prenylated oxindoles. C3-reverse prenylated oxindoles can be obtained through an $AlCl_3$-catalytic protocol starting from non-protected C3-ester indoles using 3-methyl-2-buten-1-ol (**41**) as prenyl donor.[57,58]

Xu *et al*. obtained oxindoles **43a/b** in a 2.5:1 diastereomeric ratio (d.r.) with a combined yield of 54% from *L*-tryptophan derivative **39**. This was followed by benzyl (Bn) deprotection, Boc-protection and subsequent cyclisation, through reductive amination, to give hexahydropyrroloindoline **29a** with a yield of 46% over three reaction steps. Hexahydropyrroloindoline **29a** was then coupled with *L*-Fmoc-phenylalanine. The following removal of the Fmoc-protecting group and immediate cyclisation gave de-acylated fructigenine A **44** with a yield of 72% over both steps. The last step in the reaction sequence was the acylation of compound **44** with acetic anhydride to give fructigenine A (**4a**) with an overall yield of 10% over eight steps from *L*-tryptophan derivative **39**.

1.1.1.4 Total syntheses of notoamides J (7a) and C (8a)

The notoamides are a family of natural products which have been isolated as secondary metabolites from various fungi genera, notably *Aspergillus* and *Penicillium*, which can be found in the Sea of Japan off the Noto peninsula. The notoamides belong to a class of prenylated alkaloid natural products which show a wide range of biological activities, such as antibacterial, antitumoral or insecticidal activity. Therefore, their synthesis has been of significant interest in recent years.[10,59–63]

When notoamide C (**8a**) was first isolated and its structure elucidated by Tsukamoto *et al.*, it was assigned with an (*S)*-configuration at the C3-atom of the oxindole unit. Later, they based their (*R*)-configuration of the C3-atom in the isolated notoamide J (**7a**) on these findings. However, in 2012 Williams *et al.* reported a correction of these assumptions by biochemically synthesising various notoamides and by comparison realising that notoamide C (**8a**) does in fact show (*S*)-configuration.[1,20,64] In Figure 1.1.4 the correct assignments of notoamides C (**8a**) and J (**7a**) and their epimers are shown.

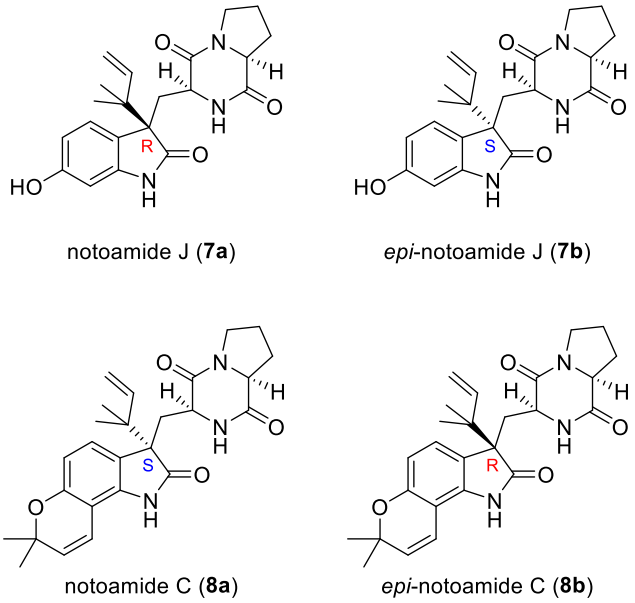
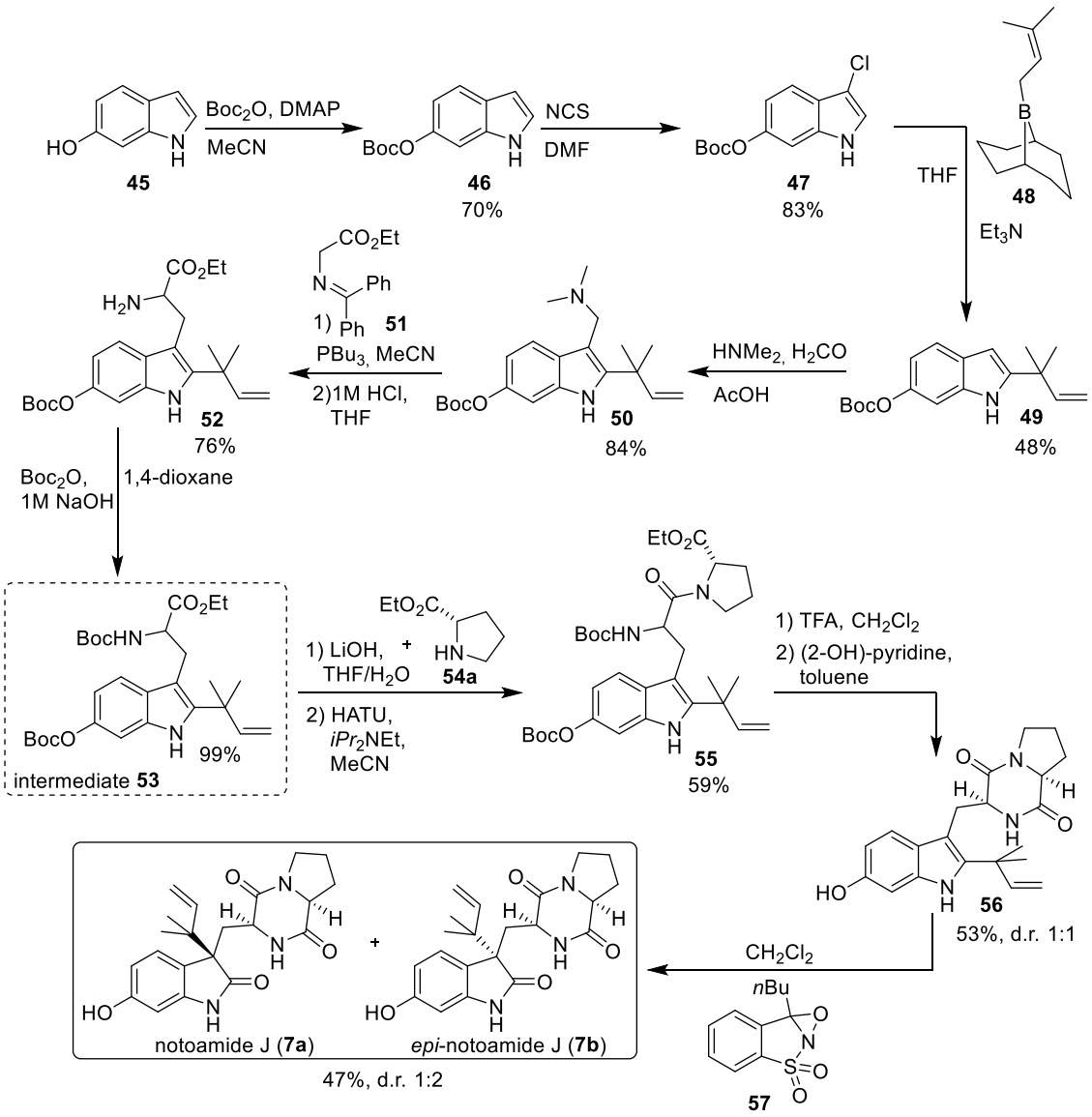


Figure 1.1.4: Absolute configuration of notoamides J (**7a**) and C (**8a**) and their epimers.[1,20,65]

Prior to the corrected configurations of the notoamides C and J, Williams and co-workers had reported two total syntheses of the incorrectly configured notoamides C and J. However, both of these syntheses also gave the now known to be correct natural products, but their stereoselectivity goals were targeted towards the corresponding epimers (Schemes 1.1.13 and 1.1.14). Williams *et al.* have since issued a correction to their paper in order to clarify this mistake.[65]

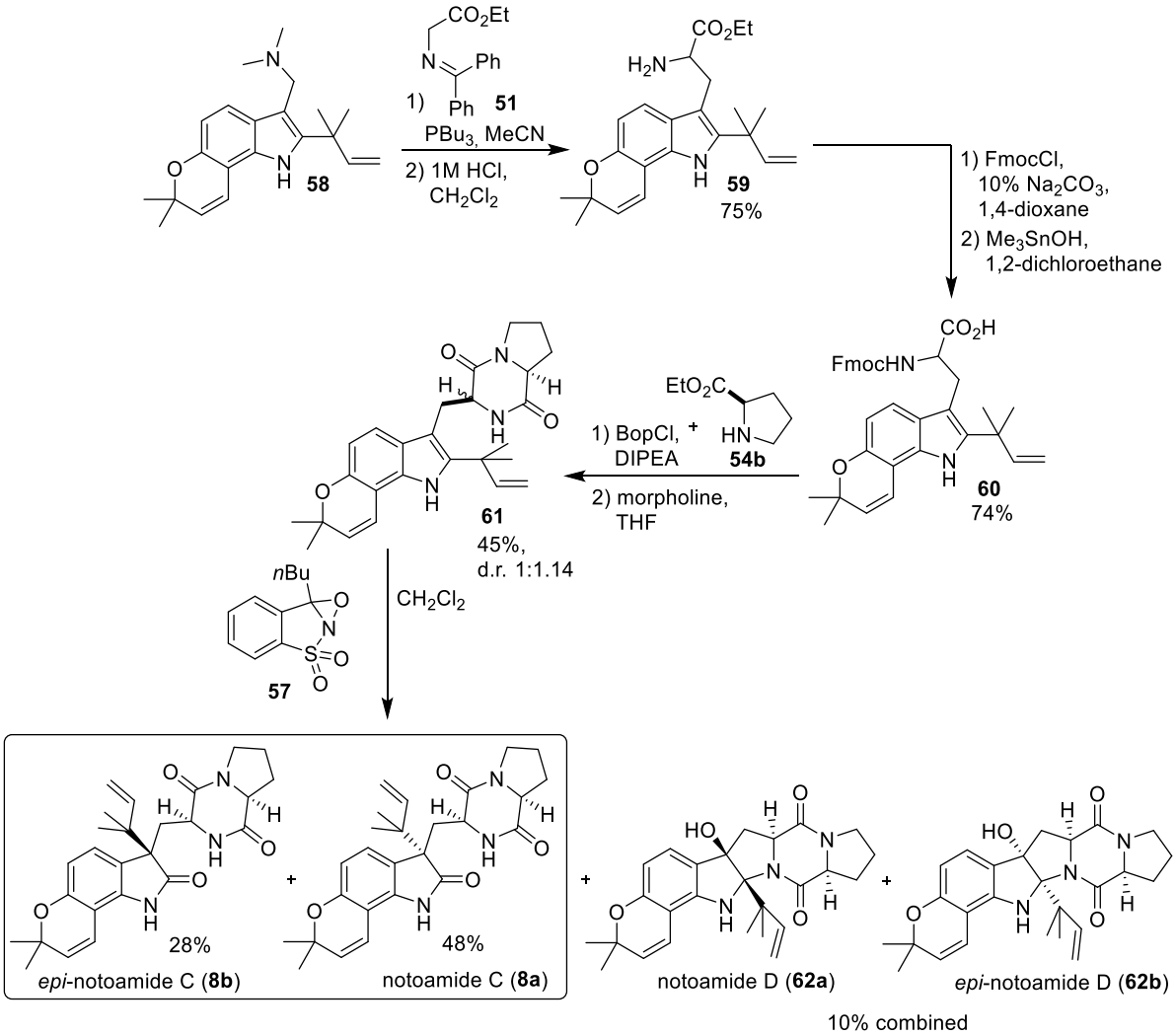
The first part of the total synthesis of notoamide J (**7a**) and its epimer **7b** was the formation of a reverse prenylated tryptophan derivative intermediate **53** (Scheme 1.1.13).[66] The necessary starting material was hydroxyl substituted indole **45**, which was synthesised *via* a modified Leimgruber-Batcho indole synthesis with an excellent yield of 89% over three steps.[67] The prepared indole **45** was, after Boc-protection, C2-reverse prenylated using a method established by Danishefsky *et al*.[8] This method required chlorination at the C3-position of intermediate **46**, using *N*-chlorosuccinimide (NCS), followed by reverse prenylation at the C2-position of intermediate **47**, with prenyl-9-borabicyclo[3.3.1]nonane **48** in the presence of triethyl amine, to give the C2-reverse prenylated compound **49**. Difficulties during the removal of excess 9-borabicyclo[3.3.1]nonane (9-BBN) led to a relatively low yield of 48% for the prenylation step. After formation of gramine **50** this was then coupled with the benzophenone imine of glycine **51** according to a modified Somei-Kametani protocol.[68] Subsequent imine hydrolysis and Boc-protection gave the intermediate **53** with a yield of 18% over seven steps from compound **45**.[66]



Scheme 1.1.13: Total synthesis of notoamide J (**7a**) and *epi*-notoamide J (**7b**) reported by Williams and co-workers.[66]

The second part of the total synthesis commenced with saponification of intermediate **53** and subsequent coupling with *L*-proline ethyl ester **54a**, using 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate (HATU) and *N,N*-diisopropylethylamine (DIPEA) as coupling reagents. Dipeptide **55** was obtained in a moderate yield of 59% over two steps from intermediate **53**. This was followed by Boc-deprotection of dipeptide **55** and subsequent cyclisation of the now free amine to form the desired DKP **56** and its corresponding diastereoisomer as a 1:1 mixture with a combined yield of 53% over two steps. The completion of the synthesis was then accomplished by treatment of DKP **56** with Davis oxaziridine **57** performing an oxidation and subsequent pinacol rearrangement. This transformation gave notoamide J (**7a**) and *epi*-notoamide J (**7b**) with a yield of 47% in a ratio of 1:2 over the last two steps.[69,70] This route afforded notoamide J (**7a**) with an overall yield of only 0.46% over 12 steps.[66]

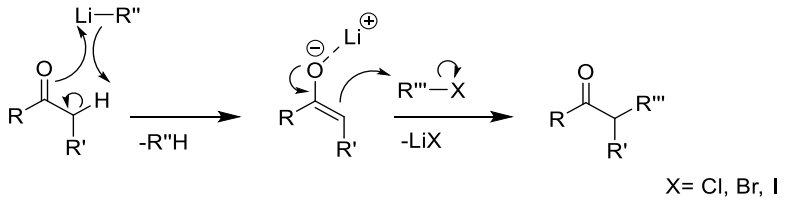
The total synthesis of notoamide C (**8a**) (Scheme 1.1.14) was performed similarly to that of notoamide J (**7a**) described above (Scheme 1.1.13). Starting from a differently substituted gramine derivative **58**, Williams *et al.* proceeded by coupling it with the same benzophenone imine derivative **51** and then hydrolysing it to obtain the amino ester **59** with a yield of 75% over two steps. The free acid **60** was next synthesised with a yield of 74% over two steps by first Fmoc-protecting the amino group and subsequent saponification of the ester. For the coupling of the free acid **60** with *D*-proline ethyl ester (**54b**) bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BopCl) and DIPEA were used as reagents. The subsequent cyclisation was performed in the presence of morpholine to give DKP **61** in a diastereomeric ratio of about 1:1 with a yield of 45% over two steps. The last step of the synthesis was again the treatment of DKP **61** with Davis oxaziridine **57** to give notoamide C (**8a**) in a yield of 48% and *epi*-notoamide C (**8b**) in a yield of 28% as the major products. However, the last reaction step also gave both diastereoisomers of notoamide D (**62a**) in a combined yield of 10%. The overall yield for notoamide C (**8a**) was 6% over six steps.[71]



Scheme 1.1.14: Total synthesis of notoamide C (**8a**), *epi*-notoamide C (**8b**), notoamide D (**62a**) and *epi*-notoamide D (**62b**).[71]

1.2 Alkylation reactions

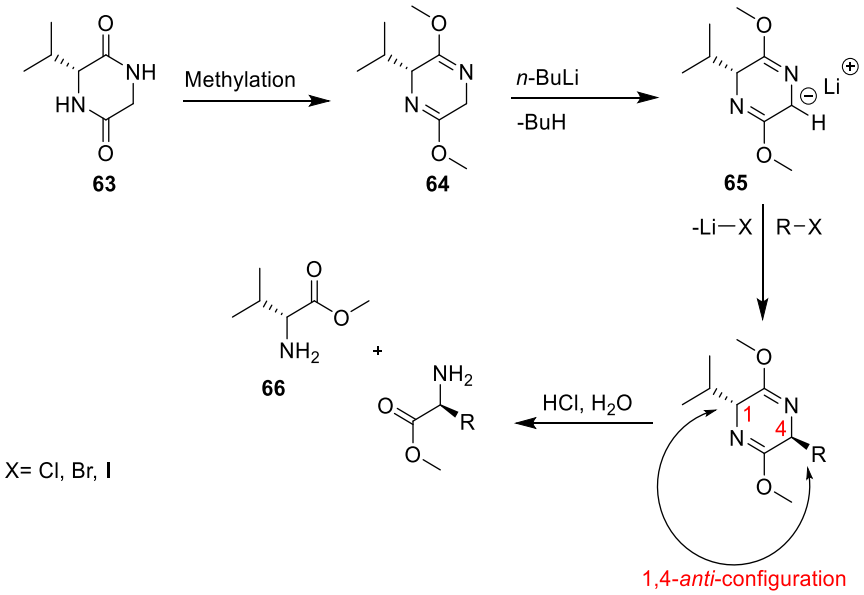
Alkylation reactions on *α*-carbon atoms of carbonyl structures have successfully been performed for a long time. In most cases a lithium base is used in order to deprotonate the desired *α*-carbon atom and form stable lithium enolates (Scheme 1.2.1). These reactions require a base that is strong enough to deprotonate different carbonylic compounds. However, the reaction temperature is usually kept very low (e.g. at -78 °C) to prevent deprotonation at other positions of the molecule. The *α*-carbon deprotonation is followed by an electrophilic addition at the enolate by alkylating agents, such as alkyl halides.[72]



Scheme 1.2.1: General mechanism of an alkylation reaction at an *α*-carbon atom of a carbonyl structure using a lithium base and an alkyl halide.[72]

1.2.1 Alkylation reactions on DKP-units

Already in 1981, Schöllkopf *et al.* successfully alkylated diketopiperazine derivatives in their attempt to synthesise (*R*)-configured amino acids. They used *L*-valine as a chiral auxiliary by coupling it with glycine in order to favour the *anti*-attack on the resulting DKP-ring **63** (Scheme 1.2.2). The DKP-ring **63** was methylated to form the bislactim ether derivative **64**, which was subsequently deprotonated by *n*-butyllithium (*n*-BuLi). The alkylation then occurs by addition of an alkyl halide, which attacks from the *anti*-position because of the sterically hindered *L*-valine substituent on the otherwise planar ring **65**. Thus, it is inevitable in these systems that the main product always shows the 1,4-*anti*-configuration. After alkylation, the dipeptide is cleaved through acidic hydrolysis giving the methyl esters of the desired amino acid and *L*-valine (**66**).[73,74]



Scheme 1.2.2: General mechanism of the Schöllkopf method.[73,74]

The Schöllkopf method or Bis-Lactim Amino Acid Synthesis can inversely be employed for the synthesis of (*S*)-configured amino acids when *D*-valine (**71**) is used as a part of the chiral starting material instead.[75]

1.2.2 Alkylation reactions on PMB-protected DKP-units

When alkylating DKP-rings the specific use of protecting groups can be of vital importance. In 1998, Davies *et al.* reported that achiral benzyl protecting groups, on the nitrogen atoms of a DKP-ring, enhance the chiral induction of the isopropyl group at the C3-atom of their DKP-ring. Molecular modelling studies showed that the resulting ring system would be planar and that the isopropyl group would direct the neighbouring benzyl group at the N4-atom into an *anti*-position. This benzyl group would in turn direct its counterpart on the N1-atom into a *syn*-position to the isopropyl group, which would effectively block the alkylation on the C6-atom from one side. This should lead to better diastereoselectivities in the alkylation reaction as opposed to reactions on similar DKP-rings, where the *N*-atoms are protected by, for example, methyl groups (Figure 1.2.1).[76]

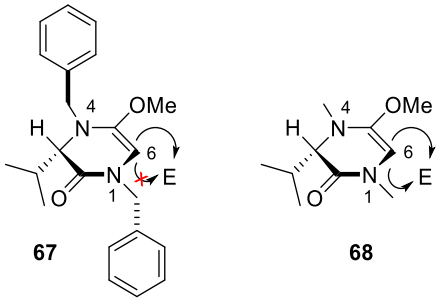
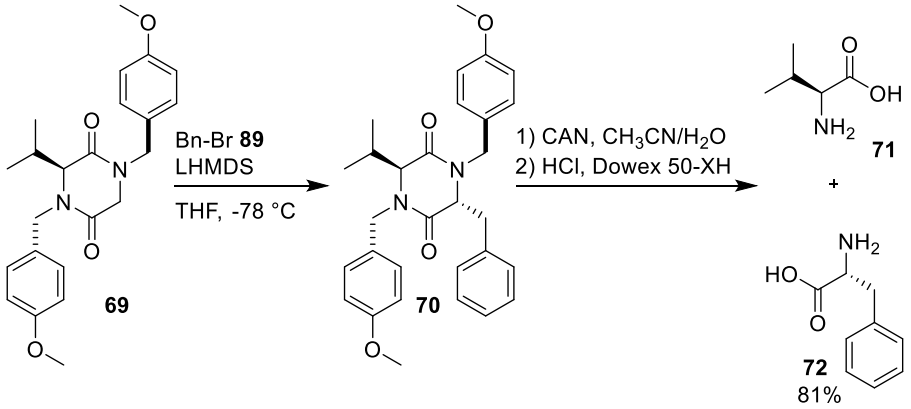


Figure 1.2.1: Electrophilic attack of substituted methyl- vs. benzyl-protected DKP-rings.[76]

With this work they wanted to design a new chiral auxiliary for the synthesis of homochiral *α*-amino acids similar to the one used in the Schöllkopf method. They showed their assumptions to be correct by using *p*-methoxybenzyl (PMB) as protecting group and consequently established an alkylation reaction on PMB-protected DKP-rings using Lithium-bis(trimethylsilyl)amide (LHMDS) as lithium base.[76]

They later applied auxiliary **69** in the synthesis of homochiral (*R*)-phenylalanine (**72**) (Scheme 1.2.3). To demonstrate the applicability of this method Davies *et al*. showed that it was also possible to de-racemise the alkylated compound to give (*S*)-phenylalanine starting from the same auxiliary **69**.[77]



Scheme 1.2.3: Synthesis of (*R*)-phenylalanine (**72**) starting from chiral auxiliary **69**.[77]

In 2008, Simpkins *et al.* reported studies of alkylation reactions on symmetrically PMB-protected DKP-rings, *via* enolate intermediates, using the method described above. They reported highly diastereocontrolled substitutions on DKP-rings containing a chiral amino acid precursor. Furthermore, the formation of racemic mixtures through the same method was demonstrated by using centrosymmetric DKP-rings. This outcome was also observed even when using a chiral lithium amide base for the formation of the lithium enolate.[78]

2 Aims and Outline

A novel diastereoselective iridium catalysed method for reverse prenylation at the C3-position of an indole unit was developed by Stark *et al.* in 2016.[4] This opened up various possibilities for the synthesis of a series of biologically active natural products or their, potentially more biologically active, derivatives.

The main aim of this thesis was to develop a novel synthetic pathway for the synthesis of reverse prenylated hexahydropyrrolo[2,3-*b*]indole natural products. The objective was to develop a unified strategy for the synthesis of those natural products by first synthesising the common core structure (Figure 2.1). The initial formation of the revers prenylated diketopiperazine structure was proposed. The following late-stage *C*- and sometimes also *N*-alkylation steps would then determine the target structure of the synthesis. Thus, giving a unified approach to various biologically active reverse prenylated hexahydropyrrolo[2,3-*b*]indole natural products with a late-stage diversification.

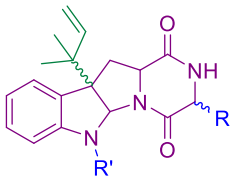
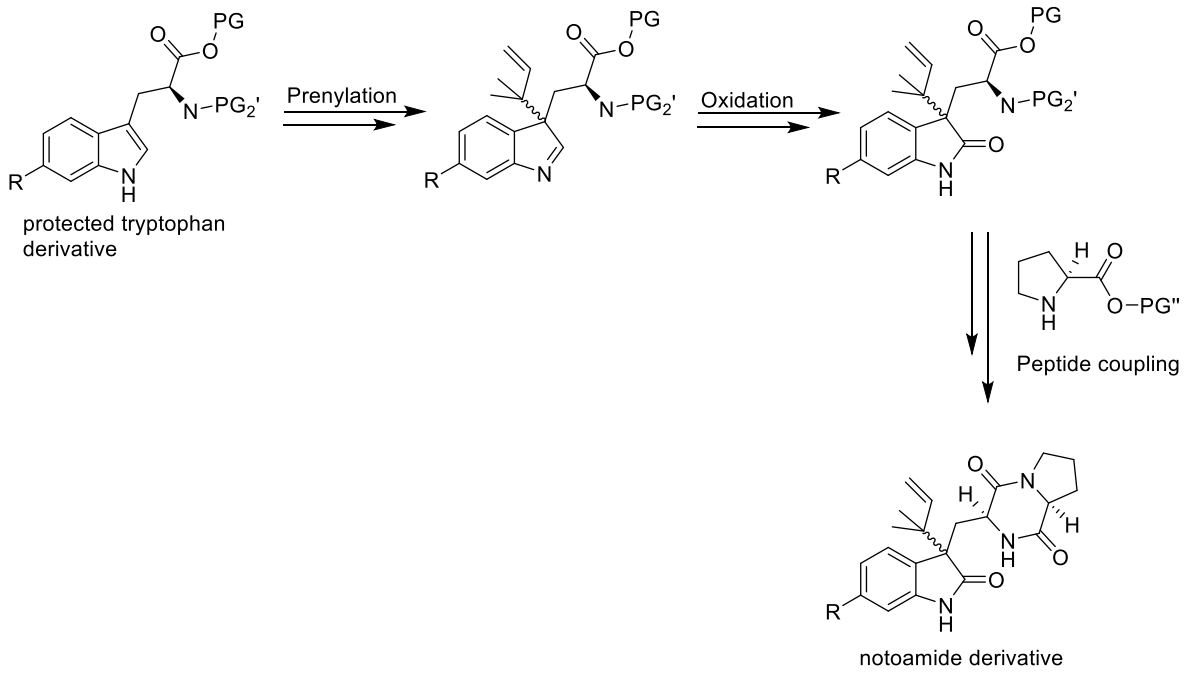


Figure 2.1: General structure of many reverse prenylated hexahydropyrrolo[2,3-*b*]indole natural products.

The late-stage modification of a uniform precursor should allow for easy access to multiple natural products or their non-natural derivatives, without the necessity of stereoselectively synthesizing unnatural amino acids. In order to show the feasibility of this approach, the two main targets of this thesis were the natural products fructigenine A (**4a**) and brevicompanine E (**5**) (Figure 1.1.2).

Furthermore, it should be demonstrated that the developed reverse prenylation reaction is also applicable for the synthesis of different biologically active reverse prenylated natural products, through the use of different nucleophiles in the reaction. The prevention of the *N*-nucleophilic attack by the *L*-tryptophan (**75a**) amino nitrogen atom followed by the addition of an *O*-nucleophilic oxidation agent should allow access to the synthesis of natural products of the notoamide family. The synthesis of a notoamide derivative would demonstrate the broad range of possible applications for the iridium catalysed reverse prenylation reaction.



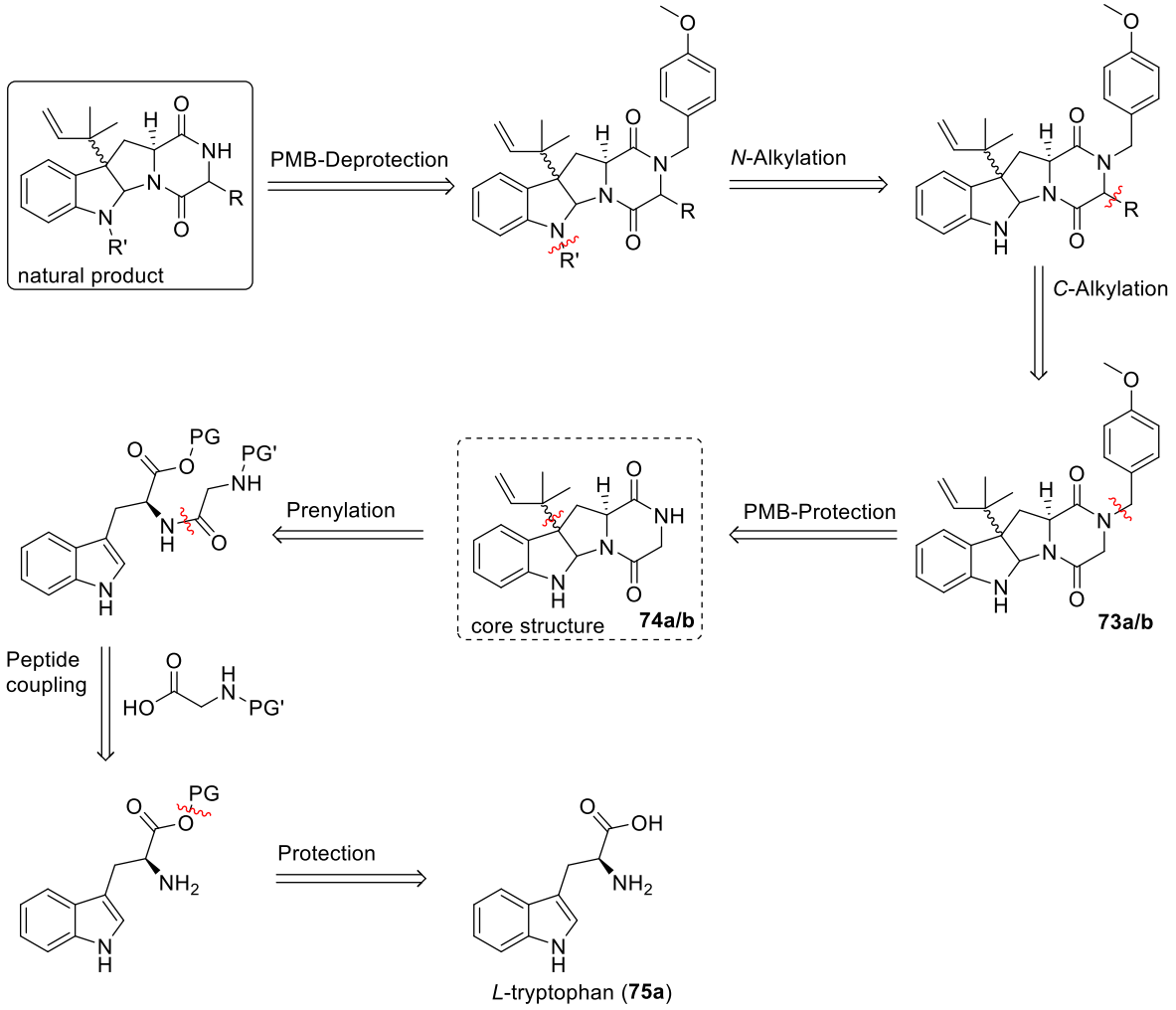
Scheme 2.1: General scheme of the synthesis of a notoamide derivative.

3 Results and Discussion

3.1 Unified approach to reverse prenylated hexahydropyrrolo[2,3-*b*] indole natural products

3.1.1 First approach towards a unified pathway to reverse prenylated hexahydropyrrolo[2,3-*b*]indole natural products

In the first part of this thesis a novel and unified pathway to synthesise a variety of reverse prenylated hexahydropyrrolo[2,3-*b*]indole natural products or their non-natural derivatives should be developed. During this the iridium catalysed reverse prenylation reaction developed in the Stark group should be employed as a key step.[4] In Scheme 3.1.1 a first retrosynthetic analysis of the aspired pathway is shown.

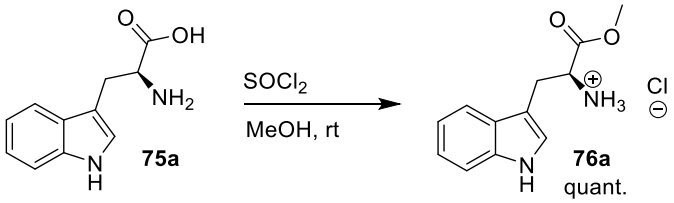


Scheme 3.1.1: Retrosynthetic analysis of a unified pathway to reverse prenylated hexahydropyrrolo[2,3-*b*]indole natural products.

The last step of any natural product synthesis *via* this pathway needs to be the deprotection of the PMB-group, in order to get the desired compound over six or seven reaction steps. For the total synthesis of many natural products an *N*-acylation at the former indole nitrogen atom is needed as the second to last step of the sequence. The *C*-alkylation reaction at the DKP-ring of the protected core structures **73a/b** is the step of the reaction sequence which determines the diversification of the pathway and needs to be altered according to which natural product shall be synthesised. Therefore, the introduction of the PMB-group to the core structures **74a/b** will be necessary beforehand, in order to direct the different alkyl groups into the desired configuration and to prevent alkylation at the *N*-atom of the DKP-ring. The one-pot reverse prenylation reaction followed by the deprotection of the glycine substructure of the dipeptide will provide access to the unprotected core structures **74a/b**, which can function as a precursor for many natural products. The starting material for the reverse prenylation reaction should be achieved by coupling of a protected *L*-tryptophan derivative with a protected glycine derivative to form a dipeptide. The protecting group on the glycine derivative shall be chosen in a way that allows it to be easily cleaved in a one-pot reaction after the prenylation step. The reaction sequence should start from *L*-tryptophan (**75a**), which is first protected at the acid function of the molecule.

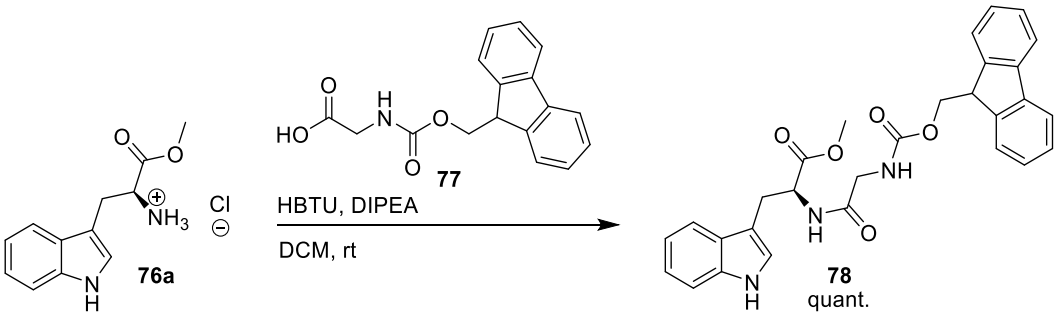
3.1.1.1 Synthesis of the core structures 74a/b

As shown in the retrosynthetic analysis (Scheme 3.1.1) the first step of the reaction sequence is the protection of the free hydroxyl group of the acid moiety of *L*-tryptophan (**75a**). This was done by esterification with thionyl chloride in methanol (Scheme 3.1.2). The conversion to *L*-tryptophan methyl ester hydrochloride (**76a**) was quantitative and could be performed on large scales of up to 0.5 mol in order to provide starting material for many sections of this thesis.[79]



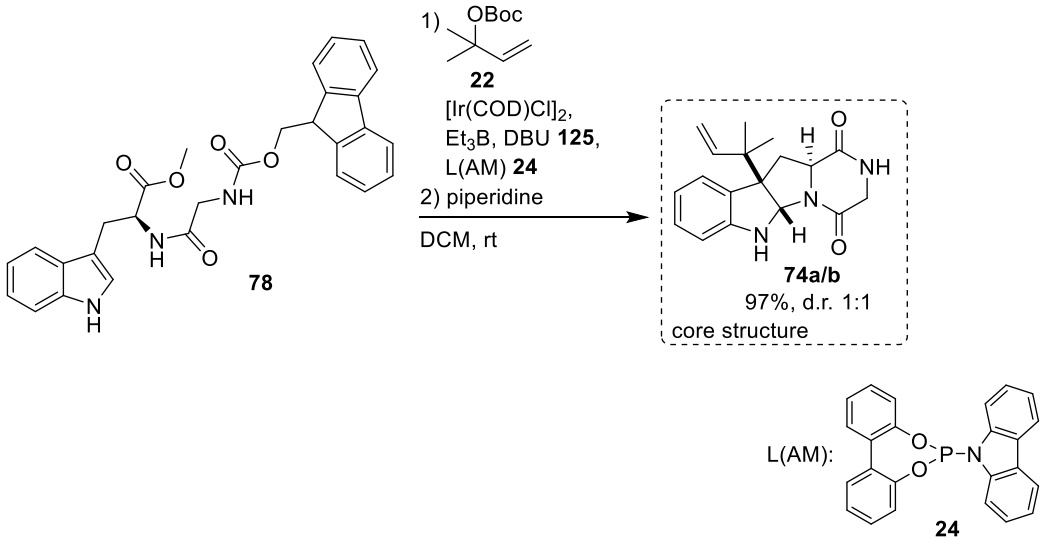
Scheme 3.1.2: Esterification of *L*-tryptophan (**75a**) with thionyl chloride.

The second step of the reaction sequence was the peptide coupling of *L*-tryptophan methyl ester hydrochloride (**76a**) with commercially available Fmoc-protected glycine **77**. The resulting dipeptide **78** was formed quantitatively by using HBTU as coupling agent and DIPEA as base in dichloromethane (DCM) at room temperature (Scheme 3.1.3).[80,81]



Scheme 3.1.3: Peptide coupling of *L*-tryptophan methyl ester hydrochloride (**76a**) with Fmoc-protected glycine **77**.

The last two steps towards the formation of the core structures **74a/b** of reverse prenylated hexahydropyrrolo[2,3-*b*]indole natural products was the iridium catalysed reverse prenylation reaction, followed by the deprotection of the Fmoc-group, which was believed to lead to an immediate closure of the DKP-ring (Scheme 3.1.4).[4] Therefore, piperidine was added to the reaction mixture after the reverse prenylation reaction had been stirring overnight and no further conversion could be observed.[82]



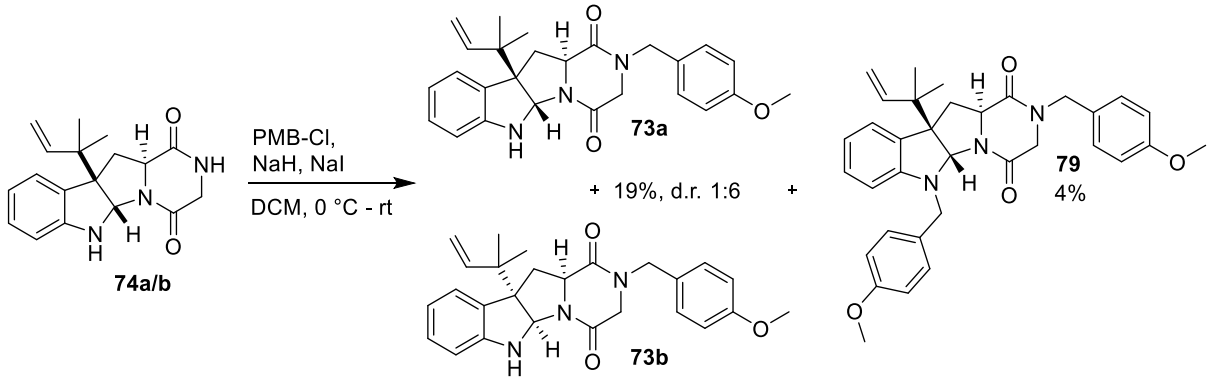
Scheme 3.1.4: Iridium catalysed reverse prenylation reaction and following deprotection to the core structures **74a/b**.

The best result for the core structures **74a/b** could be achieved through the use of the achiral ligand **24** and triethylborane as borane additive. Thus, the reverse prenylated core structures **74a/b** were obtained with a yield of 97% in a diastereomeric ratio of 1:1. The reverse prenylation reaction of dipeptide **78** was also performed with chiral ligands and a different borane. For the yields and diastereomeric ratios of these reactions see Section 3.1.4.

However, the separation of the isomers could not be realised at this stage. It was assumed that the separation might be possible at a later stage of the reaction sequence when the molecules have a different electronical surrounding, e.g. that the dipole moment of the compounds might have changed after the PMB-protection of the amide of the DKP-ring.

3.1.1.2 PMB-Protection of the core structure 74

The PMB-protection of the amide function of the core structures **74a/b** turned out to not work very well (Scheme 3.1.5).[83] The reaction should have followed a nucleophilic substitution mechanism using PMB-chloride as reagent and sodium hydride as base. The addition of sodium iodide to the reaction turned out to be crucial for any product formation. Even then the desired products **73a/b** could only be obtained with a combined yield of 19%. In addition, the double protected compound **79** was also formed but only in a yield of 4%. Interestingly, the double protected compound could only be detected in the *exo*-form **79**. A second attack of the PMB-group seems to be sterically hindered in the *endo*-form. This might explain the diastereomeric excess of compound **73b** of the single protected substrates, even though the starting material **74a/b** was employed as the 1:1 diastereomeric mixture.



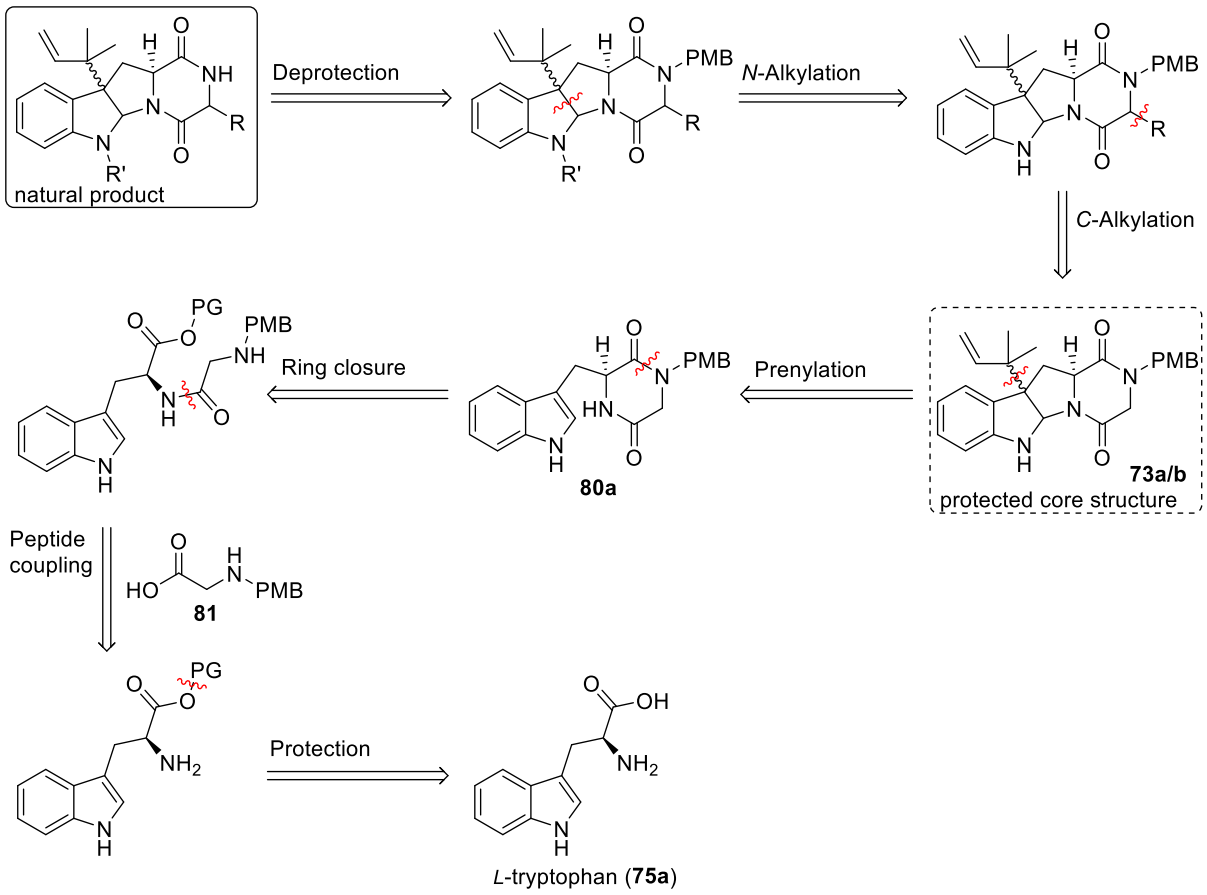
Scheme 3.1.5: PMB-Protection of the core structures **74a/b**.

The low yield of this reaction could be explained by the relatively low acidity of the amide proton (p*K*a of about 15) of the DKP-ring.[84] One reason for this is the tautomerisation to the corresponding lactim and the lack of a by-product which is PMB-substituted at the oxygen atom of the molecule is due to the even lower acidity of the lactim proton compared to the amide proton.

However, the separation of the diastereoisomers of **73** was possible, which is essential for the development of an efficient unified total synthesis of reverse prenylated hexahydropyrrolo[2,3-*b*]indole natural products. Even the reported diastereoselective reverse prenylation reaction with the best stereoselectivities (>20:1) always yielded some amounts of the undesired compound.[4] Accordingly, the separation of the corresponding diastereoisomers in order to go on with the reaction sequence to form a specific natural product is inevitable.

3.1.2 Modified approach towards a unified pathway to reverse prenylated hexahydropyrrolo[2,3-*b*]indole natural products

As preliminary experiments (Section 3.1.1) suggested that a regioselective and high yielding PMB-protection would not easily be achieved a slightly altered approach to a unified pathway for the synthesis of reverse prenylated hexahydropyrrolo[2,3-*b*]indole natural products needed to be conceived. This is depicted in Scheme 3.1.6 and aims to form the PMB-protected core structures **73a/b** through introduction of the PMB-protecting group already in the second step of the planned reaction sequence. By coupling the protected *L*-tryptophan derivative with PMB-protected glycine **81** the resulting dipeptide already contains the desired group for the *C*-alkylation step.



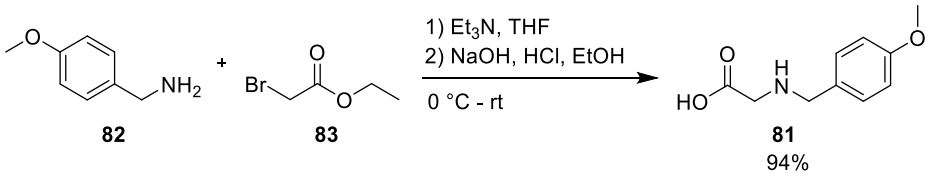
Scheme 3.1.6: Modified retrosynthetic analysis of a unified pathway to reverse prenylated hexahydropyrrolo[2,3-*b*]indole natural products.

As the protecting group on the glycine section of the dipeptide shall remain in the molecule after the prenylation step, the closure of the DKP-ring might be necessary before the prenylation reaction in order to achieve the desired PMB-protected core structures **73a/b**. With these in hand, the following reaction steps in the sequence are the same as in the previously proposed pathway (Scheme 3.1.1).

3.1.2.1 Synthesis of the PMB-protected core structures 73a/b

The first step of the reaction was again the esterification of *L*-tryptophan (**75a**) as described in Section 3.1.1.1.

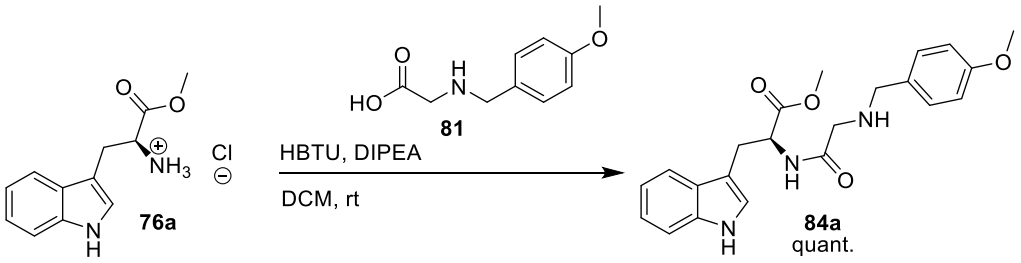
PMB-protected glycine **81** was synthesised via a two-step procedure (Scheme 3.1.7).



Scheme 3.1.7: Synthesis of PMB-protected glycine **81**.[85]

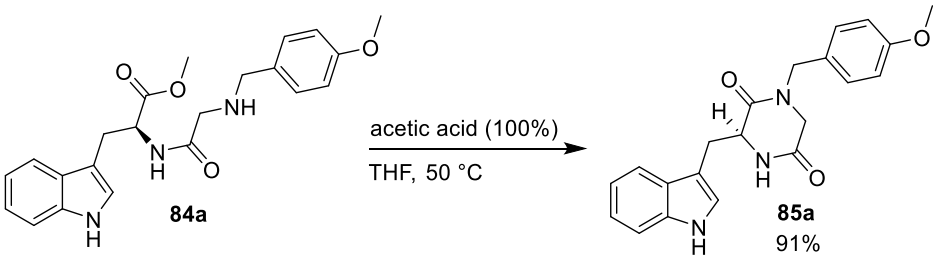
Thus, starting from *p*-methoxybenzylamine (**82**) and ethyl bromoacetate (**83**) a nucleophilic substitution (S_N2) followed by basic ester hydrolysis was performed.[85] The resulting PMB-protected glycine **81** was obtained with a very good yield of 94% over two steps.

Glycine derivative **81** was then used in the peptide coupling reaction with *L*-tryptophan methyl ester hydrochloride (**76a**) leading to the PMB-protected dipeptide **84a** (Scheme 3.1.8).[80,81] This reaction worked as well as the previously performed peptide coupling (Section 3.1.1.1) resulting in a quantitative yield.



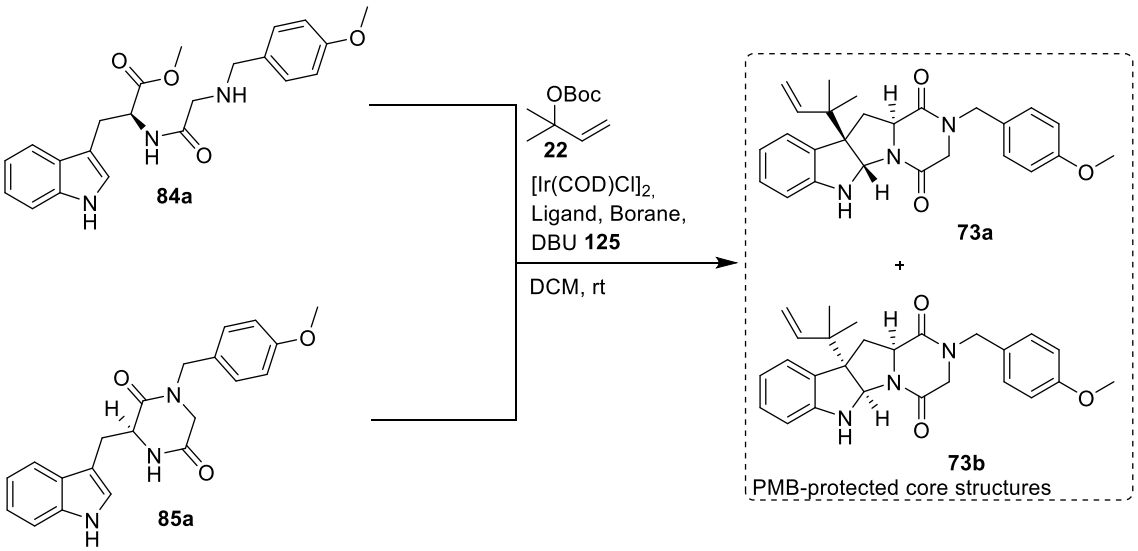
Scheme 3.1.8: Peptide coupling of *L*-tryptophan methyl ester hydrochloride (**76a**) with PMB-protected glycine **81**.

As it was not certain that the amide bond formation to the closed DKP-ring would occur immediately during the reverse prenylation reaction the ring closure should also be performed beforehand. Therefore, dipeptide **84a** was stirred at 50 °C in tetrahydrofurane (THF) in the presence of acetic acid (Scheme 3.1.9). The elimination of methanol and the resulting ring closure led to the formation of diketopiperazine **85a** with a yield of 91%.[86]



Scheme 3.1.9: Ring closure of dipeptide **84a** to diketopiperazine **85a**.

However, both the open dipeptide **84a** and diketopiperazine **85a** were submitted to the iridium catalysed reverse prenylation reaction conditions (Scheme 3.1.10). This was done in order to determine which substrate was best suited for the natural product synthesis, regarding the ring closure to the DKP-structure, the yield and the influence of the different substrates on the stereoselectivity of the reaction.[4]



Scheme 3.1.10: Reverse prenylation reaction for the synthesis of the PMB-protected core structures **73a/b**.

The reverse prenylation reaction was performed several times with both compounds. The studies with various ligands and boranes are described in Section 3.1.4 of this thesis. The best yield was achieved when diketopiperazine **85a** was employed with the achiral ligand **24**. This gave the PMB-protected core structures **73a/b** in a diastereomeric ratio of 1:1 and a yield of 99%.

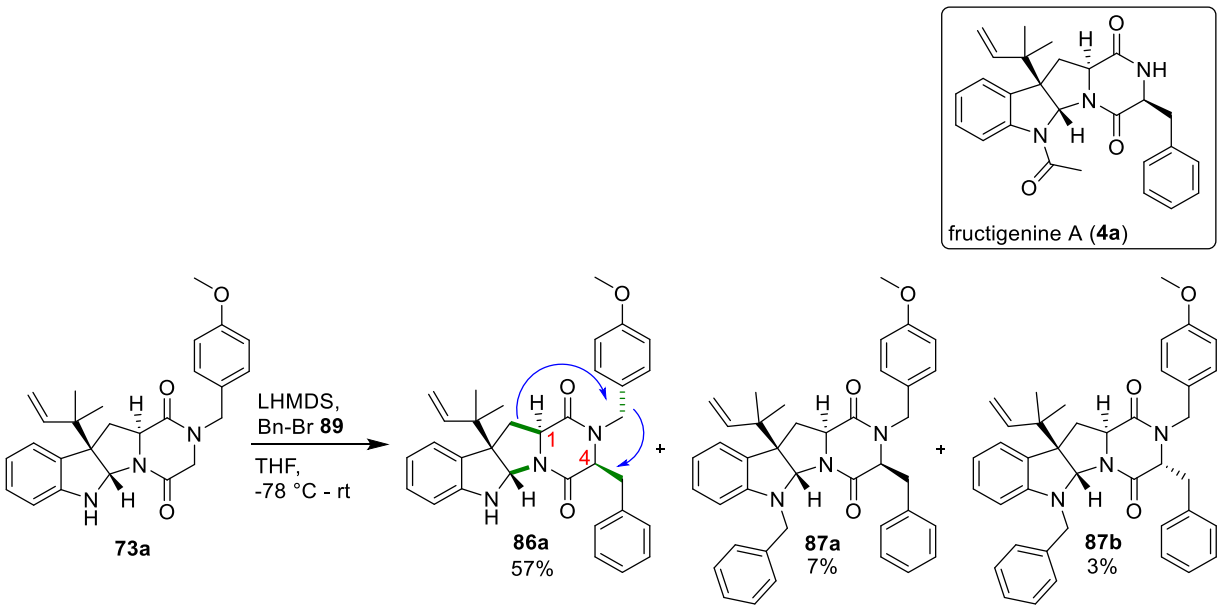
Taken together, the PMB-protected core structures **73a/b** were successfully synthesised over five steps (including the formation of diketopiperazine **85a**) with a yield of 85%.

3.1.2.2 Studies of alkylation reactions on reverse prenylated compounds

To proceed with the development of a unified pathway towards reverse prenylated hexahydropyrrolo[2,3-*b*]indole natural products the PMB-protected core structures **73a/b** needed to be alkylated at the methylene group of the DKP-ring.[76,77] Most natural products containing an alkylated DKP-ring do not show the previously described 1,4-*anti*-configuration (Section 1.2.1) but a 1,4-*syn*-configuration. This is due to the directing effect of the PMB-group described in Section 1.2.2. As the hexahydropyrrolo[2,3-*b*]indole ring-system is pointing upwards, due to the stereochemistry of the amino acid *L*-tryptophan (**75a**), the PMB-group is facing downwards. This is in turn directing the attack of the alkylating agents from the opposite side into the desired configuration. The directing effects are highlighted in alkylated product **86a** in Scheme 3.1.11.

In all alkylation reactions described in this section 1.1 equivalents (eq.) of the base LHMDS were used, as the use of higher amounts of base (2 eq.) led to an increase in the formation of double alkylated product (DAP). In accordance to the expectations (Section 1.2.1), only one isomer of the single alkylated products of all performed alkylation reactions was achieved.

The first alkylation reaction that was tried was the benzylation of *L*-*exo*-compound **73a** in order to get to the natural product fructigenine A (**4a**). The outcome of the alkylation reaction is depicted in Scheme 3.1.11.



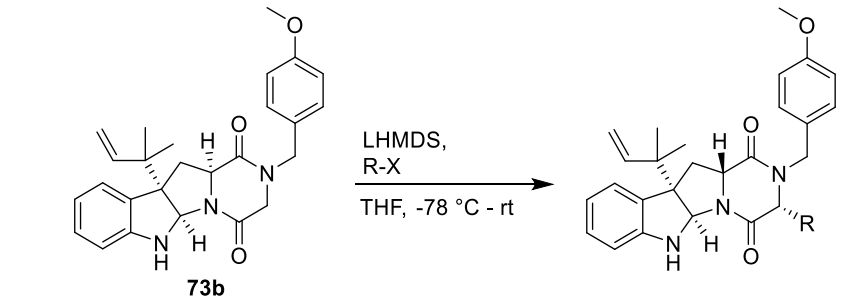
Scheme 3.1.11: *C*-Alkylation reaction of **73a** using benzyl bromide (**89**) as alkylating agent.

As alkylating agent benzyl bromide (**89**) was chosen. The desired compound **86a** could be obtained with a yield of 57%. In addition, the formation of the double alkylated products (DAP) **87a** and **87b** with a combined yield of 10% was also observed. The second alkylation happened at the nitrogen atom of the former indole unit as this position is the second most acidic position of the molecule (p*K*a of about 11).[84]

Interestingly, even a small amount of 1,4-*anti*-configured product **87b**, as the configuration between the alkyl group and the ring-system, was formed. The benzyl group might have been directed into this configuration because of the second bulky group at the nitrogen atom. However, the yield of the *syn*-configured product **87a** is still twice as big compared to **87b**. Overall, the yield of the DAPs **87a/b** compared to the desired product **86a** is still quite small.

In order to optimise the yield and the overall conversion of the alkylation reaction several studies have been performed. The formation of DAP could be observed during many of those reactions. However, if not noted differently, the amounts of DAP that were formed were so small, that it was refrained from isolating it. The first part of the studies describe the right choice of the alkyl halide as alkylating agent. By trying differently halogenated alkyl derivatives it should be determined which halide is best suited as a leaving group for this type of reaction.

Table 3.1.1: Studies of the different halogen atoms as leaving groups.



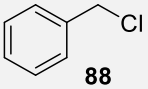
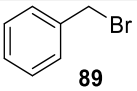
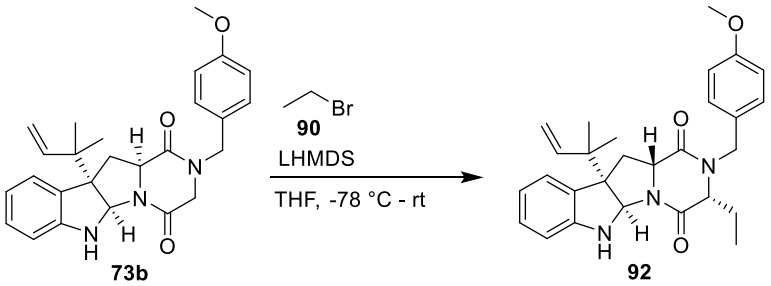
Entry	Alkylating agent	Amount	Yield	Comment
1	 **88**	2.0 eq.	6%	no DAP
2	 **89**	2.0 eq.	38%	DAP
3	 **90**	5.0 eq.	5%	DAP
4	 **91**	5.0 eq.	17%	DAP

Table 3.1.1 gives the outcome of the alkylation reactions using different halides. The expected reactivity trends, depending on the polarisability of the halide atoms, could be observed.[87] This is evident in the yields which increased up to threefold each time the halide was changed. However, the use of chloride seems to suppress the formation of double alkylated product. But as the yield when using benzyl chloride (**88**) was so significantly lower than when using benzyl bromide (**89**) this circumstance is to no advantage to the outcome of the reaction.

As a next step it was studied whether the increase of equivalents of alkylating reagent in the reaction mixture would lead to an increase in the yield of the alkylation reaction. Therefore, two different amounts of ethyl bromide (**90**) were submitted to the otherwise unchanged reaction conditions. The results of this investigation are given in Table 3.1.2.

Table 3.1.2: Comparison of the amounts of alkylating agent used.

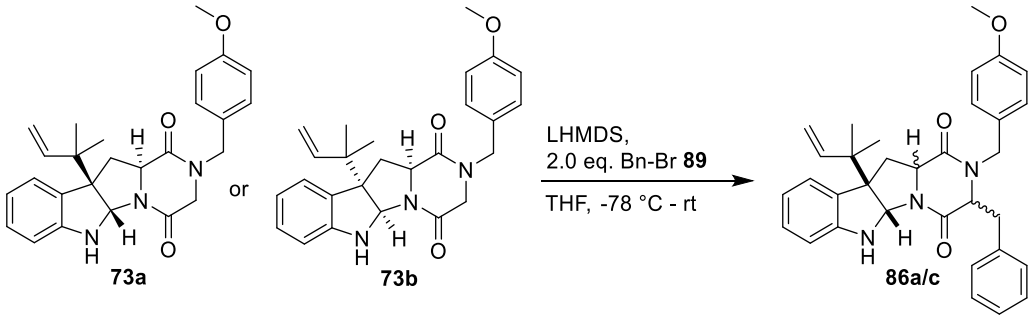


Entry	Alkylating agent	Amount	Yield	Comment
1	Br **90**	2.0 eq.	6%	DAP
2	Br **90**	5.0 eq.	5%	DAP

It could be observed that the increase to 5.0 eq. of ethyl bromide (**90**), as opposed to 2.0 eq., did not lead to an increase of the desired product **92**. The yield was even slightly lower than with only 2.0 eq. of ethyl bromide (**90**).

Even though most of the reverse prenylated hexahydropyrrolo[2,3-*b*]indole natural products show the *exo*-configuration both the *L-exo* compound **73a** and the *L-endo*-compound **73b** were available due to the extensive studies of the reverse prenylation reaction during the work for this thesis (Section 3.1.4). Therefore, the differences in the behaviour of those isomers in the *C*-alkylation reaction should be investigated. Table 3.1.3 gives the outcomes of these reactions. Benzyl bromide (**89**) was chosen as alkylating agent, as the desired product **86a** would later be needed in the pathway towards the total synthesis of fructigenine A (**4a**).

Table 3.1.3: Comparison of the alkylation reaction of *L-exo*-compound **73a** to *L-endo*-compound **73b**.



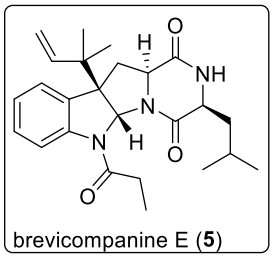
73a **73b** **86a/c**

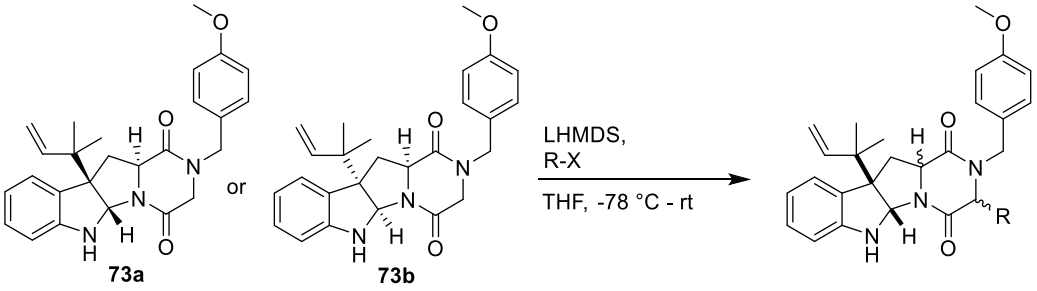
Entry	Substrate	Yield	Comment
1	**73a** (*exo*)	57%	DAP
2	**73b** (*endo*)	38%	DAP

The *L-exo*-compound **73a** gave a yield of 57% when alkylated with benzyl bromide (**89**). Compared to this the *L-endo*-compound **73b** gave a lower yield of only 38%. Interestingly, the outcome of the reaction seems to not only be influenced by the configuration of the DKP-ring but also by the configuration of the reverse prenyl group. A reason for this might be the lower thermodynamic stability of the *endo*-configured reverse prenylated hexahydropyrrolo[2,3-*b*]indole compounds as discussed in detail in Sections 3.1.4 and 3.2. The formation of small amounts of double alkylated products **87a/b** was observed in both reactions.

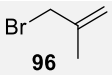
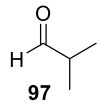
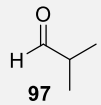
In accordance to the aim of developing a total synthesis for the natural product brevicompanine E (**5**) the introduction of an isobutyl group into the *L-exo*-compound **73a** was tried (Table 3.1.4). Unfortunately, this turned out not to be possible. The use of both isobutyl bromide (**93**) and isobutyl iodide (**94**) did not show any conversion. Neither the addition of silver triflate in order to activate the alkyl halide **94**, nor the addition of another 0.5 eq. of base or the addition of an excess of isobutyl iodide (**93**) to the reaction could lead to any product formation. Thus, the assumption was made that the isopropyl group may be too sterically hindered to attack at the methylene group of the DKP-ring. In order to still synthesise a brevicompanine E (**5**) derivative it was attempted to use isopropyl iodide (**95**) as alkylating agent. However, both attempts (with and without the addition of silver triflate) did not lead to the desired product as well. Finally, the alkylation reaction using 3-bromo-2-methylpropene (**96**) worked quite nicely with the best yield for an alkylation reaction so far of 65%. Again, the formation of small amounts of DAP was observed.

Table 3.1.4: *C*-Alkylation reactions towards the synthesis of brevicompanine E (**5**).

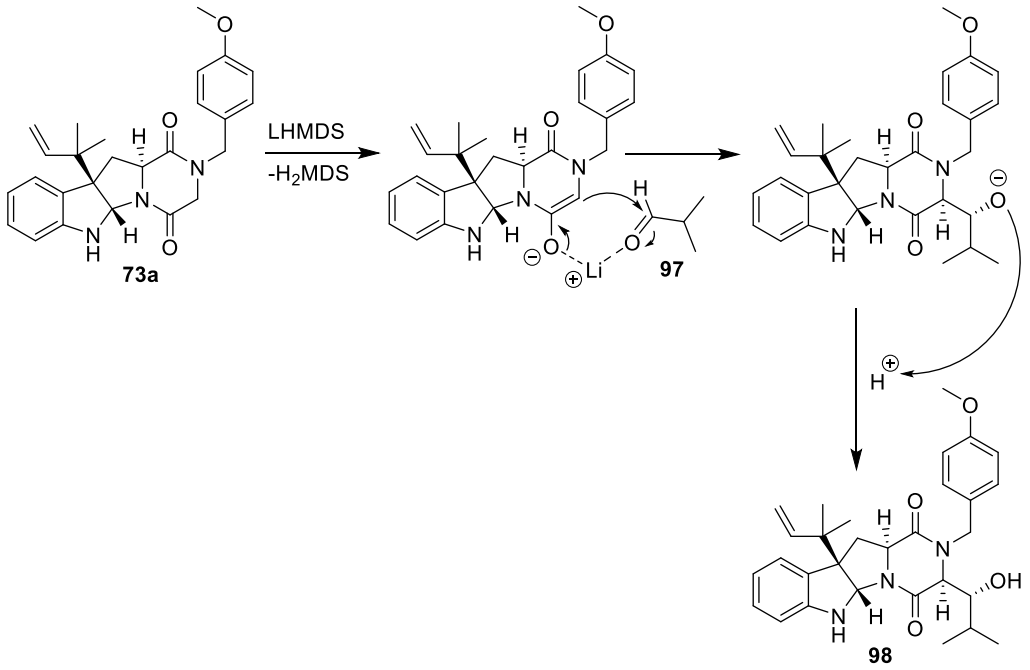




X = Br, I

Entry	Substrate	Alkylating agent	Amount	Addition	Yield	Comment
1	**73a**	 **93**	2.0 eq.	/	0%	plus 0.5 eq. of LHMDS
2	**73a**	 **94**	2.0 eq. - excess	1.2 eq. AgOTf	0%	/
3	**73b**	 **95**	2.0 eq.	/	0%	/
4	**73b**	 **95**	2.0 eq.	1.2 eq. AgOTf	0%	/
5	**73a**	 **96**	2.0 eq.	/	65%	DAP
6	**73a**	 **97**	2.0 eq.	/	54%	no DAP
7	**73a**	 **97**	5.0 eq.	/	22%	no DAP

Another electrophilic agent, which was used and which also led to a derivative of brevicompanine E (**5**), was isobutyraldehyde (**97**). As the reagent is not an alkyl halide the mechanism behind this reaction is different to that of the alkylation with e.g. 3-bromo-2-methylpropene (**96**). The introduction of isobutyraldehyde (**97**) follows an aldol-type addition.[88] This is shown in Scheme 3.1.12.



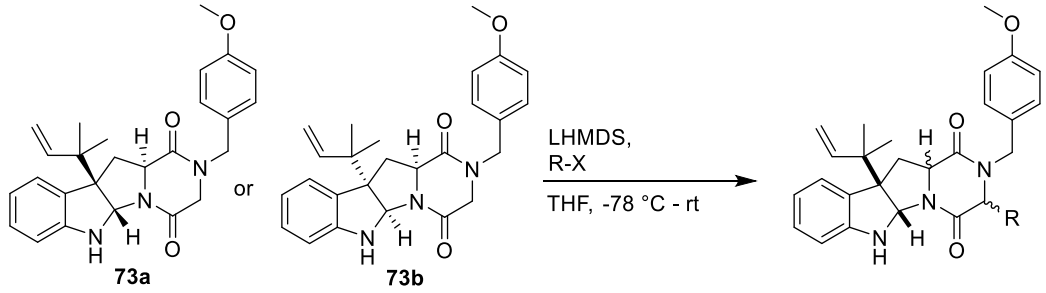
Scheme 3.1.12: Mechanism of the aldol-type addition leading to alkylated product **98**.[88]

After deprotonation and coordination to the lithium cation the newly formed enolate attacks the carbonyl function of the aldehyde. The resulting alkoxide gets protonated, usually by quenching the reaction with water, and the desired product is formed. Two new stereocentres are built during this reaction. The stereochemistry follows the Zimmermann-Traxler model, which states that *E*-enolates will be directed into *anti*-configuration during the aldol-type reaction, due to the six-membered transition state having chair-conformation.[89]

The yields for this addition were good, especially with 54% when 2.0 eq. of the aldehyde **97** were used. When using 5.0 eq. the yield dropped to 22%. This was not expected but might be explained by side reactions taking place with higher amounts of aldehyde **97** present. An aldol reaction between two isobutyraldehyde (**97**) molecules might be possible as well.

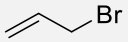
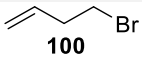
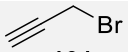
A few other alkylating agents were also tested in order to broaden the scope of the derivatives of reverse prenylated hexahydropyrrolo[2,3-*b*]indole compounds that can be synthesised *via* the newly established method. These are shown in Table 3.1.5. The reactions using allyl bromide (**99**) and propargyl bromide (**101**) worked with moderate yields and the formation of DAP in both cases. The reaction using 4-bromo-1-butene (**100**) only gave a yield of 6%, but interestingly no formation of DAP at all. The reaction using methyl iodide (**102**) gave no desired product but the DAP with a very good yield of 83%. This might be explained by the small size of the molecule, which can therefore attack quickly and simultaneously at nearly every part of the substrate.

Table 3.1.5: Different alkylating agents used in further studies of the *C*-alkylation reaction.



73a **73b**

X = Br, I

Entry	Substrate	Alkylating agent	Amount	Yield	Comment
1	**73b**	 **99**	2.0 eq.	35%	DAP
2	**73a**	 **100**	5.0 eq.	6%	no DAP
3	**73b**	 **101**	5.0 eq.	25%	DAP
4	**73b**	 **102**	5.0 eq.	0%	only DAP (83%)

The alkylation reaction with an alkyl halide worked best when using either benzyl bromide (**89**), 3-bromo-2-methylpropene (**96**), allyl bromide (**99**) or propargyl bromide (**101**). In the case of benzyl bromide (**89**) this can be explained with the stabilising effect on the transition state during the S_N2 reaction due to the +M-effect of the aromatic ring.[90] Allylic halides can react after a S_N2'-type mechanism at the *γ*-carbon atom due to the ability of the double bond to flip and therefore help the halide to leave the molecule. Propargyl bromide (**101**) can be stabilised in the form of an allene-zwitterion and act accordingly.[91] 4-bromo-1-butene (**100**) on the other hand is not able to do this, because the *π*-electron system is not close enough to the halide.

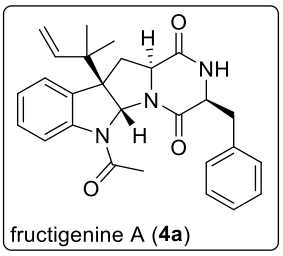
Usually, the unreacted starting material could be recovered in all reactions. In the case of the *L*-*endo*-compound **73b** the *D*-*exo*-compound **73c** was recovered instead of starting material. For more explanations and further studies of this behaviour see Section 3.2 of the present thesis.

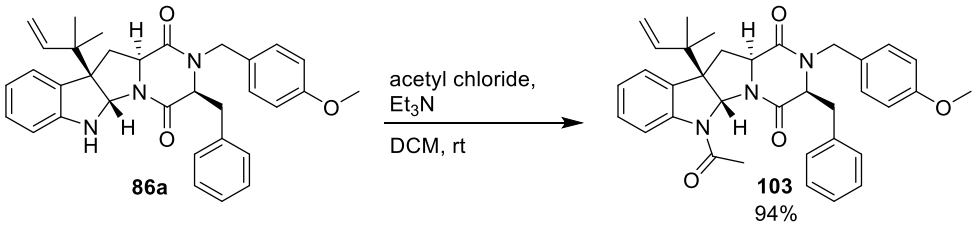
Many of the alkylation reactions described above were done in the context of the bachelor thesis of B. Sc. Daniel Schmelzer under my supervision.[92]

3.1.2.3 Towards the synthesis of fructigenine A (4a) and brevicompanine E (5)

To proceed with the development of a unified reaction sequence towards reverse prenylated hexahydropyrrolo[2,3-*b*]indole natural products and their non-natural derivatives the previously alkylated compounds (Section 3.1.2.2) needed to be modified further in order to lead to the desired natural products. As examples for the successful application of this method the natural products fructigenine A (**4a**) and brevicompanine E (**5**) were chosen as target substances for this thesis.

For a total synthesis of fructigenine A (**4a**) the benzylated compound **86a** needed to be acetylated at the nitrogen atom of the former indole unit. For a first attempt a kind of Steglich esterification was attempted using acetic anhydride and 4-dimethylaminopyridine (DMAP) in pyridine.[93,94] This turned out to be too harsh as the starting material was acetylated at multiple sites of the molecule. Therefore, conditions similar to the Schotten-Baumann reaction were tried with acetyl chloride as acetylating agent and triethylamine as base (Scheme 3.1.13).[95,96]



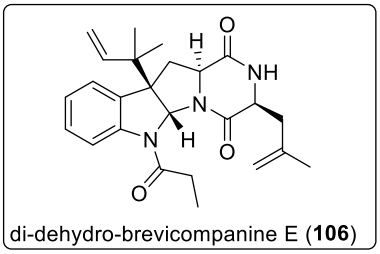


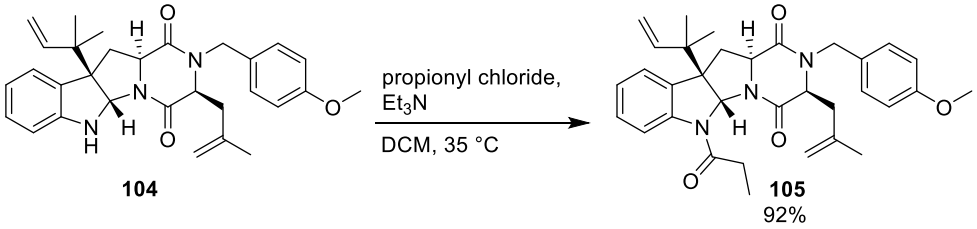
Scheme 3.1.13: *N*-Acetylation of benzylated compound **86a** with acetyl chloride.

This turned out to work very well, giving the desired acetylated product **103** in a yield of 94% on the first attempt. The acetylated precursor **103** of fructigenine A (**4a**) was successfully synthesised over six steps with an overall yield of 31%.

A very similar acylation was required for the synthesis towards the second natural product brevicompanine E (**5**), which was supposed to be synthesised during the work for this thesis as well. As the studies on the *C*-alkylation reaction showed it was not possible to introduce an isobutyl group into the molecule. It was however possible to alkylate compound **73a** quite successfully with 3-bromo-2-methylpropene (**96**). Therefore, the objective was changed to developing a total synthesis of di-dehydro-brevicompanine E (**106**).

The acylating reaction conditions used before for the acetylation of the fructigenine A (**4a**) derivative **86a** were also applied in this case. Propionyl chloride was used as reagent but initially no conversion could be observed. Only after heating the reaction mixture to 35 °C the conversion to the desired product **105** took place (Scheme 3.1.14).





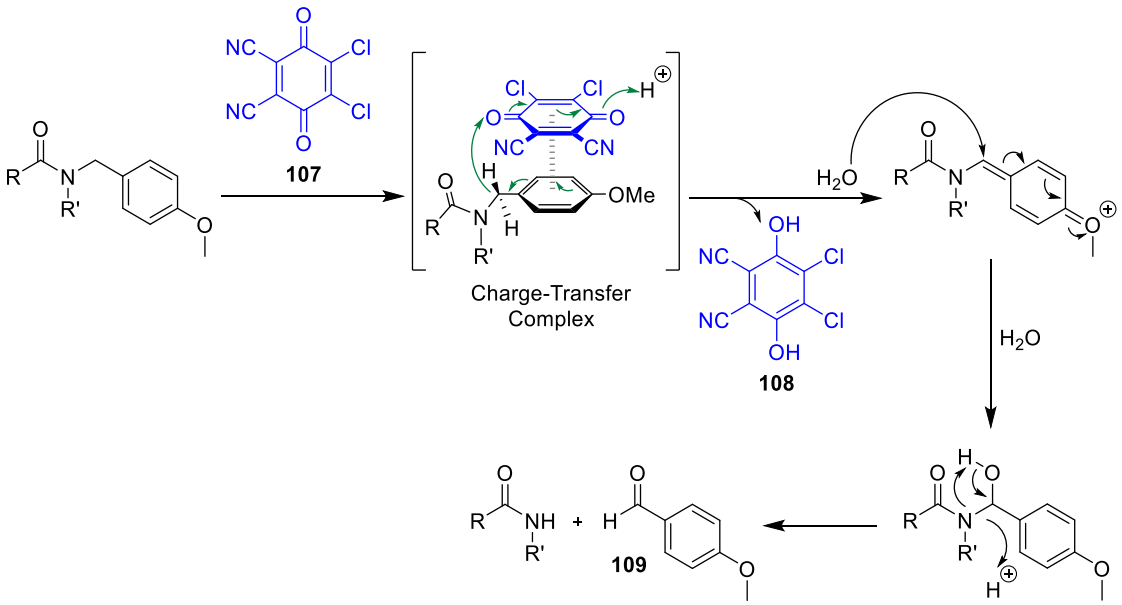
Scheme 3.1.14: *N*-Alkylation of compound **104** with propionyl chloride.

In the end this reaction worked very well giving the desired alkylated product **105** in a yield of 92%. Only the removal of the PMB-protecting group would then be left, in this case as well, in order to have the desired hexahydropyrrolo[2,3-*b*]indole natural product derivative di-dehydro-brevicompanine E (**106**) in hand.

The *N*-alkylated precursor **105** of di-dehydro-brevicompanine E (**106**) was successfully synthesised over six steps with an overall yield of 34%.

3.1.2.4 Attempted PMB-deprotection reactions

A common way to remove a PMB-protecting group off a molecule is the oxidative cleavage with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (**107**). It is known to work on PMB-protected alcohol functions as well as on amides. The mechanism behind the oxidative cleavage with DDQ (**107**) is depicted in Scheme 3.1.15. DDQ (**107**) forms a charge-transfer complex with the aromatic ring system of the PMB-group, thus dehydrogenating it and making it accessible for the nucleophilic attack of a water molecule. This leads to the recovery of the aromatic system and the subsequent formation of *p*-methoxybenzaldehyde (**109**) and the desired product.[97]

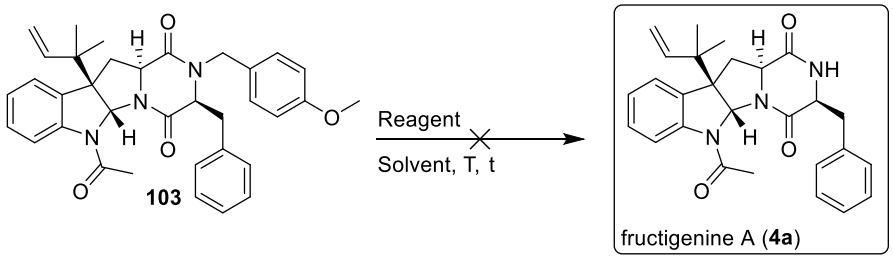


Scheme 3.1.15: Oxidative cleavage of the PMB-group with DDQ (**107**).[97]

For the oxidative removal of the PMB-group from amide moieties ceric ammonium nitrate (CAN) is often used as well.[98] The mechanism behind this cleavage is similar to the one with DDQ (**107**) described above, but with two molecules of CAN being needed for the reaction.

In Table 3.1.1 the PMB-deprotection attempts towards synthesising fructigenine A (**4a**) are listed.

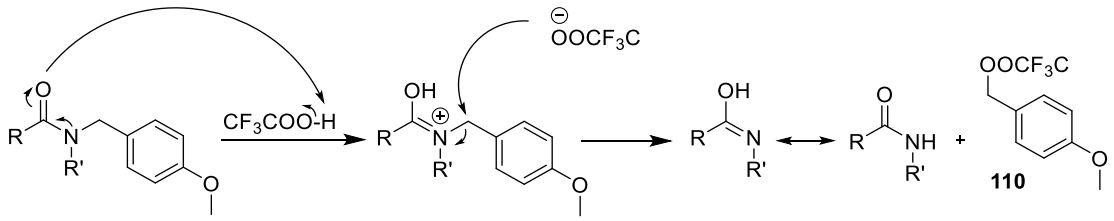
Table: 3.1.1: Attempted PMB-deprotections for the synthesis of fructigenine A (**4a**).



Entry	Reagent	Amount	Solvent	Temperature	Time	Comment
1	DDQ (**107**)	1.2 eq.	DCM:H_2O (1:1)	rt	18 h	no conversion
2	CAN	1.5 eq.	MeCN:H_2O (1:1)	50 °C	18 h	no conversion
3	CAN	1.5 eq.	THF:H_2O (99:1)	60 °C	18 h	no conversion
4	CAN	5.0 eq.	THF:H_2O (99:1)	70 °C	168 h	no conversion

The attempts to deprotect substrate **103** were not successful. The addition of DDQ (**107**) and CAN with temperatures of up to 70 °C and an excess of 4.0 eq. did all lead to no conversion of the starting material after the reaction had been stirring overnight.

After the first attempts of cleaving the PMB-group oxidatively did not work, another way of deprotecting the molecules was thought of. Even though acidic conditions did not seem ideal, because of the terminal double bond of the reverse prenyl group, the acid catalysed hydrolysis should be tried to remove the PMB-group. The mechanism behind the acidic cleavage of a PMB-protecting group by the example of trifluoroacetic acid is depicted in Scheme 3.1.16.[99]

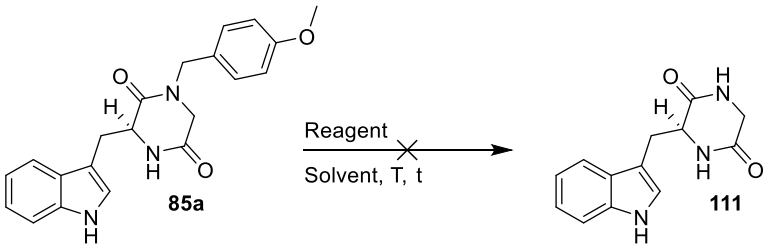


Scheme 3.1.16: Mechanism for the PMB-deprotection of an amide *via* acid catalysed hydrolysis.[99]

Here the acid protonates the amide function activating an attack at the *α*-carbon atom of the PMB-group, which subsequently leads to the formation of the desired product, after amide-iminol tautomerism, and *p*-methoxy-benzyl compound **110**. The terminal double bond was supposed to be stable enough or even sterically hindered enough to survive the mild acidic conditions needed to cleave the PMB-group. To regenerate the acid anisole can be added to the reaction mixture as a proton source.

To save on target material **103** further PMB-deprotecting reactions were first tried on diketopiperazine **85a**, the PMB-protected amide function of which should be similar enough to those of the target structures to work nicely as a test substrate. The attempted PMB-deprotection reactions using compound **85a** as substrate are listed in Table 3.1.2.

Table 3.1.2: Attempted PMB-deprotections of diketopiperazine **85a**.



Entry	Reagent	Amount	Solvent	Temperature	Time	Comment
1	CAN	2.0 eq.	1,4-dioxane	80 °C	16 h	no conversion
2	CAN	1.5 eq.	THF:H_2O (99:1)	80 °C + microwave (150W)	0.5 h	decomposition
3	CAN / anisole	1.5 eq. each	THF:H_2O (99:1)	80 °C + microwave (150W)	0.5 h	decomposition
4	TFA	neat	/	97 °C	12 h	decomposition
5	TFA / anisole	1:1	/	90 °C	18 h	no conversion
6	Blue light / Ru-cat. / $K_2S_2O_8$	460 nm / 0.1 mol% / 1.0 eq.	MeCN:H_2O (1:1)	rt	15 h	no conversion

The use of CAN at 80 °C, or even with the microwave and the addition of anisole as intercepting reagent to help bring the equilibrium to the side of the formation of *p*-methoxybenzaldehyde (**109**), did not lead to any formation of the desired product **111**. The use of microwave irradiation for 30 min at 150 W led to decomposition of the starting material **85a** in both cases. The attempted acidic hydrolysis led to decomposition in the case of using trifluoroacetic acid neat and to no conversion when anisole was added to the reaction mixture in stoichiometric amounts.[99,100] A last but promising attempt to cleave the PMB-group was the photocatalytic removal with $[Ru(bpy)_3]Cl_2$ as catalyst and potassium persulfate as oxidating agent under blue light with a wavelength of 460 nm. Due to the longer durability of the ruthenium catalyst a 1:1 mixture of acetonitrile and water was chosen as solvent for the reaction. However, no conversion could be obtained after the reaction had been running for 15 hours.[101]

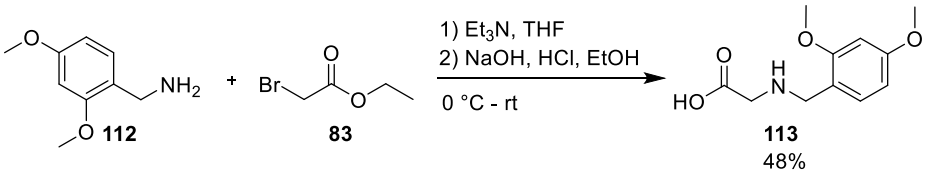
3.1.3 Rerunning the pathway using the DMB-protecting group

As the deprotection of the PMB-group was unsuccessful a different protecting group needed to be found, which had to fulfil the same requirements as the PMB-group, but would be easier to cleave. The new protecting group needed to be stable to basic conditions in order to still be intact during deprotonation and alkylation. The cleavage through acidic conditions or hydrolysis should be avoided because of the terminal double bond of the reverse prenyl group. In addition, the new group should also be a benzene derivative so that it can direct the introduction of the alkyl group in the *C*-alkylation step to the desired face of the enolate.

The 2,4-dimethoxybenzyl- (DMB) group seemed to be the right choice because it should also be cleaved oxidatively, but more readily because of its two, as opposed to only one, electron donating groups.[102]

3.1.3.1 Synthesis of the DMB-protected diketopiperazine 115 and reverse prenylated core structures 116a/b

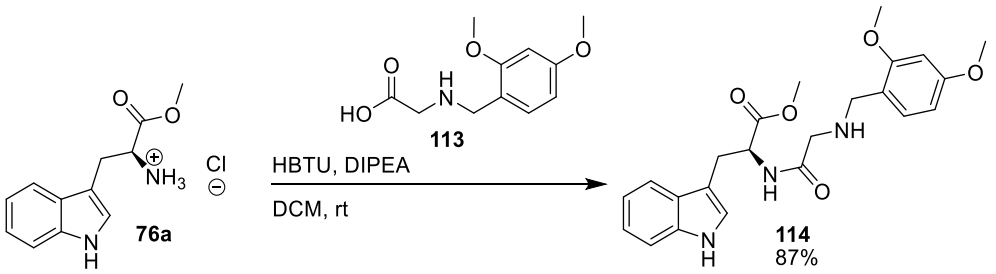
To introduce the DMB-protecting group the DMB-protected glycine derivative **113** was formed. This was also performed *via* a S_N2-type reaction of 2,4-dimethoxybenzylamine (**112**) with bromo acetate (**83**), followed by basic saponification with a yield of 48% (Scheme 3.1.17).[85]



Scheme 3.1.17: Synthesis of DMB-protected glycine **113**.

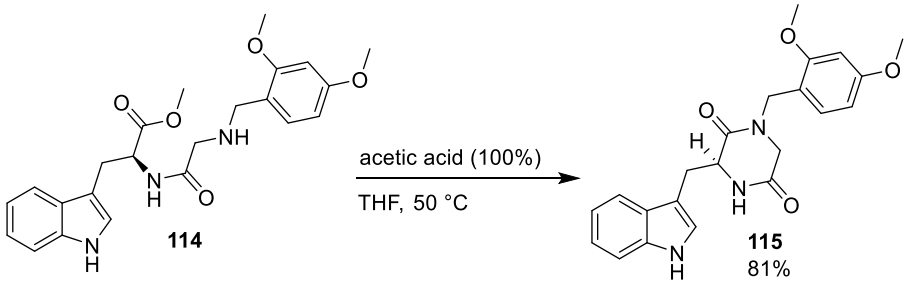
The significantly lower yield compared to the PMB-protected glycine derivative **81** might result from problems during the work-up process. Compound **81** was very easily precipitated and did not need any further purification. Compound **113** on the other hand did not precipitate and needed to be purified by column chromatography on silica gel. The high polarity of the free acid **113** made this a difficult procedure and this might have resulted in the loss of substance. If the DMB-deprotection had been successful the purification of this step would have been optimised, but as the DMB-group later turned out not to be suitable for the desired reaction sequence further work on improving the yield of substance **113** was dismissed.

With DMB-protected glycine **113** in hand the peptide coupling with *L*-tryptophan methyl ester hydrochloride (**76a**) was performed (Scheme 3.1.18). HBTU and DIPEA were used as coupling reagent and base in this case as well. The resulting dipeptide **114** could be obtained with a good yield of 87%.[80,81]



Scheme 3.1.18: Peptide coupling of *L*-tryptophan methyl ester hydrochloride (**76a**) with DMB-protected glycine **113**.

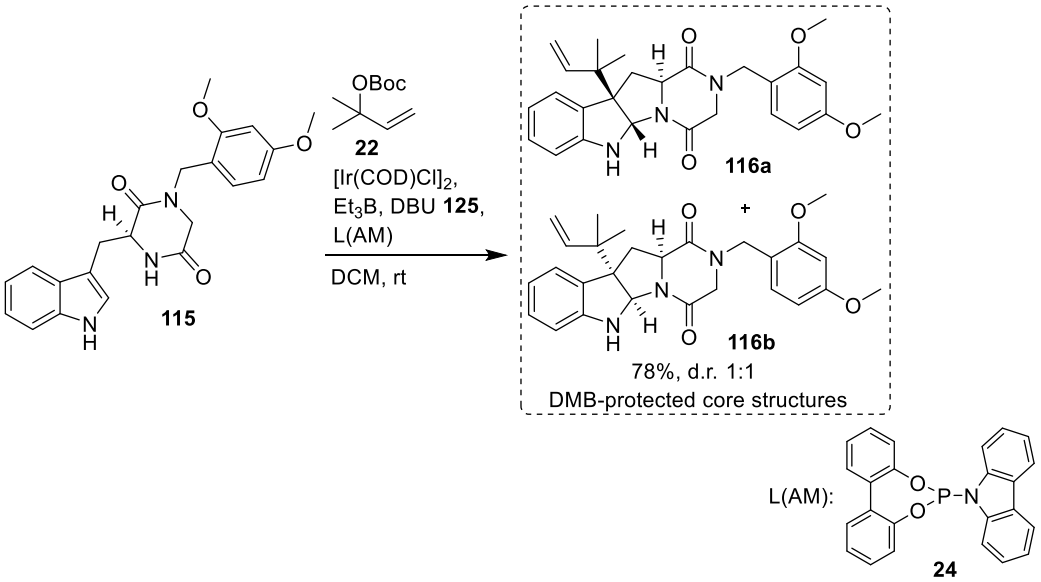
The ring closure to diketopiperazine **115** was then successfully performed with a yield of 81%, following the already established reaction procedure of the acid catalysed condensation of methanol through addition of acetic acid in THF at 50 °C (Scheme 3.1.19).[86]



Scheme 3.1.19: Ring closure of dipeptide **114** to diketopiperazine **115**.

Already at this stage of the reaction sequence several attempts to remove the DMB-group from the DKP-ring have been tried (Section 3.1.3.2). Although the electronic surrounding is not the same, compared to a reverse prenylated compound where the hexahydropyrrolo[2,3-*b*]indole system is fully closed, it might have given some indications as to whether this protecting group was the right choice. However, the removal of the DMB-group from diketopiperazine **115** was not successful (Table 3.1.3).

Nevertheless, the reverse prenylated compounds **116a/b** were formed in order to further study the removal of the DMB-protecting group on a reverse prenylated hexahydropyrrolo[2,3-*b*]indole system. In Scheme 3.1.20 the iridium catalysed reverse prenylation reaction on DMB-protected diketopiperazine **115** with achiral ligand **24** is shown.[4]



Scheme 3.1.20: Iridium catalysed reverse prenylation reaction of diketopiperazine **115**.

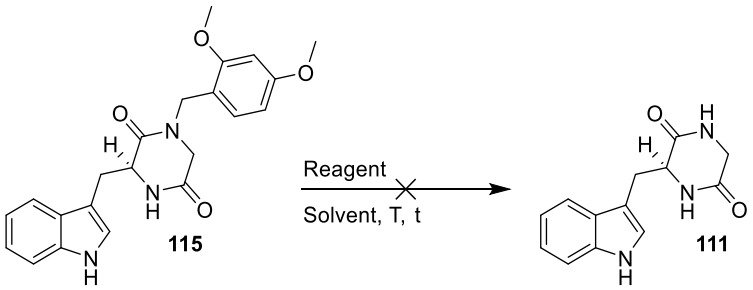
The reaction gave the prenylated compounds **116a/b** in a diastereomeric ratio of 1:1 with a yield of 78%. Further studies of the reverse prenylation reaction on this compound, e.g. with different ligands or boranes, were not performed, as the removal of the DMB-group turned out not to be successful on compounds **116a/b** as well (Section 3.1.3.2).

The DMB-protected reverse prenylated core structures **116a/b** were synthesised over five steps with an overall yield of 26% in a diastereomeric ratio of 1:1.

3.1.3.2 Attempted DMB-deprotection reactions

The removal of the DMB-protecting group was tried before any alkylation reactions were performed on the DMB-protected core structures **116a/b** in order to find out whether it would even be worthwhile to further pursue the pathway with the DMB-group. Therefore, the first deprotection attempts were performed once the DMB-protected diketopiperazine **115** was in hand. The results are given in Table 3.1.3. Many of the reaction conditions which were tried are the same as the ones tried for the removal of the PMB-group, as the mechanism behind the cleavage should be the same for both compounds. It was believed that the removal of the DMB-group would be possible, as opposed to the one of the PMB-group, because of the second methoxy group in the molecule. However, the deprotection of the DMB-group from the diketopiperazine **115** was not successful.[97,98,100,102]

Table 3.1.3: Attempted DMB-deprotections of diketopiperazine **115**.



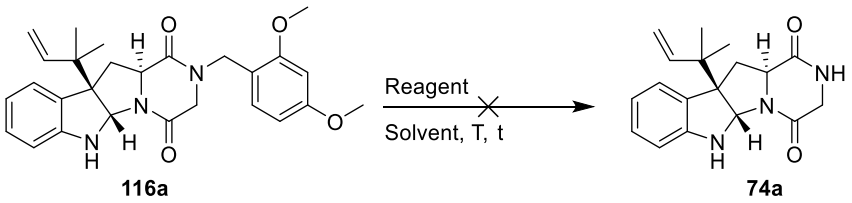
Entry	Reagent	Amount	Solvent	Temperature	Time	Comment
1	CAN	1.5 eq.	THF:H_2O (99:1)	rt	20 h	no conversion
2	CAN	2.0 eq.	THF:H_2O (99:1)	55 °C	8 h	no conversion
3	CAN / anisole	1.5 eq. each	THF:H_2O (99:1)	rt	16 h	no conversion
4	DDQ (**107**)	1.5 eq.	DCM:H_2O (1:1)	rt	8 h	decomposition
5	DDQ (**107**)	5.0 eq.	$CHCl_3$	55 °C	7 h	decomposition
6	TFA	0.1 wt%	/	rt	3 h	decomposition
7	TFA	0.1 wt%	/	-20 °C	6 h	no conversion
8	TFA	neat	/	rt	5 h	decomposition
9	TFA / anisole	1:1	/	rt	6 h	decomposition
10	*p*-TsOH *H_2O	4.0 eq.	Toluene	rt	15 h	no conversion
11	formic acid (88%)	neat	/	rt	8 h	decomposition
12	acetic acid (88%)	neat	/	rt	9 h	decomposition

Five attempts of an oxidative cleavage with DDQ (**107**) or CAN were performed at either room temperature or 55 °C. Anisole was added to the reaction with CAN and DDQ (**107**) in an excess and even tried dissolved in chloroform, where the reaction could have taken place not only at the phase boundary of the reaction mixture. The reactions using CAN showed no conversion, whereas the reactions performed with DDQ (**107**) gave decomposition of the starting material **115**. In addition, seven attempts of DMB-deprotection of diketopiperazine **115** using an acid were performed. TFA in various concentrations, *p*-toluenesulfonic acid in toluene, formic acid and acetic acid were tried as deprotection reagents at room temperature but none led to the desired product **111**.

TFA led to decomposition, except when stirred at -20 °C where it showed no conversion at all. *p*-Toluenesulfonic acid led to no conversion as well, and every other attempt led to decomposition.

With the DMB-deprotection being unsuccessful on the diketopiperazine **115** the electronic environment of the reverse prenylated compound **116a** was believed to be sufficiently different, due to its` higher rigidity and loss of aromaticity at the five membered ring of the indole unit, in order for the deprotection to work. Therefore another four deprotection attempts were performed on the DMB-protected, *exo*-configured, reverse prenylated hexahydropyrrolo[2,3-*b*]indole compound **116a**. These are listed in Table 3.1.4.

Table 3.1.4: Attempted DMB-deprotections of reverse prenylated core structure **116a**.



Entry	Reagent	Amount	Solvent	Temperature	Time	Comment
1	CAN	2.0 eq.	THF:H_2O (99:1)	rt	16 h	decomposition
2	DDQ (**107**)	2.0 eq.	DCM:H_2O (1:1)	rt	16 h	no conversion
3	TFA / anisole	1:1	/	rt	7 h	decomposition
4	acetic acid (88%)	neat	/	rt	16 h	no conversion

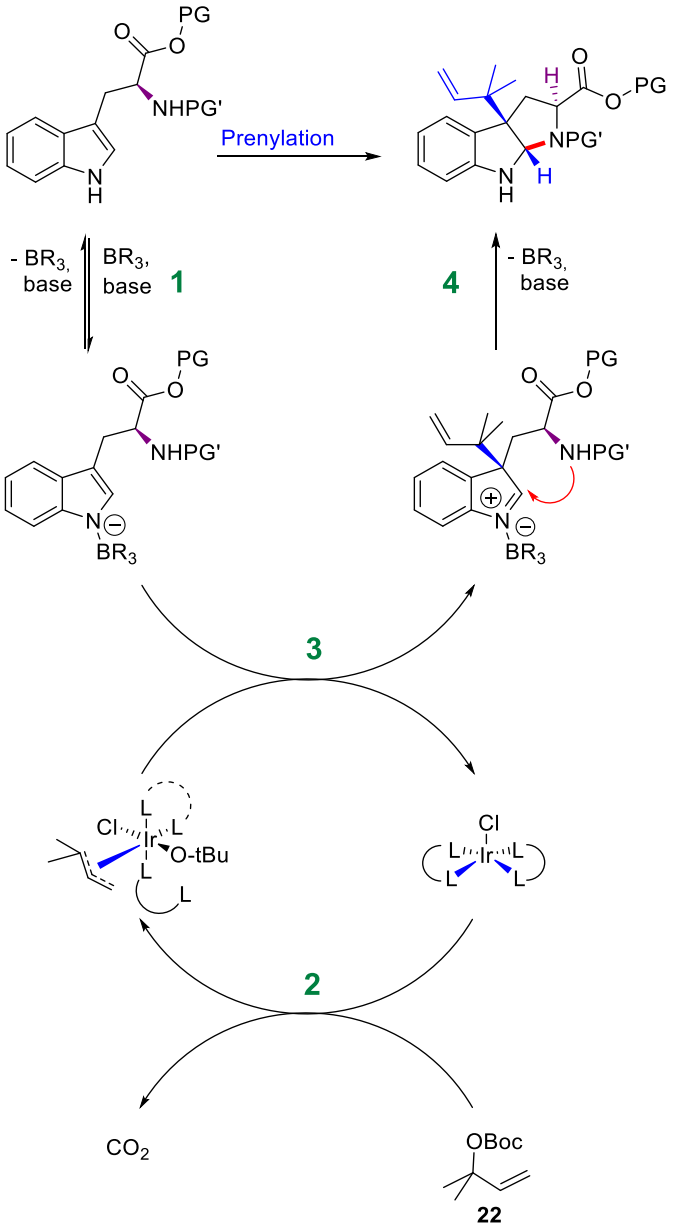
Both CAN and DDQ (**107**) were tried as oxidative reagents, as well as TFA (with anisole) and acetic acid to catalyse a hydrolysis. All reactions were performed at room temperature. The reactions using CAN and TFA led to decomposition. The reactions using DDQ (**107**) and acetic acid showed no conversion.

With these results it was concluded that both the PMB- and the DMB-protecting groups might not be the right choices for the development of a unified pathway towards reverse prenylated hexahydropyrrolo[2,3-*b*]indole natural products. A different protecting group with a different cleavage mechanism still has to be found.

3.1.4 Studies of the iridium catalysed reverse prenylation reaction

During the work on this thesis a variety of compounds were submitted to the iridium catalysed revers prenylation reaction developed in the Stark group.[4] As these compounds differ from the ones described in the initial publication in size or their electronic environment they should be submitted to further studies of the reverse prenylation reaction conditions.

The mechanism behind the reverse prenylation reaction towards prenylated hexahydropyrrolo[2,3-*b*]indole compounds has not yet been fully determined. However, there is a mechanistic proposal which satisfactorily describes the outcome of the reactions performed so far. This is shown in Scheme 3.1.21.

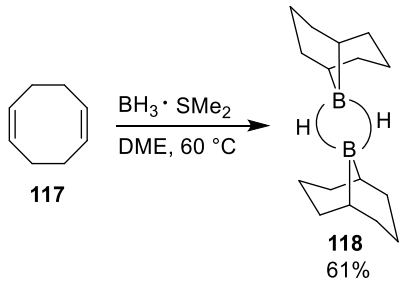


Scheme 3.1.21: Proposed mechanism for the iridium catalysed reverse prenylation reaction developed by Stark *et al*.[4]

As a first step of the reaction the nitrogen atom of the indole unit is deprotonated by the base and subsequently forms an ate-complex with the borane. Simultaneously, the previously formed iridium catalyst reacts with the allyl carbonate releasing carbon dioxide and forming a cationic *π*-allyl complex. This is then transferred to the indole ate-complex formed in the first step. Depending on the chirality of the iridium-ligand complex and also on the type of the borane, the addition of the prenyl moiety takes place stereoselectively. As a last step the nitrogen atom of the amino group attacks the iminium ate-complex to form the closed hexahydropyrrolo[2,3-*b*]indole motif.

The specific role of the borane in regard to the stereoselectivity of the reaction is not fully understood yet. 9-OBBN (**142**) was previously determined to be one of the boranes influencing the stereoselectivity.[4] To investigate this behaviour further it was decided to determine whether eight carbon atoms in 9-OBBN (**142**) is indeed the optimal chain length or could be optimised. For this reason 9-hexyl-9-borabicyclo[3.3.1]nonane (9-HBBN) (**119**) and 9-decyl-9-borabicyclo[3.3.1]nonane (9-DBBN) (**120**) were synthesised and submitted to the reverse prenylation reaction conditions as examples of boranes containing shorter and longer chains compared to 9-OBBN (**142**).

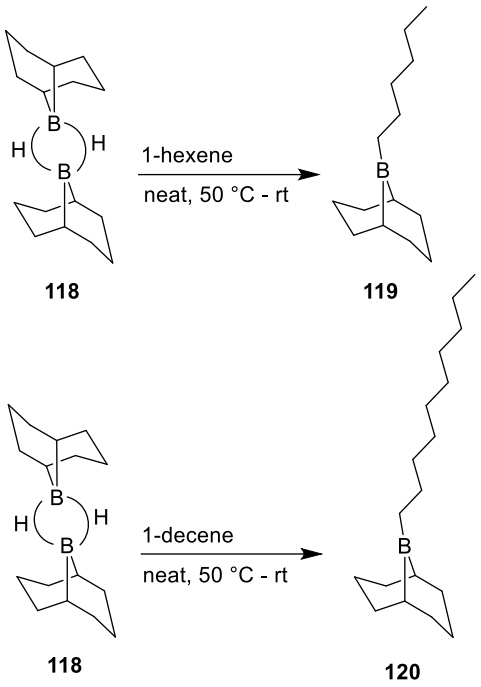
In order to do so the 9-BBN-dimer (**118**) needed to be synthesised first. This was achieved through addition of borane dimethyl sulfide complex to 1,5-cyclooctadiene (**117**) (Scheme 3.1.22).[103]



Scheme 3.1.22: Synthesis of 9-BBN-dimer **118**.[103]

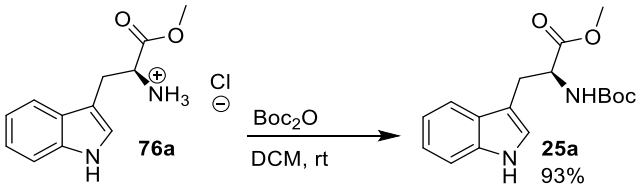
The 9-BBN-dimer (**118**) was successfully synthesised with a yield of 61%.

With 9-BBN-dimer (**118**) in hand the 9-BBN-derivatives **119** and **120** were synthesised (Scheme 3.1.23) following the procedure for the synthesis of 9-OBBN (**142**) described by Stark *et al*.[4] As both compounds are pyrophoric specific yields for these reactions were not determined.



Scheme 3.1.23: Synthesis of 9-HBBN (**119**) and 9-DBBN (**120**).

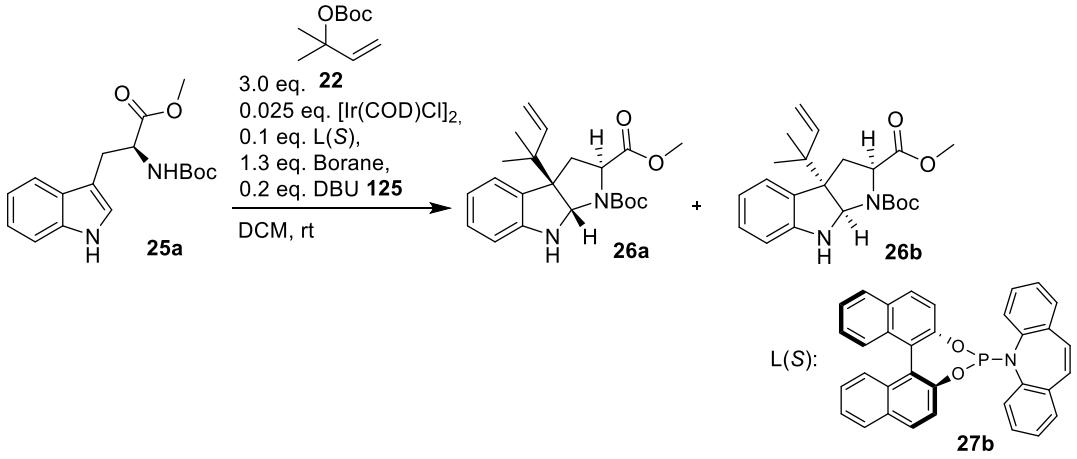
Afterwards, the boranes were submitted as additives to the reverse prenylation reaction conditions. To be able to compare the results accurately the same substrate **25a** as used in the publication for the iridium catalysed reverse prenylation reaction was used as the test substrate.[4] Therefore, substrate **25a** had to be synthesised by Boc-protection of previously synthesised *L*-tryptophan methyl ester hydrochloride (**76a**) as described in Section 3.1.1.1.



Scheme 3.1.24: Boc-protection of *L*-tryptophan methyl ester hydrochloride **76a**.[104]

Scheme 3.1.24 shows the Boc-protection to the desired compound **25a** with a very good yield of 93%.[104] The results for the reverse prenylation reaction using the boranes with different chain lengths and compound **25a** as starting material are given in Table 3.1.5.

Table 3.1.5: Comparison of the different 9-BBN-boranes.



Entry	Borane	d.r. (26a:26b)	Yield
1	9-OBBN (**142**)	7:1	not determined
2	9-HBBN (**119**)	5:1	94%
3	9-DBBN (**120**)	4:1	95%

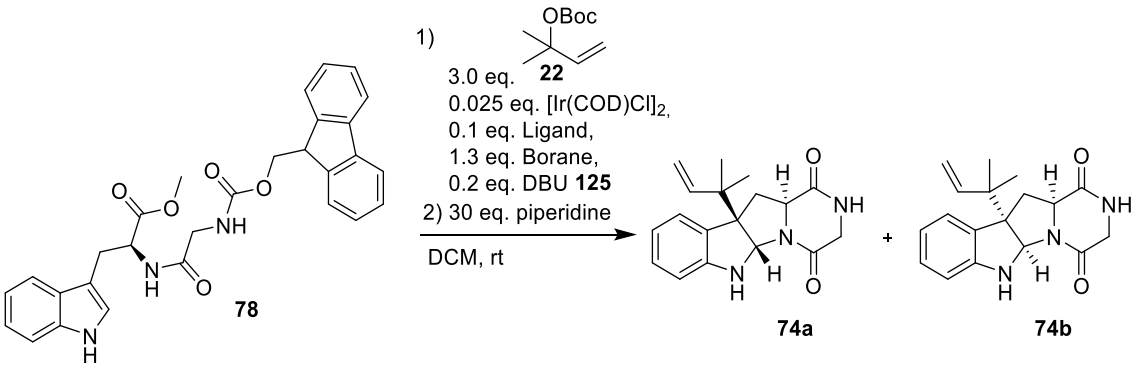
Table 3.1.5 shows that the stereoselectivity, influenced by the borane during the iridium catalysed reverse prenylation reaction, is highest when using 9-OBBN (**142**) as borane with a diastereomeric ratio of 7:1 (**26a**:**26b**). The decrease of the chain length to only six carbon atoms led to a diastereomeric ratio of only 5:1. The increase to ten carbon atoms led to an even lower ratio of only 4:1. The yields however do not seem to be affected by these modifications. In the publication introducing the reverse prenylation reaction a yield for the same reaction with 9-OBBN (**142**) as seen in entry 1 of Table 3.1.5 was not given, but the yield for the same reaction using the *R*-configured ligand **27a** is given with 95%.[4] Therefore, the yields for all three boranes are nearly identical and can be disregarded in the considerations of the borane most suited for the reverse prenylation reaction. Thus, 9-OBBN (**142**) still seems to be the best choice as borane compared to its derivatives containing shorter or longer alkyl chains.

In order to get further insight into the scope and limitations of the iridium catalysed reverse prenylation reaction the behaviour of several, during the work on this thesis newly synthesised, compounds should be investigated. Most of those compounds were expected to behave differently due to their difference in size or electronic environment.

The following section gives an overview over the majority of the prenylation reactions performed as part of this thesis. Comparisons between the prenylating reagents (e.g. ligands or pre-formed catalysts) are given, as well as between the different substrates submitted to the reaction conditions. If not noted in the tables differently all reactions were performed with a scale of 0.1 mmol of starting material and were stirred overnight.

In Table 3.1.6 the reverse prenylation reactions performed towards the synthesis of the common core structures **74a/b** are given. The iridium catalysed reverse prenylation reaction of dipeptide **78** was not studied in regard to every possible ligand or borane, but the reactions that were performed can be taken into account when comparing the different substrates for this type of reaction. The reactions have been performed as a one-pot reverse prenylation and subsequent Fmoc-deprotection in order to obtain the cyclised core structures **74a/b**.

Table 3.1.6: Reverse prenylation and subsequent Fmoc-deprotection reactions of DP **78** to the core structures **74a/b**.

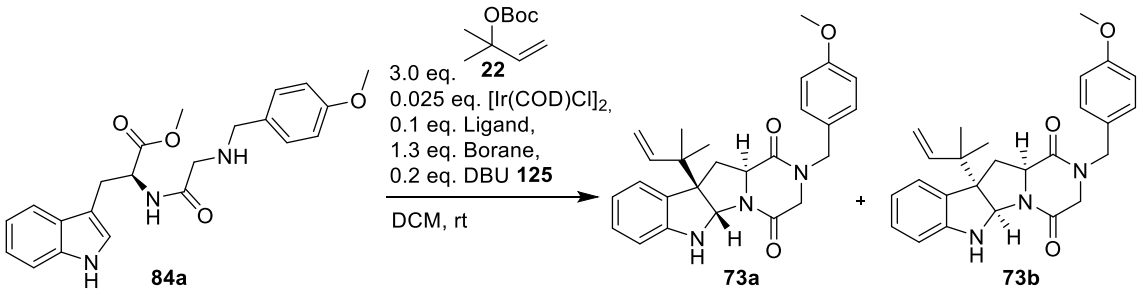


Entry	Ligand	Borane	d.r. (74a:74b)	Yield	Comment
1	L(AM) **24**	Et_3B	1:1	97%	2.0 mmol scale
2	L(*R*) **27a**	9-OBBN (**142**)	1:6	55%	/
3	L(*S*) **27b**	9-OBBN (**142**)	3:1	46%	/

The stereoselectivities of these reactions were quite low compared to the ones from the original publication.[4] It can also be seen here that the yields regarding the reactions with 9-OBBN (**142**), together with a chiral ligand, are not as good as the one with triethylborane and the achiral ligand. They are also significantly lower as compared to the test substrate from the comparisons of the different 9-BBN-boranes (Table 3.1.5). It is assumed that the size of the substrate and therefore the steric hindrance during the reverse prenylation reaction is one possible explanation for this outcome. Furthermore, it could be observed that the conversion takes place much faster with triethylborane as compared to 9-OBBN (**142**). In the case of 9-OBBN (**142**) complete conversion of the starting material could not be obtained before the catalyst lost its activity.

In Table 3.1.7 the reverse prenylation reactions using dipeptide **84a** are given with the use of the boranes 9-OBBN (**142**) or triethylborane.

Table 3.1.7: Reverse prenylation reactions of DP **84a** with triethylborane and 9-OBBN (**142**).



Entry	Ligand	Borane	d.r. (73a:73b)	Yield	Comment
1	L(AM) **24**	Et_3B	1:1	62%	/
2	L(AM) **24**	9-OBBN (**142**)	1:1	57%	/
3	L(*R*) **27a**	Et_3B	(>99:1)	40%	intermediate **121a/b** (44%)
4	L(*R*) **27a**	9-OBBN (**142**)	(>99:1)	37%	intermediate **121a/b** (46%)
5	L(*S*) **27b**	Et_3B	(>99:1)	34%	intermediate **121a/b** (46%)
6	L(*S*) **27b**	9-OBBN (**142**)	(>99:1)	52%	intermediate **121a/b** (34%)

In all reactions using a chiral ligand the formation of compounds **121a/b** could be observed (Figure 3.1.1). They turned out to be a prenylated derivative of starting material **84a** without the DKP-ring being closed. Therefore, they can be seen as an isolated intermediate of the reaction.

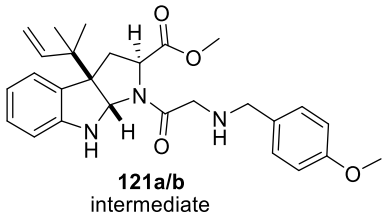


Figure 3.1.1: Open intermediates **121a/b** of the reverse prenylation reaction of DP **84a** with a chiral ligand.

Interestingly, the non-cyclised intermediate **121** always obtained both *endo*- and *exo*-compounds (d.r.=1:1) in equal amounts. This was the case regardless of which borane/ligand combinations were used.

Accordingly, it was first believed that the *L*-*exo*-product **73a** was the major product of the reaction in all cases and that, somehow, the configuration of the ligand does not have any impact on the stereoselectivity of the reaction other than the induction of chirality in general. However, the occurrence of a stereoablative process for the formation of compound **73a** is unlikely as the same outcome did not occur during the reaction of dipeptide **78** with a chiral ligand or when using triphenylborane. Later experiments led to the discovery of an inversion taking place of the *endo*-configured compounds to their corresponding *exo*-configured counterparts (3.2). This might lead to the assumption that any formed *L*-*endo*-product **73b** directly inverted to the thermodynamically more favoured *D*-*exo*-compound **73c** and that, for some reason, this was not possible for intermediate **121b**. However, to determine the reason of these findings further studies will be necessary as the NMR-spectra of the *exo*-structures **73a/c** are identical and all efforts to try and obtain crystal structures of these molecules were unsuccessful.

The yields for the expected products **73a/b** are generally lower than compared to the test substrate **25a** from the original publication.[4] Compared to dipeptide **78** the yields are slightly lower in the case of the (*R*)-configured ligand **27a**, but slightly higher in the case of the (*S*)-configured ligand **27b**. Taken into account that intermediate **121a/b** might also be transformed into poducts **73a/b** the overall conversion of these reactions is quite high.

In the initial publication of the iridium catalysed reverse prenylation reaction a third borane (triphenylborane) was introduced as well, giving very good yields and selectivities for the presented reactions.[4] To achieve these results the iridium catalyst was submitted to an additive beforehand and an imidazolium complex was formed. The publication mentions the use of a benzyl substituted imidazolium complex (pre-cat.1). As part of the present thesis also the phenyl substituted imidazolium complex (pre-cat.2) should be studied and compared to the benzylated derivative. Both pre-formed catalysts are depicted in Figure 3.1.2. Additionally, triazabicyclodecene (TBD) is used as base in these reactions, instead of DBU (**125**). As the handling of the pre-catalysts is difficult, due to their hygroscopicity, triphenylborane as borane additive was only used for the studies of the reverse prenylation reactions as opposed to during the development of a natural product synthesis during the work for this thesis.

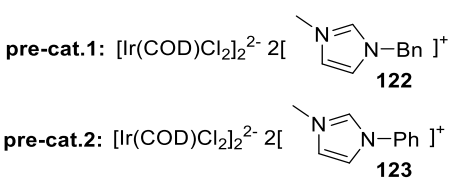
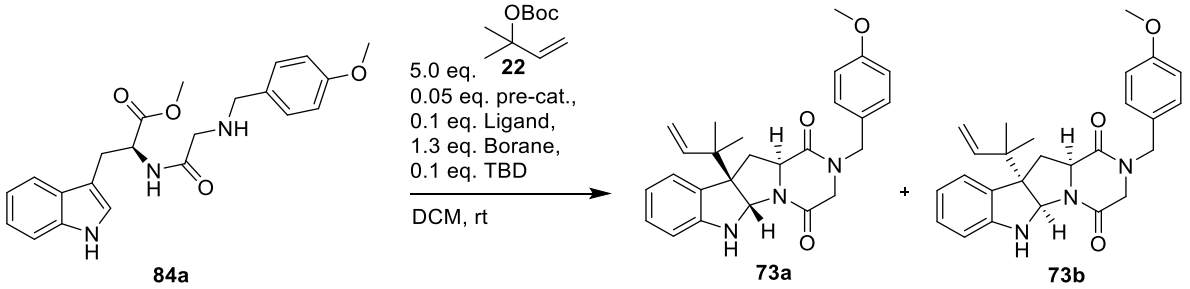


Figure 3.1.2: Pre-catalysts for the reverse prenylation reaction with triphenylborane.

The reverse prenylation reactions with dipeptide **84a** using triphenylborane and the pre-formed catalysts are given in Table 3.1.8. The stereoselectivities are acceptable in general, but not as good as compared to using both triethylborane or 9-OBBN (**142**) and the chiral ligands **27a/b** with a non-cyclised dipeptide as starting material. Interestingly, there was no conversion to any desired product when pre-cat.2 was used with dipeptide **84a** as starting material. The yields for the reactions using the benzylated imidazolium ion **122** in pre-cat.1 are generally higher as compared to using 9-OBBN (**142**). However, the yield for the use of the achiral ligand **24** with triphenylborane and pre-cat.1 is lower than when using triethylborane.

Table 3.1.8: Reverse prenylation reactions of DP **84a** with triphenylborane and the pre-catalysts.*

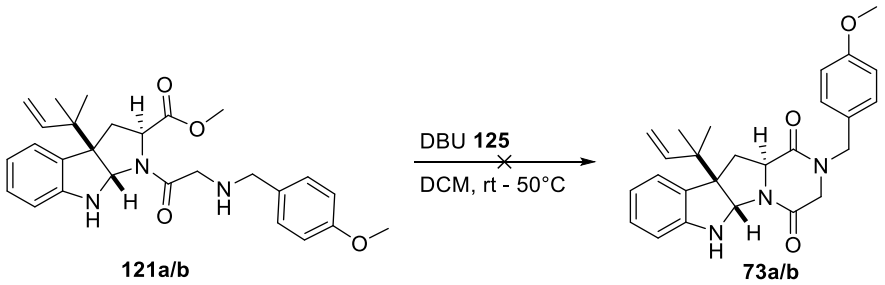


Entry	Ligand	Borane + pre-cat.	d.r. (73a:73b)	Yield	Comment
1	L(AM) **24**	Ph_3B + pre-cat.1	1:1	75%	/
2	L(AM) **24**	Ph_3B + pre-cat.2	/	0%	only intermediate **121a/b** (71%)
3	L(*R*) **27a**	Ph_3B + pre-cat.1	20:1	65%	/
4	L(*R*) **27a**	Ph_3B + pre-cat.2	/	0%	only intermediate **121a/b** (58%)
5	L(*S*) **27b**	Ph_3B + pre-cat.1	1:15	67%	/
6	L(*S*) **27b**	Ph_3B + pre-cat.2	/	0%	only intermediate **121a/b** (63%)

*The yields and selectivities given in this table were determined via ^{1}H-NMR-spectroscopy using *N*-MP as internal reference.

Interestingly, all reactions using the new phenyl substituted pre-cat.2 gave the intermediates **121a/b** exclusively, regardless of the ligand (d.r.=1:1). Additionally, it should be tried to close the open ring of the intermediates **121a/b** (Scheme 3.1.25). As the DKP-ring closure happens automatically during the reverse prenylation reaction in case of the *exo*-configured compounds and when the achiral ligand **24** is used it was believed to be possible to close the ring under basic reaction conditions. DBU (**125**) was chosen as the same base used in the prenylation reaction and the substrate stirred in DCM in the presence of DBU (**125**).

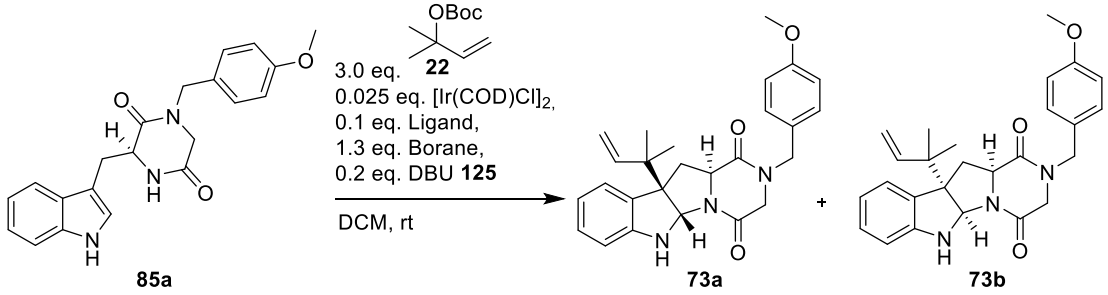
Because no conversion could be observed at room temperature the reaction mixture was then heated to 50 °C. At 50 °C the starting material decomposed so that no cyclised product **73a/b** could be obtained and the reaction could not be retried under acidic condition.



Scheme 3.1.25: Attempted DKP-ring closure of intermediates **121a/b**.

The previously synthesised diketopiperazine **85a** was also submitted to the various reaction conditions of the iridium catalysed reverse prenylation reaction. Table 3.1.9 shows the reactions with triethylborane and 9-OBBN (**142**).

Table 3.1.9: Reverse prenylation reactions of DKP **85a** with triethylborane and 9-OBBN (**142**).



Entry	Ligand	Borane	d.r. (73a:73b)	Yield
1	L(AM) **24**	Et_3B	1:1	99%
2	L(AM) **24**	9-OBBN (**142**)	1:1	48%
3	L(*R*) **27a**	Et_3B	1:2	63%
4	L(*R*) **27a**	9-OBBN (**142**)	1:2	38%
5	L(*S*) **27b**	Et_3B	3:1	52%
6	L(*S*) **27b**	9-OBBN (**142**)	8:1	23%

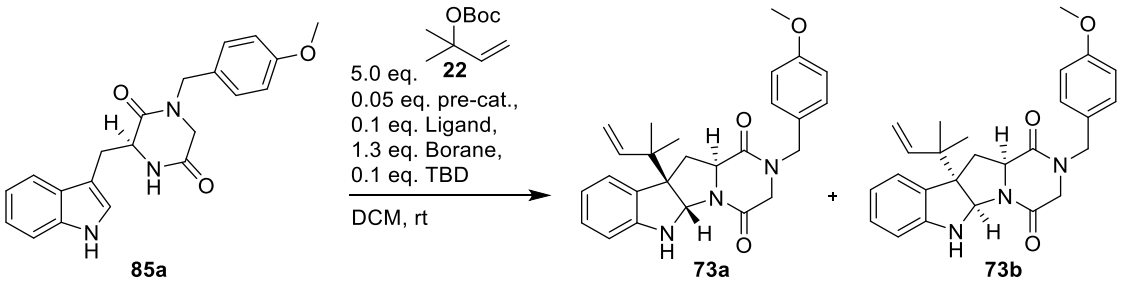
Compared to the test substrate **25a** the stereoselectivities are lower. Due to the formation of the intermediate **121** and the possible formation of D-*exo*-configured product **73c** during the reaction, the selectivities cannot be compared to the ones from dipeptide **84a**. Furthermore, the low stereoselectivity of the reaction with 9-OBBN (**142**) and the (*R*)-configured chiral ligand **27a** shows an irregularity which cannot be explained. This result is particularly curious as the same reaction using the (*S*)-configured ligand **27b** gives a nice selectivity of 8:1 (**73a**:**73b**).

The yields are slightly higher as compared to the yields of the dipeptide **84a**. This can be explained by the lack of formation of intermediate **121**. The yield of the reaction of triethylborane with the achiral ligand **24** is even close to the yields of the test substrate **25a**.

Considering the better yields, the lack of formation of intermediate **121** and that the handling of the substance is also much easier the use of diketopiperazine **85a** is preferable as opposed to the use of dipeptide **84a** in the reverse prenylation reaction when pursuing a total synthesis of a natural product or derivative thereof.

Diketopiperazine **85a** was also subjected to the reverse prenylation reaction conditions with triphenylborane and the pre-catalysts 1 and 2 (Table 3.1.10). The diastereoselectivities are much better when the benzyl substitute imidazolium pre-cat.1 is used. In the case of phenyl substituted pre-cat.2 the selectivities are even worse than with 9-OBBN (**142**).

Table 3.1.10: Reverse prenylation reactions of DKP **85a** with triphenylborane and the pre-catalysts.



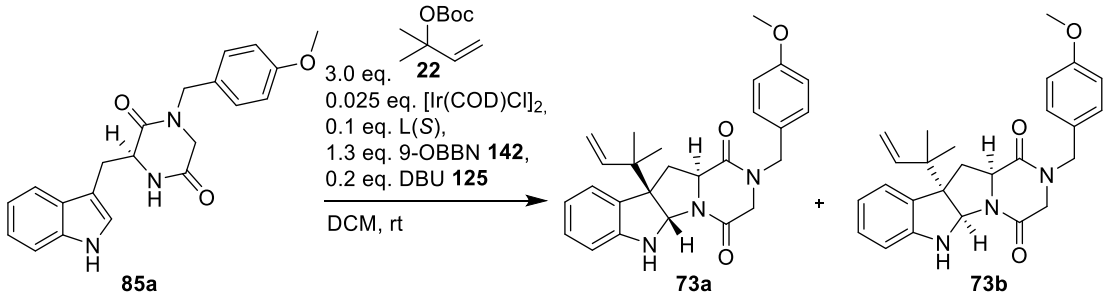
Entry	Ligand	Borane + pre-cat.	d.r. (73a:73b)	Yield
1	L(AM) **24**	Ph_3B + pre-cat.1	1:1	46%
2	L(AM) **24**	Ph_3B + pre-cat.2	1:1	65%
3	L(*R*) **27a**	Ph_3B + pre-cat.1	20:1	19%
4	L(*R*) **27a**	Ph_3B + pre-cat.2	4:1	78%
5	L(*S*) **27b**	Ph_3B + pre-cat.1	1:15	67%
6	L(*S*) **27b**	Ph_3B + pre-cat.2	1:5	65%

The yields are generally higher than when using 9-OBBN (**142**) and a chiral ligand. The exception is again a reaction of the (*R*)-configured ligand **27a**, this time with pre-cat.1. Compared to the test substrate **25a** from the original publication the yields are slightly lower.[4]

Overall, the stereoselectivities and yields seem to be best when triphenylborane is used together with pre-cat.1 and the already closed diketopiperazine **85a** as substrate. In the context of a natural product synthesis this would be the best method to choose. However, if the stereoselectivity outcome of the reaction does not matter triethylborane in combination with the achiral ligand leads to a nearly quantitative yield regardless of the substrate.

The scalability of the reverse prenylation reaction should also be tested. As test system diketopiperazine **85a** as substrate with chiral ligand **27b** and 9-OBBN (**142**) as borane were chosen. A range of 0.1 mmol to 5.0 mmol were tested and the results are given in Table 3.1.11.

Table 3.1.11: Upscale of the reverse prenylation reaction with DKP **85a** as substrate.



Entry	Scale [mmol]	d.r. (73a:73b)	Yield	Comment
1	0.1	2:1	15%	/
2	0.2	9:1	32%	/
3	0.5	9:1	35%	/
4	1.0	7:1	18%	/
5	2.0	4:1	20%	/
6	5.0	5:1	25%	unknown side product

The reverse prenylation reaction worked best with scales of 0.2 and 0.5 mmol of starting material. A lower amount of 0.1 mmol and higher amounts led to decreasing yields and also decreasing stereoselectivities. The use of 5.0 mmol of diketopiperazine **85a** even led to the formation of an unknown side product, which decreases the amount of recoverable starting material.

3.2 Inversion of *endo*- to *exo*-prenylated compounds

During the studies of the *C*-alkylation reactions on reverse prenylated hexahydropyrrolo[2,3-*b*]indole compounds described in Section 3.1.2.2 an interesting discovery was made. The shifts of the peaks in the ^{1}H-NMR-spectrum of the reisolated starting material, when *L-endo*-compound **73b** was used, matched the ones of the *L-exo*-compound **73a**. As an inversion of the *L-endo*- **73b** to the *L-exo*-isomer **73a** under basic conditions was found very unlikely, it was assumed that rather the *L-endo*-compound **73b** inverts to the *D-exo*-compound **73c** during this reaction. This is demonstrated in Figure 3.2.1 along with a thin layer chromatography (TLC) plate of an alkylation reaction, on which the formation of the new and also slightly differently coloured spot of the putative corresponding diastereoisomer is visible.

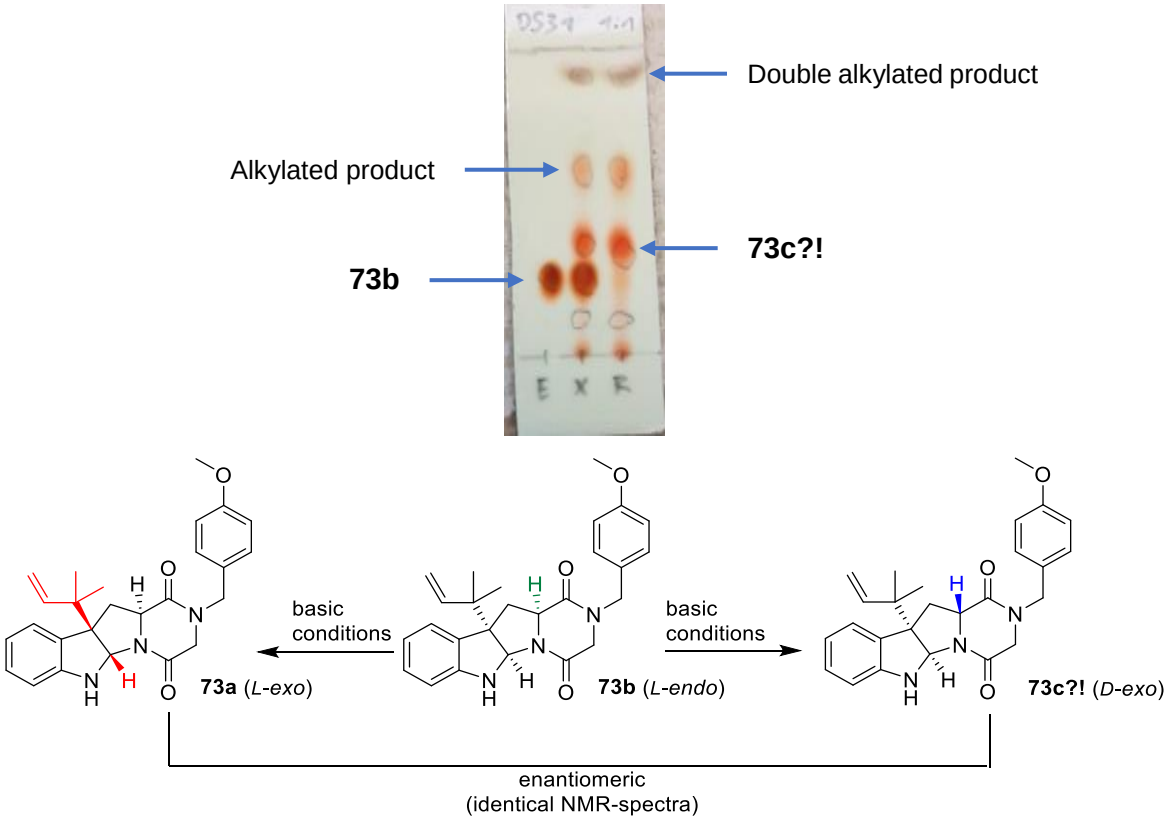


Figure 3.2.1: TLC-plate of an alkylation reaction with *L-endo*-compound **73b** and possible inversions of the same compound.

Together with the comparison of the ^{1}H-NMR-spectra this was an indication of the inversion of reverse prenylated *endo*-compounds to their corresponding *exo*-isomers under basic reaction conditions. Additionally, Kawasaki *et al*. had described a similar inversion during their synthesis of fructigenine A (**4a**) in 2009 using sodium hydroxide as base (Scheme 1.1.11).

3.2.1 Confirmation and further studies on the inversion of *endo*- to *exo*- prenylated compounds

To verify the assumption that the reverse prenylated *endo*-configured compounds invert into their *exo*-configured counterpart under basic reaction conditions several experiments were performed.

To determine at which positions of the molecule the base attacks during the alkylation reaction a reaction was performed in which the *L*-*exo*-compound **73a** was stirred with 1.1 eq. of LHMDS (the same base and amount previously used during the alkylation reactions) but without an alkylating reagent. After stirring over night at room temperature the reaction mixture was quenched with deuterated methanol. In this way it was not only possible to see which sites of the molecule the base attacked at, but also allows for quantification through ^{1}H-NMR-analysis. For this first study the *L*-*exo*-compound **73a** was used because the resulting ^{1}H-NMR-spectrum of a partly occurred, not yet confirmed, inversion might have been more difficult to analyse.

Figure 3.2.2 shows an excerpt of the ^{1}H-NMR-spectrum of the previously described experiment, in which the positions of the molecule attacked by the base are highlighted.

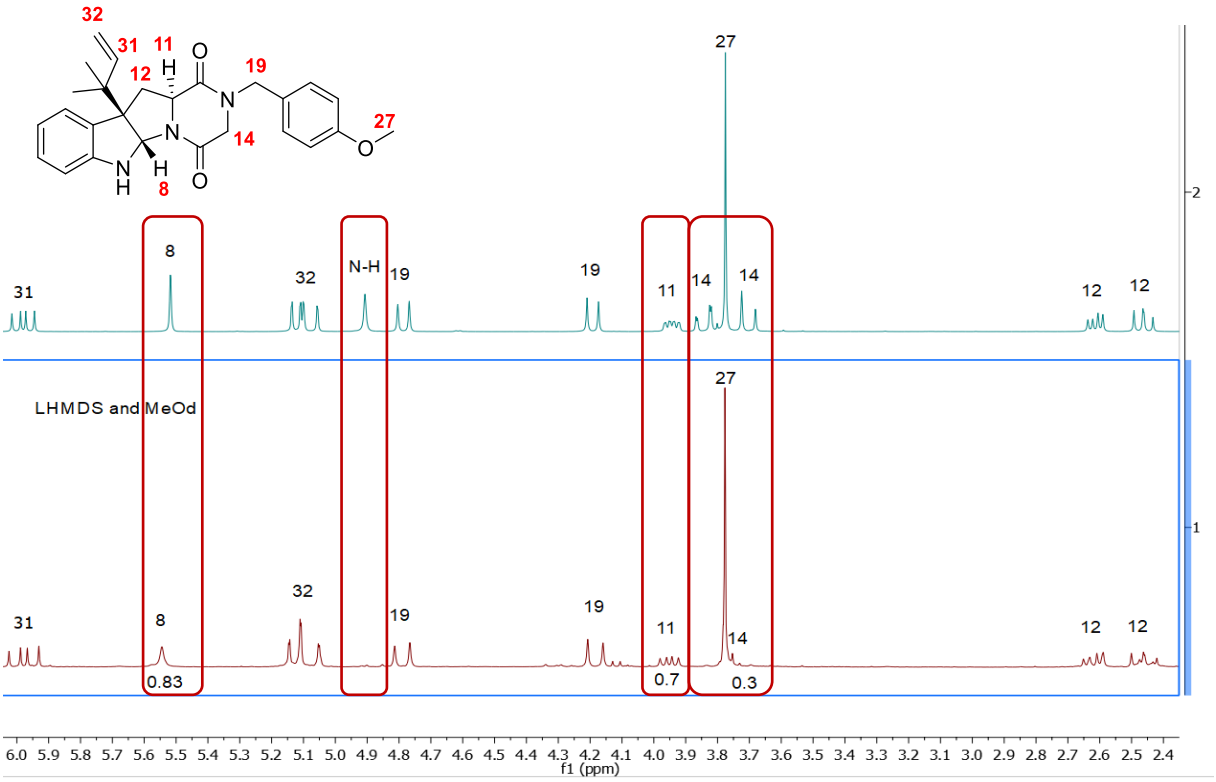
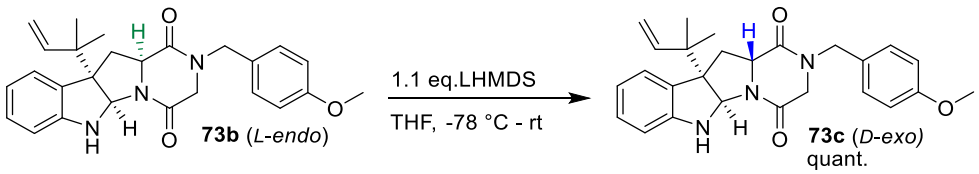


Figure 3.2.2: Comparison of excerpts of the ^{1}H-NMR-spectrum of *L*-*exo*-compound **73a** before and after the deprotonation quenched with deuterated methanol.

It could be determined that the proton-deuterium-exchange happens at four different sites of the molecule according to their acidity. The amino proton of the former indole unit, as well as the protons of the methylene group of the DKP-ring, were almost completely substituted with deuterium. This is in accordance with the results of the previously performed alkylation reactions giving both the desired single and also the double alkylated products (Section 3.1.2.2). The proton at the aminal carbon atom and the one at C-11 are both exchanged with 20% and 30% respectively as well. This is shows that the inversion at the C-11 position is possible.

L-*endo*-Compound **73b** was also submitted to basic reaction conditions (1.1 eq. of LHMDS) without quenching it with deuterated methanol in order to find out to which extend the *L*- to *D*- inversion takes place (Scheme 3.2.1).



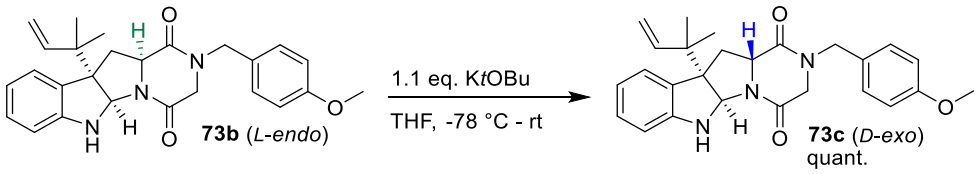
Scheme 3.2.1: Inversion of *L*-*endo*-compound **73b** to *D*-*exo*-compound **73c**.

Gratifyingly, the yield of the reaction was quantitative so that a complete conversion from *L*-*endo*-compound **73b** to the apparently thermodynamically more stable *D*-*exo*-compound **73c** was achieved.

To fully determine that the isolated product really is compound **73c** it had to be compared to compound **73c** received through synthesis starting from *D*-tryptophan (**75b**). The NMR-spectra as well as the optical rotation of both compounds were evaluated. This and further syntheses are described in Section 3.2.2. Thus, it could be established that the inversion from compound **73b** to compound **73c** did take place in this reaction.

During the studies on the substitution with deuterium it became clear that a larger amount of protons were removed from the molecule than stoichiometrically possible. This means that the inversion could possibly work with catalytic amounts of base.

Additionally, the inversion should also be traced by ^{1}H-NMR-spectroscopy. To this end, a base that does not contain protons which might interfere with the substrate signals needed to be chosen. Potassium *tert*-butoxide was chosen and first submitted to the standard reaction conditions to see whether the inversion takes place in general. The quantitative inversion using potassium *tert*-butoxide as base is shown in Scheme 3.2.2.



Scheme 3.2.2: Inversion with 1.1 eq. of potassium *tert*-butoxide as base.

In order to find out which base is more potent for the inversion of compound **73b** to compound **73c** an experiment was set up in which 0.1 eq. of either LHMDS and potassium *tert*-butoxide were employed. The conversion of both reactions was determined after stirring for 48 hours at room temperature. In the case of LHMDS as base 19% of the inverted product **73c** were obtained, whereas when using the same amount of potassium *tert*-butoxide 32% of compound **73b** were obtained. Both are strong non-nucleophilic bases with LHMDS being the slightly stronger base of the two. However, the better yields using potassium *tert*-butoxide might stem from the sizes of the molecules as LHDMS is much bigger and might be more sterically hindered to attack at the stereocentre. Additionally, the acidity of the tertiary amide proton is lower than that of the methylene group of the DKP-ring, as can be observed by the quantity of the proton-deuterium-exchange in the ^{1}H-NMR-spectrum (Figure 3.2.2).

Then the ^{1}H-NMR-experiment was set up using potassium *tert*-butoxide as base in deuterated THF as solvent. As part of this investigation it was also envisaged to find out how much potassium *tert*-butoxide would be needed to get full conversion of the *endo*- to the corresponding *exo*-compound.

In Figure 3.2.3 an excerpt of the ^{1}H-NMR-spectra is shown following the inversion from *L-endo*-compound **73b** to *D-exo*-compound **73c**. The inversion of the protons 8 and 24 can be followed easiest and are marked in the spectrum. Each addition of another 0.1 eq. of potassium *tert*-butoxide is depicted, as well as the according time the reaction had been running (after the last addition of potassium *tert*-butoxide) when the spectra were recorded.

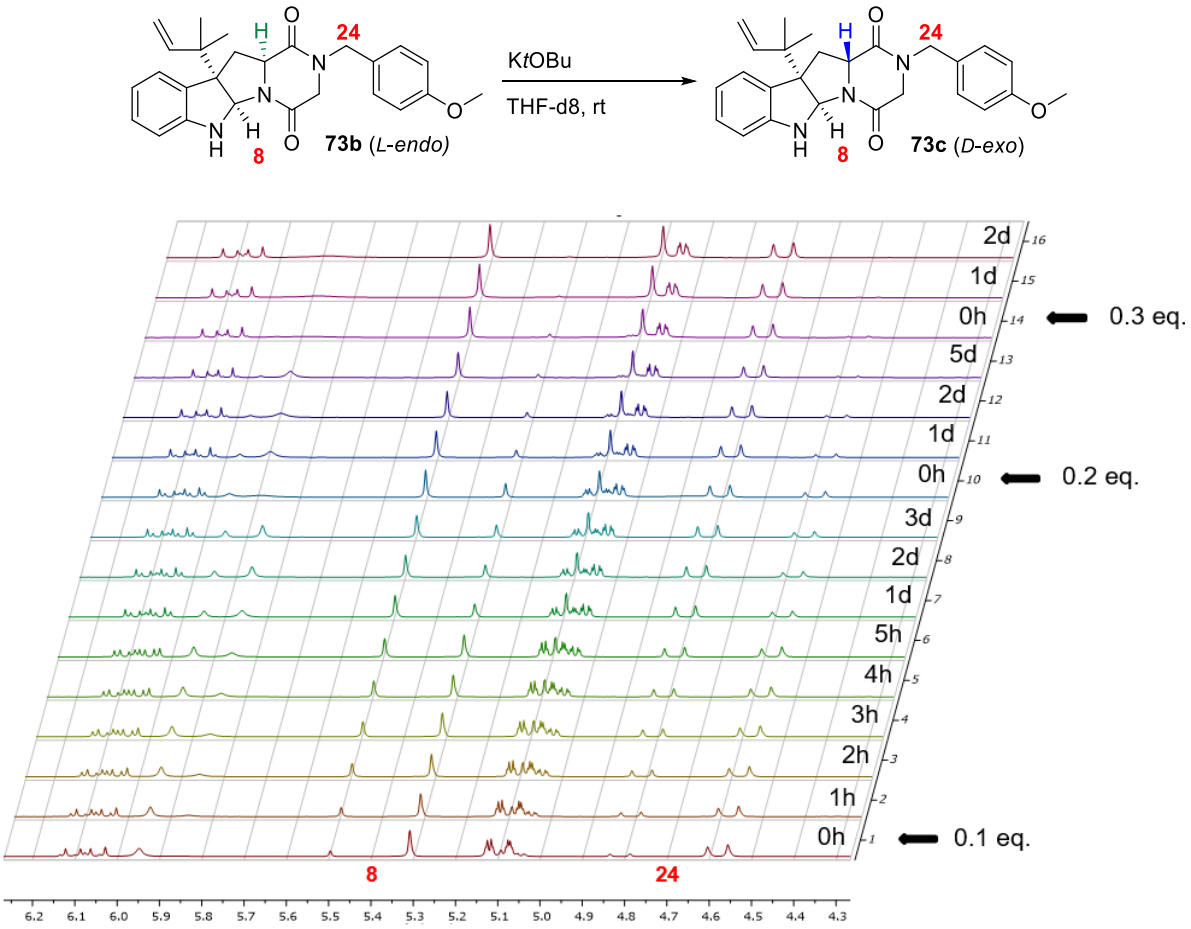
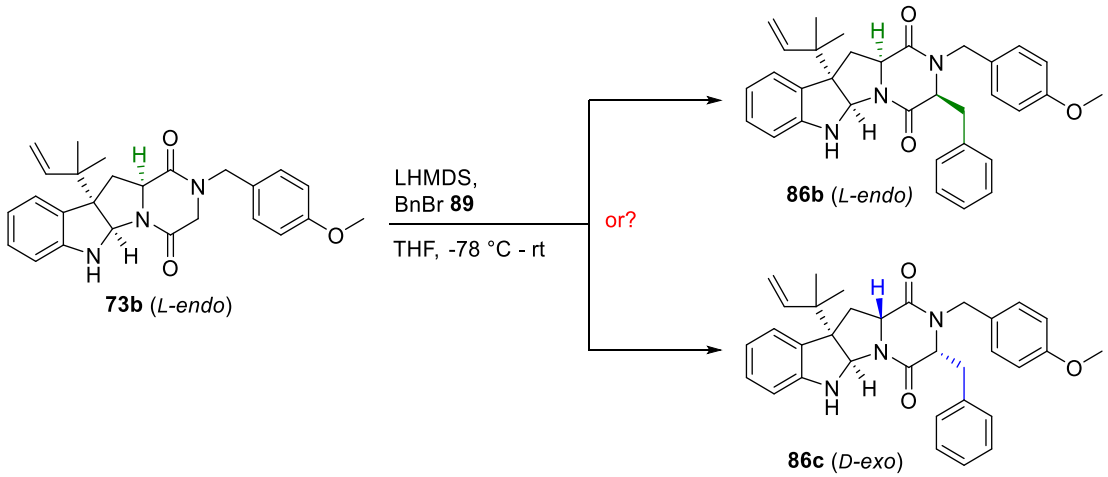


Figure 3.2.3: Tracing of the conversion from *L-endo* **73b** to *D-exo* **73c** using ^{1}H-NMR spectroscopy.

It is apparent that the inversion was nearly complete after the addition of 0.2 eq. of potassium *tert*-butoxide and a reaction time of more than two days after the second addition. Full conversion could then be observed after the addition of another 0.1 eq. of base and another day of reaction time. Stagnation of the inversion could generally be observed after about three days of reaction time following each addition of 0.1 eq. of base.

The next question that arose from these findings was the configuration of the products of the *C*-alkylation reactions studied in Section 3.1.2.2, where *L-endo*-compound **73b** was used as starting material. Two possible outcomes were conceivable depending on the speed of the alkylation reaction, or rather the deprotonation by the base at the methylene group of the DKP-ring, compared to the speed of the inversion.

In Scheme 3.2.3 the two possible outcomes of the alkylation of *L-endo*-compound **73b** are shown. In this Scheme the alkylation using benzyl bromide (**89**) as reagent was chosen to demonstrate the possible products of the reaction.



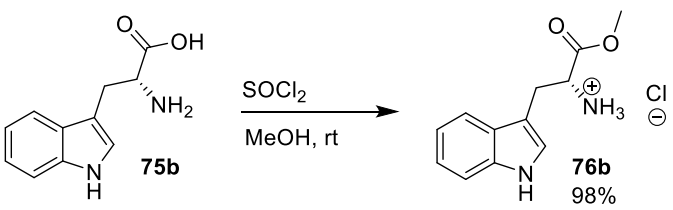
Scheme 3.2.3: Possible outcomes of the benzylation of *L-endo*-compound **73b** depending on the speed of the alkylation *vs*. the inversion.

As described in Sections 1.2.2 and 3.1.2.2 the benzyl group will always be directed in *1,4-syn*-configuration to the ring system on the opposite side. If the attack of the base at the methylene group of the DKP-ring and the subsequent alkylation should happen faster than the inversion the *L-endo*-configured compound **86b** would occur. If, however, the inversion would happen faster than the deprotonation and subsequent alkylation at the methylene group of the DKP-ring the *D-exo*-configured compound **86c** with the benzyl group pointing to the back would be obtained.

3.2.2 Comparison of the alkylated compounds derived from *D*-tryptophan (75b)

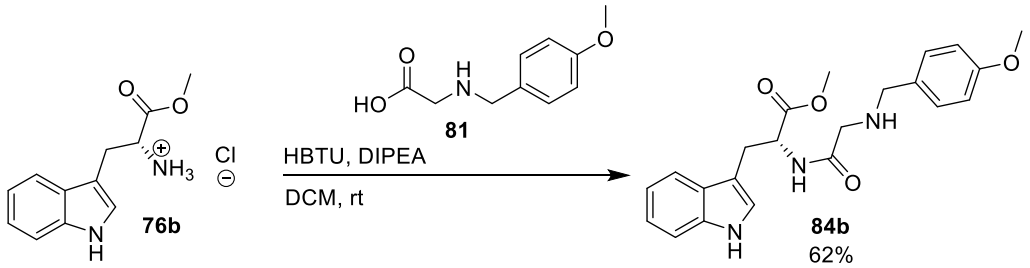
In order to find out whether or not the inversion of the stereocentre of an *endo*-configured substrate happens faster than the *C*-alkylation reaction at the DKP-ring an alkylated compound containing the *D*-configuration needed to be synthesised from scratch. The alkyl group chosen for this reaction sequence was the benzyl group so that the *D-exo*-benzylated substrate **86c** could afterwards be compared to the product of an alkylation of the *L-endo*-prenylated compound **73b** with benzyl bromide (**89**).

For the first step of this reaction sequence the acid function of *D*-tryptophan (**75b**) was protected by esterification with thionyl chloride in methanol (Scheme 3.2.4).[79] This gave *D*-tryptophan methyl ester hydrochloride (**76b**) with a nearly quantitative yield of 98%.



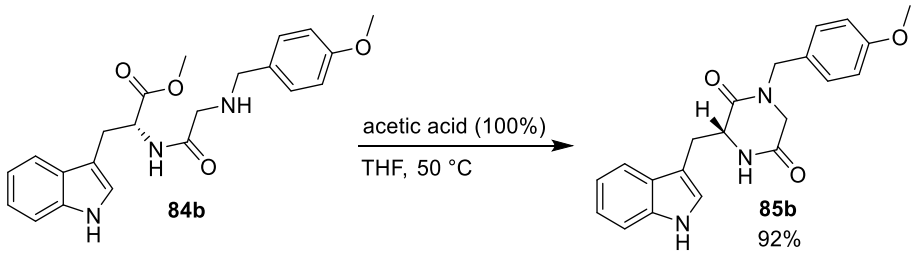
Scheme 3.2.4: Esterification of *D*-tryptophan (**75b**) with thionyl chloride.

Afterwards, the previously synthesised PMB-protected glycine derivative **81** (Section 3.1.2.1) was coupled with *D*-tryptophan derivative **76b** to form dipeptide **84b** with an unoptimised yield of 62% (Scheme 3.2.5).[80,81,85]



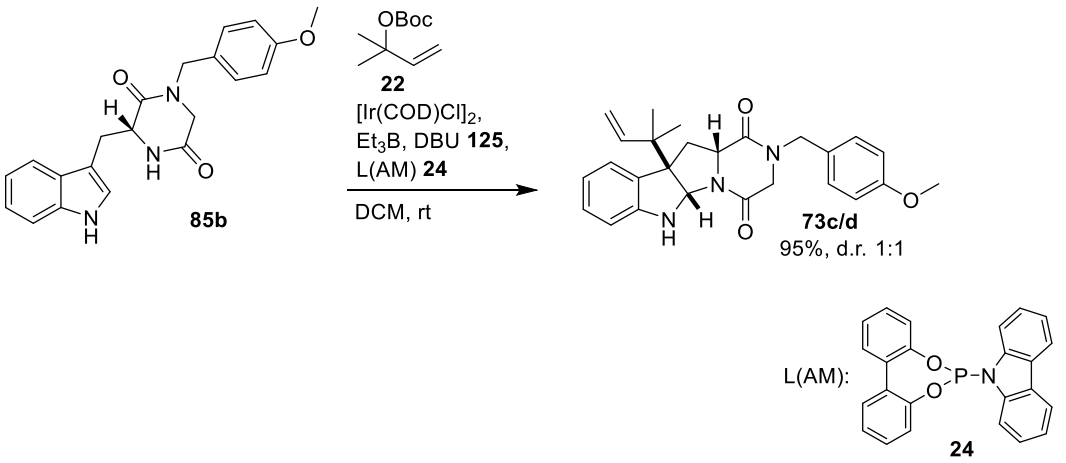
Scheme 3.2.5: Peptide coupling of *D*-tryptophan methyl ester hydrochloride **76b** with PMB-protected glycine **81**.

The following ring closure to diketopiperazine **85b** worked very well again with a yield of 92% through the acetic acid catalysed condensation reaction (Scheme 3.2.6).[86]



Scheme 3.2.6: Ring closure of dipeptide **84b** to the diketopiperazine **85b**.

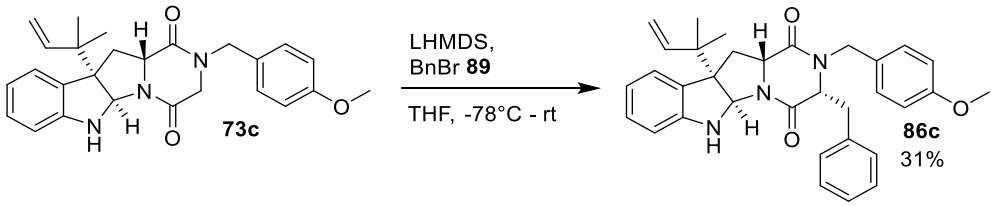
In Scheme 3.2.7 the iridium catalysed reverse prenylation reaction to the non-natural PMB-protected, *D*-configured core structures **73c/d** is shown. As the goal of this reaction sequence was the formation of just enough substance to do the alkylation reaction on a *D*-configured compound, no prenylation reactions of compound **85b** were performed with regard to the different ligands or boranes.[4] A yield of 95% and a diastereomeric ratio of 1:1 for this reaction demonstrated that the *D*-configured compounds behave as the enantiomeric series, whose extensive studies are described in Section 3.1.4.



Scheme 3.2.7: Achiral reverse prenylation reaction of diketopiperazine **85b**.

Though not many reverse prenylated natural products containing the *D*-configuration are known, the successful synthesis of compounds **73c/d** provides a first access towards them *via* an iridium catalysed reverse prenylation reaction. Further studies would be needed in order to prove that this can also be performed diastereoselectively using the protocol developed in the Stark group as well.[4] Interestingly, the applicability of the inversion of the *endo*- to the *exo*-compounds might immediately render this access useless as a route starting from the more common and therefore much cheaper *L*-tryptophan (**75a**) would be more desirable.

The last step towards the synthesis of compound **86c**, needed for the comparison with the *L*-*endo*-alkylated substrate, was the *C*-alkylation reaction with benzyl bromide (**89**) (Scheme 3.2.8).[76]

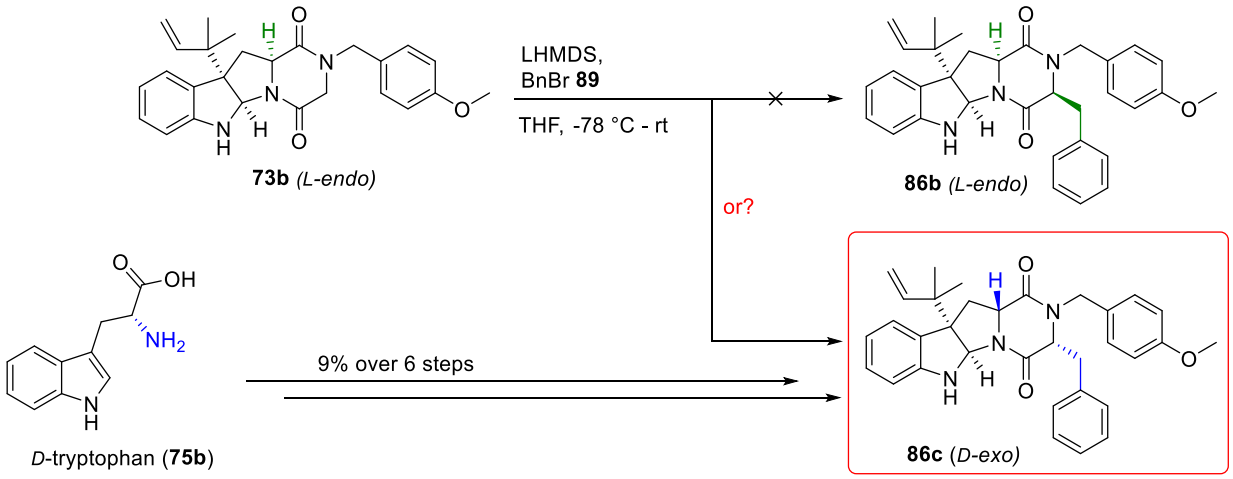


Scheme 3.2.8: Alkylation reaction of the *D*-*exo,* PMB-protected core structure **73c** with benzyl bromide (**89**).

The *C*-alkylation reaction was performed with a yield of 31% of the desired product **73c**.

In the end the *D*-tryptophan (**75b**) derived, benzylated, compound **86c**, which shows the *exo*-configuration, was synthesised with an overall yield of 9% over six reaction steps.

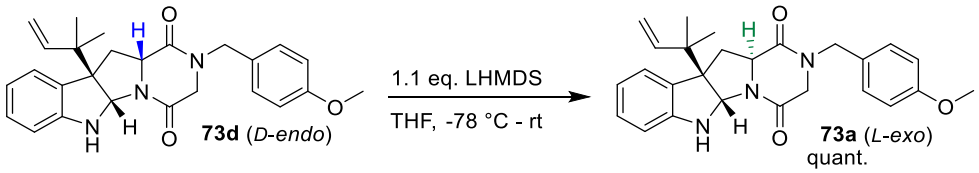
The comparison of the ^{1}H-NMR-spectra of the benzylated compound **86a** and of the product from the benzylation of **73b** shows that the inversion is in fact faster than the deprotonation at the methylene group and subsequent alkylation of compound **73b** to **86b**. This is depicted in Scheme 3.2.9. Formation of compound **86b** could not be observed at all, whereas the spectra of compounds **86a** and **86c** were identical, even in the shifts of the peaks, which verifies that both compounds have *exo*-configuration. The optical rotation of the obtained compounds further undermined the formation of *D-exo*-configured compound **86c**, as the values of both *exo*-configured, benzylated compounds **86a** and **86c** are nearly identical but with opposite signs (plus or minus). With a concentration of 0.50 g/100 mL in chloroform *L-exo*-configured compound **86a** shows a rotation value of -191°, whereas *D-exo*-configured compound **86c** shows a rotation value of +198° at the same concentration and in the same solvent.



Scheme 3.2.9: Outcome of the comparison of the speed of the alkylation reaction starting from *L-endo*-derived compound **73b**.

This outcome suggests that the products of all *C*-alkylation reactions, in which *L-endo*-derived compound **73b** was used as starting material, show *D-exo*-configuration.

With *D-endo*-compound **73d** in hand the reciprocal conversion to the *L-exo*-compound **73a** was also tested (Scheme 3.2.10).

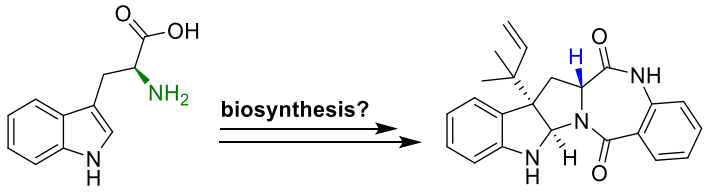


Scheme 3.2.10: Inversion of *D-endo*-compound **73d** to *L-exo*-compound **73a**.

This inversion worked as well as the reciprocal one, further demonstrating that the *exo*-compounds of reverse prenylated hexahydropyrrolo[2,3-*b*]indoles are thermodynamically more stable than their corresponding *endo*-isomers in general. This is in accordance with the understanding that the reaction only takes place in one direction. An inversion from an *exo*- to an *endo*-compound has never been observed. This means that a *D*-*endo*-configured compound cannot be realised starting from a more available *L*-*exo*-configured starting material. However, to the best of our knowledge, no reverse prenylated hexahydropyrrolo[2,3-*b*]indole natural product containing *D*-*endo*-configuration exists.[10,11]

3.2.3 A new biomimetic approach towards *D*-configured natural products?

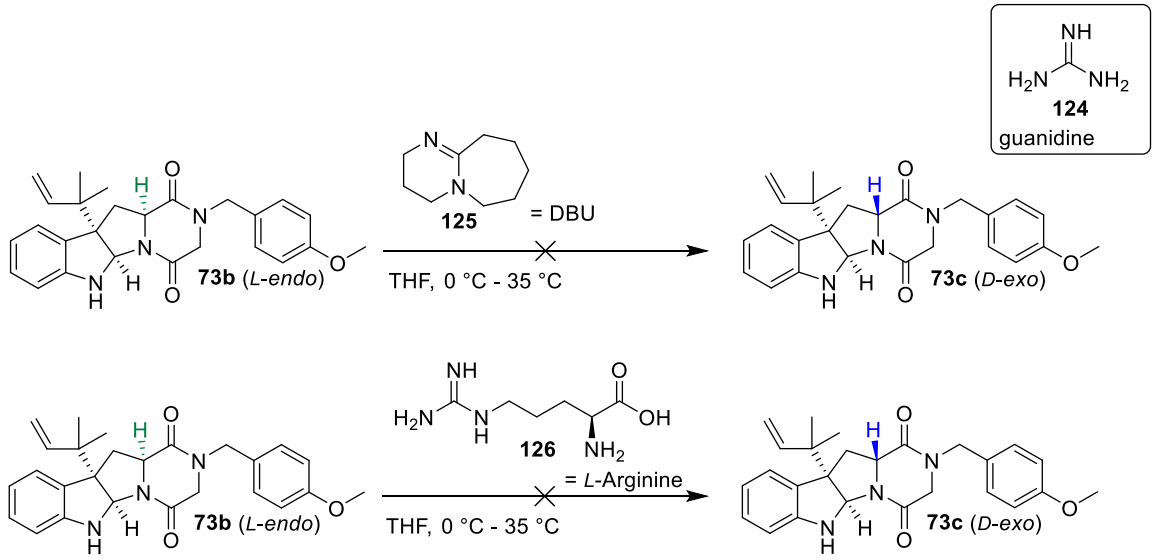
The discovery of the inversion from *L*-*endo*- to *D*-*exo*-compounds is not only interesting for the development of new total syntheses of *D*-tryptophan (**75b**) derived natural products. It might also suggest that nature does the same inversion in the biosynthesis of these molecules. This would mean that *D*-tryptophan (**75b**) would not be necessary for the biosynthesis of reverse prenylated hexahydropyrrolo[2,3-*b*]indole natural products at all, but that, no matter what the configuration of the desired product is, the *L*-form of the amino acid is always the starting material (Scheme 3.2.11).



L-tryptophan (**75a**) aszonalenine (**3**)

Scheme 3.2.11: Possible connection between *L*-tryptophan (**75a**) as starting material for the synthesis of a *D*-configured natural product.

To further establish this theory it was decided to study the inversion from **73b** to **73c** with the help of a more biomimetic base (Scheme 3.2.12). DBU **125** as an amidine base and *L*-arginine **126** as a similar compound to the base guanidine **124** were tried.[105]



Scheme 3.2.12: Attempted, more biomimetic inversion of the stereocentre.

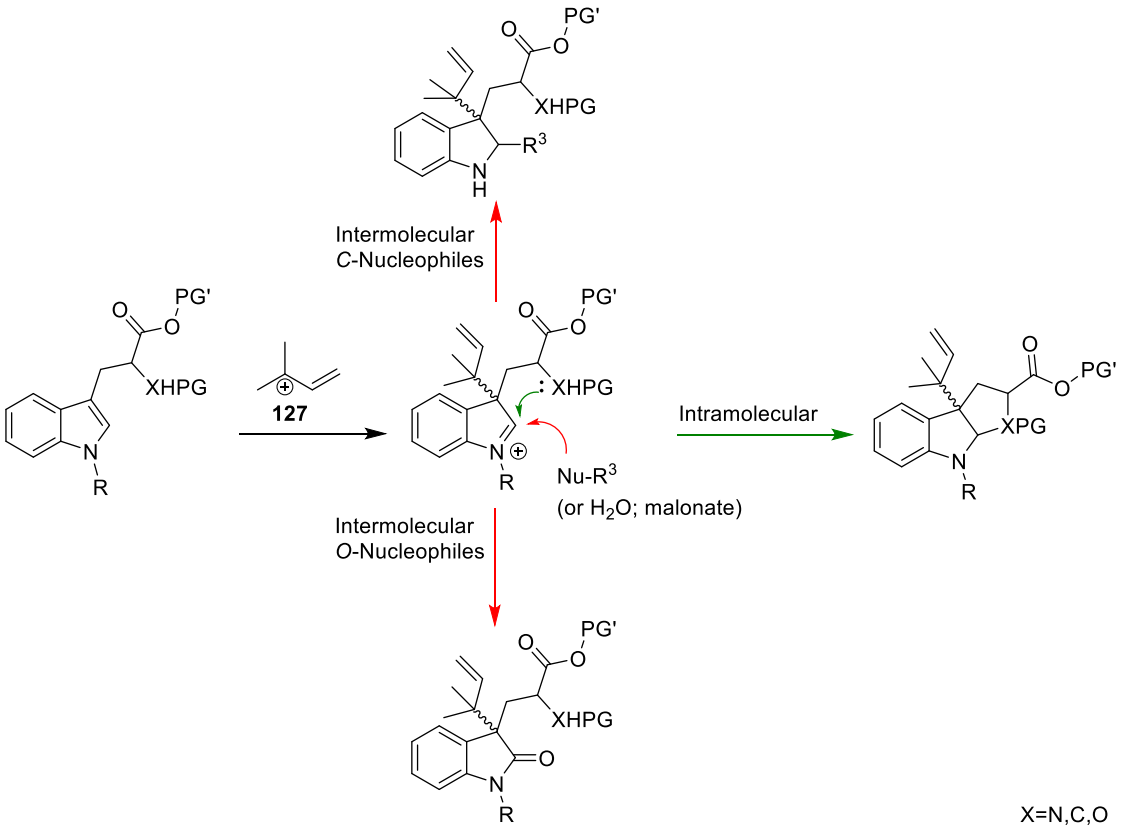
However, there was no conversion to the desired *D-exo*-compound **73c** in both cases. Even by raising the reaction temperature to 35 °C, which is still a temperature common in biological environments, no formation of **73c** could be observed. This does not mean that the biosynthesis does not happen *via* this pathway, as a specific spatial arrangement with the correct corresponding functional groups might additionally be needed to catalyse the inversion. But, unfortunately, the concept could not be established further during the work on this thesis.

3.3 Synthesis of notoamide derivatives

3.3.1 Variation of the nucleophile during the reverse prenylation reaction

In order to show the broad applicability of the iridium catalysed reverse prenylation reaction the second part of this thesis focused on applications of this method to form structurally different derivatives of natural products.

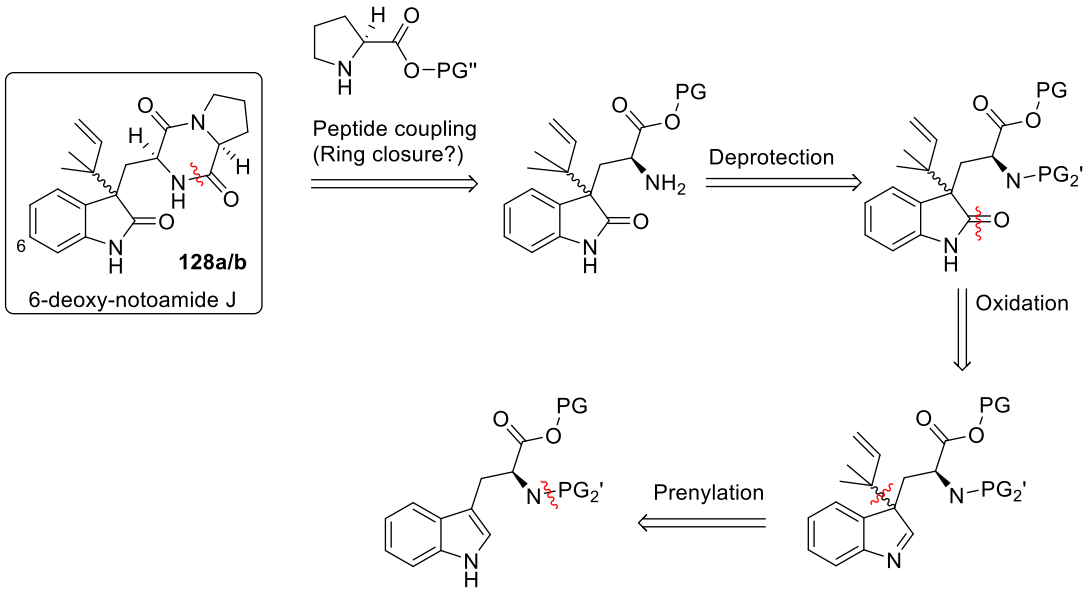
Scheme 3.3.1 gives an overview how the use of different nucleophiles can lead to a variety of reverse prenylated compounds. Depending on the starting material, a diversification through a different intramolecular nucleophilic attack may be possible. Additionally, the use of different nucleophiles (N, C, O), as additional reagents in this reaction, can lead to a broad range of C2-substituted molecules as well.



Scheme 3.3.1: Overview over possible variations of the nucleophile during the iridium catalysed reverse prenylation reaction.

The specific aim of the present work was to study whether *O*-nucleophiles can be employed intermolecularly on the imines formed during the reverse prenylation reaction developed in the Stark group in order to give access to the synthesis of a different class of reverse prenylated natural products. Therefore, a derivative of the notoamide family (Section 1.1.3.4) should be synthesised during the work on this thesis. The retrosynthetic analysis for a synthesis of 6-deoxy-notoamide J (**128a**) or its corresponding epimer **128b**, which is a derivative of notoamide C (**8a**), is shown in Scheme 3.3.2.

Deprotection of the amino function and peptide coupling with a proline derivative should give one of the desired notoamide derivatives **128a/b** or an open chained version of the molecule, which lastly would have to be cyclised to form the desired products **128a/b**. Preceding this would be the oxidation of the imine to give the desired reverse prenylated oxindole or lactim derivative. The imine is resulting from the iridium catalysed reverse prenylation reaction of a protected *L*-tryptophan derivative. It is important that the primary amino function of *L*-tryptophan (**75a**) is adequately protected so that the ring closure during the reverse prenylation reaction would be prevented. The total synthesis should start with the protection of the acid function of *L*-tryptophan (**75a**).

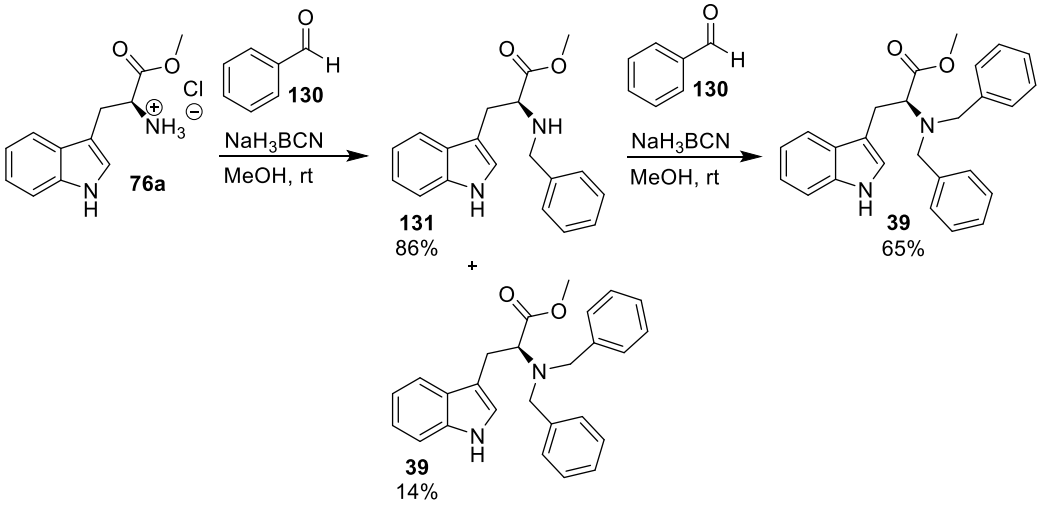


Scheme 3.3.2: Retrosynthetic analysis for the synthesis of notoamide derivatives.

3.3.2 Total synthesis of derivatives of the notoamide family

In the total synthesis of the notoamide derivatives the first step of the reaction sequence was also the esterification of *L*-tryptophan (**75a**) as described in Section 3.1.1.1.

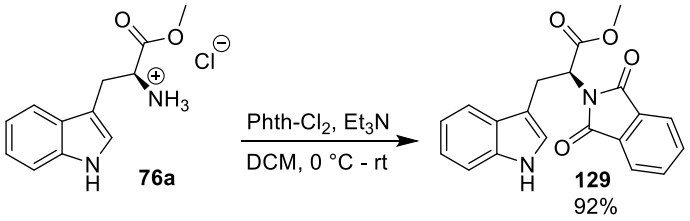
Then the protection of the amino group of *L*-tryptophan methyl ester hydrochloride (**76a**) followed. For the desired formation of the imine moiety during the reverse prenylation reaction the chosen protecting group needed to render a non-nucleophilic nitrogen atom. Therefore, a common Boc- or Fmoc-protecting group could not be chosen and double benzyl protected *L*-tryptophan methyl ester **39** was synthesised.[106]



Scheme 3.3.4: Double benzyl protection of *L*-tryptophan methyl ester hydrochloride (**76a**).

Scheme 3.3.4 shows the benzyl protection with sodium cyanoborohydride and benzaldehyde (**130**). The mechanism behind this is that of the reductive amination, while sodium cyanoborohydride is a comparatively mild reduction agent.[107,108] It was believed that an excess of base and alkylating agent, along with a longer reaction time, would lead to the formation of double alkylated product. However, the protection did not work as well as expected. The major product isolated from the reaction was the single benzylated compound **131** with a yield of 86%. The starting material **76a** was fully converted and the desired product obtained with a yield of only 14%. In order to get more double protected material **39** the single protected compound **130** was submitted to the same reaction conditions again. This gave the desired product **39** with a yield of 65%.

Such low conversions and yields to the desired product, already in the second step of the planned route, was not desirable for a total synthesis. Therefore, it was decided that the route should be pursued with the phthalimide (phth) protected substrate **129** instead, although the removal of the phthalimide group does not always work well (Scheme 3.3.3).[109]

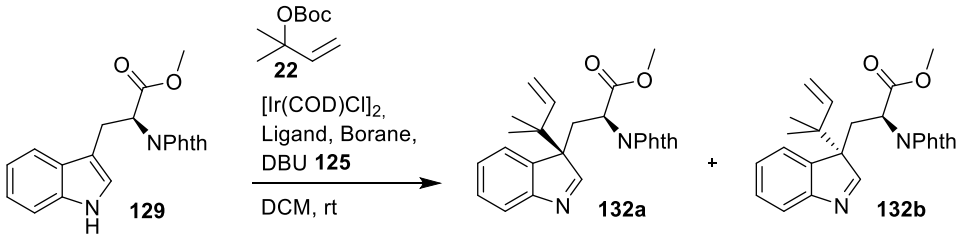


Scheme 3.3.3: Phthalimide protection of L-tryptophan methyl ester hydrochloride (**76a**).

This reaction worked very well with a yield of 92%.

The results of the reverse prenylation reactions of compound **129** are given in Table 3.3.1. The reaction was performed with both chiral ligands **27a** and **27b** and worked with moderate yields and diastereoselectivities.[4]

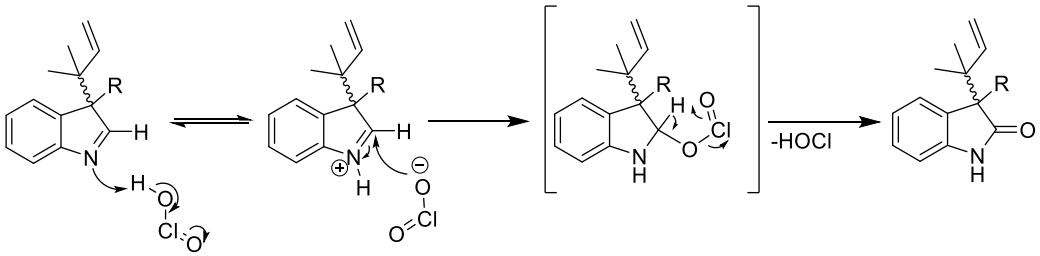
Table 3.3.1: Reverse prenylation reactions for the formation of the imines **132a/b**.



Entry	Ligand	Borane	d.r. (132a:132b)	Yield
1	L(*R*) **27a**	9-OBBN (**142**)	1:3	40%
2	L(*S*) **27b**	9-OBBN (**142**)	6:1	61%

The obtained imine compounds **132a** and **132b** turned out to be very unstable and needed to be handled with great care. Decomposition of the material started almost immediately at room temperature. Although this rendered the analysis of the obtained compounds and of their stereoselective ratios quite difficult the outcome is according to the expectations. The *anti*-configured compound **132b** was obtained in lower yields and selectivities, which might be explained through a lower thermodynamic stability of this compound or a matched/mismatched effect during the reverse prenylation reaction.

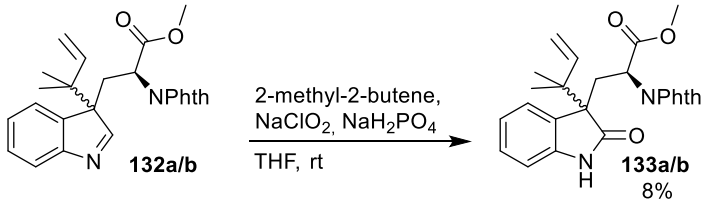
The next step in the reaction sequence was the oxidation to the oxindole compounds **133a/b**. The Pinnick oxidation was chosen for this purpose. It is mostly known for the oxidation of aldehydes to their corresponding carboxylic acids, but the transformation of imines to amides should work as well.[110] The mechanism of a Pinnick reaction at a reverse prenylated imine system is shown in Scheme 3.3.5.[111]



Scheme 3.3.5: Mechanism of the Pinnick oxidation of a reverse prenylated imine compound.[111]

Before the reaction takes place at the imine function the active oxidant chlorous acid is formed from chlorite under acidic conditions. Afterwards, the chlorous acid adds to the imine followed by a concerted fragmentation giving the desired oxindole compound. During this hypochlorous acid is formed by transferral of the *α*-hydrogen atom of the imine on to the chloride.

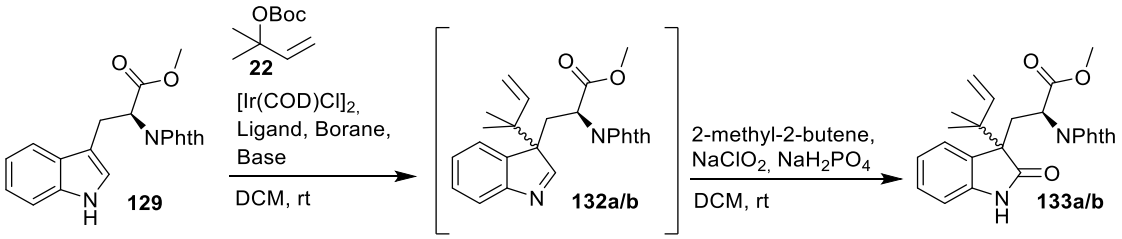
Scheme 3.3.6 shows the Pinnick oxidation to oxindoles **133a/b**. Only a yield of 8% for the oxidised compounds **133a/b** could be obtained. This may be because of the instability of the starting materials **132a/b**.



Scheme 3.3.6: Pinnick oxidation of imines **132a/b**.

Because of the low yields of the Pinnick oxidation described above, it was attempted to perform the reverse prenylation reaction and the Pinnick oxidation as a one-pot reaction. For this purpose the Pinnick reagents were simply added to the reaction mixture after no further conversion of the reverse prenylation reaction was detectable. The results of these reactions are listed in Table 3.3.2.

Table 3.3.2: One-pot prenylation and oxidation of phthalimide protected *L*-tryptophan methyl ester **129**.



Entry	Ligand	Borane	Base	d.r. (133a:133b)	Yield
1	L(AM) **24**	Et_3B	DBU **125**	2:1	82%
2	L(*R*) **27a**	9-OBBN (**142**)	DBU **125**	1:2	87%
3	L(*S*) **27b**	9-OBBN (**142**)	DBU **125**	3:1	89%
4	L(*R*) **27a**	Ph_3B + pre-cat.1	TBD	1:6	32%
5	L(*S*) **27b**	Ph_3B + pre-cat.1	TBD	7:1	38%

In general, the one-pot reverse prenylation and Pinnick oxidation reactions worked quite well. The yields for the reactions using triethylborane or 9-OBBN (**142**) are very good. However, the yields in case of triphenylborane with pre-cat.1 are relatively low but the stereoselectivity outcomes are better than when using 9-OBBN (**142**). Interestingly, the use of triethylborane and the achiral ligand **24** did not give the 1:1 diastereomeric mixture of compounds **133a/b**. Furthermore, did the reported “boron-switch” of the stereoselectivities when using the same ligand and substrate but a different achiral borane not take place for substrate **129**. This might be the case because of the lower rigidity of substrate **129** as compared to e.g. DKP **85a**.

An excess of the *syn*-configured compound **133a** was formed, which indicates that this might be the thermodynamically more favoured configuration for reverse prenylated oxindoles and that they are synthesised *via* substrate controlled pathways in nature as well. Furthermore, can a slight matched/mismatched effect be observed during the one-pot prenylation-oxidation reaction described in Table 3.3.2, which is another possible reason for the excess of *syn*-isomer **133a** in these reactions.

The exact stereochemistry of the reverse prenylated and oxidised compounds was determined as a crystal structure of the *syn*-configured compound **133a** could be obtained. The crystal structure and the corresponding compound are depicted in Figure 3.3.1.

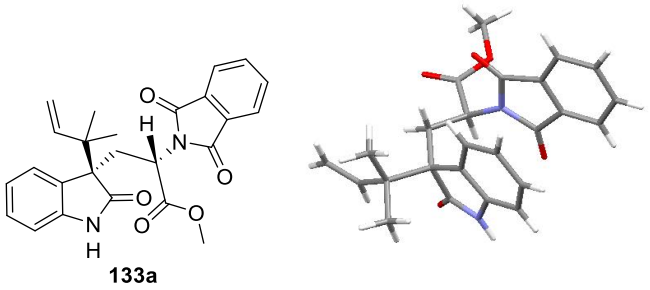
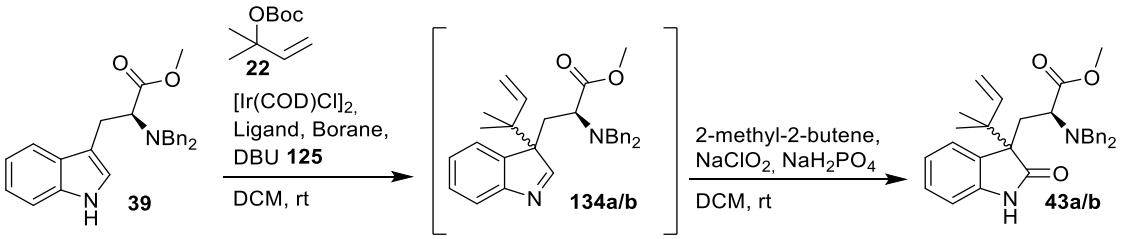


Figure 3.3.1: Crystal structure of reverse prenylated and oxidised compound **133a**.

As the double benzylated compound **39** was already in hand the reaction conditions of the one-pot reverse prenylation and Pinnick oxidation were also tried on this compound (Table 3.3.3).

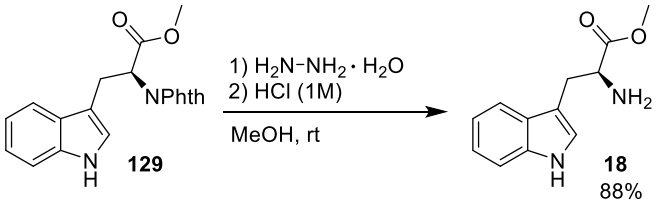
Table 3.3.3: One-pot prenylation and oxidation of double benzyl protected *L*-tryptophan methyl ester **39**.



Entry	Ligand	Borane	d.r. (43a:43b)	Yield
1	L(AM) **24**	9-OBBN (**142**)	6:1	52%
2	L(*S*) **27b**	9-OBBN (**142**)	3:1	34%

The *syn*-compound **43a** was obtained in an even higher excess in this reaction with achiral ligand **24**. However, 9-OBBN (**142**) was used in this reaction, instead of triethylborane, so the reactions are not comparable completely, yet the outcome of a 1:1 mixture for the reaction using the achiral ligand would have been predicted in this case as well. The yields for this reaction are lower compared to the ones of the phthalimide protected compounds **133a/b**.

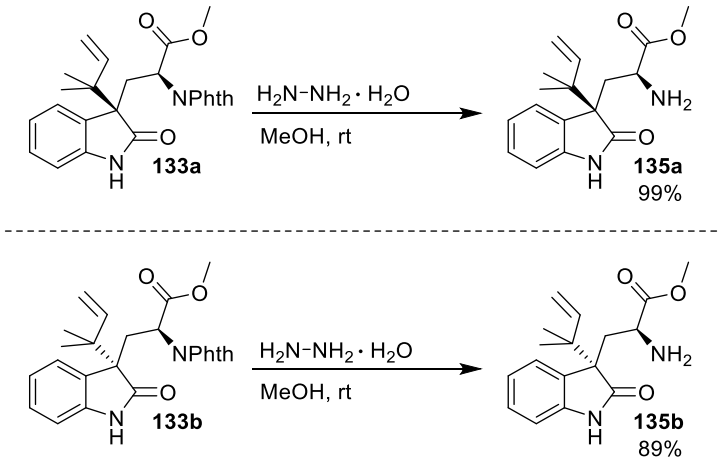
After the successful prenylation-oxidation procedure the phthalimide group had to be removed next. As it is well known that such deprotections can be tricky or require harsh reaction conditions the deprotection of the phthalimide group was first tried on the protected *L*-tryptophan derivative **129** as a simple model substrate (Scheme 3.3.7).[112,113]



Scheme 3.3.7: Attempted phthalimide cleavage of compound **129** to *L*-tryptophan methyl ester **18**.

The removal of the phthalimide group worked very nicely with a yield of 88% of *L*-tryptophan methyl ester **18**.

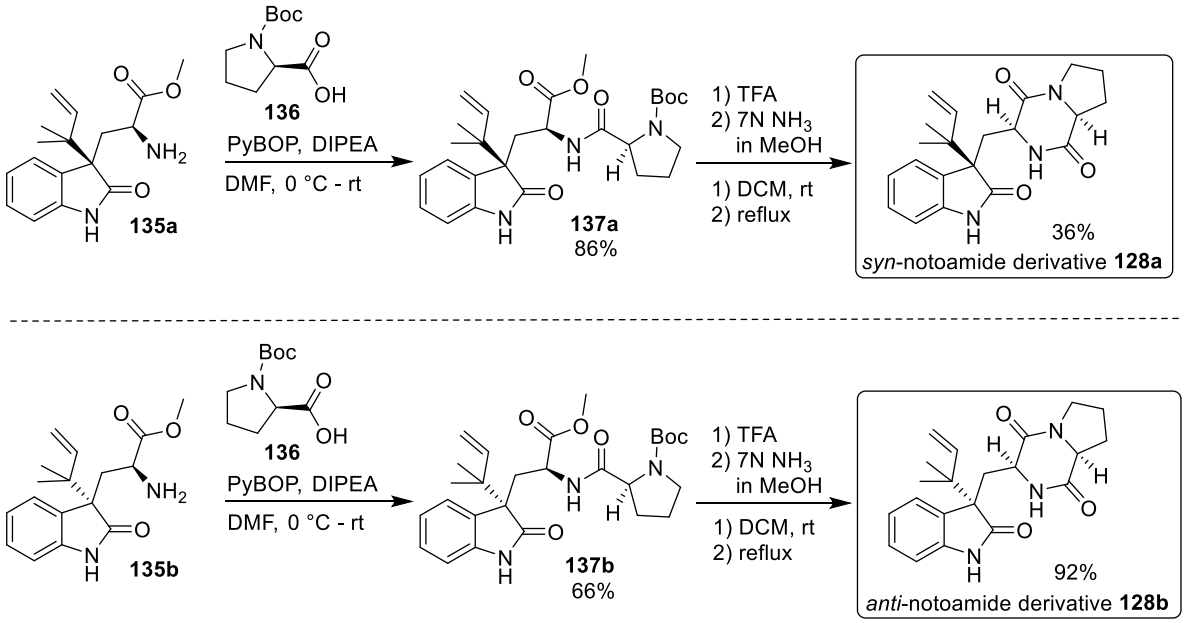
When the phthalimide deprotection was first tried on the oxindole compounds **133a/b** no desired product could be obtained. Only after the omission of hydrochloric acid from the reaction mixture the desired products **133a/b** were isolated (Scheme 3.3.8).



Scheme 3.3.8: Deprotection of the reverse prenylated oxindols **133a/b**.

In the end the deprotections worked very well with a nearly quantitative yield of 99% in the case of the *syn*-compound **315a** and a yield of 89% of the *anti*-compound **135b**. The slightly better yield for the *syn*-compound **135a** also indicates a higher stability of this substance.

The last two steps towards the synthesis of the notoamide derivatives **128a/b** were the peptide coupling with a protected *L*-proline derivative **136** and the Boc-deprotection and subsequent DKP-ring closure.[8,114] These reactions are shown in Scheme 3.3.9.



Scheme 3.3.9: Peptide coupling and ring closure to the desired notoamide derivatives **128a/b**.

The peptide coupling worked well in both cases. Again, the yield for the *syn*-configured compound **137a** was better with 86% compared to 66% of that of dipeptide **137b**. In order for the peptide coupling to succeed benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBOP) had to be used as coupling agent. HBTU did not give any conversion to the desired products **137a/b**. This might be because of the more rigid ring system of the Boc-protected *L*-proline **136**. Unfortunately, the Boc-deprotection with TFA and the subsequent DKP-ring closure under basic conditions worked very poorly in the case of the *syn*-derivative **128a** with a yield of only 36%. The yield of the corresponding *anti*-compound **128b**, on the other hand, was nearly quantitative with 92%.

Figure 3.3.2 shows the successfully synthesised notoamide derivatives with their corresponding natural products.[1,20]

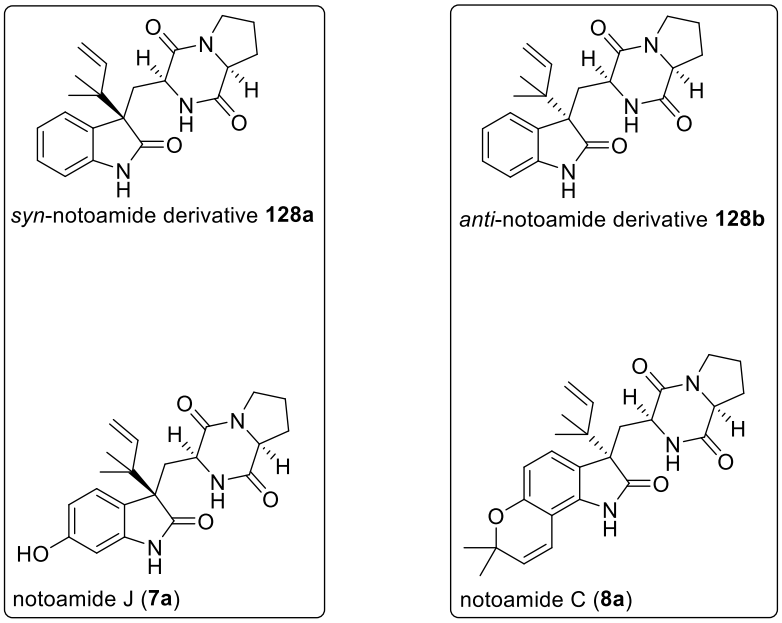
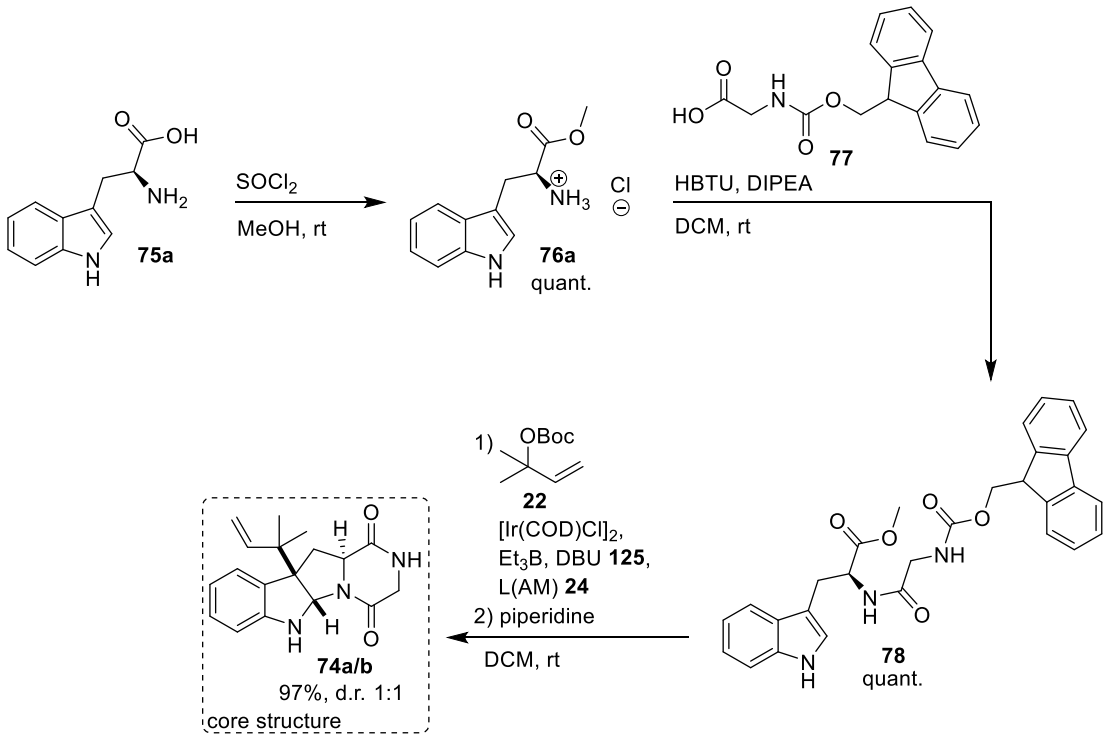


Figure 3.3.2: The synthesised notoamides and their natural product derivatives.[1,20]

6-Deoxy-notoamide J (**128a**) could successfully be synthesised with an overall yield of 15% over six consecutive steps. The *anti*-configured notoamide derivative **128b** could be synthesised successfully with a yield of 13% over six steps.

4 Conclusion and Outlook

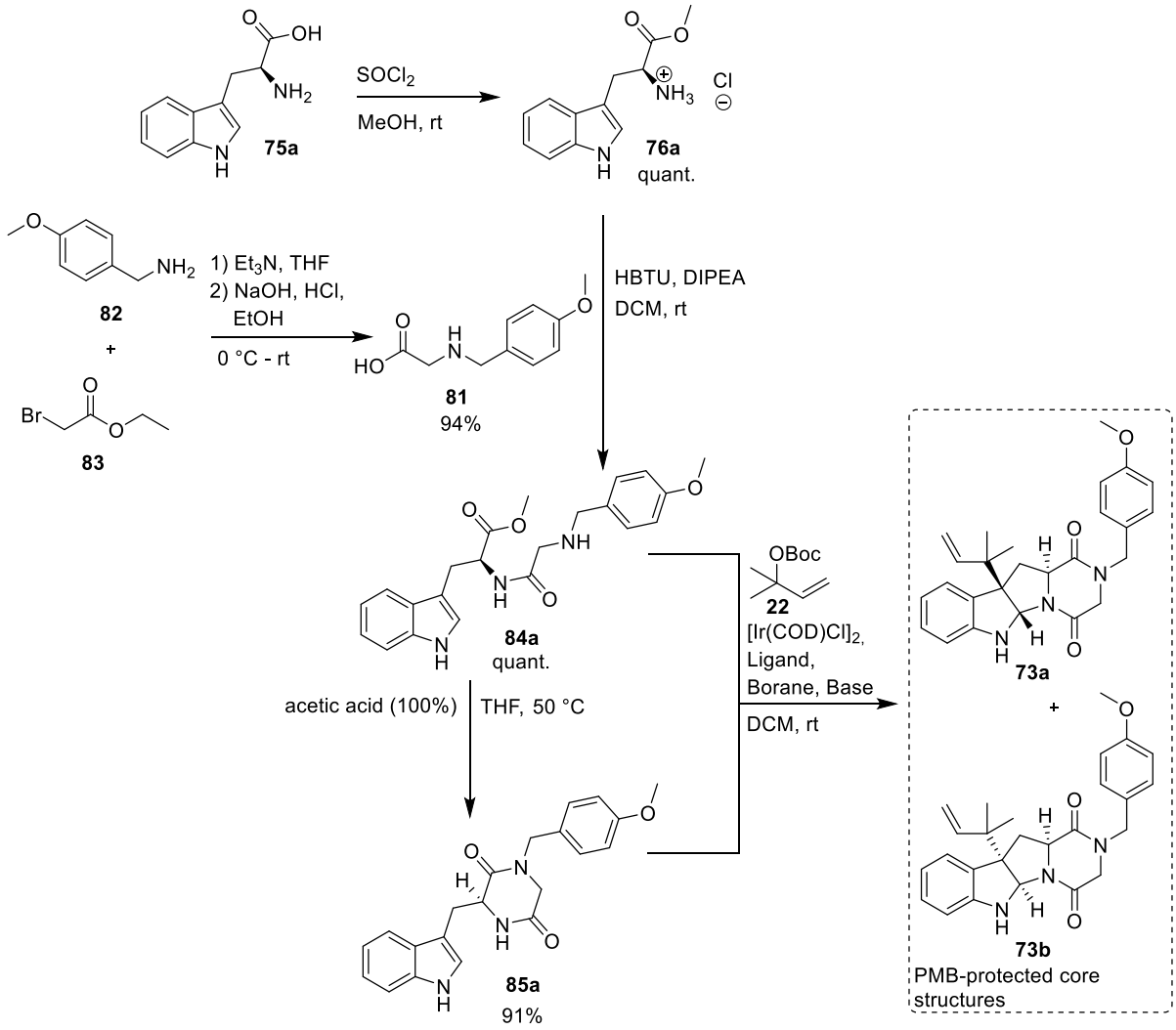
In the first attempt to develop a unified pathway towards reverse prenylated hexahydropyrrolo[2,3-*b*]indole natural products the core structures **74a/b** of these natural products were successfully synthesised with a yield of 97% over three steps in a diastereomeric ratio of 1:1 (Scheme 4.1).



Scheme 4.1: Synthesis of the core structures **74a/b** of reverse prenylated hexahydropyrrolo[2,3-*b*]indole natural products.

The separation of the diastereoisomers was not possible at this stage and the PMB-protection of the core structures **74a/b** did not work well.

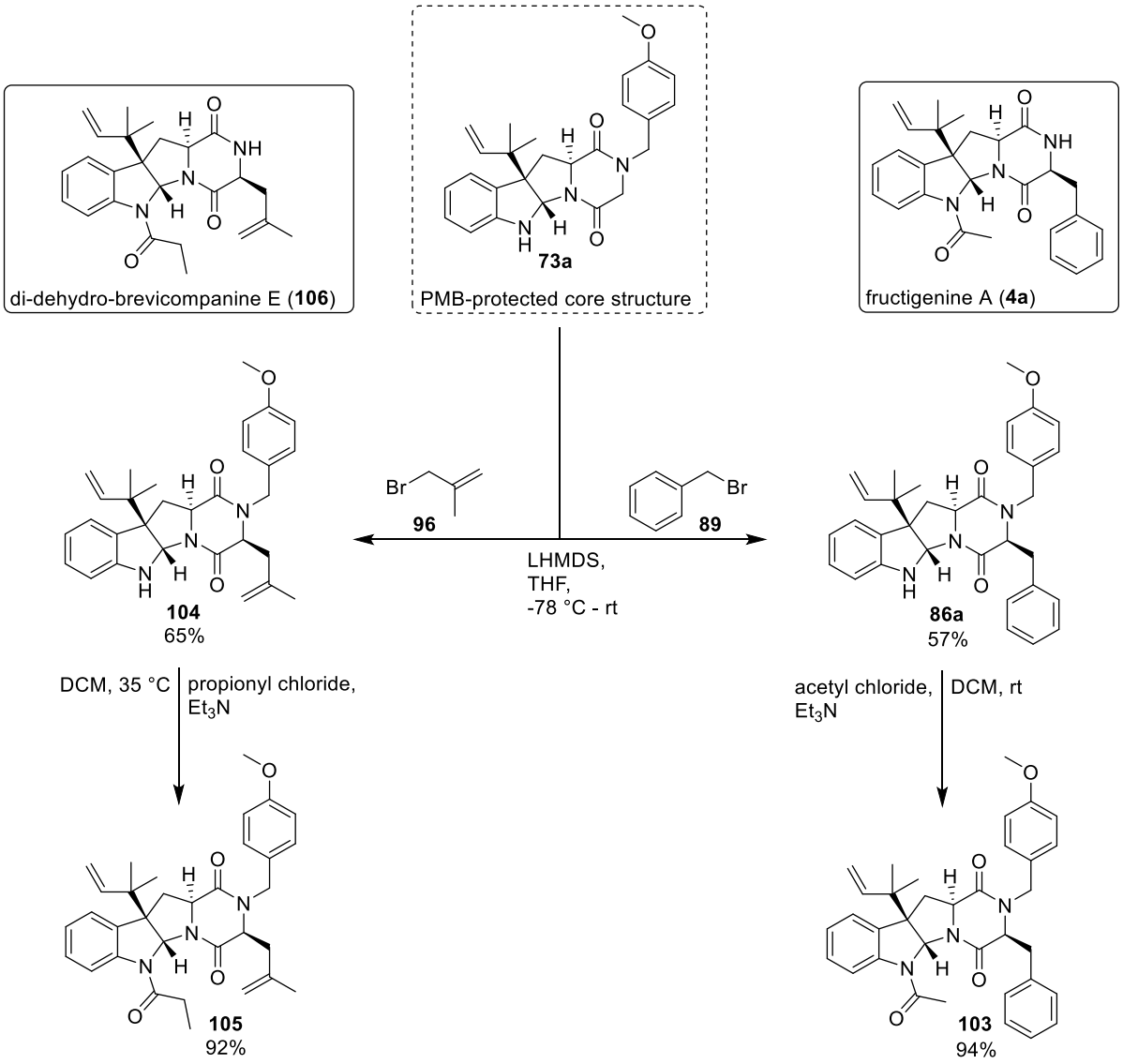
Therefore, the proposed pathway was altered to introduce the PMB-protecting group at an earlier stage of the reaction sequence. Scheme 4.2 shows the reactions performed in order to synthesise the PMB-protected core structures **73a/b** of reverse prenylated hexahydropyrrolo[2,3-*b*]indole natural products, which were separable *via* column chromatography at this stage.



Scheme 4.2: Synthesis of the PMB-protected core structures **73a/b** of reverse prenylated hexahydropyrrolo[2,3-*b*]indole natural products.

The core structures **73a/b** were synthesised with very good yields by protection of *L*-tryptophan **75a** to the corresponding methyl ester hydrochloride **76a**, synthesising and then coupling PMB-protected glycine **81** with the protected *L*-tryptophan derivative **75a** to form dipeptide **84a**, closure of the DKP-ring of dipeptide **84a** and finally submitting both the dipeptide **84a** and the diketopiperazine **85a** to the iridium catalysed reverse prenylation reaction conditions. Extensive studies of the reverse prenylation reaction were conducted on both compounds **84a** and **85a**, among others, for specific scopes and yields of these reactions see Tables 3.1.7 to 3.1.11.

The next steps towards a unified pathway for the synthesis of reverse prenylated hexahydropyrrolo[2,3-*b*]indole natural products were the *C*- and *N*-alkylation reactions of the PMB-protected core structures **73a/b**. The pursuit of this pathway towards the synthesis of the natural product fructigenine A (**4a**) and the derivative of natural product brevicompanine E (**5**) are shown in Scheme 4.3.

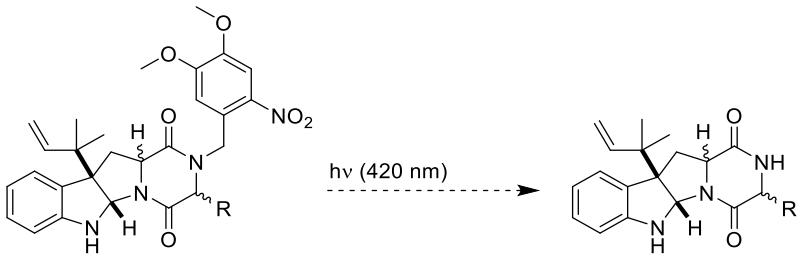


Scheme 4.3: Synthesis of the PMB-protected precursors of fructigenine A (**4a**) and di-dehydro-brevicompanine E (**106**) from the PMB-protected core structure **73a**.

The *C*-alkylation reactions were performed with moderate yields, followed by *N*-alkylation reactions with very good yields. Overall, the PMB-protected precursors for fructigenine A (**4a**) and brevicompanine E derivative **106** could be synthesised over six steps each with yields of 31% and 34% respectively.

Unfortunately, the PMB-deprotection, which would have been the last step in the reaction sequence, did not work. Many attempts with different reagents were performed but none worked. Therefore, the reaction sequence towards the protected core structures was repeated with DMB as protecting group. The DMB-protected core structures **116a/b** were successfully synthesised with a yield of 24% over five steps in a diastereomeric ratio of 1:1. However, as the removal of the DMB-group turned out to be equally unsuccessful further steps in this pathway were not performed.

In order to finish the development of a unified pathway for the synthesis of reverse prenylated hexahydropyrrolo[2,3-*b*]indole natural products a cleavable protecting group still needs to be found. A substituted benzyl protecting group is of vital importance as the directing effects of this type of compounds are necessary for the successful employment of the developed reaction sequence. As the acidic and oxidative cleavage of benzyl derived groups do not seem to be possible on those compounds a photochemical protecting group might be the right choice.[115] In Scheme 4.4 an example of a photochemical protecting group and its cleavage from a reverse prenylated hexahydropyrrolo[2,3-*b*]indole compound is given.[116]



Scheme 4.4: Possible deprotection of a 4,5-dimethoxy-2-nitrobenzyl protected reverse prenylated hexahydropyrrolo[2,3-*b*]indole derivative.[116]

It should be possible to cleave this particular group under exposure of light with a wavelength of 420 nm. There are different nitrobenzyl derivatives that might work for this purpose and should therefore be tried to be implemented in this pathway.[116,117]

The broad applicability of the proposed pathway should also be demonstrated. Therefore, studies of the *C*-alkylation reaction at the DKP-ring of the PMB-protected core structures **73a/b** were performed. Figure 4.1 gives an overview over the alkylated compounds that were obtained in these studies, their yields and the alkylating agents used in their synthesis.

As a next step these compounds, especially the non-natural derivatives, should be tested for their biological activities. The non-protected core structures **74a/b** were submitted to a first test of their antibiotic activity against *Escherichia coli* bacteria. The negative outcome of this test does not mean that the differently alkylated derivatives could not show other results as the side chains may be essential for any biological activity.

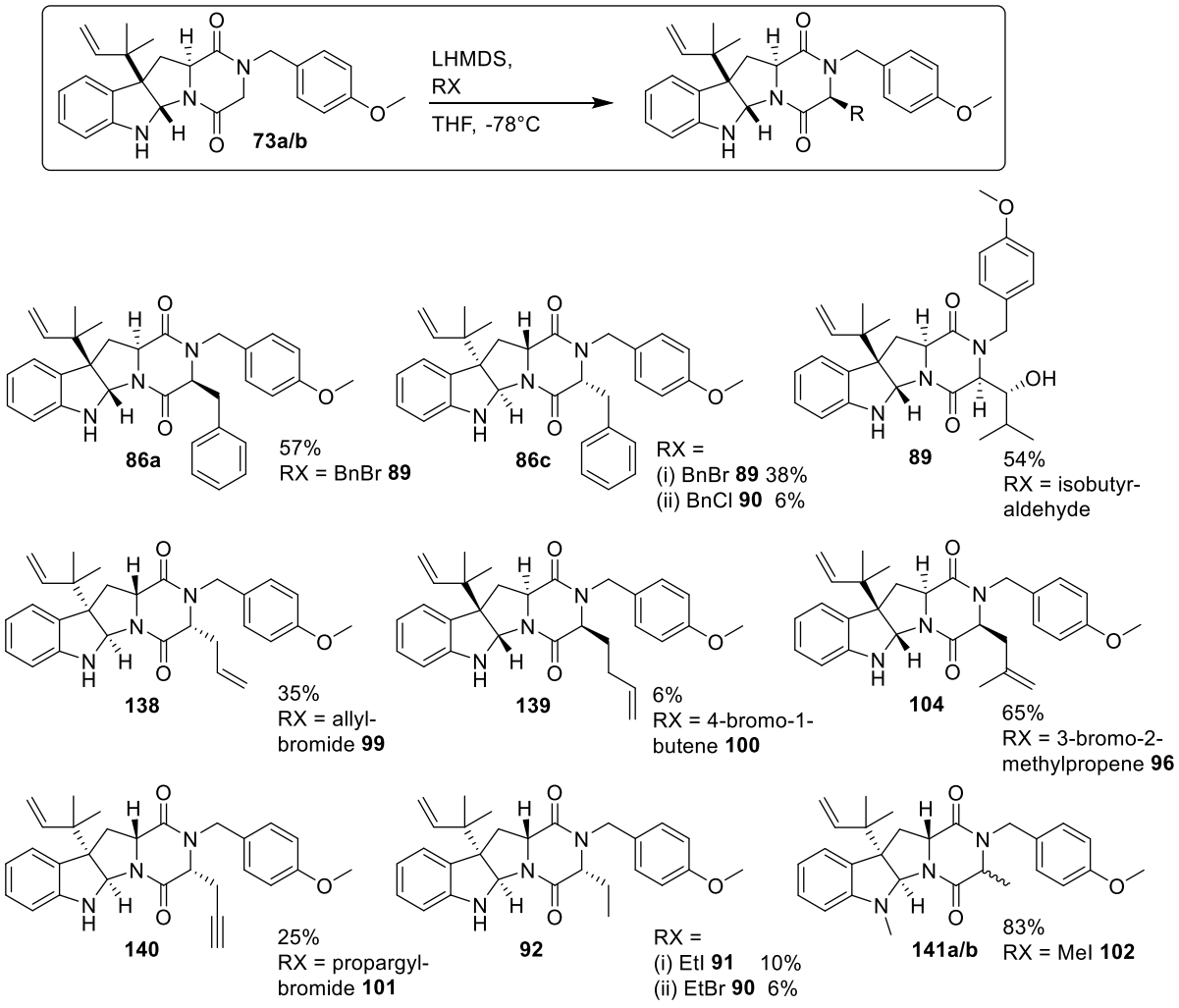
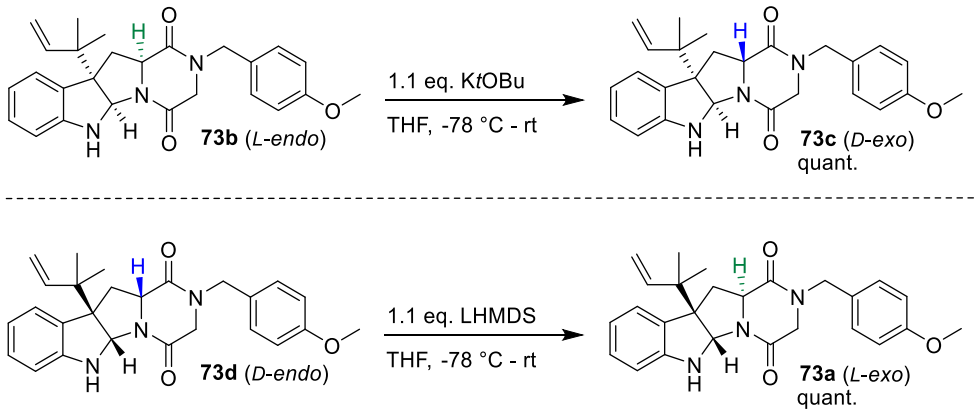


Figure 4.1: The successfully alkylated derivatives of the PMB-protected reverse prenylated hexahydropyrrolo[2,3-*b*]indole core structures **73a/b**.

During the studies of the *C*-alkylation reactions it was discovered that the *L-endo* core structure **73b** inverts to its corresponding diastereoisomer *D-exo* compound **73c**. Further studies on these findings revealed that the inversion does also take place from the *D-endo* compound **73d** to the *L-exo* compound **73a**, which led to the conclusion that the *exo*-compounds generally are the thermodynamically more stable isomers (Scheme 4.5). In addition, the inversion could be determined to be faster than the alkylation reaction and also that catalytic amounts of base are enough to achieve a full conversion. Though the assumption that nature might only use *L*-configured amino acids as starting material for its biosynthesis of both *exo*- and *endo*-configured reverse prenylated hexahydropyrrolo[2,3-*b*]indole natural products, as well as compounds derived from both *L*- and *D*-configured amino acids, could not be verified in this thesis. Further research on this topic, e.g. screening of more biomimetic bases for the reaction to work, is of great interest.

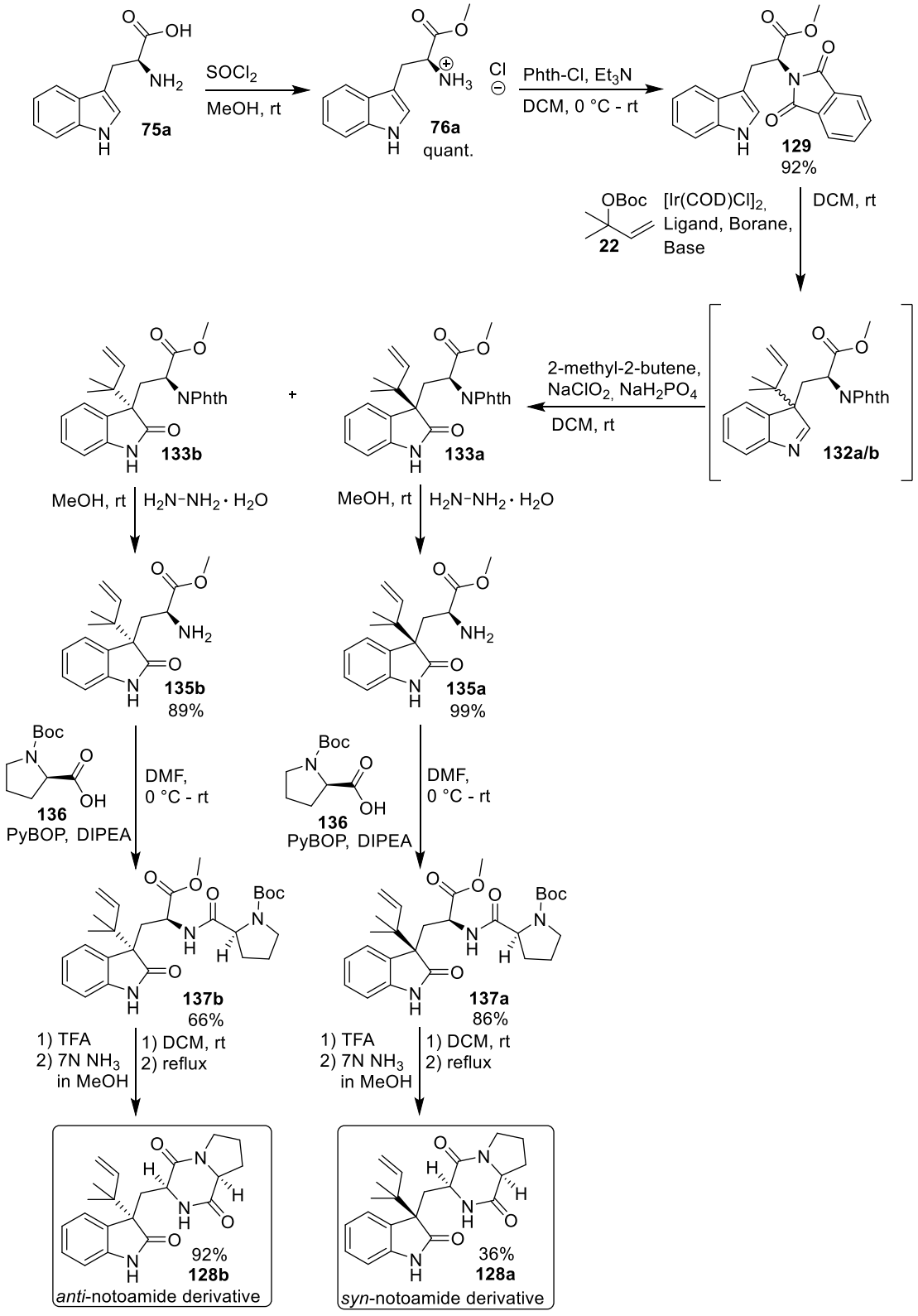


Scheme 4.5: Inversion of the stereocentre from *L-endo* compound **73b** to *D-exo* compound **73c** and from *D-endo* compound **73d** to *L-exo* compound **73a**.

These interesting findings also show the limitation of the developed unified approach towards reverse prenylated hexahydropyrrolo[2,3-*b*]indole compounds as only two out of eight possible alkylated isomers can be synthesised this way. However, as the majority of natural products of both the *L*- and the *D*-series of this class exhibit *exo*-configuration the developed reaction sequence can be employed for the total synthesis of most known reverse prenylated hexahydropyrrolo[2,3-*b*]indole natural products.

In the second part of the present thesis the broad applicability of the iridium catalysed reverse prenylation reaction should be demonstrated by the synthesis of a derivative of the notoamide family of natural products, namely 6-deoxy-notoamide J (**128a**) (Scheme 4.6). This was successfully achieved by first synthesising phth-protected *L*-tryptophan methyl ester **129** and subsequently successfully submitting it to a one-pot reverse prenylation and Pinnick oxidation reaction developed during the work on this thesis. The resulting reverse prenylated oxindole compounds **133a** and **133b** were afterwards relieved of the phthalimide group and coupled with Boc-protected *L*-proline **136**. The last steps towards the desired notoamide derivatives **128a** and **128b** were the one-pot Boc-deprotection and DKP-ring closure. This gave *syn*-notoamide J derivative **128a** with an overall yield of 15% over six steps and *anti*-notoamide C derivative **128b** with an overall yield of 13%, also over six step.

In the future a total synthesis of notoamides J (**7a**) and C (**8a**) should be developed based on the findings of this thesis. Therefore, either a selective oxidation reaction to introduce the hydroxy group present in notoamide J (**7a**) needs to be found, or *L*-tryptophan derivatives need to be synthesised from scratch to already contain a C6-substituted indole moiety in the molecule. In addition, further studies of different compounds for the reverse prenylation reaction might be performed in order to develop total syntheses of other interesting biologically active reverse prenylated natural products and their derivatives.



Scheme 4.6: Synthesis of notoamide derivatives **128a/b**.

5 Experimental

5.1. Materials and instrumentation

5.1.1 General remarks

Unless otherwise stated, all reactions were performed at a room temperature of 22 °C and at 1013 hPa atmospheric pressure. Reactions which are sensitive to oxygen or absorption of humidity were performed in previously baked out vessels and under a nitrogen atmosphere.

5.1.2 Chemicals and solvents

The applied chemicals were purchased from the companies *Acros Organics*, *Alfa Aesar*, *VWR*, *ABCR*, *Sigma Aldrich* and *TCI* in the best available quality and were used without further purification.

Solvents were used as purchased from the manufacturer (pure; absolute, dried over molecular sieve (H_2O $\leq$0.01%), $\geq$99.5%) e.g. acetonitrile, dichloromethane, dimethyl sulfoxide, methanol, tetrahydrofuran or toluene. Additionally, solvents were either used from the solvent drying system “MB SPS-800” from the *Mbraun* company or were freshly distilled, e.g. chloroform, dichloromethane, diethyl ether, ethanol, ethyl acetate, petroleum ether, methanol, tetrahydrofuran or toluene. In the case of petroleum ether the solvent boiling point range was 40-65 °C.

5.1.3 Chromatography

For the preparation of thin layer chromatograms (TLCs) silica gel sheets (ALUGRAM(R) - Xtra SIL G/UV254, 0.20 mm) from the *Macherey-Nagel* company were used. The detection of spots was done using UV-light (254 nm) or *via* staining with either ceric ammonium molybdate (phosphomolybdic acid (25 g), $Ce(SO_4)_2 \cdot 2\ H_2O$ (10 g), H_2SO_4 conc. (60 mL), H_2O (940 mL)), Ninhydrin (Ninhydrin (0.8 g), EtOH (200 mL)), Vanillin (Vanillin (8.6 g), H_2SO_4 conc. (2.5 mL), EtOH (200 mL)) or potassium permanganate (potassium permanganate (2.4 g), potassium carbonate (16 g), sodium hydroxide (4 mL, 5%), H_2O (240 mL)) and later treatment with hot air. The eluents used are given with each compound and the corresponding R_f-values display the altitude relative to the solvent front.

For the column chromatography silica gel 60 Å (grain size 40-63 µm) from the *Fluka* company was used. The eluent is given with each corresponding compound.

5.1.4 Infrared spectroscopy

The IR-spectra were recorded with the FT-IR spectrometer “ALPHA Platinum ATR” from the *Bruker* company. Absorption maxima (ν_{max}) are given in wavenumbers [cm^{-1}].

5.1.5 Mass spectroscopy

High resolution ESI-mass spectra were recorded in the positive mode with the “6224 ESI-TOF” instrument from the *Agilent* company, within a mass range of 110 – 3200 *m/z*. For the interpretation of the mass spectra both the recorded and the calculated values for the mass of the peaks are given in the *m/z* ratios.

5.1.6 Melting points

The determination of the melting points was done with the “Melting Point M-565” from the *Büchi* company.

5.1.7 NMR-spectroscopy

^{1}H-, ^{13}C- and 2D-NMR-experiments were recorded using the following spectrometers from the Bruker company:

- FT-300 (300 or 76 MHz)
- Avance I-400 (400 or 101 MHz)
- Avance II-400 (400 or 101 MHz)
- DRX-500 (500 or 126 MHz)
- Avance III-600 (600 or 151 MHz)

The NMR-spectra were interpreted using the *MestReNova* or *Topspin* software. The exact assignments of the signals to their corresponding *H*- or *C*-atoms was done with the help of ^{1}H,-^{1}H-COSY-, HSQC- and HMBC-spectra. The determination of the stereochemistry was done with the help of NOESY-spectra. The signal of the corresponding deuterated solvent was used as an internal standard ($CHCl_3$-d_1: δ = 7.26 ppm; MeOH-d_4: δ = 3.31 ppm; DMSO-d_6: δ = 2.50 ppm). The numbering of the carbon atoms can be seen in each illustration before the synthesis instructions of each molecule and does not always coincide with the IUPAC nomenclature rules.

5.1.8 Optical Rotation

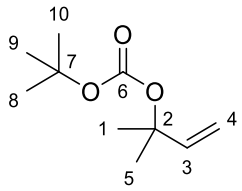
The optical rotation was recorded with a “P8000 Polarimeter” from the *A. Krüss GmbH*. The specific rotation value was determined using the formular $[\alpha]_{\lambda}^{T} = \frac{\alpha \bullet 100}{c \bullet l}$ with *α* being the measured optical rotation, *c* being the concentration in g/100 mL, *T* being the temperature and *l* being the cell path length dm.

5.1.9 Crystal structures

The single crystal x-ray diffraction measurements was conducted at the Institute of Inorganic Chemistry of the Department of Chemistry at the University of Hamburg. They were measured on a four-circle single crystal diffractometer “SuperNova” from the *Rigaku* company. The software *Olex* was used for the calculations of the structures. The visualisation of the structures was done with the help of the *Mercury* software.

5.2. Synthesis of the prenylating reagents

5.2.1 Synthesis of *tert*-butyl (2-methylbut-3-en-2-yl) carbonate (22)



22

$C_{10}H_{18}O_3$

[186.25]

To a solution of 15.8 mL (12.9 g, 0.150 mol, 1.1 eq.) of 2-methylbut-3-en-2-ol in 300 mL dry THF under a nitrogen atmosphere were added 100 mL (0.150 mol, 1.1 eq.) of *n*-BuLi (1.6 M in *n*-hexane) at 0 °C. After stirring for 20 min 29.1 mL (29.7 g, 0.136 mol, 1.0 eq.) of di-*tert*-butyldicarbonate were added and the solution stirred again for three hours at room temperature. Afterwards, the reaction mixture was reduced to a third of its volume under reduced pressure, diluted with diethyl ether and washed successively with a solution of sodium carbonate, sodium chloride and three times with water.

The residual solvents were dried over sodium sulfate and removed under reduced pressure to afford the desired product **22** (21.9 g, 0.118 mol, 87%) as a clear liquid.

The synthesis of *tert*-butyl (2-methylbut-3-en-2-yl) carbonate (**22**) was performed according to the procedure of Carreira *et al.* and the analytical data matched literature values.[49]

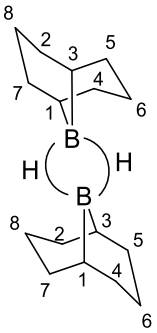
R_f value (PE/EtOAc 10:1 (v/v)): 0.89.

^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] 6.10 (dd, *J* = 17.5, 10.9 Hz, 1H, C3-H), 5.18 (d, *J* = 17.5 Hz, 1H, C4-H), 5.10 (d, *J* = 11.1 Hz, 1H, C4-H), 1.52 (s, 6H, C1/5-H), 1.46 (s, 9H, C8-10-H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ [ppm] 152.05 (C-6), 142.46 (C-3), 113.14 (C-4), 81.42 (C-7), 81.36 (C-2), 28.00 (C-1/5), 26.56 (C-8/9/10).

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 2980.79, 2935.38, 1736.86, 1472.21, 1457.80, 1415.51, 1367.45, 1280.74, 1253.75, 1119.52, 989.45, 922.29, 897.77, 842.51, 793.78, 713.27.

5.2.2 Synthesis of 9-borabicyclo[3.3.1]nonane dimer (118)



118

$C_{16}H_{30}B_2$

[244.03]

To a solution of 47.4 mL (38.0 g, 0.500 mol, 1.0 eq.) of borane dimethyl sulfide complex in 160 mL dry DME were added dropwise 64.0 mL (0.499 mol, 0.99 eq.) of cycloocta-1,5-diene (**117**) under a nitrogen atmosphere in the course of one hour, in which the temperature did not rise above 60 °C. Afterwards, about 100 mL of DME were removed through distillation under reduced pressure, during which clear crystals started to precipitate.

The residue was recrystallised twice from freshly dried DME and the residual solvent removed under reduced pressure to afford the desired product **118** (37.4 g, 0.310 mol, 61%) as clear crystals.

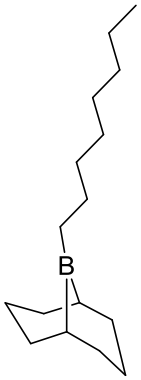
The synthesis of the 9-borabicyclo[3.3.1]nonane dimer (**118**) was performed according to the procedure of the *Organicum* and the analytical data matched literature values.[118]

^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] 2.06 – 1.11 (m, 30H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ [ppm] 33.07 (C-2/4/5/6/7/8), 23.66 (C-1/3).

As this substrate is pyrophoric, it has been refrained from collecting further analytical data.

5.2.3 Synthesis of 9-octyl-9-borabicyclo[3.3.1]nonane (142)



142

$C_{16}H_{31}B$

[234.23]

A solution of 2.44 g (10.0 mmol, 1.0 eq.) of 9-borabicyclo[3.3.1]nonane dimer (**118**) in 6.3 mL (4.5 g, 40 mmol, 4.0 eq.) of 1-octene was stirred for 30 min at room temperature under a nitrogen atmosphere. Afterwards, the solution was heated to 50 °C and stirred for another hour.

The residual solvent was removed under reduced pressure to afford the desired product **142** quantitatively as a clear liquid.

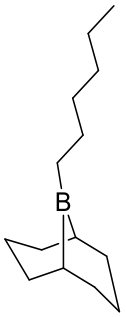
The synthesis of 9-octyl-9-borabicyclo[3.3.1]nonane (**142**) was performed according to the procedure of Stark *et al.*[4]

As this substrate is pyrophoric it was refrained from collecting further analytical data. Additionally, because of the high overlap of signals, it was also refrained from assigning the signals from the NMR-spectra to their corresponding atoms.

^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] 1.92 – 1.79 (m, 6H), 1.73 – 1.61 (m, 6H), 1.56 – 1.44 (m, 2H), 1.40 – 1.16 (m, 14H), 0.92 – 0.86 (m, 3H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ [ppm] 76.65, 41.86, 33.06, 32.90, 31.87, 29.56, 29.27, 27.09, 25.58, 24.38, 23.17, 22.61, 14.04.

5.2.4 Synthesis of 9-hexyl-9-borabicyclo[3.3.1]nonane (119)



119

$C_{14}H_{27}B$

[206.18]

A solution of 0.500 g (2.05 mmol, 1.0 eq.) of 9-borabicyclo[3.3.1]nonane dimer (**118**) in 1.0 mL (0.69 g, 8.2 mmol, 4.0 eq.) of 1-hexene was stirred for 30 min at room temperature under a nitrogen atmosphere. Afterwards, the solution was heated to 50 °C and stirred for another hour.

The residual solvent was removed under reduced pressure to afford the desired product **119** quantitatively as a clear liquid.

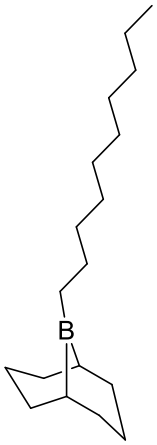
The synthesis of 9-hexyl-9-borabicyclo[3.3.1]nonane (**119**) was performed according to the procedure of Stark *et al.*[4]

As this substrate is pyrophoric it was refrained from collecting further analytical data. Additionally, because of the high overlap of signals, it was also refrained from assigning the signals from the NMR-spectra to their corresponding atoms.

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] 1.76 (dq, J = 13.2, 4.8 Hz, 6H), 1.68 – 1.53 (m, 6H), 1.42 (td, J = 7.9, 3.8 Hz, 2H), 1.34 – 1.27 (m, 2H), 1.23 (q, J = 4.7, 2.5 Hz, 5H), 1.15 (dp, J = 12.8, 4.4, 3.7 Hz, 3H), 0.88 – 0.74 (m, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ [ppm] 33.16, 32.66, 31.95, 24.44, 23.27, 22.71, 14.14.

5.2.5 Synthesis of 9-decyl-9-borabicyclo[3.3.1]nonane (120)



120

$C_{18}H_{35}B$

[262.29]

A solution of 0.500 g (2.05 mmol, 1.0 eq.) of 9-borabicyclo[3.3.1]nonane dimer (**118**) in 1.2 mL (6.2 mmol, 3.0 eq.) of 1-decene was stirred for 30 min at room temperature under a nitrogen atmosphere. Afterwards, the solution was heated to 50 °C and stirred for another hour.

The residual solvent was removed under reduced pressure to afford the desired product **120** quantitatively as a clear liquid.

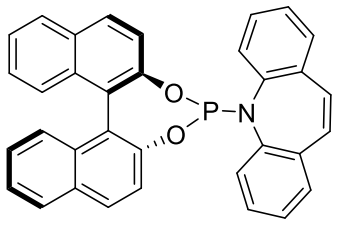
The synthesis of 9-decyl-9-borabicyclo[3.3.1]nonane (**120**) was performed according to the procedure of Stark *et al.*[4]

As this substrate is pyrophoric it was refrained from collecting further analytical data. Additionally, because of the high overlap of signals, it was also refrained from assigning the signals from the NMR-spectra to their corresponding atoms.

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] 1.80 – 1.67 (m, 6H), 1.58 (t, J = 5.8 Hz, 6H), 1.38 (t, J = 7.2 Hz, 2H), 1.29 – 1.22 (m, 2H), 1.22 – 1.05 (m, 16H), 0.77 (t, J = 6.7 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ [ppm] 33.16, 33.01, 31.97, 29.72, 29.40, 24.49, 23.28, 22.73, 14.11.

5.2.6 Synthesis of *(R)*-5*H*-dibenzo[*b,f*]azepinyl-binapht-[2,2‘]-diylphosphoramidit (27a)



27a

$C_{34}H_{22}NO_2P$

[507.52]

To 1.15 g (4.00 mmol, 1.0 eq.) of (*R*)-(+)-1,1′-bi(2-naphthol) were added 5.3 mL (60 mmol, 15 eq.) of phosphorous trichloride under a nitrogen atmosphere and stirred at room temperature. To start the reaction catalytic amounts (11.6 mg, 0.120 mmol, 0.03 eq.) of *N*-methylpyrrolidon were added and the solution was heated to 50 °C for 30 min. After cooling to room temperature the excess phosphorous trichloride was carefully removed under reduced pressure. The residue was diluted with 50 mL dry THF and added to a solution of 0.850 g (4.40 mmol, 1.1 eq.) of iminostilbene in 50 mL dry THF, in which were added 2.6 mL (4.2 mmol, 1.05 eq.) of *n*-BuLi (1.6 M in *n*-hexane) at -80 °C and which was previously stirred for 20 min. After stirring for another hour at -80 °C the solvent was removed under reduced pressure.

The residue was purified by column chromatography (PE/toluene = 2:1) to afford the desired product **27a** (1.20 g, 2.36 mmol, 59%) as a light yellow solid.

The synthesis of *(R)*-5*H*-dibenzo[*b,f*]azepinyl-binapht-[2,2‘]-diylphosphoramidit (**27a**) was performed according to the procedure of Carreira *et al*.[119]

As this substrate is very sensitive and unstable it was refrained from collecting further analytical data. Additionally, because of the high overlap of signals, it was also refrained from assigning the signals from the NMR-spectra to their corresponding atoms.

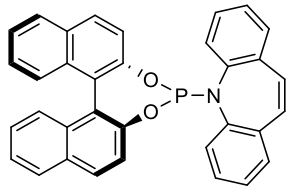
R_f value (PE/EtOAc 1:1 (v/v)): 0.61.

^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] 7.99 (d, *J* = 8.8 Hz, 1H), 7.91 (d, *J* = 8.1 Hz, 1H), 7.77 (d, *J* = 7.9 Hz, 1H), 7.63 (d, *J* = 8.8 Hz, 1H), 7.47 – 7.33 (m, 3H), 7.32 – 7.15 (m, 10H), 7.14 - 7.09 (m, 1H), 7.03 – 6.90 (m, 2H), 6.87 (d, *J* = 8.8 Hz, 1H), 6.54 (td, *J* = 7.8, 1.5 Hz, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ [ppm] 150.08, 148.87, 143.19, 142.68, 136.61, 135.35, 133.02, 132.32, 131.67, 131.59, 131.48, 130.45, 130.35, 129.31, 129.22, 129.13, 129.11, 129.05, 128.69, 128.54, 128.44, 128.37, 128.00, 127.25, 126.94, 126.83, 126.29, 126.19, 125.79, 124.97, 124.45, 122.27, 121.60, 121.27.

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3053.92, 1618.75, 1588.91, 1504.41, 1483.49, 1456.10, 1431.35, 1367.85, 1322.14, 1280.86, 1235.05, 1200.64, 1153.52, 1106.22, 1069.06, 1037.21, 978.07, 937.88, 868.20, 819.83, 799.37, 749.78, 694.79, 682.47, 639.01, 629.78, 619.20, 585.23, 558.88, 545.00, 519.43, 494.63, 482.84, 469.23, 460.65, 414.03, 402.34.

5.2.7 Synthesis of (*S*)-5*H*-dibenzo[b,f]azepinyl-binapht-[2,2‘]-diylphosphoramidit (27b)



27b

$C_{34}H_{22}NO_2P$

[507.52]

To 1.23 g (4.27 mmol, 1.0 eq.) of (*S*)-(-)-1,1′-bi(2-naphthol) were added 8.81 g (64.0 mmol, 15 eq.) of phosphorous trichloride under a nitrogen atmosphere and stirred at room temperature. To start the reaction catalytic amounts (12.2 mg, 0.130 mmol, 0.03 eq.) of *N*-methylpyrrolidon were added and the solution was heated to 50 °C for 30 min. After cooling to room temperature the excess phosphorous trichloride was carefully removed under reduced pressure. The residue was diluted with 50 mL dry THF and added to a solution of 0.910 g (4.70 mmol, 1.1 eq.) of iminostilbene in 50 mL dry THF, in which were added 2.8 mL (4.5 mmol, 1.05 eq.) of *n*-BuLi (1.6 M in *n*-hexane) at -80 °C and which was previously stirred for 20 min. After stirring for another hour at -80 °C the solvent was removed under reduced pressure.

The residue was purified by column chromatography (PE/toluene = 2:1) to afford the desired product **27b** (1.39 g, 2.73 mmol, 64%) as a light yellow solid.

The synthesis of *(S)*-5*H*-dibenzo[*b,f*]azepinyl-binapht-[2,2']-diylphosphoramidit (**27b**) was performed according to the procedure of Carreira *et al.* and the analytical data matched literature values.[119]

As this substrate is very sensitive and unstable it was refrained from collecting further analytical data. Additionally, because of the high overlap of signals, it was also refrained from assigning the signals from the NMR-spectra to their corresponding atoms.

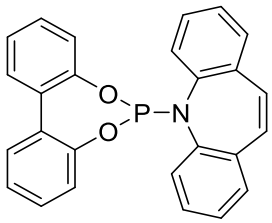
R_f value (PE/EtOAc 1:1 (v/v)): 0.61.

^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] 7.99 (d, *J* = 8.8 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.76 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.62 (d, *J* = 8.7 Hz, 1H), 7.43 (d, *J* = 8.9 Hz, 1H), 7.39 (ddd, *J* = 8.2, 6.2, 1.7 Hz, 1H), 7.36 (ddd, *J* = 8.1, 6.6, 1.3 Hz, 1H), 7.28 (d, *J* = 8.5 Hz, 1H), 7.24 (d, *J* = 3.1 Hz, 1H), 7.23 – 7.14 (m, 8H), 7.12 – 7.08 (m, 1H), 7.02 – 6.94 (m, 1H), 6.93 (td, *J* = 7.4, 1.3 Hz, 1H), 6.85 (d, *J* = 8.8 Hz, 1H), 6.53 (td, *J* = 7.7, 1.6 Hz, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ [ppm] 150.09, 150.01, 142.97, 142.67, 136.60, 136.57, 135.33, 133.01, 132.30, 131.67, 131.58, 131.48, 130.45, 130.34, 129.31, 129.21, 129.14, 129.11, 129.05, 128.69, 128.54, 128.44, 128.00, 127.24, 126.94, 126.84, 126.30, 126.19, 125.79, 124.98, 124.44, 122.28, 121.59, 121.25.

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3053.49, 1618.81, 1588.88, 1504.33, 1483.57, 1456.38, 1431.29, 1367.84, 1322.34, 1280.96, 1234.96, 1200.75, 1153.63, 1106.22, 1069.11, 1037.13, 978.22, 938.11, 868.24, 819.86, 799.41, 749.81, 694.65, 682.55, 639.03, 629.78, 619.30, 585.19, 558.88, 545.11, 519.73, 494.82, 482.83, 469.27, 460.75, 414.28, 402.21.

5.2.8 Synthesis of 5-(dibenzo[d,f][1,3,2]dioxaphosphepin-6-yl)-5*H*-dibenzo[b,f] azepine (24)



24

$C_{26}H_{18}NO_2P$

[407.40]

To 1.52 g (8.16 mmol, 1.0 eq.) of [1,1′-biphenyl]-2,2'-diol were added 8.81 g (64.0 mmol, 15 eq.) of phosphorous trichloride under a nitrogen atmosphere and stirred at room temperature. To start the reaction catalytic amounts (24.3 mg, 0.245 mmol, 0.03 eq.) of *N*-methylpyrrolidon were added and the solution was heated to 50 °C for 30 min. After cooling to room temperature the excess phosphorous trichloride was carefully removed under reduced pressure. The residue was diluted with 50 mL dry THF and added to a solution of 1.74 g (8.98 mmol, 1.1 eq.) of iminostilbene in 50 mL dry THF, in which were added 5.4 mL (8.6 mmol, 1.05 eq.) of *n*-BuLi (1.6 M in *n*-hexane) at -80 °C and which was previously stirred for 20 min. After stirring for another hour at -80 °C the solvent was removed under reduced pressure.

The residue was purified by column chromatography (PE/toluene = 2:1) to afford the desired product **24** (2.43 g, 5.96 mmol, 73%) as a light yellow solid.

The synthesis of 5-(dibenzo[d,f][1,3,2]dioxaphosphepin-6-yl)-5*H*-dibenzo[b,f]azepine (**24**) was performed according to the procedure of Carreira *et al*.[119]

As this substrate is very sensitive and unstable it was refrained from collecting further analytical data. Additionally, because of the high overlap of signals, it was also refrained from assigning the signals from the NMR-spectra to their corresponding atoms.

R_f value (PE/EtOAc 1:1 (v/v)): 0.90.

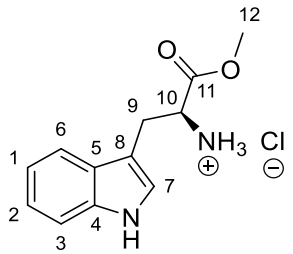
^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] 8.04 (ddd, *J* = 39.6, 7.7, 1.3 Hz, 2H), 7.59 (ddd, *J* = 20.7, 7.6, 1.8 Hz, 2H), 7.48 (d, *J* = 8.2 Hz, 2H), 7.46 – 7.39 (m, 2H), 7.39 – 7.31 (m, 2H), 7.29 (dd, *J* = 7.8, 1.8 Hz, 2H), 7.27 – 7.19 (m, 2H), 7.17 (ddd, *J* = 8.5, 7.2, 1.4 Hz, 2H), 7.04 (dt, *J* = 8.0, 1.3 Hz, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ [ppm] 151.37, 141.77, 131.13, 130.28, 129.89, 125.93, 122.24, 121.69, 120.47, 119.91, 119.57, 114.52, 110.70.

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3417.34, 3051.09, 1597.43, 1497.11, 1484.40, 1472.73, 1450.69, 1434.96, 1386.05, 1336.23, 1325.95, 1297.66, 1269.69, 1252.73, 1233.31, 1192.84, 1178.91, 1158.14, 1148.57, 1116.35, 1093.49, 1030.57, 1021.09, 973.04, 944.86, 890.92, 863.27, 851.79, 772.65, 744.87, 722.16, 709.53, 695.25, 624.08, 612.82, 598.08, 569.27, 516.01, 485.20, 472.14, 443.92, 417.73, 379.88.

5.3. Protecting and coupling of amino acids

5.3.1 Synthesis of (*S*)-3-(1*H*-indol-3-yl)-1-methoxy-1-oxopropan-2-aminium chloride (76a)



76a

$C_{12}H_{15}ClN_2O_2$

[254.71]

To a suspension of 10.0 g (49.0 mmol, 1.0 eq.) of *L*-tryptophan (**75a**) in 500 mL methanol were slowly added 5.3 mL (8.7 g, 73 mmol, 1.5 eq.) of thionyl chloride at 0 °C and under a nitrogen atmosphere. After stirring overnight at room temperature, the solvent was nearly completely removed under reduced pressure and a faintly purple solid precipitated through addition of 150 mL of diethyl ether. The solid was then washed several times with diethyl ether until it was purely white.

The residual solvent was removed under reduced pressure to afford the desired product **76a** quantitatively (12.5 g, 49.0 mmol) as a fine white powder.

The synthesis of (*S*)-3-(1*H*-indol-3-yl)-1-methoxy-1-oxopropan-2-aminium chloride (**76a**) was performed according to the procedure of Liu *et al.* and the analytical data matched literature values.[79,120]

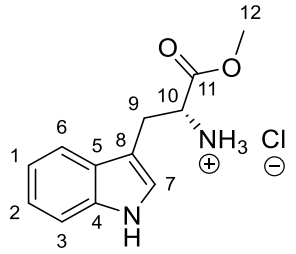
R_f value (EtOAc (deactivated over Ammonia)): 0.24.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm] 11.12 (d, J = 2.6 Hz, 1H, indole N-H), 8.63 (s, 3H, N-H_3), 7.51 (d, J = 7.9 Hz, 1H, C3-H), 7.41 – 7.34 (m, 1H, C6-H), 7.25 (d, J = 2.5 Hz, 1H, C7-H), 7.09 (ddd, J = 8.1, 7.0, 1.2 Hz, 1H, C2-H), 7.01 (ddd, J = 8.0, 7.0, 1.1 Hz, 1H, C1-H), 4.21 (t, J = 6.2 Hz, 1H, C10-H), 3.65 (s, 3H, C12-H), 3.34 – 3.20 (m, 2H, C9-H).

^{13}C-NMR (101 MHz, DMSO-d$_6$): δ [ppm] 169.71 (C-11), 136.16 (C-4), 126.84 (C-5), 124.94 (C-8), 121.11 (C-2), 118.57 (C-1), 117.94 (C-3), 111.52 (C-6), 106.26 (C-7), 52.71 (C-10), 52.59 (C-12), 26.05 (C-9).

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3389.61, 3269.69, 2925.94, 1747.19, 1579.53, 1506.33, 1459.50, 1444.20, 1436.81, 1351.68, 1340.18, 1285.66, 1257.34, 1229.49, 1210.84, 1193.28, 1138.90, 1107.66, 1074.97, 1058.37, 1008.17, 937.73, 889.64, 849.93, 818.29, 749.55, 731.79, 659.80, 597.10, 516.88, 463.50, 425.86.

5.3.2 Synthesis of (*R*)-3-(1*H*-indol-3-yl)-1-methoxy-1-oxopropan-2-aminium chloride (76b)



76b

$C_{12}H_{15}ClN_2O_2$

[254.71]

To a suspension of 10.2 g (50.0 mmol, 1.0 eq.) of *D*-tryptophan (**75b**) in 300 mL methanol were slowly added 7.3 mL (12 g, 0.10 mol, 2.0 eq.) of thionyl chloride at 0 °C and under a nitrogen atmosphere. After stirring for 48 h at room temperature, the solvent was nearly completely removed under reduced pressure and a faintly purple solid precipitated through addition of 150 mL of diethyl ether. The solid was then washed several times with diethyl ether until it was purely white.

The residual solvent was removed under reduced pressure to afford the desired product **76b** (12.4 g, 48.8 mmol, 98%) as a fine white powder.

The synthesis of (*R*)-3-(1*H*-indol-3-yl)-1-methoxy-1-oxopropan-2-aminium chloride (**76b**) was performed according to the procedure of Liu *et al.* and the analytical data matched literature values.[79,120]

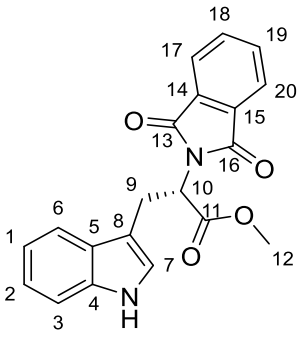
R_f value (EtOAc (deactivated over Ammonia)): 0.23.

^{1}H-NMR (400 MHz, MeOD): δ [ppm] 7.57 (dt, *J* = 7.9, 1.0 Hz, 1H, C3-H), 7.42 (dt, *J* = 8.1, 0.9 Hz, 1H, C6-H), 7.23 (s, 1H, C7-H), 7.17 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H, C2-H), 7.10 (ddd, *J* = 8.0, 7.1, 1.1 Hz, 1H, C1-H), 4.35 (dd, *J* = 7.4, 5.5 Hz, 1H, C10-H), 3.83 (s, 3H, C12-H), 3.49 (ddd, *J* = 15.2, 5.5, 0.8 Hz, 1H, C9-H), 3.39 (ddd, *J* = 15.2, 7.4, 0.7 Hz, 1H, C9-H).

^{13}C-NMR (101 MHz, MeOD): δ [ppm] 170.82 (C-12), 138.34 (C-4), 128.17 (C-5), 125.57 (C-9), 122.97 (C-2), 120.34 (C-1), 118.80 (C-3), 112.69 (C-6), 107.46 (C-8), 54.63 (C-11), 53.65 (C-16), 27.59 (C-10).

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3261.65, 2999.52, 2948.84, 2857.96, 2622.68, 2012.55, 1748.63, 1579.49, 1502.92, 1459.22, 1436.69, 1402.48, 1385.99, 1351.08, 1285.01, 1259.75, 1228.71, 1211.06, 1179.92, 1139.71, 1126.35, 1108.81, 1074.55, 1059.41, 1006.92, 982.45, 940.42, 888.90, 864.42, 819.69, 730.95, 703.53, 659.89, 605.66, 565.68, 463.11, 425.03, 413.04, 402.71.

5.3.3 Synthesis of methyl (*S*)-2-(1,3-dioxoisoindolin-2-yl)-3-(1*H*-indol-3-yl) propanoate (129)



129

$C_{20}H_{16}N_2O_4$

[348.35]

A suspension of 1.02 g (4.00 mmol, 1.0 eq.) of (*S*)-3-(1*H*-indol-3-yl)-1-methoxy-1-oxopropan-2-aminium chloride (**76a**) in 100 mL dichloromethane was cooled down to 0 °C under a nitrogen atmosphere. 1.2 mL (1.6 g, 16 mmol, 4.0 eq.) of triethylamine were added to form a clear solution. Afterwards, 1.5 mL (0.81 g, 4.0 mmol, 1.0 eq.) of phthaloyl dichloride were slowly added and the reaction mixture stirred overnight at room temperature. After complete conversion the reaction mixture was washed with sodium hydrogen carbonate, the aqueous layers extracted three times with dichloromethane, the combined organic layers dried over sodium sulfate and the solvent removed under reduced pressure.

The residue was purified by column chromatography (PE/EtOAc = 2:1 – 1:1) to afford the desired product **129** (1.3 g, 3.7 mmol, 92%) as yellow crystals.

The synthesis of methyl (*S*)-2-(1,3-dioxoisoindolin-2-yl)-3-(1*H*-indol-3-yl) propanoate (**129**) was performed according to the procedure of Viswanathan *et al.* and the analytical data matched literature values.[109]

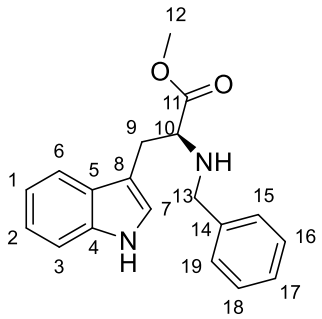
R_f value (PE/EtOAc 1:1 (v/v)): 0.46.

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] 8.00 – 7.88 (m, 1H, N-H), 7.75 (dd, *J* = 5.5, 3.1 Hz, 2H, C17/20-H), 7.66 (dd, *J* = 5.5, 3.0 Hz, 2H, C18/19-H), 7.60 (dq, *J* = 8.0, 0.9 Hz, 1H, C3-H), 7.26 (s, 1H, C6-H), 7.12 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H, C1-H), 7.05 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H, C2-H), 7.00 (d, *J* = 2.4 Hz, 1H, C7-H), 5.28 (dd, *J* = 9.6, 6.4 Hz, 1H, C10-H), 3.80 (s, 3H, C12-H), 3.78 – 3.73 (m, 2H, C9-H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ [ppm] 169.64 (C-11), 167.55 (C-13/16), 136.06 (C-4), 134.00 (C-18/19), 131.73 (C-14/15), 127.18 (C-5), 123.39 (C-17/20), 122.51 (C-7), 122.11 (C-1), 119.54 (C-2), 118.51 (C-3), 111.15 (C-6), 111.07 (C-8), 52.60 (C-10), 24.80 (C-9).

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3400.46, 2952.51, 2922.96, 1774.68, 1705.27, 1456.69, 1433.95, 1386.30, 1257.50, 1233.70, 1201.99, 1174.08, 1104.17, 1008.47, 964.30, 915.86, 880.06, 792.93, 741.65, 716.55, 698.13, 606.08, 581.35, 529.41, 424.53.

5.3.4 Synthesis of methyl benzyl-*L*-tryptophanate (131)



131

$C_{19}H_{20}N_2O_2$

[308.38]

To a solution of 1.00 g (3.90 mmol, 1.0 eq.) of (*S*)-3-(1*H*-indol-3-yl)-1-methoxy-1-oxopropan-2-aminium chloride (**76a**) in 10 mL methanol were added 1.6 mL (1.7 g, 16 mmol, 4.0 eq.) benzaldehyde (**130**) and 0.612 g (9.75 mmol, 2.5 eq.) of sodium cyanoborohydride. The reaction mixture was stirred overnight at room temperature, after which the solvent was removed under reduced pressure.

The residue was purified by column chromatography (PE/EtOAc = 2:1) to afford the desired product **131** (1.03 g, 3.35 mmol, 86%) as clear crystals.

The synthesis of methyl benzyl-*L*-tryptophanate (**131**) was performed according to the procedure of Simpkins *et al*.[106]

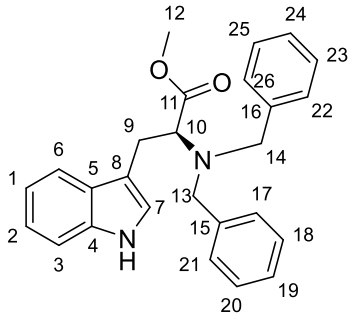
R_f value (PE/EtOAc 3:1 (v/v)): 0.25.

^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm] 10.84 (d, *J* = 2.6 Hz, 1H, indole N-H), 7.43 (d, *J* = 7.9 Hz, 1H, C6-H), 7.35 – 7.30 (m, 1H, C3-H), 7.28 (s, 2H, C15/19-H), 7.27 (s, 2H, C16/18-H), 7.24 - 7.18 (m, 1H, C17-H), 7.10 (d, *J* = 2.3 Hz, 1H, C7-H), 7.05 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H, C2-H), 6.99 – 6.93 (m, 1H, C1-H), 3.76 (d, *J* = 13.6 Hz, 1H, C13-H), 3.61 (d, *J* = 13.6 Hz, 1H, C13-H), 3.52 (s, 3H, C12-H), 3.50 (d, *J* = 6.8 Hz, 1H, C10-H), 3.35 (s, 1H, N-H), 3.04 (d, *J* = 6.6 Hz, 2H, C9-H).

^{13}C-NMR (101 MHz, DMSO-d$_6$): δ [ppm] 174.54 (C-11), 140.10 (C-14), 136.01 (C-5), 128.05 (C-16/18), 127.79 (C-15/19), 127.25 (C-8), 126.62 (C-17), 123.48 (C-7), 120.82 (C-2), 118.22 (C-6), 118.13 (C-1), 111.32 (C-3), 109.77 (C-4), 61.23 (C-10), 51.21 (C-12), 50.88 (C-13), 28.62 (C-9).

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3417.20, 3287.52, 3140.17, 3104.89, 3057.13, 3028.76, 2948.84, 2922.29, 2863.37, 1739.06, 1597.33, 1550.77, 1495.80, 1426.56, 1355.97, 1345.16, 1289.32, 1224.26, 1206.74, 1188.51, 1175.48, 1150.88, 1130.52, 1114.87, 1072.66, 1065.38, 1010.52, 992.58, 979.29, 925.42, 884.53, 869.24, 849.72, 816.96, 803.82, 766.45, 743.24, 696.97, 613.26, 602.19, 575.21, 533.15, 480.36, 458.61, 427.94.

5.3.5 Synthesis of methyl *N*,*N* dibenzyl-*L*-tryptophanate (39)



39

$C_{26}H_{26}N_2O_2$

[398.51]

To a solution of 1.01 g (3.28 mmol, 1.0 eq.) of methyl benzyl-*L*-tryptophanate (**131**) in 15 mL of methanol were added three drops of hydrochloric acid (7 N), 0.67 mL (1.7 g, 16 mmol, 4.0 eq.) of benzaldehyde (**130**) and 0.412 g (6.56 mmol, 2.0 eq.) of sodium cyanoborohydride. The reaction mixture was stirred for a week at room temperature, after which it was diluted with 5 mL each of a saturated solution of potassium hydroxide and sodium chloride.

The reaction mixture was then extracted with diethyl ether, dried over sodium sulfate and the residing solvent removed under reduced pressure.

The residue was purified by column chromatography (PE/EtOAc = 2:1) to afford the desired product **39** (0.401 g, 1.01 mmol, 31%) as clear crystals.

The synthesis of methyl *N*,*N* dibenzyl-*L*-tryptophanate (**39**) was performed according to the procedure of Simpkins *et al.* and the analytical data matched literature values.[8,106]

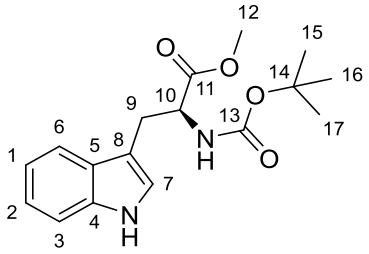
R_f value (PE/EtOAc 3:1 (v/v)): 0.81.

^{1}H-NMR (400 MHz, $CDCl_3$): *δ* [ppm] 7.91 – 7.84 (m, 1H, N-H), δ 7.37 – 7.20 (m, 12H, C2/3/16-24-H), 7.14 (d, *J* = 7.5 Hz, 1H, C6-H), 6.99 – 6.94 (m, 1H, C1-H), 6.89 (d, *J* = 2.3 Hz, 1H, C7-H), 4.01 (d, *J* = 13.8 Hz, 2H, C13a/14a-H), 3.80 (dd, *J* = 9.1, 5.7 Hz, 1H, C10-H), 3.68 (s, 3H, C12-H), 3.54 (d, *J* = 13.9 Hz, 2H, C13b/14b-H), 3.37 (dd, *J* = 14.3, 9.1 Hz, 1H, C9-H), 3.08 (ddd, *J* = 14.4, 5.7, 0.9 Hz, 1H, C9-H).

^{13}C-NMR (101 MHz, $CDCl_3$): *δ* [ppm] 173.06 (C-11), 139.68 (C-15/16), 136.25 (C-4), 128.94 (C-17/21/22/26), 128.34 (C-18/20/23/25), 127.57 (C-5), 127.07 (C-19/24), 122.83 (C-7), 121.92 (C-2), 119.34 (C-1), 118.86 (C-3), 112.30 (C-8), 111.02 (C-6), 61.53 (C-10), 54.83 (C-13/14), 51.10 (C-12), 26.38 (C-9).

IR (ATR) *ṽ* [cm^{-1}]: 3436.09, 3056.19, 3026.58, 2994.75, 2947.60, 2911.59, 2846.31, 1726.85, 1597.61, 1492.10, 1454.14, 1420.63, 1354.68, 1334.87, 1312.30, 1254.04, 1199.70, 1163.27, 1124.23, 1087.73, 1071.69, 1026.01, 986.64, 957.74, 886.59, 824.41, 807.41, 782.18, 738.43, 698.95, 577.87, 517.27, 501.98, 455.80, 426.74.

5.3.6 Synthesis of methyl (*tert*-butoxycarbonyl)-*L*-tryptophanate (25a)



25a

$C_{17}H_{22}N_2O_4$

[318.37]

To a suspension of 2.55 g (10.0 mmol, 1.0 eq.) of (*S*)-3-(1*H*-indol-3-yl)-1-methoxy-1-oxopropan-2-aminium chloride (**76a**) and 2.40 g (11.0 mmol, 1.1 eq.) of di-*tert*-butyl dicarbonate in 20 mL dichloromethane were added 3.1 mL (2.2 g, 22 mmol, 2.2 eq.) of triethylamine to form a clear solution. The reaction mixture was stirred overnight at room temperature. After complete conversion the reaction mixture was washed several times with a 1 M solution of citric acid and then several times with brine. The organic layer was dried over magnesium sulfate and the solvent removed under reduced pressure to afford the desired product **25a** (2.97 g, 9.30 mmol, 93%) as a white solid without further purification.

The synthesis of methyl (*tert*-butoxycarbonyl)-*L*-tryptophanate (**25a**) was performed according to the procedure of Liu *et al.* and the analytical data matched literature values.[104,121]

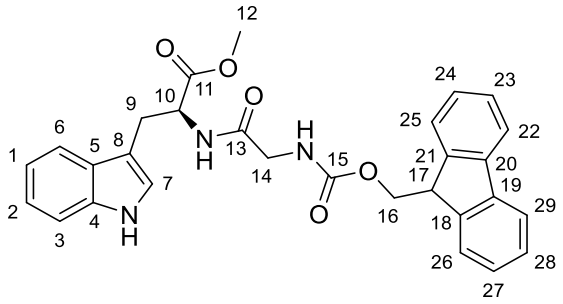
R_f value (EtOAc): 0.70.

^{1}H-NMR (400 MHz, $CDCl_3$): *δ* [ppm] 8.14 (s, 1H, indole N-H), 7.55 (d, *J* = 7.8 Hz, 1H, C6-H), 7.35 (d, *J* = 8.0 Hz, 1H, C3-H), 7.23 – 7.16 (m, 1H, C1-H), 7.12 (t, *J* = 7.4 Hz, 1H, C2-H), 7.00 (d, *J* = 2.2 Hz, 1H, C7-H), 5.08 (d, *J* = 8.2 Hz, 1H, N-H), 4.65 (dt, *J* = 8.4, 5.5 Hz, 1H, C10-H), 3.68 (s, 3H, C12-H), 3.29 (dd, *J* = 5.5, 2.8 Hz, 2H, C9-H), 1.43 (s, 9H, C15/16/17-H).

^{13}C-NMR (101 MHz, $CDCl_3$): *δ* [ppm] 172.77 (C-11), 155.25 (C-13), 136.10 (C-5), 127.69 (C-4), 122.71 (C-7), 122.20 (C-1), 119.62 (C-2), 118.77 (C-6), 111.16 (C-3), 110.25 (C-8), 79.84 (C-14), 54.17 (C-10), 52.25 (C-12), 28.34 (C-15/16/17), 27.99 (C-9).

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3382.23, 3318.15, 3057.83, 2975.20, 2948.99, 2932.76, 1735.47, 1689.68, 1651.32, 1619.49, 1519.39, 1491.93, 1458.53, 1440.23, 1390.34, 1367.34, 1355.14, 1345.44, 1292.65, 1277.43, 1250.04, 1218.30, 1163.82, 1149.67, 1123.66, 1095.74, 1076.66, 1054.63, 1035.53, 1011.06, 982.44, 923.73, 878.13, 853.76, 827.41, 782.58, 750.48, 708.14, 679.82, 617.29, 559.89, 539.01, 462.83, 423.05.

5.3.7 Synthesis of methyl (((9*H*-fluoren-9-yl)methoxy)carbonyl)glycyl-*L*-tryptophanate (78)



78

$C_{29}H_{27}N_3O_5$

[497.55]

A suspension of 0.635 g (2.50 mmol, 1.0 eq.) of (*S*)-3-(1*H*-indol-3-yl)-1-methoxy-1-oxopropan-2-aminium chloride (**76a**) and 1.11 g (3.85 mmol, 1.5 eq.) of Fmoc-glycine **77** in 10 mL of dichloromethane was stirred for ten minutes at room temperature under a nitrogen atmosphere. Then 1.42 g (3.85 mmol, 1.5 eq.) of HBTU and 1.2 mL (0.82 g, 6.8 mmol, 2.7 eq.) of DIPEA were added to form a clear solution and the reaction mixture was stirred for 6.5 hours. Afterwards, the solvent was removed under reduced pressure.

The residue was purified by column chromatography (PE/EtOAc = 1:4) to afford the desired product **78** quantitatively (1.24 g, 2.50 mmol) as clear crystals.

The synthesis of methyl (((9*H*-fluoren-9-yl)methoxy)carbonyl)glycyl-*L*-tryptophanate (**78**) was performed according to the procedures of Speicher *et al.* and Alewood *et al.* and the analytical data matched literature values.[80,81,122]

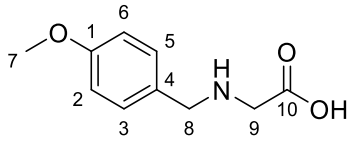
R_f value (PE/EtOAc 1:4 (v/v)): 0.78.

^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] 7.96 (s, 1H, indole N-H), 7.78 (d, *J* = 7.5 Hz, 2H, C25/26-H), 7.62 – 7.54 (m, 2H, C22/29-H), 7.49 (d, *J* = 7.8 Hz, 1H, C3-H), 7.41 (t, *J* = 7.5 Hz, 2H, C24/27-H), 7.35 – 7.27 (m, 3H, C23/28/6-H), 7.16 (ddd, *J* = 8.2, 7.0, 1.3 Hz, 1H, C1-H), 7.10 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H, C2-H), 6.94 (d, *J* = 2.4 Hz, 1H, C7-H), 6.39 (d, *J* = 7.9 Hz, 1H, Trp N-H), 5.29 (d, *J* = 6.7 Hz, 1H, Gly N-H), 4.94 (dt, *J* = 7.8, 5.3 Hz, 1H, C8-H), 4.37 (d, *J* = 7.0 Hz, 2H, C16-H), 4.20 (d, *J* = 7.1 Hz, 1H, C17-H), 3.83 (d, *J* = 5.7 Hz, 2H, C14-H), 3.69 (s, 3H, C12-H), 3.33 (d, *J* = 5.3 Hz, 2H, C9-H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ [ppm] 172.14 (C-15), 168.85 (C-11), 143.89 (C-13), 141.37 (C-4), 136.23 (C-5), 135.27 (C-18/21), 127.87 (C-24/27), 127.56 (C-19/20), 127.22 (C-23/28), 125.22 (C-22/29), 123.24 (C-7), 122.23 (C-1), 120.10 (C-25/26), 119.69 (C-2), 118.37 (C-3), 111.54 (C-6), 109.49 (C-8), 67.36 (C-16), 53.04 (C-10), 52.56 (C-12), 47.13 (C-17), 44.49 (C-14), 27.57 (C-9).

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3308.27, 3055.63, 2949.97, 1711.72, 1662.96, 1513.31, 1446.66, 1340.80, 1212.08, 1103.50, 1044.33, 1008.10, 939.92, 737.45, 664.95, 620.27, 583.85, 534.96, 459.88, 424.96, 382.94.

5.3.8 Synthesis of (4-methoxybenzyl)glycine (81)



81

$C_{10}H_{13}NO_3$

[195.22]

To a solution of 4.8 mL (5.0 g, 37 mmol, 1.05 eq.) of *p*-methoxybenzylamine (**82**) in 15 mL of THF were added 9.8 mL (7.1 g, 79 mmol, 2.2 eq.) of triethylamine and the mixture was stirred at room temperature for ten minutes. Afterwards, the reaction mixture was cooled to 0 °C and 3.9 mL (5.9 g, 35 mmol, 1.0 eq.) of bromo acetate (**83**) were added dropwise. The mixture was then stirred overnight and during this time allowed to reach room temperature again. Then the mixture was filtered over a pad of silica gel and the solvent removed under reduced pressure. The residue was collected in 10 mL of ethanol and diluted with sodium hydroxide (2.80 g, 70.0 mmol, 2.0 eq.) which was previously solved in 60 mL of ethanol. The reaction mixture was stirred overnight at room temperature. The next day the solution was acidified to reach a pH-value of 6-7 with 4 N hydrochloric acid until the formed solid was completely dissolved. Afterwards, the solvent was removed under reduced pressure, the residue dissolved in methanol and the undissolving parts cleaved *via* filtration. The solvent was removed under reduced pressure and the residue dissolved in dichloromethane. The obtained solid was filtrated and dried under high vacuum to give the desired product **81** (6.4 g, 33 mmol, 94%).

The synthesis of (4-methoxybenzyl)glycine (**81**) was performed according to the procedure from the dissertation of F. Fini and the analytical data matched literature values.[85]

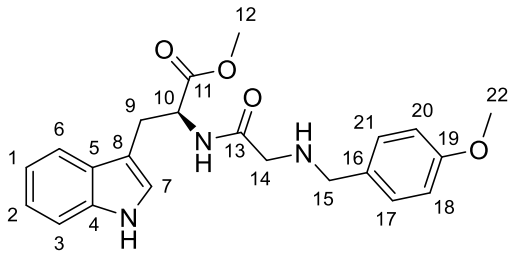
R_f value (DCM/MeOH 2:1 (v/v)): 0.20.

^{1}H-NMR (300 MHz, MeOD): *δ* [ppm] 7.45 (d, *J* = 8.7 Hz, 2H, C2/6-H), 7.02 (d, *J* = 8.7 Hz, 2H, C3/5-H), 4.20 (s, 2H, C9-H), 3.85 (s, 3H, C7-H), 3.69 (s, 2H, C8-H).

^{13}C-NMR (76 MHz, MeOD): *δ* [ppm] 170.71 (C-10), 162.13 (C-1), 132.57 (C-3/5), 124.62 (C-4), 115.49 (C-2/6), 55.78 (C-7), 51.42 (C-8), 49.63 (C-9).

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3468.65, 2985.46, 2935.27, 2833.20, 2756.85, 2632.91, 2420.76, 1762.79, 1690.54, 1612.92, 1586.51, 1516.43, 1466.25, 1433.11, 1404.64, 1341.22, 1300.18, 1274.08, 1249.00, 1179.73, 1114.45, 1053.86, 1030.24, 998.72, 921.08, 834.31, 816.85, 756.56, 717.11, 683.05, 620.99, 559.64, 524.41, 499.35, 392.66.

5.3.9 Synthesis of methyl (4-methoxybenzyl)glycyl-*L*-tryptophanate (84a)



84a

$C_{22}H_{25}N_3O_2$

[395.45]

A suspension of 3.67 g (14.4 mmol, 1.2 eq.) of (*S*)-3-(1*H*-indol-3-yl)-1-methoxy-1-oxopropan-2-aminium chloride (**76a**) and 2.34 g (12.0 mmol, 1.0 eq.) of (4-methoxybenzyl)glycine (**78**) in 40 mL of dichloromethane was stirred for ten minutes at room temperature under a nitrogen atmosphere. Then 6.83 g (18.0 mmol, 1.5 eq.) of HBTU and 5.5 mL (4.2 g, 33 mmol, 2.7 eq.) of DIPEA were added to form a clear solution and the reaction mixture was stirred for three days at room temperature. The reaction mixture was then filtered through a pad of silica gel and the solvent was removed under reduced pressure.

The residue was purified by column chromatography (dichloromethane/methanol = 100:1 plus 3% triethylamine) to afford the desired product **84a** quantitatively (4.63 g, 12.0 mmol) as clear a light yellow solid.

The synthesis of methyl (4-methoxybenzyl)glycyl-*L*-tryptophanate (**84a**) was performed according to the procedures of Speicher *et al.* and Alewood *et al*.[80,81]

R_f value (EtOAc): 0.27.

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] 8.24 (s, 1H, indole N-H), 7.74 (d, *J* = 8.2 Hz, 1H, Trp N-H), 7.55 (dd, *J* = 7.9, 1.2 Hz, 1H, C3-H), 7.33 (dt, *J* = 8.2, 0.9 Hz, 1H, C6-H), 7.18 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H, C1-H), 7.09 (ddd, *J* = 7.9, 7.0, 1.0 Hz, 1H, C2-H), 7.02 – 6.98 (m, 2H, C18/20-H), 6.96 (d, *J* = 2.4 Hz, 1H, C7-H), 6.81 – 6.75 (m, 2H, C17/21-H), 4.96 (dt, *J* = 8.2, 5.6 Hz, 1H, C10-H), 3.78 (s, 3H, C12-H), 3.70 (s, 3H, C22-H), 3.58 – 3.46 (m, 2H, C15-H), 3.39 – 3.28 (m, 2H, C9-H), 3.24 (d, *J* = 1.8 Hz, 2H, C14-H) 2.81 (s, 1H, Gly N-H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ [ppm] 172.54 (C-11), 171.63 (C-13), 158.80 (C-19), 136.22 (C-16), 131.58 (C-4), 129.42 (C-18/20), 128.06 (C-5), 123.06 (C-7), 122.59 (C-1), 119.71 (C-2), 118.72 (C-3), 113.90 (C-17/21), 111.39 (C-6), 110.20 (C-8), 55.43 (C-12), 53.11 (C-15), 52.53 (C-10), 52.48 (C-22), 51.81 (C-14), 27.79 (C-9).

ESI-MS [*m/z*]: calc.: 396.1923 $[M]+H^+$.

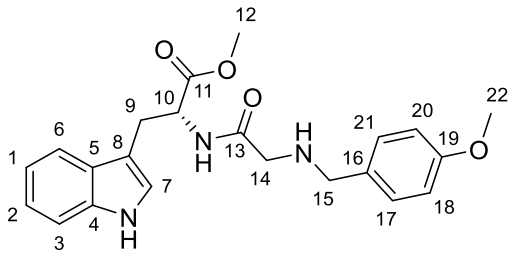
found: 396.1931 $[M]+H^+$.

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3287.31, 3057.16, 3001.94, 2950.32, 2926.76, 2837.68, 2810.34, 1745.17, 1645.64, 1611.08, 1584.46, 1510.10, 1458.05, 1433.91, 1418.22, 1355.89, 1333.67, 1300.04, 1247.22, 1197.27, 1175.95, 1119.66, 1107.16, 1024.57, 1011.16, 979.45, 959.22, 925.04, 849.76, 836.03, 816.12, 790.69, 762.67, 742.56, 714.94, 645.18, 574.19, 559.30, 528.44, 519.55, 484.74, 450.61, 433.73.

Rotation value (*c* 1.0, $CHCl_3$) $[\alpha]_D^{20}$**:** +19.2°.

Melting point: 93 °C.

5.3.10 Synthesis of methyl (4-methoxybenzyl)glycyl-*D*-tryptophanate (84b)



84b

$C_{22}H_{25}N_3O_2$

[395.45]

A suspension of 3.13 g (12.3 mmol, 1.2 eq.) of (*R*)-3-(1*H*-indol-3-yl)-1-methoxy-1-oxopropan-2-aminium chloride (**76b**) and 2.00 g (10.2 mmol, 1.0 eq.) of (4-methoxybenzyl)glycine (**78**) in 40 mL of dichloromethane was stirred for ten minutes at room temperature under a nitrogen atmosphere. Then 5.80 g (15.3 mmol, 1.5 eq.) of HBTU and 4.7 mL (3.6 g, 28 mmol, 2.7 eq.) of DIPEA were added to form a clear solution and the reaction mixture was stirred for three days at room temperature. The reaction mixture was then filtered through a pad of silica gel and the solvent was removed under reduced pressure.

The residue was purified by column chromatography (dichloromethane/methanol = 100:1 with 3% triethylamine) to afford the desired product **84b** (2.49 g, 6.30 mmol, 62%) as a light yellow solid.

The synthesis of methyl (4-methoxybenzyl)glycyl-*D*-tryptophanate (**84b**) was performed according to the procedures of Speicher *et al.* and Alewood *et al*.[80,81]

R_f value (EtOAc): 0.27.

^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] 8.35 – 8.26 (m, 1H, indole N-H), 7.74 (d, *J* = 8.2 Hz, 1H, NTrp-H), 7.55 (dd, *J* = 7.8, 1.0 Hz, 1H, C3-H), 7.34 (dd, *J* = 8.1, 1.0 Hz, 1H, C6-H), 7.17 (ddd, *J* = 8.3, 7.0, 1.2 Hz, 1H, C1-H), 7.09 (ddd, *J* = 7.9, 7.0, 1.0 Hz, 1H, C2-H), 6.99 (d, *J* = 8.5 Hz, 2H, C18/20-H), 6.96 (d, *J* = 2.4 Hz, 1H, C7-H), 6.80 – 6.75 (m, 2H, C17/21-H), 4.96 (dt, *J* = 8.2, 5.6 Hz, 1H, C10-H), 3.78 (s, 3H, C12-H), 3.69 (s, 3H, C22-H), 3.57 – 3.46 (m, 2H, C15-H), 3.35 – 3.31 (m, 2H, C9-H), 3.23 (d, *J* = 1.5 Hz, 2H, C14-H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ [ppm] 172.53 (C-11), 170.99 (C-13), 159.02 (C-19), 136.23 (C-16), 130.64 (C-4), 129.63 (C-18/20), 127.69 (C-5), 123.04 (C-7), 122.26 (C-1), 119.67 (C-2), 118.66 (C-3), 113.97 (C-17/21), 111.45 (C-6), 110.13 (C-8), 55.38 (C-12), 52.89 (C-15), 52.61 (C-10), 52.49 (C-22), 51.28 (C-14), 27.75 (C-9).

ESI-MS [*m/z*]: calc.: 396.1923 [M]+H$^+$.

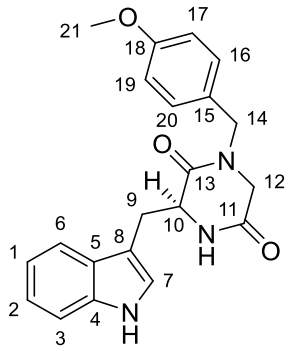
found: 396.1938 [M]+H$^+$.

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3306.95, 3055.71, 3001.34, 2950.39, 2835.01, 1738.11, 1655.29, 1610.68, 1584.51, 1509.58, 1456.21, 1436.55, 1340.53, 1300.48, 1242.98, 1205.11, 1174.47, 1150.83, 1107.00, 1073.30, 1029.74, 1009.84, 987.95, 929.85, 848.53, 815.71, 739.89, 635.33, 582.06, 559.05, 518.08, 460.22, 425.59.

Rotation value (*c* 0.50, $CHCl_3$) $[\alpha]_D^{20}$**:** -34.6°.

Melting point: 47 °C.

5.3.11 Synthesis of (*S*)-3-((1*H*-indol-3-yl)methyl)-1-(4-methoxybenzyl)piperazine-2,5-dione (85a)



85a

$C_{21}H_{21}N_3O_3$

[363.41]

To a solution of 1.00 g (2.53 mmol, 1.0 eq.) of methyl (4-methoxybenzyl)glycyl-*L*-tryptophanate (**84a**) in 30 mL dry THF were added 0.58 mL (0.61 g, 10 mmol, 4.0 eq.) of acetic acid (100%) and stirred for 16 hours at 50 °C. The reaction mixture was diluted with toluene, the solvent removed under reduced pressure and the residue purified *via* column chromatography using ethyl acetate as eluent. This procedure gave the desired product **85a** (0.831 g, 2.29 mmol, 91%) as a colourless solid.

R_f value (EtOAc): 0.18.

^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] 8.28 (s, 1H, indole N-H), 7.64 (d, *J* = 8.0 Hz, 1H, C3-H), 7.36 (d, *J* = 8.1 Hz, 1H, C6-H), 7.22 (t, *J* = 7.5 Hz, 1H, C2-H), 7.15 (t, *J* = 7.4 Hz, 1H, C1-H), 6.95 (dd, *J* = 8.8, 2.3 Hz, 3H, C7/16/20-H), 6.83 – 6.68 (m, 2H, C17/19-H), 6.41 (d, *J* = 2.5 Hz, 1H, DKP N-H), 4.51 (d, *J* = 14.4 Hz, 1H, C14-H), 4.35 (td, *J* = 5.9, 2.9 Hz, 1H, C10-H), 4.08 (d, *J* = 14.4 Hz, 1H, C14-H), 3.77 (s, 3H, C21-H), 3.48 (d, *J* = 17.6 Hz, 1H, C12-H), 3.34 (t, *J* = 5.2 Hz, 2H, C9-H), 3.00 (d, *J* = 17.7 Hz, 1H, C12-H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ [ppm] 166.10 (C-13), 165.82 (C-11), 159.45 (C-18), 136.37 (C-4), 129.94 (C-16/20), 127.12 (C-15), 127.05 (C-5), 124.20 (C-7), 122.70 (C-2), 120.17 (C-1), 119.10 (C-3), 114.30 (C-17/19), 111.44 (C-6), 109.19 (C-8), 55.97 (C-10), 55.42 (C-21), 49.04 (C-14), 48.44 (C-12), 30.90 (C-9).

ESI-MS [*m/z*]: calc.: 364.1661 $[M]+H^+$.

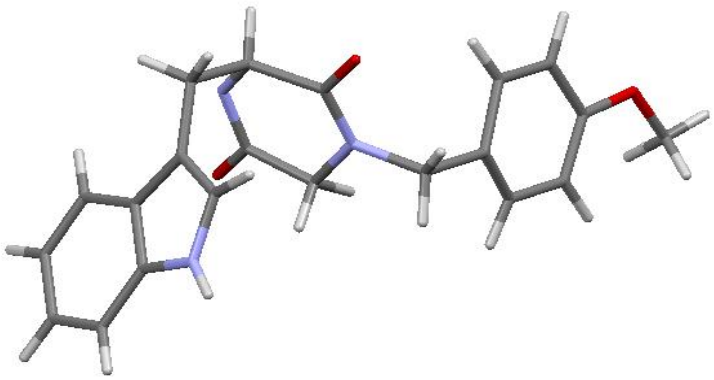
found: 364.1657 $[M]+H^+$.

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3256.16, 2925.35, 2853.13, 1681.30, 1645.91, 1625.66, 1613.09, 1586.44, 1511.79, 1457.20, 1434.35, 1337.87, 1321.83, 1305.50, 1245.16, 1176.43, 1152.23, 1130.46, 1106.30, 1075.15, 1057.06, 1032.16, 907.55, 844.98, 807.61, 730.65, 686.02, 633.20, 600.86, 556.86, 516.81, 459.86, 423.61.

Rotation value (*c* 0.25, $CHCl_3$) $[\alpha]_D^{20}$**:** -12.0°.

Melting point: 128 °C.

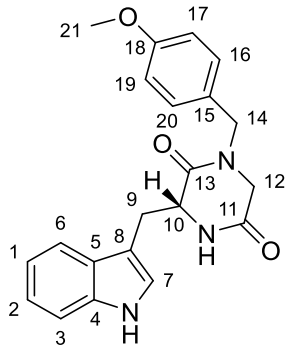
Crystal data:



Cell	a = 28.4428(5) Å;	α = 90°
	b = 6.22970(10) Å;	β = 97.659(2)°
	c = 12.2268(2) Å;	γ = 90°
	V = 2147.14(6) Å^3	
	from 10640 reflns. between θ_{min} = 3.6° and θ_{max} = 76.1°	

Z	4
Crystal system, space group	monoclinic, *C2y*
Crystal size	0.35 x 0.12 x 0.08
Crystal colour, morphology	colourless, needle
F(000)	780
D_x	1.134 Mg m^{-3}
θ_{min}, θ_{max}	3.14°, 75.0°
Completeness at θ_{max}	1.000
Radiation type	Cu *Kα* (*λ* = 1.54184 Å)
Temperature	100 K
μ	0.621 mm^{-1}
Diffractometer	Rigaku SuperNova
T_{min}, T_{max}	0.6529, 1.000
hkl range	*h*: -35→35, *k*: -7→7, *l*: -15→15
No. of reflections	19255 measured, 4323 independent, 4189 ($I > 2\sigma(I)$)
R_{int}	0.0282
$\sin(\theta_{max})/\lambda$	-0.256 $Å^{-1}$
$R[F^2 > 2\sigma(F^2)]$	0.0495
$wR(F^2)$	0.1421
S	1.062
w	$1/(\sigma^2(F_o^2)+(0.0858P)^2+1.8692P)$ with $P=(F_o^2+2F_c^2)/3$
$(\Delta/\sigma)_{max}$	0.001
$\Delta\rho_{max}$, $\Delta\rho_{min}$	0.495 e $Å^3$, -0.375 e $Å^3$
No. of reflections	4189
No. of parameters / restraints	232 / 1

5.3.12 Synthesis of (*R*)-3-((1*H*-indol-3-yl)methyl)-1-(4-methoxybenzyl)piperazine-2,5-dione (85b)



85b

$C_{21}H_{21}N_3O_3$

[363.41]

To a solution of 1.25 g (3.16 mmol, 1.0 eq.) of methyl (4-methoxybenzyl)glycyl-*D*-tryptophanate (**84b**) in 30 mL dry THF were added 0.36 mL (0.38 g, 6.3 mmol, 2.0 eq.) of acetic acid (100%) and stirred for 16 hours at 50 °C. The reaction mixture was diluted with toluene, the solvent removed under reduced pressure and the residue purified *via* column chromatography using ethyl acetate as eluent. This procedure gave the desired product **85b** (1.05 g, 2.89 mmol, 92%) as a colourless solid.

R_f value (EtOAc): 0.23.

^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] 8.19 (s, 1H, indole N-H), 7.64 (d, *J* = 7.9 Hz, 1H, C3-H), 7.38 (d, *J* = 8.1 Hz, 1H, C6-H), 7.23 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H, C2-H), 7.18 – 7.14 (m, 1H, C1-H), 7.01 (s, 1H, C7-H), 6.99 – 6.95 (m, 2H, C16/20-H), 6.81 – 6.75 (m, 2H, C17/19-H), 6.23 - 6.17 (m, 1H, DKP N-H), 4.52 (d, *J* = 14.5 Hz, 1H, C14-H), 4.36 (ddd, *J* = 6.7, 4.0, 2.3 Hz, 1H, C10-H), 4.10 (d, *J* = 14.4 Hz, 1H, C14-H), 3.78 (s, 3H, C21-H), 3.51 (d, *J* = 17.6 Hz, 1H, C12-H), 3.36 (dd, *J* = 7.2, 5.4 Hz, 2H, C9-H), 3.04 (d, *J* = 17.6 Hz, 1H, C12-H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ [ppm] 165.99 (C-13), 165.78 (C-11), 159.50 (C-18), 136.41 (C-4), 129.97 (C-16/20), 127.10 (C-15), 127.08 (C-5), 124.17 (C-7), 122.77 (C-2), 120.23 (C-1), 119.10 (C-3), 114.32 (C-17/19), 111.45 (C-6), 109.29 (C-8), 55.98 (C-10), 55.44 (C-21), 49.09 (C-14), 48.49 (C-12), 30.95 (C-9).

ESI-MS [*m/z*]: calc.: 364.1661 $[M]+H^+$.

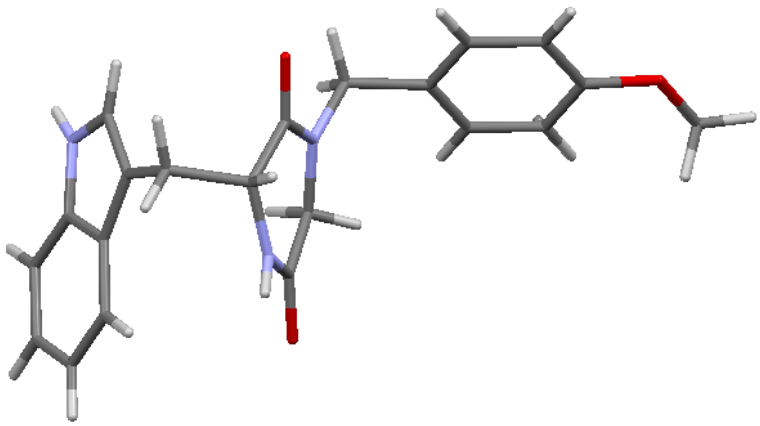
found: 364.1658 $[M]+H^+$.

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3254.46, 3150.81, 2927.18, 2832.12, 1735.83, 1685.72, 1652.72, 1623.43, 1585.86, 1546.18, 1512.36, 1472.09, 1434.27, 1369.52, 1346.62, 1338.31, 1321.68, 1305.72, 1279.57, 1246.79, 1193.02, 1177.98, 1152.15, 1106.87, 1075.50, 1056.22, 1032.47, 955.53, 871.63, 844.44, 808.92, 756.82, 739.25, 706.12, 685.72, 633.18, 600.60, 556.76, 514.81, 453.88, 443.14, 424.35, 396.49.

Rotation value (*c* 0.25, $CHCl_3$) $[\alpha]_D^{20}$**:** +16.0°.

Melting point: 133 °C.

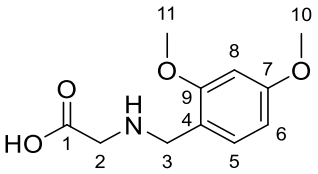
Crystal data:



Cell	a = 28.4477 (7) Å; α = 90° b = 6.2333 (2) Å; β = 97.385 (2)° c = 12.2470 (3) Å; γ = 90° V = 2153.66 (10) Å from 9897 reflns. between θ_{min} = 3.6° and θ_{max} = 76.3°
Z	4
Crystal system, space group	monoclinic, C2y
Crystal size	0.32 x 0.12 x 0.07
Crystal colour, morphology	clear colourless, needle
F(000)	768.0
D_x	1.121 Mg m^{-3}
θ_{min}, θ_{max}	3.13°, 76.3°
Completeness at θ_{max}	0.999
Radiation type	Cu *Kα* (λ = 1.54184 Å)

Temperature	100 K
μ	0.619 mm^{-1}
Diffractometer	Rigaku SuperNova
T_{min}, T_{max}	0.648, 1.000
hkl range	*h*: -35→35, *k*: -7→7, *l*: -15→15
No. of reflections	18605 measured, 4438 independent, 4271 ($I > 2\sigma(I)$)
R_{int}	0.0455
$\sin(\theta_{max})/\lambda$	0.527 $Å^{-1}$
$R[F^2 > 2\sigma(F^2)]$	0.04400
$wR(F^2)$	0.1180
S	1.076
w	$1/(\sigma^2(F_o^2)+(0.0723P)^2+0.7629P)$ with $P=(F_o^2+2F_c^2)/3$
$(\Delta/\sigma)_{max}$	0.001
$\Delta\rho_{max}$, $\Delta\rho_{min}$	0.277 e $Å^3$, -0.204 e $Å^3$
No. of reflections	4271
No. of parameters / restraints	244 / 122

5.3.13 Synthesis of (2,4-dimethoxybenzyl)glycine (113)



113

$C_{11}H_{15}NO_4$

[225.24]

To a solution of 5.5 mL (5.0 g, 37 mmol, 1.05 eq.) of 2,4-dimethoxybenzylamine (**112**) in 15 mL of THF were added 9.8 mL (7.1 g, 79 mmol, 2.2 eq.) of triethylamine and the mixture was stirred at room temperature for ten minutes. Afterwards, the reaction mixture was cooled to 0 °C and 3.9 mL (5.9 g, 35 mmol, 1.0 eq.) of bromo acetate (**83**) were added dropwise. The mixture was then stirred overnight and during this time allowed to reach room temperature again. Then the mixture was filtered over a pad of silica gel and the solvent removed under reduced pressure. The residue was collected in 10 mL of ethanol and diluted with sodium hydroxide (2.80 g, 70.0 mmol, 2.0 eq.) which was previously solved in 60 mL of ethanol. The reaction mixture was stirred overnight at room temperature. The next day the solution was acidified to reach a pH-value of 6-7 with 4 N hydrochloric acid until the formed solid was completely dissolved. Afterwards, the solvent was removed under reduced pressure.

The residue was purified by column chromatography (ethanol/acetic acid/water = 6:1:1) to afford the desired product **113** (3.8 g, 17 mmol, 48%) as a light yellow solid.

The synthesis of (2,4-dimethoxybenzyl)glycine (**113**) was performed according to the procedure from the dissertation of F. Fini.[85]

R_f value (EtOH/AcOH/H_2O 4:1:1 (v/v)): 0.80.

^{1}H-NMR (500 MHz, MeOD): δ [ppm] 7.26 (d, 1H, C5-H), 6.36 – 6.28 (m, 2H, C6/8-H), 4.00 (s, 2H, C3-H), 3.69 (s, 3H, C10/11-H), 3.68 (s, 3H, C10/11-H) 3.27 (s, 2H, C2-H).

^{13}C-NMR (126 MHz, MeOD): δ [ppm] 171.3 (C-1), 161.6 (C-7/9), 159.0 (C-7/9), 132.7 (C-5), 112.1 (C-4), 104.6 (C-6/8), 98.2 (C-6/8), 55.3 (C-10/11), 55.3 (C-10/11), 48.3 (C-2), 44.2 (C-3).

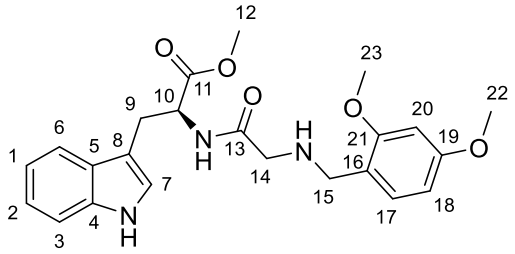
ESI-MS [*m/z*]: calc.: 248.0893 $[M]+Na^{+}$.

found: 248.0900 $[M]+Na^{+}$.

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 2939.00, 2836.82, 1716.75, 1612.56, 1585.81, 1509.35, 1455.62, 1437.69, 1419.58, 1331.59, 1290.16, 1269.72, 1206.47, 1157.56, 1131.95, 1118.30, 1026.27, 925.22, 828.32, 729.72, 702.26, 638.77, 585.08, 489.37, 466.23.

Melting point: 53 °C.

5.3.14 Synthesis of methyl (2,4-dimethoxybenzyl)glycyl-*L*-tryptophanate (114)



114

$C_{23}H_{27}N_3O_5$

[425.49]

A suspension of 2.17 g (8.52 mmol, 1.2 eq.) of (*S*)-3-(1*H*-indol-3-yl)-1-methoxy-1-oxopropan-2-aminium chloride (**76a**) and 1.60 g (7.10 mmol, 1.0 eq.) of (2,4-dimethoxybenzyl)glycine (**113**) in 25 mL of dichloromethane was stirred for ten minutes at room temperature under a nitrogen atmosphere. Then 4.06 g (10.7 mmol, 1.5 eq.) of HBTU and 3.3 mL (2.5 g, 19 mmol, 2.7 eq.) of DIPEA were added to form a clear solution and the reaction mixture was stirred for three days at room temperature. The reaction mixture was then filtered through a pad of silica gel and the solvent was removed under reduced pressure.

The residue was purified by column chromatography (dichloromethane/methanol = 100:1 plus 3% triethylamine) to afford the desired product **114** (2.63 g, 6.18 mmol, 87%) as a light yellow solid.

The synthesis of methyl (2,4-dimethoxybenzyl)glycyl-*L*-tryptophanate (**114**) was performed according to the procedures of Speicher *et al.* and Alewood *et al*.[80,81]

R_f value (EtOAc): 0.65.

^{1}H-NMR (400 MHz, $CDCl_3$): *δ* [ppm] 8.44 (s, 1H, N-H), 7.53 (d, *J* = 7.9 Hz, 1H, C6-H), 7.35 (d, *J* = 8.2 Hz, 1H, C1-H), 7.18 – 7.13 (m, 1H, C2-H), 7.09 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H, C3-H), 7.04 (d, *J* = 8.2 Hz, 1H, C7-H), 6.89 (d, *J* = 8.3 Hz, 1H, C17-H), 6.41 (d, *J* = 2.4 Hz, 1H, C20-H), 6.37 (dd, *J* = 8.3, 2.4 Hz, 1H, C18-H), 4.85 (dt, *J* = 7.9, 5.6 Hz, 1H, C10-H), 4.36 (d, *J* = 3.0 Hz, 2H, C15-H), 3.91 (s, 2H, C14-H), 3.77 (s, 3H, C22/23-H), 3.74 (s, 3H, C22/23-H), 3.66 (s, 3H, C12-H), 3.28 (d, *J* = 5.6 Hz, 2H, C9-H).

^{13}C-NMR (101 MHz, $CDCl_3$): *δ* [ppm] 172.7 (C-11/13), 169.1 (C-11/13), 161.0 (C-18/20), 158.5 (C-18/20), 136.2 (C-4), 129.5 (C-17), 127.6 (C-5), 123.4 (C-7), 122.1 (C-2), 119.6 (C-1), 118.6 (C-6), 116.0 (C-16), 111.4 (C-3), 110.1 (C-8), 104.0 (C-18), 98.9 (C-20), 55.5 (C-22/23), 55.3 (C-22/23), 53.43 (C-10), 52.4 (C-12), 49.2 (C-15), 48.8 (C-14), 27.9 (C-9).

ESI-MS [*m/z*]: calc.: 426.2023 $[M]+H^+$.

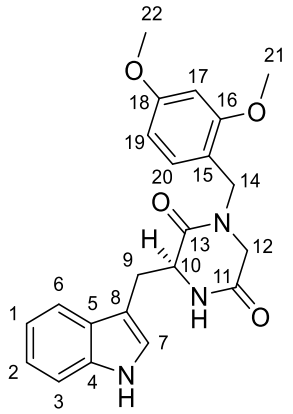
found: 426.1999 $[M]+H^+$.

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3271.26, 2932.62, 2837.31, 1739.80, 1651.32, 1611.79, 1587.52, 1505.67, 1455.71, 1435.50, 1373.77, 1339.49, 1288.04, 1260.14, 1234.47, 1205.60, 1155.12, 1128.76, 1029.95, 989.25, 933.00, 830.75, 741.09, 634.18, 584.06, 559.16, 509.66, 460.88, 425.27.

Rotation value (*c* 0.20, $CHCl_3$) $[\alpha]_D^{20}$**:** +19.0°.

Melting point: 81 °C.

5.3.15 Synthesis of (*S*)-3-((1*H*-indol-3-yl)methyl)-1-(2,4-dimethoxybenzyl)piperazine-2,5-dione (115)



115

$C_{22}H_{23}N_3O_4$

[393.44]

To a solution of 0.320 g (0.752 mmol, 1.0 eq.) of methyl (2,4-dimethoxybenzyl)glycyl-*L*-tryptophanate (**114**) in 10 mL dry THF were added 0.086 mL (0.90 g, 1.5 mmol, 2.0 eq.) of acetic acid (100%) and stirred for four hours at 50 °C and overnight at room temperature. The reaction mixture was diluted with toluene and the solvent removed under reduced pressure.

The residue was purified by column chromatography using ethyl acetate as eluent to afford the desired product **115** (0.240 g, 0.610 mmol, 81%) as a colourless solid.

R_f value (EtOAc): 0.20.

^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] 8.36 (s, 1H, N-H), 7.61 (d, J = 7.9 Hz, 1H, C3-H), 7.35 (dd, J = 8.1, 1.0 Hz, 1H, C6-H), 7.20 (ddd, J = 8.1, 7.0, 1.2 Hz, 1H, C1-H), 7.13 (ddd, J = 8.1, 7.3, 1.0 Hz, 1H, C2-H), 7.04 (d, J = 8.1 Hz, 1H, C20-H), 6.93 (d, J = 2.3 Hz, 1H, C7-H), 6.38 (m, 2H, C17/19-H), 4.53 (d, J = 14.2 Hz, 1H, C14-H), 4.28 (m, 1H, C10-H), 4.20 (d, J = 14.2 Hz, 1H, C14-H), 3.79 (s, 3H, C21/22-H), 3.72 (s, 3H, C21/22-H), 3.67 (d, J = 10.6 Hz, 1H, C12-H), 3.37 (dd, J = 14.6, 3.9 Hz, 1H, C9-H), 3.25 (dd, J = 14.6, 7.3 Hz, 1H, C9-H), 3.19 (d, J = 17.9 Hz, 1H, C12-H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ [ppm] 166.5 (C-11/13), 165.8 (C-11/13), 160.9 (C-16/18), 158.8 (C-16/18), 136.4 (C-5), 131.8 (C-20), 127.0 (C-4), 124.1 (C-7), 122.6 (C-1), 120.0 (C-2), 119.0 (C-3), 115.8 (C-15), 111.3 (C-6), 109.3 (C-8), 104.6 (C-17), 98.4 (C-19), 55.9 (C-10), 55.5 (C-21/22), 55.4 (C-21/22), 49.1 (C-12), 44.0 (C-14), 30.7 (C-9).

ESI-MS [*m/z*]: calc.: 394.1761 $[M]+H^+$.

found: 394.1769 $[M]+H^+$.

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3258.80, 2934.24, 2836.57, 1733.16, 1644.32, 1611.69, 1587.56, 1506.74, 1455.79, 1435.54, 1358.81, 1321.33, 1288.04, 1257.86, 1206.44, 1178.57, 1155.83, 1126.83, 1110.76, 1031.01, 933.53, 828.68, 783.92, 740.71, 632.41, 584.34, 555.08, 509.79, 460.21, 424.04.

Rotation value (*c* 0.29, $CHCl_3$) $[\alpha]_D^{20}$**:** -19.7°.

Melting point: 130 °C.

5.4. Prenylation reactions

The following prenylation reactions were all executed after procedures established by Stark *et al*. as they were given in the supporting information of the corresponding publication. According to these procedures the catalyst was formed beforehand and added to the rest of the reaction mixture as a preformed solution.[4]

General reaction procedure A:

Catalyst preformation: 2.5 mol% $[Ir(COD)Cl]_2$ and 10 mol% Ligand (see according substrate) were placed in a vial equipped with a stirring bar then evacuated and flushed two times with nitrogen. After that dichloromethane was added to reach a 0.1 M concentration and stirred for ten minutes, while the colour turns from orange to cherry red.

The substrate (1.0 eq.) was placed in a Schlenk tube equipped with a magnetic stirring bar, evacuated and flushed two times with nitrogen. 9-Octyl-9-borabicyclo[3.3.1]nonane (**142**) (1.3 eq.) was added and the vessel was evacuated and flushed with nitrogen. After that dichloromethane and 1,8-diazabicyclo[5.4.0]undec-7-en (**125**) (0.20 eq.) were added to reach a final concentration of 0.25 M. The homogeneous solution was stirred for ten minutes at room temperature. Then *tert*-butyl-2-methylbut-3-en-2-yl carbonate (**22**) (3.0 eq.) and the preformed catalyst were added. After complete conversion of the starting material as judged by TLC, the reaction mixture was diluted with diethyl ether, poured into a separation funnel with 3% H_2O_2 and extracted three times with diethyl ether. The combined organic layers were dried with sodium sulphate and the solvent removed under reduced pressure.

General reaction procedure B:

Formation of pre-cat-1: $[Ir(COD)Cl]_2$ (1.0 eq.) and 3-benzyl-1-methyl-1*H*-imidazol-3-ium chloride (2.0 eq.) or 3-phenyl-1-methyl-1*H*-imidazol-3-ium chloride (2.0 eq.) (see according substrate) were placed in a Schlenk tube, evacuated and flushed with nitrogen. Then dichloromethane was added under stirring. The colour of the solution turned from orange-red to yellow within ten minutes after which the bulk of the solvent was removed under a stream of nitrogen and further dried under high vacuum in the Schlenk tube.

Catalyst preformation: 2.5 mol% (pre-cat-1) and 5 mol% Ligand (see according substrate) were placed in a vial equipped with a stirring bar, then evacuated and flushed two times with nitrogen. After that dichloromethane and 1,5,7-triazabicyclo-[4.4.0]dec-5-ene were added to reach a 0.1 M concentration and stirred for ten min while the colour turns from orange to cherry red.

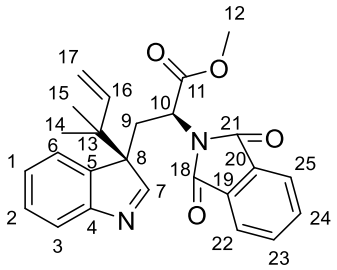
The substrate (1.0 eq.) and triphenylborane (1.3 eq.) were placed in a Schlenk tube equipped with a magnetic stirring bar, evacuated and flushed two times with nitrogen. After that dichloromethane and the preformed catalyst were added to reach a final concentration of 0.25 M. The homogeneous solution was stirred for 30 min at room temperature. Then *tert*-butyl-2-methylbut-3-en-2-yl carbonate (**22**) (5.0 eq.) was added. After complete conversion of the starting material as judged by TLC, the reaction mixture was diluted with diethyl ether, poured into a separation funnel with 2 M aqueous sodium hydroxide and washed three times with 2 M aqueous sodium hydroxide. The combined organic layers were dried with sodium sulphate and the solvent removed under reduced pressure.

General reaction procedure C:

Catalyst preformation: 2.5 mol% $[Ir(COD)Cl]_2$ and 10 mol% Ligand (see according substrate) were placed in a vial equipped with a stirring bar then evacuated and flushed two times with nitrogen. After that dichloromethane was added to reach a 0.1 M concentration and stirred for ten minutes while the colour turns from orange to cherry red.

The substrate (1.0 eq.) was placed in a Schlenk tube equipped with a magnetic stirring bar, evacuated and flushed two times with nitrogen. After that dichloromethane, triethylborane (1 M in *n*-hexane, 1.3 eq.) and 1,8-diazabicyclo[5.4.0]undec-7-en (**125**) (0.20 eq.) were added to reach a final concentration of 0.2 M. The homogeneous solution was stirred for ten minutes at room temperature. Then *tert*-butyl-2-methylbut-3-en-2-yl carbonate (**22**) (3.0 eq.) and the preformed catalyst were added. After complete conversion of the starting material as judged by TLC, the reaction mixture was diluted with diethyl ether, poured into a separation funnel with 3% H_2O_2 and extracted three times with diethyl ether. The combined organic layers were dried with sodium sulphate and the solvent removed under reduced pressure.

5.4.1 Synthesis of (2*R*)-methyl 2-(1,3-dioxoisoindolin-2-yl)-3-(3-(2-methylbut-3-en-2-yl)-3*H*-indol-3-yl)propanoate (132a)



132a

$C_{25}H_{24}N_2O_4$

[416.47]

This reaction was performed according to the general reaction procedure **A** in which 88.0 mg (0.250 mmol, 1.0 eq.) of (*S*)-2-(1,3-dioxoisoindolin-2-yl)-3-(1*H*-indol-3-yl) propanoate (**129**) were used as starting material and chiral compound **27b** as ligand.

The residue was purified by column chromatography (PE/EtOAc = 1:1) to afford the desired product **132a** and its corresponding diastereoisomer **132b** (63.3 mg, 0.152 mmol, 61%) as a clear to light yellow liquid with a ratio of 1:6, *anti/syn*, **132a**/**132a**.

The synthesis of (2*R*)-methyl 2-(1,3-dioxoisoindolin-2-yl)-3-(3-(2-methylbut-3-en-2-yl)-3*H*-indol-3-yl)propanoate (**132a**) was performed according to the procedure of Stark *et al.*[4]

R_f value (PE/EtOAc 1:1 (v/v)): 0.29.

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] 7.83 (s, 1H, C7-H), 7.79 (dd, *J* = 5.5, 3.1 Hz, 2H, C22/25-H), 7.71 (dd, *J* = 5.5, 3.1 Hz, 2H, C23/24-H), 7.52 – 7.46 (m, 1H, C6-H), 7.45 – 7.38 (m, 1H, C3-H), 7.37 – 7.29 (m, 2H, C1/2-H), 5.96 (dd, *J* = 17.4, 10.8 Hz, 1H, C16-H), 5.18 (dd, *J* = 10.9, 1.1 Hz, 2H, C17-H), 4.06 (dd, *J* = 12.2, 3.1 Hz, 1H, C10-H), 3.63 (s, 3H, C12-H), 3.51 (dd, *J* = 14.8, 12.1 Hz, 1H, C9-H), 2.97 (dd, *J* = 14.8, 3.2 Hz, 1H, C9-H), 1.03 (s, 3H, C14-H), 0.94 (s, 3H, C15-H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ [ppm] 177.22 (C-11), 169.69 (C-18/21), 167.32 (C-7), 156.50 (C-22/25), 143.57 (C-16), 137.98 (C-4), 134.30 (C-19/20), 131.78 (C-23/24), 128.86 (C-2), 126.27 (C-6), 123.97 (C-3), 123.74 (C-1), 121.88 (C-5), 114.69 (C-17), 65.75 (C-8), 53.09 (C-12), 49.31 (C-10), 41.98 (C-13), 28.97 (C-9), 23.44 (C-14), 23.08 (C-15).

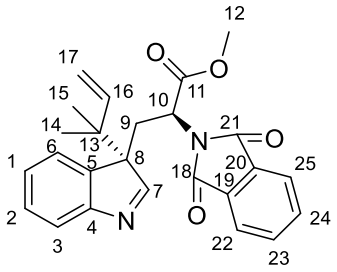
ESI-MS [*m/z*]: calc.: 417.1814 [M]+H$^+$.

found: 417.1812 [M]+H$^+$.

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 2954.85, 2921.66, 2852.17, 1777.54, 1744.34, 1714.52, 1465.16, 1382.70, 1261.40, 1221.46, 1129.31, 1104.99, 1088.13, 1005.47, 954.51, 916.06, 873.84, 785.52, 774.57, 747.06, 718.59, 645.21, 617.31, 580.46, 529.52, 437.42.

Rotation value (*c* 3.0, CHCl$_3$) $[\alpha]_D^{20}$**:** -28.2°.

5.4.2 Synthesis of (2*S*)-methyl 2-(1,3-dioxoisoindolin-2-yl)-3-(3-(2-methylbut-3-en-2-yl)-3*H*-indol-3-yl)propanoate (132b)



132b

$C_{25}H_{24}N_2O_4$

[416.47]

This reaction was performed according to the general reaction procedure **A** in which 88.0 mg (0.250 mmol, 1.0 eq.) of (*S*)-2-(1,3-dioxoisoindolin-2-yl)-3-(1*H*-indol-3-yl) propanoate (**129**) were used as starting material and chiral compound **27b** as ligand.

The residue was purified by column chromatography (PE/EtOAc = 1:1) to afford the desired product **132b** and its corresponding diastereoisomer **132a** (63.3 mg, 0.152 mmol, 61%) as a clear to light yellow liquid with a ratio of 1:6, *anti/syn*, **132b**/**132a**.

The synthesis of (2*S*)-methyl 2-(1,3-dioxoisoindolin-2-yl)-3-(3-(2-methylbut-3-en-2-yl)-3*H*-indol-3-yl)propanoate (**132b**) was performed according to the procedure of Stark *et al.*[4]

R_f value (PE/EtOAc 1:1 (v/v)): 0.21.

^{1}H-NMR (400 MHz, $CDCl_3$): *δ* [ppm] 8.26 (s, 1H, C7-H), 7.60 (p, *J* = 2.2 Hz, 4H, C22-25-H), 7.40 (d, *J* = 7.7 Hz, 1H, C6.-H), 7.07 (dd, *J* = 7.4, 1.1 Hz, 1H, C3-H), 6.84 (td, *J* = 7.6, 1.2 Hz, 1H, C1-H), 6.64 (td, *J* = 7.5, 1.1 Hz, 1H, C2-H), 5.98 (dd, *J* = 17.3, 10.8 Hz, 1H, C16-H), 5.16 (dd, *J* = 10.7, 1.0 Hz, 1H, C17-H), 5.07 (dd, *J* = 17.4, 1.0 Hz, 1H, C17-H), 4.21 (dd, *J* = 10.4, 3.3 Hz, 1H, C10-H), 3.65 (s, 3H, C12-H), 3.21 (dd, *J* = 14.9, 3.4 Hz, 1H, C9-H), 3.11 (dd, *J* = 14.9, 10.4 Hz, 1H, C9-H), 0.97 (s, 6H, C14/15-H).

^{13}C-NMR (101 MHz, $CDCl_3$): *δ* [ppm] 177.58 (C-11), 169.84 (C-18/21), 166.97 (C-7), 156.00 (C-22/25), 144.10 (C-16), 139.35 (C-4), 134.01 (C-19/20), 131.82 (C-23/24), 127.84 (C-2), 125.77 (C-6), 123.41 (C-3), 123.26 (C-1), 121.93 (C-5), 114.99 (C-17), 66.07 (C-8), 53.00 (C-12), 48.73 (C-10), 42.56 (C-13), 29.38 (C-9), 23.33 (C-14), 22.32 (C-15).

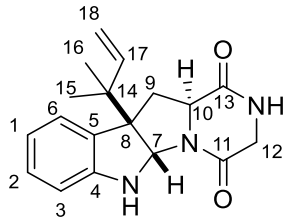
ESI-MS [*m/z*]: calc.: 417.1814 $[M]+H^+$.

found: 417.1816 $[M]+H^+$.

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3391.82, 2924.09, 2854.82, 1775.15, 1744.16, 1711.68, 1613.17, 1466.49, 1436.95, 1385.65, 1336.36, 1243.93, 1206.79, 1171.96, 1105.84, 1087.27, 1071.98, 1006.08, 975.06, 918.06, 878.73, 843.11, 792.17, 773.33, 740.32, 717.37, 620.30, 568.08, 529.27, 426.65.

Rotation value (*c* 0.30, $CHCl_3$) $[\alpha]_D^{20}$**:** +21.0°.

5.4.3 Synthesis of (11a*S*)-10b-(2-methylbut-3-en-2-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (74)



74

$C_{18}H_{21}N_3O_2$

[311.38]

In the course of this thesis the preparation of this substrate was performed following both the general reaction procedures **A** and **C** using methyl (((9*H*-fluoren-9-yl)methoxy)carbonyl)glycyl-*L*-tryptophanate (**78**) as starting material as well as the ligands **27a**, **27b** or **24**. In order to get more details regarding the scale and yield of these reactions see Table 3.1.6.

The synthesis of (11a*S*)-10b-(2-methylbut-3-en-2-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (**74**) was performed according to the procedure of Stark *et al.*[4]

R_f value (DCM/MeOH 40:1 (v/v)): 0.35.

^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] 7.15 (dt, *J* = 7.5, 1.3 Hz, 1H, C6-H), 7.08 (dtd, *J* = 13.5, 7.6, 1.2 Hz, 1H, C2-H), 6.81 (d, *J* = 4.1 Hz, 0.5H, DKP N-H), 6.74 (dtd, *J* = 10.8, 7.5, 1.0 Hz, 1H, C1-H), 6.68 (d, *J* = 4.1 Hz, 0.5H, DKP N-H), 6.57 (dd, *J* = 10.1, 7.6 Hz, 1H, C3-H), 5.95 (ddd, *J* = 17.4, 14.4, 10.9 Hz, 1H, C17-H), 5.51 (d, *J* = 23.4 Hz, 1H, C7-H), 5.37 (s, 0.5H, indole N-H), 5.17 – 5.04 (m, 2H, C18-H), 4.99 (s, 0.5H, indole N-H), 4.09 (td, *J* = 8.9, 1.7 Hz, 0.5H, C10-H), 3.99 (ddd, *J* = 17.5, 5.2, 1.9 Hz, 1H, C12-H), 3.93 (ddd, *J* = 11.3, 6.2, 1.9 Hz, 0.5H, C10-H), 3.84 (ddd, *J* = 17.6, 14.0, 4.1 Hz, 1H, C12-H), 2.82 (dd, *J* = 13.8, 8.9 Hz, 0.5H, C9-H), 2.54 (dd, *J* = 12.7, 6.2 Hz, 0.5H, C9-H), 2.45 (ddd, *J* = 19.8, 13.3, 10.2 Hz, 1H, C9-H), 1.13 (d, *J* = 10.9 Hz, 3H, C15/16-H), 0.99 (d, *J* = 11.3 Hz, 3H, C15/16-H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ [ppm] 169.68 (d, *J* = 15.0 Hz, C-13), 164.82 (d, *J* = 249.9 Hz, C-11), 149.30 (d, *J* = 199.7 Hz, C-4), 143.58 (d, *J* = 8.3 Hz, C-17), 130.31 (d, *J* = 310.7 Hz, C-5), 128.74 (d, *J* = 53.6 Hz, C-2), 125.51 (d, *J* = 79.3 Hz, C-6), 118.97 (d, *J* = 12.2 Hz, C-1), 114.80 (d, *J* = 19.3 Hz, C-18), 109.24 (d, *J* = 20.2 Hz, C-3), 78.78 (d, *J* = 250.8 Hz, C-7), 61.59 (d, *J* = 14.4 Hz, C-8), 57.71 (d, *J* = 172.7 Hz, C-10), 46.69 (d, *J* = 25.0 Hz, C-12), 41.36 (d, *J* = 94.1 Hz, C-14), 36.55 (d, *J* = 23.9 Hz, C-9), 22.77 (d, *J* = 50.4 Hz, C-15/16).

ESI-MS [*m/z*]: calc.: 312.1712 $[M]+H^+$.

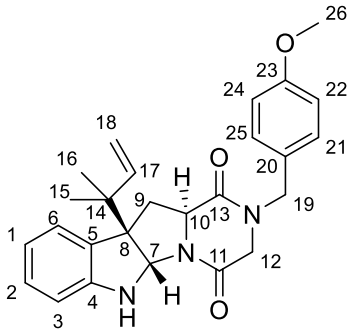
found: 312.1702 $[M]+H^+$.

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3233.44, 3081.30, 2965.13, 2873.63, 1652.48, 1604.50, 1483.88, 1437.98, 1382.76, 1366.34, 1313.63, 1265.01, 1211.18, 1152.94, 1098.34, 1077.50, 1062.74, 1019.08, 1004.00, 971.48, 916.24, 789.43, 738.51, 694.55, 650.26, 558.49, 507.76, 446.97, 414.10.

Rotation value (*c* 1.0, $CHCl_3$, *endo/exo* 1:1) $[\alpha]_D^{20}$**:** -152°.

Melting point: 114 °C.

5.4.4 Synthesis of (10b*R*,11a*S*)-2-(4-methoxybenzyl)-10b-(2-methylbut-3-en-2-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (73a)



73a

$C_{26}H_{29}N_3O_3$

[431.53]

In the course of this thesis the preparation of this substrate was performed following both the general reaction procedures **A**, **B** and **C** using both methyl (4-methoxybenzyl)glycyl-*L*-tryptophanate (**84a**) and (*S*)-3-((1*H*-indol-3-yl)methyl)-1-(4-methoxybenzyl)piperazine-2,5-dione (**85a**) as starting materials as well as the ligands **27a**, **27b** or **24**. In order to get more details regarding the scale and yield of these reactions see Tables 3.1.7 to 3.1.11.

The synthesis of (10b*R*,11a*S*)-2-(4-methoxybenzyl)-10b-(2-methylbut-3-en-2-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (**73a**) was performed according to the procedure of Stark *et al.*[4]

The stereochemistry of this compound was confirmed by NOESY experiments in comparison to its corresponding diastereoisomer **73b**.

R_f value (PE/EtOAc 1:1 (v/v)): 0.57.

^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] 7.16 (d, *J* = 7.6 Hz, 1H, C3-H), 7.14 (d, *J* = 8.6 Hz, 2H, C22/24-H), 7.08 (t, *J* = 7.5 Hz, 1H, C2-H), 6.86 – 6.80 (m, 2H, C21/25-H), 6.75 (t, *J* = 7.4 Hz, 1H, C1-H), 6.55 (d, *J* = 7.7 Hz, 1H, C6-H), 5.98 (dd, *J* = 17.3, 10.7 Hz, 1H, C17-H), 5.52 (s, 1H, C7-H), 5.15 – 5.04 (m, 2H, C18-H), 4.90 (s, 1H, N-H), 4.79 (d, *J* = 14.3 Hz, 1H, C19-H), 4.19 (d, *J* = 14.4 Hz, 1H, C19-H), 3.95 (ddd, *J* = 11.2, 6.2, 1.9 Hz, 1H, C10-H), 3.85 (dd, *J* = 17.3, 2.1 Hz, 1H, C12-H), 3.78 (s, 3H, C26-H), 3.71 (d, *J* = 17.2 Hz, 1H, C12-H), 2.62 (dd, *J* = 12.7, 6.1 Hz, 1H, C9-H), 2.47 (dd, *J* = 12.8, 11.2 Hz, 1H, C9-H), 1.12 (s, 3H, C15/16-H), 1.01 (s, 3H, C15/16-H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ [ppm] 166.85 (C-13), 163.60 (C-11), 159.60 (C-23), 150.08 (C-4), 143.64 (C-17), 129.94 (C-21/25), 129.06 (C-5), 129.02 (C-2), 127.43 (C-20), 125.25 (C-3), 119.03 (C-1), 114.63 (C-18), 114.42 (C-22/24), 109.29 (C-6), 77.67 (C-7), 61.86 (C-8), 59.00 (C-10), 55.43 (C-26), 50.88 (C-12), 49.02 (C-19), 40.99 (C-14), 36.87 (C-9), 23.00 (C-15/16), 22.62 (C-15/16).

ESI-MS [*m/z*]: calc.: 432.2287 $[M]+H^+$.

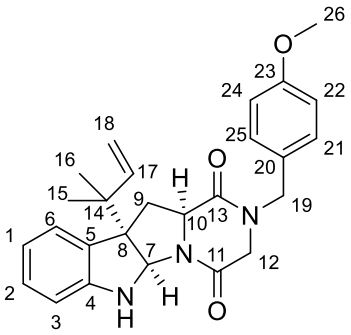
found: 432.2286 $[M]+H^+$.

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3327.95, 2963.66, 2835.58, 1652.57, 1606.50, 1511.49, 1482.13, 1442.65, 1417.96, 1382.31, 1362.51, 1302.07, 1273.04, 1244.41, 1210.83, 1174.78, 1149.52, 1104.92, 1081.54, 1061.13, 1031.45, 980.44, 913.73, 847.06, 817.79, 784.21, 740.26, 672.76, 644.31, 629.57, 597.98, 568.73, 516.03, 497.48, 462.56, 431.69, 414.18.

Rotation value (*c* 0.50, $CHCl_3$) $[\alpha]_D^{20}$**:** -329°.

Melting point: 65 °C.

5.4.5 Synthesis of (10b*S*,11a*S*)-2-(4-methoxybenzyl)-10b-(2-methylbut-3-en-2-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (73b)



73b

$C_{26}H_{29}N_3O_3$

[431.53]

In the course of this thesis the preparation of this substrate was performed following both the general reaction procedures **A**, **B** and **C** using both methyl (4-methoxybenzyl)glycyl-*L*-tryptophanate (**84a**) and (*S*)-3-((1*H*-indol-3-yl)methyl)-1-(4-methoxybenzyl)piperazine-2,5-dione (**85a**) as starting materials as well as the ligands **27a**, **27b** or **24**. In order to get more details regarding the scale and yield of these reactions see Tables 3.1.7 to 3.1.11.

The synthesis of (10b*S*,11a*S*)-2-(4-methoxybenzyl)-10b-(2-methylbut-3-en-2-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (**73b**) was performed according to the procedure of Stark *et al.*[4]

The stereochemistry of this compound was confirmed by NOESY experiments in comparison to its corresponding diastereoisomer **73a**.

R_f value (PE/EtOAc 1:1 (v/v)): 0.43.

^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] 7.20 (dd, *J* = 7.5, 1.1 Hz, 1H, C3-H), 7.11 (td, *J* = 7.6, 1.2 Hz, 1H, C2-H), 6.99 – 6.95 (m, 2H, C21/25-H), 6.81 – 6.77 (m, 2H, C22/24-H), 6.76 (dd, *J* = 7.5, 1.0 Hz, 1H, C1-H), 6.58 (d, *J* = 7.8 Hz, 1H, C6-H), 5.95 (dd, *J* = 17.3, 10.8 Hz, 1H, C17-H), 5.46 (s, 1H, N-H), 5.35 (s, 1H, C7-H), 5.18 – 5.07 (m, 2H, C18-H), 4.55 (d, *J* = 14.5 Hz, 1H, C19-H), 4.25 (d, *J* = 14.5 Hz, 1H, C19-H), 4.16 – 4.07 (m, 1H, C10-H), 3.85 (dd, *J* = 17.3, 1.6 Hz, 1H, C12-H), 3.78 (s, 2H, C26-H), 3.64 (d, *J* = 17.3 Hz, 1H, C12-H), 2.86 (dd, *J* = 13.8, 8.9 Hz, 1H, C9-H), 2.62 (dd, *J* = 13.9, 8.3 Hz, 1H, C9-H), 1.14 (s, 3H, C15/16-H), 0.98 (s, 3H, C15/16-H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ [ppm] 167.19 (C-13), 165.83 (C-11), 159.75 (C-23), 148.93 (C-4), 144.00 (C-27), 131.69 (C-5), 129.99 (C-21/25), 128.73 (C-2), 127.76 (C-20), 126.26 (C-3), 119.29 (C-1), 115.04 (C-18), 114.66 (C-22/24), 109.53 (C-6), 80.10 (C-7), 62.31 (C-8), 57.93 (C-10), 55.68 (C-26), 51.35 (C-12), 49.22 (C-19), 41.94 (C-14), 36.70 (C-9), 22.88 (C-15/16).

ESI-MS [*m/z*]: calc.: 432.2287 $[M]+H^+$.

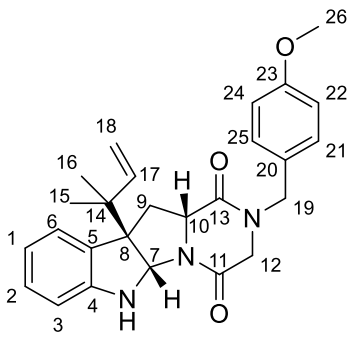
found: 432.2283 $[M]+H^+$.

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3377.47, 2961.93, 2932.46, 2873.03, 1734.85, 1658.57, 1607.60, 1511.64, 1484.19, 1464.60, 1439.32, 1416.41, 1381.83, 1365.94, 1345.28, 1302.55, 1243.64, 1206.52, 1172.66, 1092.00, 1068.78, 1031.88, 919.26, 845.07, 818.85, 777.60, 743.23, 692.76, 658.34, 624.22, 606.20, 574.55, 515.09, 464.70, 435.55, 407.43.

Rotation value (*c* 0.50, $CHCl_3$) $[\alpha]_D^{20}$**:** +150°.

Melting point: 57 °C.

5.4.6 Synthesis of (10b*R*,11a*R*)-2-(4-methoxybenzyl)-10b-(2-methylbut-3-en-2-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (73d)



73d

$C_{26}H_{29}N_3O_3$

[431.53]

This reaction was performed according to the general reaction procedure **C** in which 182 mg (0.501 mmol, 1.0 eq.) of (*R*)-3-((1*H*-indol-3-yl)methyl)-1-(4-methoxybenzyl)piperazine-2,5-dione (**85b**) were used as starting material and the achiral compound **24** as Ligand.

The residue was purified by column chromatography (PE/EtOAc = 1:1) to afford the desired product **73d** and its corresponding diastereoisomer **73c** (20.6 mg, 0.477 mmol, 95%) as a colourless solid with a ratio of 1:1, *endo/exo*, **73d**/**73c**.

The synthesis of (10b*R*,11a*R*)-2-(4-methoxybenzyl)-10b-(2-methylbut-3-en-2-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (**73d**) was performed according to the procedure of Stark *et al.*[4]

The stereochemistry of this compound was confirmed by NOESY experiments in comparison to its corresponding diastereoisomer **73c**.

R_f value (PE/EtOAc 1:1 (v/v)): 0.25.

^{1}H-NMR (600 MHz, $CDCl_3$): δ [ppm] 7.21 – 7.18 (m, 1H, C3-H), 7.11 (td, *J* = 7.6, 1.2 Hz, 1H, C2-H), 6.97 (d, *J* = 8.6 Hz, 2H, C21/25-H), 6.79 (d, *J* = 8.6 Hz, 2H, C22/24-H), 6.77 (dd, *J* = 7.5, 1.1 Hz, 1H, C1-H), 6.58 (d, *J* = 7.8 Hz, 1H, C6-H), 5.95 (dd, *J* = 17.3, 10.8 Hz, 1H, C17-H), 5.35 (s, 1H, C7-H), 5.19 – 5.08 (m, 2H, C18-H), 4.55 (d, *J* = 14.5 Hz, 1H, C19-H), 4.25 (d, *J* = 14.5 Hz, 1H, C19-H), 4.16 – 4.08 (m, 1H, C10-H), 3.85 (dd, *J* = 17.4, 1.7 Hz, 1H, C12-H), 3.78 (s, 3H, C26-H), 3.65 (d, *J* = 17.3 Hz, 1H, C12-H), 2.86 (dd, *J* = 13.8, 9.0 Hz, 1H, C9-H), 2.62 (dd, *J* = 13.8, 8.3 Hz, 1H, C9-H), 1.14 (s, 3H, C15/16-H), 0.98 (s, 3H, C15/16-H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] 166.92 (C-13), 165.58 (C-11), 159.49 (C-23), 148.56 (C-4), 143.72 (C-17), 131.48 (C-5), 129.72 (C-21/25), 128.48 (C-2), 127.48 (C-20), 125.98 (C-3), 119.11 (C-1), 114.79 (C-18), 114.39 (C-22/24), 109.36 (C-6), 79.81 (C-7), 62.06 (C-8), 57.69 (C-10), 55.41 (C-26), 51.08 (C-12), 48.96 (C-19), 41.67 (C-14), 36.43 (C-9), 22.61 (C-15/16).

ESI-MS [*m/z*]: calc.: 432.2287 $[M]+H^+$.

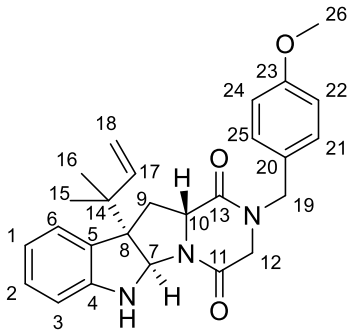
found: 432.2278$[M]+H^+$.

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3367.56, 2964.98, 2934.50, 2835.90, 1721.40, 1658.89, 1606.93, 1511.18, 1484.01, 1464.20, 1438.28, 1415.88, 1382.55, 1366.34, 1344.75, 1302.08, 1242.43, 1207.06, 1172.13, 1091.41, 1069.20, 1030.14, 918.92, 845.53, 817.55, 777.26, 743.28, 658.61, 605.03, 574.21, 514.44, 461.73, 434.50, 408.39.

Rotation value (*c* 0.25, $CHCl_3$) $[\alpha]_D^{20}$**:** -154°.

Melting point: 62 °C.

5.4.7 Synthesis of (10b*S*,11a*R*)-2-(4-methoxybenzyl)-10b-(2-methylbut-3-en-2-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (73c)



73c

$C_{26}H_{29}N_3O_3$

[431.53]

This reaction was performed according to the general reaction procedure **C** in which 182 mg (0.501 mmol, 1.0 eq.) of (*R*)-3-((1*H*-indol-3-yl)methyl)-1-(4-methoxybenzyl)piperazine-2,5-dione (**85b**) were used as starting material and the achiral compound **24** as ligand.

The residue was purified by column chromatography (PE/EtOAc = 1:1) to afford the desired product **73c** and its corresponding diastereoisomer **73d** (20.6 mg, 0.477 mmol, 95%) as a colourless solid with a ratio of 1:1, *endo/exo*, **73d**/**73c**.

The synthesis of (10b*R*,11a*R*)-2-(4-methoxybenzyl)-10b-(2-methylbut-3-en-2-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (**73d**) was performed according to the procedure of Stark *et al.*[4]

The stereochemistry of this compound was confirmed by NOESY experiments in comparison to its corresponding diastereoisomer **73d**.

R_f value (PE/EtOAc 1:1 (v/v)): 0.38.

^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] 7.17 (d, *J* = 7.8 Hz, 1H, C3-H), 7.14 (d, *J* = 8.6 Hz, 1H, C22/24-H), 7.11 – 7.07 (m, 1H, C2-H), 6.86 – 6.80 (m, 2H, C21/25-H), 6.77 (t, *J* = 7.5 Hz, 1H, C1-H), 6.59 (d, *J* = 7.7 Hz, 1H, C6-H), 5.98 (dd, *J* = 17.3, 10.8 Hz, 1H, C17-H), 5.55 (s, 1H, C7-H), 5.16 – 5.04 (m, 2H, C18-H), 4.79 (d, *J* = 14.4 Hz, 1H, N-H), 4.19 (d, *J* = 14.3 Hz, 1H, C19-H), 3.99 – 3.91 (m, 1H, C10-H), 3.86 (dd, *J* = 17.3, 2.1 Hz, 1H, C12-H), 3.78 (s, 3H, C26-H), 3.71 (d, *J* = 17.2 Hz, 1H, C12-H), 2.62 (dd, *J* = 12.7, 6.1 Hz, 1H, C9-H), 2.47 (dd, *J* = 12.7, 11.2 Hz, 1H, C9-H), 1.12 (s, 3H, C15/16-H), 1.01 (s, 3H, C15/16-H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ [ppm] 166.80 (C-13), 163.60 (C-11), 159.61 (C-23), 150.06 (C-4), 143.59 (C-17), 129.94 (C-21/25), 129.08 (C-5), 129.00 (C-2), 127.41 (C-20), 125.25 (C-3), 119.06 (C-1), 114.70 (C-18), 114.44 (C-22/24), 109.30 (C-6), 77.66 (C-7), 61.92 (C-8), 58.99 (C-10), 55.39 (C-26), 50.89 (C-12), 48.99 (C-19), 41.00 (C-14), 36.94 (C-9), 23.05 (C-15/16), 22.61 (C-15/16).

ESI-MS [*m/z*]: calc.: 432.2287 $[M]+H^+$.

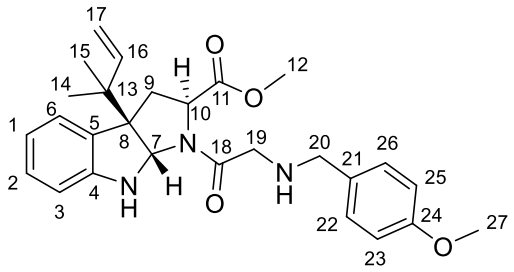
found: 432.2292 $[M]+H^+$.

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3339.21, 2966.79, 2835.78, 1735.17, 1653.06, 1606.49, 1511.42, 1481.92, 1442.50, 1417.47, 1383.11, 1354.64, 1302.15, 1272.70, 1243.31, 1210.68, 1174.55, 1149.26, 1104.31, 1081.53, 1060.43, 1031.51, 980.14, 915.31, 846.93, 817.34, 783.74, 741.74, 672.82, 630.10, 602.01, 568.17, 517.63, 496.75, 462.10, 431.58, 416.67.

Rotation value (*c* 0.13, $CHCl_3$) $[\alpha]_D^{20}$**:** +358°.

Melting point: 83 °C.

5.4.8 Synthesis of methyl (2*S*,3a*R*)-1-((4-methoxybenzyl)glycyl)-3a-(2-methylbut-3-en-2-yl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole-2-carboxylate (121a)



121a

$C_{27}H_{33}N_3O_4$

[463.57]

In the course of this thesis this substrate was formed as a by-product during prenylation reactions following the general reaction procedure **B** using methyl (4-methoxybenzyl)glycyl-*L*-tryptophanate (**84a**) as starting material as well as the ligands **27a**, **27b** or **24**. In order to get more details regarding the scale and yield of these reactions see Tables 3.1.7 and 3.1.8.

The synthesis of methyl (2*S*,3a*R*)-1-((4-methoxybenzyl)glycyl)-3a-(2-methylbut-3-en-2-yl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole-2-carboxylate (**121a**) was performed according to the procedure of Stark *et al.*[4]

R_f value (EtOAc): 0.90.

^{1}H-NMR (600 MHz, $CDCl_3$): δ [ppm] 8.15 (s, 1H, indole N-H), 7.84 (d, *J* = 8.2 Hz, 1H, Gly N-H), 7.57 (d, *J* = 7.8 Hz, 1H, C3-H), 7.35 (d, *J* = 8.1 Hz, 1H, C6-H), 7.18 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H, C1-H), 7.11 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H, C2-H), 6.95 – 6.89 (m, 3H, C7/22/26-H), 6.68 (d, *J* = 8.2 Hz, 2H, C23/25-H), 5.08 – 5.02 (m, 1H, C16-H), 4.94 – 4.87 (m, 1H, C10-H), 3.77 (s, 3H, C27-H), 3.65 (s, 3H, C12-H), 3.50 (d, *J* = 13.1 Hz, 1H, C20-H), 3.33 (t, *J* = 6.1 Hz, 2H, C9-H), 3.29 (d, *J* = 12.9 Hz, 1H, C20-H), 3.08 (d, *J* = 16.6 Hz, 1H, C19-H), 2.96 (d, *J* = 16.6 Hz, 1H, C19-H), 2.92 (dd, *J* = 16.5, 7.0 Hz, 2H, C17-H), 1.69 (s, 3H, C14/15-H), 1.53 (s, 3H, C14/15-H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] 172.49 (C-11), 171.67 (C-18), 158.78 (C-24), 136.27 (C-4), 130.13 (C-22/26), 127.73 (C-5), 122.80 (C-7), 122.38 (C-1), 122.13 (C-21), 120.63 (C-16), 119.80 (C-2), 118.80 (C-3), 113.76 (C-23/25), 111.31 (C-6), 110.29 (C-8), 60.53 (C-13), 58.35 (C-20), 57.07 (C-19), 55.39 (C-27), 52.39 (C-10), 52.24 (C-12), 51.68 (C-17), 27.75 (C-9), 26.05 (C-14/15), 18.12 (C-14/15).

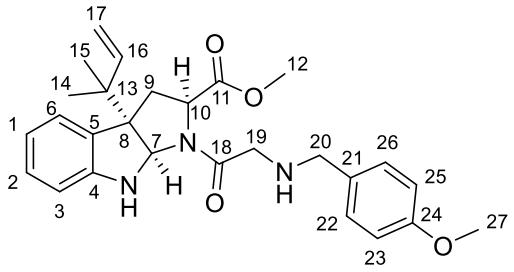
ESI-MS [*m/z*]: calc.: 464.2549 $[M]+H^+$.

found: 464.2551 $[M]+H^+$.

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3324.73, 2930.12, 2835.40, 1741.21, 1657.40, 1610.70, 1585.00, 1509.86, 1456.24, 1427.74, 1340.17, 1300.86, 1245.54, 1208.18, 1174.83, 1151.19, 1120.99, 1102.33, 1032.44, 1010.28, 963.94, 909.92, 848.54, 814.05, 735.60, 645.90, 602.73, 563.59, 521.99, 460.04, 425.99.

Rotation value (*c* 1.2, $CHCl_3$) $[\alpha]_D^{20}$**:** -15.5°.

5.4.9 Synthesis of methyl (2*S*,3a*S*)-1-((4-methoxybenzyl)glycyl)-3a-(2-methylbut-3-en-2-yl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole-2-carboxylate (121b)



121b

$C_{27}H_{33}N_3O_4$

[463.57]

In the course of this thesis this substrate was formed as a by-product during prenylation reactions following the general reaction procedure **B** using methyl (4-methoxybenzyl)glycyl-*L*-tryptophanate (**84a**) as starting material as well as the ligands **27a**, **27b** or **24**. In order to get more details regarding the scale and yield of these reactions see Tables 3.1.7 and 3.1.8.

The synthesis of methyl (2*S*,3a*S*)-1-((4-methoxybenzyl)glycyl)-3a-(2-methylbut-3-en-2-yl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole-2-carboxylate (**121b**) was performed according to the procedure of Stark *et al.*[4]

R_f value (EtOAc): 0.78.

^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] 8.22 (s, 1H, indole N-H), 7.48 (d, *J* = 7.5 Hz, 1H, Gly N-H), 7.45 (d, *J* = 7.9 Hz, 1H, C3-H), 7.28 (d, *J* = 8.1 Hz, 1H, C6-H), 7.11 (t, *J* = 7.6 Hz, 1H, C1-H), 7.03 (t, *J* = 7.4 Hz, 1H, C2-H), 6.93 (d, *J* = 8.6 Hz, 2H, C23/25-H), 6.59 (d, *J* = 2.5 Hz, 1H, C7-H), 6.54 (d, *J* = 8.5 Hz, 2H, C22/26-H), 5.80 (dd, *J* = 17.6, 10.8 Hz, 1H, C16-H), 5.06 – 4.98 (m, 2H, C17-H), 4.52 (dt, *J* = 7.6, 5.8 Hz, 1H, C10-H), 3.62 (s, 3H, C27-H), 3.49 (d, *J* = 12.9 Hz, 1H, C9-H), 3.46 (s, 3H, C12-H), 3.34 (d, *J* = 12.7 Hz, 1H, C9-H), 3.12 – 2.99 (m, 4H, C19/20-H), 1.09 (s, 3H, C14/15-H), 1.06 (s, 3H, C14/15-H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ [ppm] 173.04 (C-18), 172.43 (C-11), 158.69 (C-24), 145.48 (C-16), 136.20 (C-4), 131.75 (C-20), 130.54 (C-22/26), 129.60 (C-5), 127.63 (C-1), 122.86 (C-21), 122.19 (C-7), 119.61 (C-2), 118.79 (C-3), 113.98 (C-23/25), 113.47 (C-17), 111.28 (C-6), 110.19 (C-19), 60.08 (C-13), 55.40 (C-27), 55.00 (C-9), 52.92 (C-8), 52.39 (C-10), 52.23 (C-12), 23.99 (C-14/15), 22.82 (C-14/15).

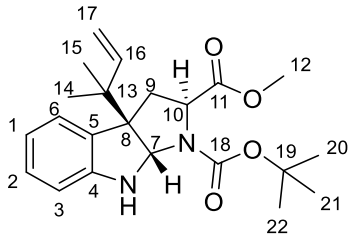
ESI-MS [*m/z*]: calc.: 464.2549 $[M]+H^+$.

found: 464.2557 $[M]+H^+$.

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3336.45, 3057.69, 2972.87, 2836.57, 1735.28, 1655.27, 1610.83, 1585.58, 1510.25, 1457.67, 1437.03, 1358.27, 1300.59, 1283.99, 1244.72, 1167.25, 1109.54, 1065.96.1032.38, 1008.99, 920.52, 852.56, 818.83, 741.23, 692.80, 636.28, 563.75, 525.48, 460.39, 426.34.

Rotation value (*c* 0.97, $CHCl_3$) $[\alpha]_D^{20}$**:** +23.1°.

5.4.10 Synthesis of 1-(*tert*-butyl) 2-methyl (2*S*,3a*R*)-3a-(2-methylbut-3-en-2-yl)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1,2(2*H*)-dicarboxylate (26a)



26a

$C_{22}H_{30}N_2O_4$

[386.49]

This reaction was performed according to the general reaction procedure **A** using methyl (*tert*-butoxycarbonyl)-*L*-tryptophanate (**25a**) as starting material and chiral substrate **27b** as ligand. The reaction was performed using 9-octyl-9-borabicyclo[3.3.1]hexane (**119**) or 9-octyl-9-borabicyclo[3.3.1]decane (**120**) as borane. In order to get more details regarding the scale and yield of these reactions see Table 3.1.5.

The synthesis of 1-(*tert*-butyl) 2-methyl (2*S*,3a*R*)-3a-(2-methylbut-3-en-2-yl)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1,2(2*H*)-dicarboxylate (**26a**) was performed according to the procedure of Stark *et al.*[4]

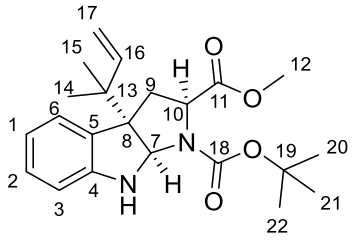
R_f value (PE/EtOAc 2:1 (v/v)): 0.80.

^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] 7.13 – 7.08 (m, 2H, C1/6-H), 6.75 (td, *J* = 7.3, 4.5 Hz, 1H, C2-H), 6.64 – 6.59 (m, 1H, N-H), 6.58 (d, *J* = 7.7 Hz, 1H, C3-H), 6.04 – 5.96 (m, 1H, C16-H), 5.42 (s, 1H, C7-H), 5.13 – 5.00 (m, 2H, C17-H), 3.94 (dd, *J* = 9.2, 7.7 Hz, 1H, C10-H), 3.71 (s, 3H, C12-H), 2.44 (dd, *J* = 12.8, 7.6 Hz, 1H, C9-H), 2.35 (dd, *J* = 12.9, 9.0 Hz, 1H, C9-H), 1.36 (s, 9H, C20/21/22-H), 1.05 (s, 3H, C14/15-H), 0.99 (s, 3H, C14/15-H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ [ppm] 173.80 (C-11), 154.15 (C-18), 150.22 (C-4), 144.28 (C-16), 129.01 (C-6), 125.37 (C-5), 124.66 (C-1), 119.87 (C-2), 114.37 (C-17), 109.80 (C-3), 81.29 (C-19), 79.59 (C-7), 62.19 (C-13), 59.77 (C-10), 52.35 (C-12), 41.45 (C-8), 37.59 (C-9), 28.59 (C-20/21/22), 23.29 (C-14/15), 22.73 (C-14/15).

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3412.63, 2973.28, 2929.42, 2872.28, 1743.29, 1684.04, 1636.96, 1609.17, 1482.19, 1467.17, 1434.86, 1389.99, 1354.35, 1327.13, 1301.80, 1275.46, 1256.61, 1228.62, 1200.67, 1169.24, 1149.31, 1129.98, 1087.01, 1052.27, 1005.26, 923.87, 889.89, 872.75, 848.15, 784.05, 774.50, 753.74, 743.51, 692.98, 674.82, 640.20, 595.89, 538.58, 514.87, 461.82, 433.86, 411.11.

5.4.11 Synthesis of 1-(*tert*-butyl) 2-methyl (2*S*,3a*S*)-3a-(2-methylbut-3-en-2-yl)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1,2(2*H*)-dicarboxylate (26b)



26b

$C_{22}H_{30}N_2O_4$

[386.49]

This reaction was performed according to the general reaction procedure **A** using methyl (*tert*-butoxycarbonyl)-*L*-tryptophanate (**25a**) as starting material and chiral substrate **27b** as ligand. The reaction was performed using 9-octyl-9-borabicyclo[3.3.1]hexane (**119**) or 9-octyl-9-borabicyclo[3.3.1]decane (**120**) as borane. In order to get more details regarding the scale and yield of these reactions see Table 3.1.5.

The synthesis of 1-(*tert*-butyl) 2-methyl (2*S*,3a*S*)-3a-(2-methylbut-3-en-2-yl)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1,2(2*H*)-dicarboxylate (**26b**) was performed according to the procedure of Stark *et al.*[4]

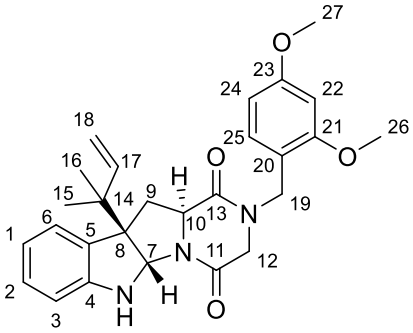
R_f value (PE/EtOAc 2:1 (v/v)): 0.75.

^{1}H-NMR (300 MHz, $CDCl_3$): δ [ppm] 7.07 – 6.95 (m, 2H, C1/3-H), 6.75 – 6.50 (m, 2H, C2/6-H), 6.05 – 5.90 (m, 1H, C16-H), 5.31 (s, 1H, C7-H), 5.16 – 4.96 (m, 2H, C17-H), 4.38 (dd, *J* = 9.2, 0.9 Hz, 1H, C10-H), 3.10 (s, 3H, C12-H), 2.60 (td, *J* = 12.7, 9.0 Hz, 1H, C9-H), 2.50 – 2.34 (m, 1H, C9-H), 1.38 (s, 9H, C20/21/22-H), 1.06 (s, 3H, C14/15-H), 0.96 (s, 3H, C14/15-H).

^{13}C-NMR (76 MHz, $CDCl_3$): δ [ppm] 172.27 (C-11), 154.08 (C-18), 151.42 (C-4), 144.13 (C-16), 129.16 (C-5), 128.86 (C-6), 125.55 (C-1), 117.92 (C-2), 114.07 (C-17), 109.05 (C-3), 80.48 (C-19), 78.77 (C-7), 62.13 (C-13), 59.73 (C-10), 51.82 (C-12), 40.97 (C-8), 36.51 (C-9), 28.39 (C-20/21/22), 22.95 (C-14/15), 22.37 (C-14/15).

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3408.90, 2973.18, 2928.28, 1755.49, 1736.25, 1689.90, 1637.46, 1607.23, 1483.02, 1466.83, 1434.610, 1387.08, 1365.36, 1338.99, 1321.52, 1276.10, 1230.74, 1204.57, 1166.00, 1121.69, 1110.17, 1084.98, 1046.73, 1021.06, 1009.90, 905.54, 863.38, 811.30, 779.16, 731.51, 690.26, 676.51, 646.54, 604.85, 518.47, 477.99, 461.42.

5.4.12 Synthesis of (5a*S*,10b*R*,11a*S*)-2-(2,4-dimethoxybenzyl)-10b-(2-methylbut-3-en-2-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (116a)



116a

$C_{27}H_{31}N_3O_4$

[461.56]

In the course of this thesis the preparation of this substrate was performed following the general reaction procedure **C** using 197 mg (0.500 mmol, 1.0 eq.) of (*S*)-3-((1*H*-indol-3-yl)methyl)-1-(2,4-dimethoxybenzyl)piperazine-2,5-dione (**115**) as starting material as well as the ligand **24**.

The residue was purified by column chromatography (PE/EtOAc = 1:1) to afford the desired product **116a** and its corresponding diastereoisomer **116b** (180 mg, 0.390 mmol, 78%) as a clear to light yellow solid with a ratio of 1:1, *exo/endo*, **116a**/**116b**.

The synthesis of (5a*S*,10b*R*,11a*S*)-2-(2,4-dimethoxybenzyl)-10b-(2-methylbut-3-en-2-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (**116a**) was performed according to the procedure of Stark *et al.*[4]

The stereochemistry of this compound was confirmed by NOESY experiments in comparison to its corresponding diastereoisomer **116b**.

R_f value (PE/EtOAc 1:1 (v/v)): 0.40.

^{1}H-NMR (600 MHz, $CDCl_3$): δ [ppm] 7.16 (dd, J = 7.5, 2.1 Hz, 1H, C3-H), 7.14 (dd, J = 7.5, 1.2 Hz, 1H, C25-H), 7.07 (dt, J = 7.6, 1.2 Hz, 1H, C1-H), 6.73 (dt, J = 7.5, 1.0 Hz, 1H, C2-H), 6.54 (d, J = 7.8 Hz, 1H, C6-H), 6.41 (s, 1H, C22-H), 6.40 (d, J = 2.4 Hz, 1H, C24-H), 5.97 (dd, J = 17.4, 10.8 Hz, 1H, C17-H), 5.50 (s, 1H, C7-H), 5.14 – 5.04 (m, 2H, C18-H), 4.91 (s, 1H, N-H), 4.69 (d, J = 14.2 Hz, 1H, C19-H), 4.33 (d, J = 14.2 Hz, 1H, C19-H), 3.92 – 3.87 (m, 2H, C10/12-H), 3.85 (d, J = 1.0 Hz, 1H, C12-H), 3.78 (s, 3H, C26/27-H), 3.77 (s, 3H, C26/27-H), 2.58 (dd, J = 12.7, 6.1 Hz, 1H, C9-H), 2.44 (dd, J = 12.7, 11.2 Hz, 1H, C9-H), 1.11 (s, 3H, C15/16-H), 1.00 (s, 3H, C15/16-H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] 166.80 (C-11/13), 164.11 (C-11/13), 160.96 (C-21), 158.76 (C-23), 150.10 (C-4), 143.67 (C-17), 131.91 (C-3), 129.14 (C-5), 128.92 (C-1), 125.22 (C-25), 118.93 (C-2), 116.14 (C-20), 114.53 (C-18), 109.23 (C-6), 104.59 (C-22), 98.51 (C-24), 77.59 (C-7), 61.79 (C-8), 58.93 (C-10), 55.50 (C-26/27), 51.35 (C-12), 43.89 (C-19), 40.95 (C-14), 36.80 (C-9), 22.97 (C-15/16), 22.59 (C-15/16).

ESI-MS [*m/z*]: calc.: 462.2387 $[M]+H^+$.

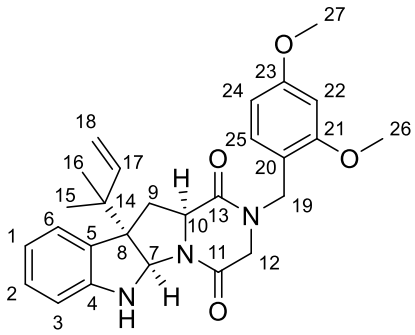
found: 462.2335 $[M]+H^+$.

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3327.52, 2964.35, 1655.16, 1608.05, 1587.97, 1507.50, 1482.14, 1440.97, 1417.05, 1382.62, 1363.83, 1338.14, 1296.12, 1251.25, 1207.40, 1181.57, 1154.07, 1129.77, 1081.64, 1032.72, 980.67, 916.60, 883.38, 833.05, 781.94, 742.12, 672.81, 643.24, 585.93, 561.68, 511.31, 463.38, 410.53, 378.99.

Rotation value (*c* 0.20, $CHCl_3$) $[\alpha]_D^{20}$**:** -231°.

Melting point: 109 °C.

5.4.13 Synthesis of (5a*R*,10b*S*,11a*S*)-2-(2,4-dimethoxybenzyl)-10b-(2-methylbut-3-en-2-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (116b)



116b

$C_{27}H_{31}N_3O_4$

[461.56]

In the course of this thesis the preparation of this substrate was performed following the general reaction procedure **C** using 0.197 mg (0.500 mmol, 1.0 eq.) of (*S*)-3-((1*H*-indol-3-yl)methyl)-1-(2,4-dimethoxybenzyl)piperazine-2,5-dione (**115**) as starting material as well as the ligand **24**.

The residue was purified by column chromatography (PE/EtOAc = 1:1) to afford the desired product **116b** and its corresponding diastereoisomer **116a** (180 mg, 0.390 mmol, 78%) as a clear to light yellow solid with a ratio of 1:1, *exo/endo*, **116a**/**116b**.

The synthesis of (5a*R*,10b*S*,11a*S*)-2-(2,4-dimethoxybenzyl)-10b-(2-methylbut-3-en-2-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (**116b**) was performed according to the procedure of Stark *et al.*[4]

The stereochemistry of this compound was confirmed by NOESY experiments in comparison to its corresponding diastereoisomer **116a**.

R_f value (PE/EtOAc 1:1 (v/v)): 0.30.

^{1}H-NMR (600 MHz, $CDCl_3$): δ [ppm] 7.21 – 7.14 (d, J = 7.5 Hz, 1H, C3-H), 7.08 (dt, J = 7.6, 1.2 Hz, 1H, C1-H), 7.01 (d, J = 8.2 Hz, 1H, C25-H), 6.74 (dt, J = 0.9, 7.5 Hz, 1H, C2-H), 6.56 (d, J = 7.9 Hz, 1H, C6-H), 6.40 – 6.38 (m, 1H, C24-H), 5.94 (dd, J = 17.4, 10.8 Hz, 1H, C17-H), 5.44 (s, 1H, N-H), 5.34 (s, 1H, C7-H), 5.12 (ddd, J = 15.8, 10.7, 0.9 Hz, 2H, C18-H), 4.54 (d, J = 14.4 Hz, 1H, C19-H), 4.33 (d, J = 14.4 Hz, 1H, C19-H), 4.07 (td, J = 9.0, 1.7 Hz, 1H, C10-H), 3.89 (dd, J = 17.7, 1.8 Hz, 1H, C12-H), 3.80 (d, J = 17.6 Hz, 1H, C12-H), 3.78 (s, 3H, C26/27-H), 3.72 (s, 3H, C26/27-H), 2.85 (dd, J = 13.8, 8.7 Hz, 1H, C9-H), 2.54 (dd, J = 13.8, 8.9 Hz, 1H, C9-H), 1.13 (s, 3H, C15/16-H), 0.97 (s, 3H, C15/16-H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] 166.87 (C-11/13), 166.09 (C-11/13), 160.91 (C-23), 158.74 (C-21), 148.65 (C-5), 143.74 (C-17), 131.74 (C-25), 131.72 (C-4), 128.42 (C-1), 125.96 (C-3), 118.93 (C-2), 116.26 (C-20), 114.74 (C-18), 109.16 (C-6), 104.65 (C-22), 98.51 (C-24), 79.69 (C-7), 61.99 (C-8), 57.59 (C-10), 55.53 (C-26/27), 55.45 (C-26/27), 51.59 (C-12), 43.98 (C-19), 41.73 (C-14), 36.97 (C-9), 22.61 (C-15/16), 22.59 (C-15/16).

ESI-MS [*m/z*]: calc.: 462.2387 $[M]+H^+$.

found: 462.2420 $[M]+H^+$.

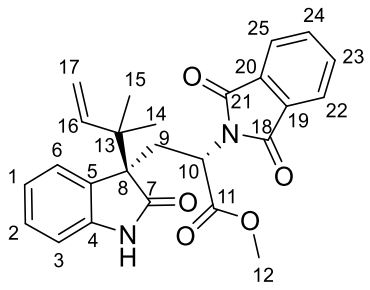
IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3372.15, 2965.43, 2935.41, 2836.40, 1659.75, 1608.21, 1588.17, 1507.29, 1484.37, 1463.55, 1437.48, 1415.54, 1382.27, 1365.97, 1342.73, 1288.20, 1258.58, 1206.78, 1155.81, 1130.54, 1068.48, 1031.84, 917.63, 833.28, 776.31, 743.27, 634.45, 582.96, 557.97, 510.71, 468.38, 406.49.

Rotation value (*c* 0.18, $CHCl_3$) $[\alpha]_D^{20}$**:** +73.3°.

Melting point: 65 °C.

5.5. Further transformed substrates

5.5.1 Synthesis of (2*R*)-methyl 2-(1,3-dioxoisoindolin-2-yl)-3-(3-(2-methylbut-3-en-2-yl)-2-oxoindolin-3-yl)propanoate (133a)



133a

$C_{25}H_{24}N_2O_5$

[432.47]

This reaction was performed as a one-pot synthesis of the prenylation reaction and the following oxidation.

In the course of this thesis the prenylation reaction leading to this substrate was performed following both the general reaction procedures **A, B** and **C** in which methyl (*S*)-2-(1,3-dioxoisoindolin-2-yl)-3-(1*H*-indol-3-yl) propanoate (**129**) was used as starting material as well as the ligands **27a**, **27b** or **24**.[4]

Afterwards, the residue was diluted with THF/H_2O 1:1 and 7 eq. of 2-methyl-2-buten and 5.0 eq. of sodium chlorite were added. Then 10 eq. of sodium hydrogen phosphate were added and the reaction mixture stirred at room temperature for four hours. After complete conversion of the starting material the reaction mixture was extracted with ethyl acetate, dried over sodium sulphate and the solvent removed under reduced pressure.

The residue was purified by column chromatography (PE/EtOAc = 2:1) to afford the desired product **133a** and its corresponding diastereoisomer **133b** as colourless crystals.

In order to get more details regarding the scale and yields of these reactions see Table 3.3.2.

R_f value (PE/EtOAc 2:1 (v/v)): 0.27.

^{1}H-NMR (500 MHz, $CDCl_3$): *δ* [ppm] 8.03 (s, 1H, N-H), 7.62 – 7.54 (m, 4H, Phth-H), 6.91 (dd, *J* = 7.6, 1.1 Hz, 1H, C3-H), 6.58 – 6.47 (m, 2H, C2/6-H), 6.26 (td, *J* = 7.4, 1.3 Hz, 1H, C1-H), 6.07 (dd, *J* = 17.4, 10.8 Hz, 1H, C16-H), 5.13 – 4.96 (m, 2H, C17-H), 4.82 (dd, *J* = 10.9, 3.9 Hz, 1H, C10-H), 3.69 (s, 3H, C12-H), 3.08 – 2.96 (m, 2H, C9-H), 1.13 (s, 3H, C14/15-H), 1.02 (s, 3H, C14/15-H).

^{13}C-NMR (126 MHz, $CDCl_3$): *δ* [ppm] 179.73 (C-11), 169.42 (C-7), 167.11 (C-18/21), 142.77 (C-16), 141.19 (C-4), 133.73 (C-22/25), 131.66 (C-19/20), 130.14 (C-5), 127.19 (C-2), 124.97 (C-3), 123.02 (C-23/24), 121.25 (C-1), 114.39 (C-17), 109.67 (C-6), 56.81 (C-8), 53.09 (C-12), 49.63 (C-10), 42.81 (C-13), 29.04 (C-9), 22.57 (C-14/15), 21.54 (C-14/15).

ESI-MS [*m/z*]: calc.: 433.1763 $[M]+H^+$.

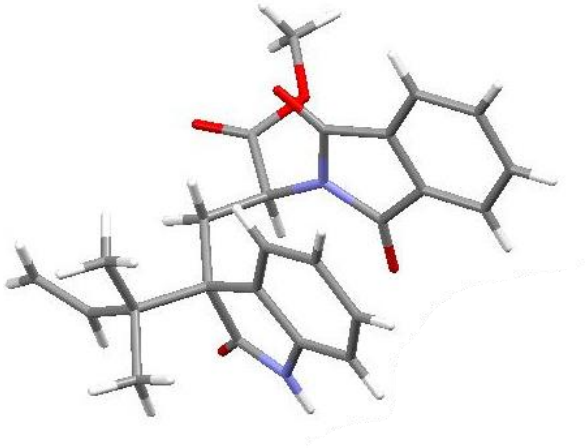
found: 433.1774 $[M]+H^+$.

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3276.55, 2959.97, 1774.70, 1743.34, 1704.33, 1615.62, 1469.61, 1435.55, 1385.92, 1329.82, 1290.86, 1258.55, 1186.38, 1154.80, 1112.14, 1088.75, 1072.71, 1031.50, 1020.22, 1006.94, 916.51, 863.04, 828.58, 786.89, 756.92, 717.03, 658.40, 634.28, 577.48, 528.99, 491.05, 458.14, 418.86, 402.40.

Rotation value (*c* 0.25, $CHCl_3$) $[\alpha]_D^{20}$**:** -1.25°.

Melting point: 69 °C.

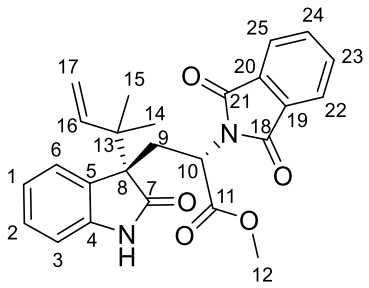
Crystal data:



Cell	a = 9.2086 (3) Å; α = 86.925 (4)° b = 10.4404 (6) Å; β = 88.212 (3)° c = 12.7210 (5) Å; γ = 66.045 (4)° V = 1116.00 (9) Å^3 from 31608 reflns. between θ_{min} = 4.6° and θ_{max} = 75.8°
Z	2
Crystal system, space group	triclinic, P1
Crystal size	0.25 x 0.2 x 0.15
Crystal colour, morphology	clear colourless, needle
F(000)	456.0
D_x	1.287 Mg m^{-3}
θ_{min}, θ_{max}	3.5°, 76.5°
Completeness at θ_{max}	0.991
Radiation type	Cu *Kα* (λ = 1.54184 Å)
Temperature	100 K
μ	0.740 mm^{-1}
Diffractometer	Rigaku SuperNova
T_{min}, T_{max}	0.8811, 1.000
hkl range	*h*: -11→11, *k*: -13→12, *l*: -15→15
No. of reflections	41096 measured, 8457 independent, 8382 ($I > 2\sigma(I)$)

R_{int}	0.0207
$\sin(\theta_{max})/\lambda$	0.581 $Å^{-1}$
$R[F^2 > 2\sigma(F^2)]$	0.0267
$wR(F^2)$	0.0731
S	0.937
w	$1/(\sigma^2(F_o^2)+(0.0494P)^2+0.2447P)$ with $P=(F_o^2+2F_c^2)/3$
$(\Delta/\sigma)_{max}$	0.000
$\Delta\rho_{max}$, $\Delta\rho_{min}$	0.416 e $Å^3$, -0.142 e $Å^3$
No. of reflections	8457
No. of parameters / restraints	592 / 3

5.5.2 Synthesis of (2*S*)-methyl 2-(1,3-dioxoisoindolin-2-yl)-3-(3-(2-methylbut-3-en-2-yl)-2-oxoindolin-3-yl)propanoate (133b)



133b

$C_{25}H_{24}N_2O_5$

[432.47]

This reaction was performed as a one-pot synthesis of the prenylation reaction and the following oxidation.

In the course of this thesis the prenylation reaction leading to this substrate was performed following both the general reaction procedures **A, B** and **C** in which methyl (*S*)-2-(1,3-dioxoisoindolin-2-yl)-3-(1*H*-indol-3-yl) propanoate (**129**) was used as starting material as well as the ligands **27a**, **27b** or **24**.[4]

Afterwards, the residue was diluted with THF/H_2O 1:1 and 7 eq. of 2-methyl-2-buten and 5.0 eq. of sodium chlorite were added. Then 10 eq. of sodium hydrogen phosphate were added and the reaction mixture stirred at room temperature for four hours. After complete conversion of the starting material the reaction mixture was extracted with ethyl acetate, dried over sodium sulphate and the solvent removed under reduced pressure.

The residue was purified by column chromatography (PE/EtOAc = 2:1) to afford the desired product **133b** and its corresponding diastereoisomer **133a** as colourless crystals.

In order to get more details regarding the scale and yields of these reactions see Table 3.3.2.

R_f value (PE/EtOAc 2:1 (v/v)): 0.23.

^{1}H-NMR (300 MHz, $CDCl_3$): δ [ppm] 7.81 (dd, *J* = 5.5, 3.1 Hz, 2H, C22/25-H), 7.62 (dd, *J* = 5.5, 3.0 Hz, 2H, C23/24-H), 7.57 (s, 1H, N-H), 7.34 – 7.21 (m, 2H, C2/3-H), 7.09 (td, *J* = 7.6, 1.1 Hz, 1H, C1-H), 6.80 (d, *J* = 7.6 Hz, 1H, C6-H), 6.01 (dd, *J* = 17.4, 10.8 Hz, 1H, C16-H), 5.15 – 4.95 (m, 2H, C17-H), 4.23 (dd, *J* = 10.9, 2.2 Hz, 1H, C9-H), 3.63 (s, 3H, C12-H), 3.20 (dd, *J* = 14.8, 10.9 Hz, 1H, C10-H), 2.91 (dd, *J* = 14.8, 2.2 Hz, 1H, C9-H), 1.13 (s, 3H, C14/15-H), 1.01 (s, 3H, C14/15-H).

^{13}C-NMR (76 MHz, $CDCl_3$): δ [ppm] 179.45 (C-11), 169.77 (C-7), 167.43 (C-18/21), 142.85 (C-16), 142.10 (C-4), 134.11 (C-22/25), 131.88 (C-19/20), 129.17 (C-5), 128.72 (C-2), 125.97 (C-3), 123.67 (C-23/24), 122.02 (C-1), 114.42 (C-17), 110.02 (C-6), 56.93 (C-8), 53.09 (C-12), 49.14 (C-10), 42.36 (C-13), 30.41 (C-9), 22.10 (C-14/15), 21.95 (C-14/15).

ESI-MS [*m/z*]: calc.: 433.1763 $[M]+H^+$.

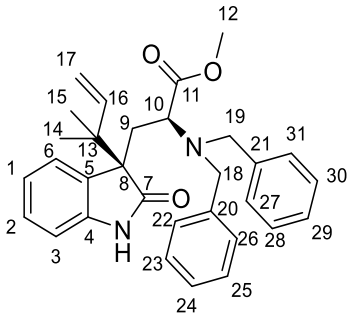
found: 433.1770 $[M]+H^+$.

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3280.13, 2957.92, 1776.44, 1711.71, 1617.99, 1470.64, 1435.58, 1384.27, 1335.03, 1257.03, 1186.20, 1112.27, 1088.24, 1070.24, 1029.49, 918.31, 891.75, 825.61, 788.45, 754.27, 715.26, 677.96, 654.69, 622.50, 568.17, 529.01, 489.08, 451.64, 408.59.

Rotation value (*c* 0.25, $CHCl_3$) $[\alpha]_D^{20}$**:** -73.6°.

Melting point: 61 °C.

5.5.3 Synthesis of methyl-(*S*)-2-(dibenzylamino)-3-((*R*)-3-(2-methylbut-3-en-2-yl)-2-oxoindolin-3-yl)propanoate (43a)



43a

$C_{31}H_{34}N_2O_3$

[482.62]

This reaction was performed as a one-pot synthesis of the prenylation reaction and the following oxidation.

In the course of this thesis the prenylation reaction leading to this substrate was performed following both the general reaction procedures **A** and **C** in which methyl *N*,*N* dibenzyl-*L*-tryptophanate (**39**) was used as starting material as well as the ligands **27a**, **27b** or **24**.[4]

Afterwards, the residue was diluted with THF/H_2O 1:1 and 7 eq. of 2-methyl-2-buten and 5.0 eq. of sodium chlorite were added. Then 10 eq. of sodium hydrogen phosphate were added and the reaction mixture stirred at room temperature for four hours. After complete conversion of the starting material the reaction mixture was extracted with ethyl acetate, dried over sodium sulphate and the solvent removed under reduced pressure.

The residue was purified by column chromatography (PE/EtOAc = 3:1) to afford the desired product **43a** and its corresponding diastereoisomer **43b** as a light yellow solid.

In order to get more details regarding the scale and yields of these reactions see Table 3.3.3.

R_f value (PE/EtOAc 3:1 (v/v)): 0.48.

^{1}H-NMR (600 MHz, $CDCl_3$): *δ* [ppm] 8.39 (s, 1H, N-H), 7.28 – 7.14 (m, 10H, C22-31-H), 7.09 (ddd, *J* = 7.7, 4.9, 4.0 Hz, 1H, C2-H), 6.76 (dd, *J* = 4.1, 0.9 Hz, 2H, C1/3-H), 6.72 (dd, *J* = 7.7, 0.8 Hz, 1H, C6-H), 5.99 (dd, *J* = 17.4, 10.8 Hz, 1H, C16-H), 5.13 – 4.90 (m, 2H, C17-H), 3.81 (d, *J* = 14.0 Hz, 2H, C18/19-H), 3.53 (s, 3H, C12-H), 3.33 (d, *J* = 14.0 Hz, 2H, C18/19-H), 2.90 (dd, *J* = 9.9, 2.4 Hz, 1H, C10-H), 2.75 (dd, *J* = 13.6, 10.0 Hz, 1H, C9-H), 2.15 (dd, *J* = 13.6, 2.5 Hz, 1H, C9-H), 1.09 (s, 3H, C14/15-H), 0.96 (s, 3H, C14/15-H).

^{13}C-NMR (151 MHz, $CDCl_3$): *δ* [ppm] 180.75 (C-11), 172.32 (C-7), 143.14 (C-16), 141.81 (C-4), 139.46 (C-20/21), 129.66 (C-5), 128.69 (C-22/26/27/31), 128.24 (C-23/25/28/30), 127.95 (C-2), 126.93 (C-24/29), 125.91 (C-1), 121.61 (C-3), 114.04 (C-17), 109.25 (C-6), 58.26 (C-10), 56.86 (C-8), 54.93 (C-18/19), 51.05 (C-12), 42.64 (C-13), 32.93 (C-9), 22.01 (C-14/15), 21.81 (C-14/15).

ESI-MS [*m/z*]: calc.: 483.2648 $[M]+H^+$.

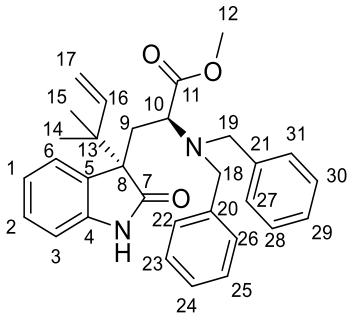
found: 483.2662 $[M]+H^+$.

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 2955.29, 2927.09, 2857.48, 1734.88, 1648.58, 1618.46, 1585.31, 1454.52, 1368.10, 1275.63, 1252.52, 1160.42, 1073.97, 1029.31, 961.76, 915.83, 855.21, 793.37, 745.22, 697.95, 574.09, 492.52, 464.11.

Rotation value (*c* 0.23, $CHCl_3$) $[\alpha]_D^{20}$**:** -53.9°.

Melting point: 53 °C.

5.5.4 Synthesis of methyl-(*S*)-2-(dibenzylamino)-3-((*S*)-3-(2-methylbut-3-en-2-yl)-2-oxoindolin-3-yl)propanoate (43b)



43b

$C_{31}H_{34}N_2O_3$

[482.62]

This reaction was performed as a one-pot synthesis of the prenylation reaction and the following oxidation.

In the course of this thesis the prenylation reaction leading to this substrate was performed following both the general reaction procedures **A** and **C** in which methyl *N*,*N* dibenzyl-*L*-tryptophanate (**39**) was used as starting material as well as the ligands **27a**, **27b** or **24**.[4]

Afterwards, the residue was diluted with THF/H_2O 1:1 and 7 eq. of 2-methyl-2-buten and 5.0 eq. of sodium chlorite were added. Then 10 eq. of sodium hydrogen phosphate were added and the reaction mixture stirred at room temperature for four hours. After complete conversion of the starting material the reaction mixture was extracted with ethyl acetate, dried over sodium sulphate and the solvent removed under reduced pressure.

The residue was purified by column chromatography (PE/EtOAc = 3:1) to afford the desired product **43b** and its corresponding diastereoisomer **43a** as a light yellow solid.

In order to get more details regarding the scale and yields of these reactions see Table 3.3.3.

R_f value (PE/EtOAc 3:1 (v/v)): 0.20.

^{1}H-NMR (300 MHz, $CDCl_3$): δ [ppm] 7.69 (s, 1H, indole N-H), 7.54 (m, 2H, C22-31-H), 7.42 - 7.29 (m, 4H, C22-31-H), 7.17 (d, *J* = 12.9 Hz, 5H, C2/22-31-H), 6.90 (t, *J* = 45.4 Hz, 3H, C1/3/6-H), 6.07 (m, 1H, C16-H), 5.09 (m, 2H, C17-H), 4.54 (d, *J* = 15.7 Hz, 2H, C18/19-H), 4.28 (m, 1H, C10-H), 4.07 (m, 1H, C9-H), 3.25 (m, 4H, C9/12-H), 2.90 (m, 2H, C18/19-H), 1.19 (s, 3H, C14/15-H), 1.10 (s, 3H, C14/15-H).

^{13}C-NMR (76 MHz, $CDCl_3$): δ [ppm] 179.44 (C-11), 172.02 (C-7), 139.46 (C-16), 137.79 (C-4), 136.25 (C-20/21), 129.66 (C-5), 128.86 (C-22/26/27/31), 128.61 (C-23/25/28/30), 128.50 (C-2), 128.20 (C-24/29), 127.73 (C-1), 121.94 (C-3), 114.38 (C-17), 109.67 (C-6), 57.28 (C-10), 55.09 (C-8), 52.02 (C-18/19), 51.04 (C-12), 39.83 (C-13), 29.83 (C-9), 22.29 (C-14/15), 21.83 (C-14/15).

ESI-MS [*m/z*]: calc.: 483.2648 $[M]+H^+$.

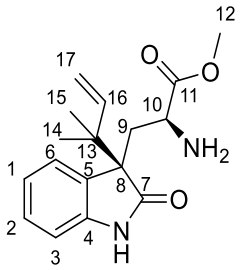
found: 483.2663 $[M]+H^+$.

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3250.88, 3062.16, 3029.058, 2923.33, 2850.92, 1727.87, 1618.86, 1471.75, 1453.44, 1365.21, 1327.51, 1190.42, 1169.43, 1127.23, 1072.99, 1027.35, 962.79, 915.51, 871.93, 815.18, 744.98, 697.00, 675.49, 597.11, 574.88, 536.74, 489.20.

Rotation value (*c* 0.17, $CHCl_3$) $[\alpha]_D^{20}$**:** -18.2°.

Melting point: 51 °C.

5.5.5 Synthesis of methyl-(*S*)-2-amino-3-((*R*)-3-(2-methylbut-3-en-2-yl)-2-oxoindolin-3-yl)propanoate (135a)



135a

$C_{17}H_{22}N_2O_3$

[302.36]

To a solution of 0.433 g (1.00 mmol, 1.0 eq.) of (2*R*)-methyl 2-(1,3-dioxoisoindolin-2-yl)-3-(3-(2-methylbut-3-en-2-yl)-2-oxoindolin-3-yl)propanoate (**133a**) in 10 mL of methanol, with a drop of dichloromethane, were added 0.15 mL (0.096 g, 3.0 mmol, 3.0 eq.) of hydrazine hydrate and the reaction mixture stirred for four hours at room temperature. Afterwards, the mixture was washed with a saturated solution of sodium hydrogen carbonate, extracted with ethyl acetate and dried over sodium sulfate. Then the solvent was removed under reduced pressure.

The residue was purified by column chromatography using ethyl acetate as eluent to afford the desired product **135a** (0.298 g, 0.986 mmol, 99%) as a colourless solid.

The synthesis of methyl-(*S*)-2-amino-3-((*R*)-3-(2-methylbut-3-en-2-yl)-2-oxoindolin-3-yl)propanoate (**135a**) was performed according to the procedure of Sen *et al*.[113]

R_f value (EtOAc): 0.15.

^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] 8.87 (s, 1H, indole N-H), 7.22 – 7.15 (m, 2H, C2/3-H), 6.97 (td, *J* = 7.6, 1.1 Hz, 1H, C1-H), 6.90 – 6.87 (m, 1H, C6-H), 6.05 (dd, *J* = 17.4, 10.8 Hz, 1H, C16-H), 5.12 – 4.94 (m, 2H, C17-H), 3.56 (s, 3H, C12-H), 3.28 (t, *J* = 6.4 Hz, 1H, C10-H), 2.58 (dd, *J* = 14.2, 6.7 Hz, 1H, C9-H), 2.22 (dd, *J* = 14.1, 6.3 Hz, 1H, C9-H), 1.10 (s, 3H, C14/15-H), 1.01 (s, 3H, C14/15-H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ [ppm] 180.93 (C-11), 175.29 (C-7), 142.99 (C-16), 142.18 (C-4), 130.53 (C-5), 128.25 (C-3), 126.10 (C-2), 121.41 (C-1), 114.19 (C-17), 109.68 (C-6), 56.75 (C-8), 52.40 (C-10), 52.02 (C-12), 42.73 (C-13), 36.30 (C-9), 22.16 (C-14/15), 21.69 (C-14/15).

ESI-MS [*m/z*]: calc.: 303.1703 [M]+H$^+$.

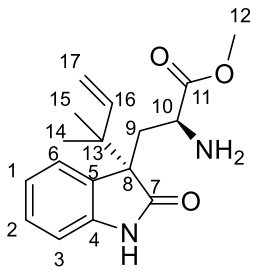
found: 303.1700 [M]+H$^+$.

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3213.91, 3082.57, 2967.84, 2880.38, 1698.01, 1615.62, 1594.10, 1469.99, 1437.29, 1414.59, 1381.62, 1365.82, 1329.23, 1199.13, 1154.92, 1111.93, 1009.96, 972.04, 916.82, 861.15, 823.61, 745.88, 675.21, 641.97, 588.59, 492.95, 429.30.

Rotation value (*c* 0.66, $CHCl_3$) $[\alpha]_D^{20}$**:** +55.2°.

Melting point: 47 °C.

5.5.6 Synthesis of methyl-(*S*)-2-amino-3-((*S*)-3-(2-methylbut-3-en-2-yl)-2-oxoindolin-3-yl)propanoate (135b)



135b

$C_{17}H_{22}N_2O_3$

[302.36]

To a solution of 0.137 g (0.317 mmol, 1.0 eq.) of (2*S*)-methyl 2-(1,3-dioxoisoindolin-2-yl)-3-(3-(2-methylbut-3-en-2-yl)-2-oxoindolin-3-yl)propanoate (**133b**) in 10 mL of methanol, with a drop of dichloromethane, were added 0.15 mL (0.048 g, 0.95 mmol, 3.0 eq.) of hydrazine hydrate and the reaction mixture stirred for three hours at room temperature. Afterwards, the mixture was washed with a solution of sodium hydrogen carbonate, extracted with ethyl acetate and dried over sodium sulfate. Then the solvent was removed under reduced pressure.

The residue was purified by column chromatography using ethyl acetate as eluent to afford the desired product **135b** (84.9 mg, 0.281 mmol, 89%) as a colourless solid.

The synthesis of methyl-(*S*)-2-amino-3-((*S*)-3-(2-methylbut-3-en-2-yl)-2-oxoindolin-3-yl)propanoate (**135b**) was performed according to the procedure of Sen *et al*.[113]

R_f value (EtOAc): 0.10.

^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] 8.50 (s, 1H, indole N-H), 7.19 (td, *J* = 7.7, 1.2 Hz, 1H, C2-H), 7.12 (dd, *J* = 7.5, 1.1 Hz, 1H, C3-H), 6.97 (td, *J* = 7.6, 1.1 Hz, 1H, C1-H), 6.89 – 6.84 (m, 1H, C6-H), 6.02 (dd, *J* = 17.4, 10.8 Hz, 1H, C16-H), 5.12 – 4.88 (m, 2H, C17-H), 3.56 (s, 3H, C12-H), 2.94 (dd, *J* = 10.5, 4.2 Hz, 1H, C10-H), 2.36 (dd, *J* = 14.1, 4.2 Hz, 1H, C9-H), 2.22 (dd, *J* = 14.0, 10.5 Hz, 1H, C9-H), 1.11 (s, 3H, C14/15-H), 0.99 (s, 3H, C14/15-H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ [ppm] 182.31 (C-11), 176.43 (C-7), 143.25 (C-16), 142.55 (C-4), 129.36 (C-5), 128.13 (C-2), 126.31 (C-3), 121.19 (C-1), 113.99 (C-17), 109.56 (C-6), 56.79 (C-8), 52.73 (C-10), 52.12 (C-12), 42.34 (C-13), 35.61 (C-9), 21.95 (C-14/15), 21.91 (C-14/15).

ESI-MS [*m/z*]: calc.: 303.1703 $[M]+H^+$.

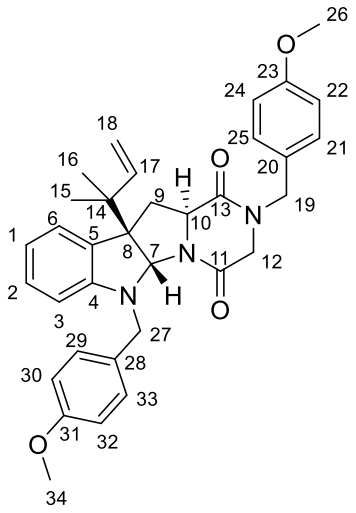
found: 303.1710 $[M]+H^+$.

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3202.78, 2923.78, 2853.46, 1714.68, 1616.40, 1509.56, 1469.35, 1392.03, 1372.75, 1330.07, 1290.84, 1259.92, 1208.11, 1157.76, 1116.62, 1094.59, 1025.91, 930.57, 795.52, 750.87, 711.63, 664.72, 642.13, 603.23, 582.61, 534.42, 524.52, 492.53, 471.57, 382.28.

Rotation value (*c* 0.37, $CHCl_3$) $[\alpha]_D^{20}$**:** -22.3°.

Melting point: 53 °C.

5.5.7 Synthesis of (10b*R*,11a*S*)-2,6-bis(4-methoxybenzyl)-10b-(2-methylbut-3-en-2-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (79)



79

$C_{34}H_{37}N_3O_4$

[551.68]

A solution of 46.7 mg (0.150 mmol, 1.0 eq.) of (11a*S*)-10b-(2-methylbut-3-en-2-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (**74**) in 2 mL of dry dichloromethane was cooled to 0 °C under a nitrogen atmosphere. Afterwards, 11.9 mg (0.496 mmol, 3.3 eq.) of sodium hydride were added and the reaction mixture stirred for ten minutes before 0.157 g (1.05 mmol, 7.0 eq.) of sodium iodide and 0.31 mL (0.35 g, 2.3 mmol, 15 eq.) of *p*-methoxybenzyl chloride were added and the reaction mixture was stirred for two days, during which it was allowed to reach room temperature. Then the mixture was diluted with ethanol and the solvent was removed under reduced pressure.

The residue was purified by column chromatography (PE/EtOAc = 3:1) to afford the product **79** (3.5 mg, 0.0063 mmol, 4.2%) as a colourless oil.

The synthesis of (10b*R*,11a*S*)-2,6-bis(4-methoxybenzyl)-10b-(2-methylbut-3-en-2-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (**79**) was performed according to the procedure of Tsuchiya *et al*.[83]

R_f value (PE/EtOAc 1:1 (v/v)): 0.83.

^{1}H-NMR (400 MHz, $CDCl_3$): *δ* [ppm] 7.23 (d, *J* = 8.6 Hz, 2H, C29/33-H), 7.18 – 7.12 (m, 3H, C3/21/25-H), 7.05 (t, *J* = 7.7 Hz, 1H, C2-H), 6.85 (d, *J* = 8.6 Hz, 2H, C30/32-H), 6.81 – 6.76 (m, 2H, C22/24-H), 6.66 (t, *J* = 7.5 Hz, 1H, C1-H), 6.34 (d, *J* = 7.8 Hz, 1H, C6-H), 5.86 (dd, *J* = 17.6, 11.2 Hz, 1H, C17-H), 5.82 (s, 1H, C7-H), 5.09 – 4.97 (m, 2H, C18-H), 4.78 (d, *J* = 14.4 Hz, 1H, C19-H), 4.64 (d, *J* = 15.8 Hz, 1H, C27-H), 4.43 (d, *J* = 15.9 Hz, 1H, C27-H), 4.21 (d, *J* = 14.3 Hz, 1H, C19-H), 4.05 (dd, *J* = 11.5, 5.6 Hz, 1H, C10-H), 3.81 (s, 1H, C12-H), 3.79 (s, 3H, C26-H), 3.75 (s, 3H, C34-H), 3.69 (d, *J* = 17.2 Hz, 1H, C12-H), 2.61 (dd, *J* = 12.4, 5.9 Hz, 1H, C9-H), 2.34 (t, *J* = 12.0 Hz, 1H, C9-H), 1.04 (s, 3H, C15/16-H), 0.87 (s, 3H, C15/16-H).

^{13}C-NMR (101 MHz, $CDCl_3$): *δ* [ppm] 166.04 (C-13), 161.98 (C-11), 159.64 (C-23), 158.77 (C-31), 151.03 (C-4), 143.55 (C-17), 130.82 (C-28), 130.00 (C-21/25),129.40 (C-5), 129.02 (C-2), 128.70 (C-29/33), 127.29 (C-20), 125.31 (C-3), 117.49 (C-1), 114.70 (C-18), 114.43 (C-22/24), 113.85 (C-30/32), 106.06 (C-6), 81.27 (C-7), 60.54 (C-10), 58.60 (C-8), 55.46 (C-26), 55.36 (C-34), 50.34 (C-12), 48.84 (C-19/27), 41.38 (C-14), 39.94 (C-9), 23.27 (C-15/16), 22.43 (C-15/16).

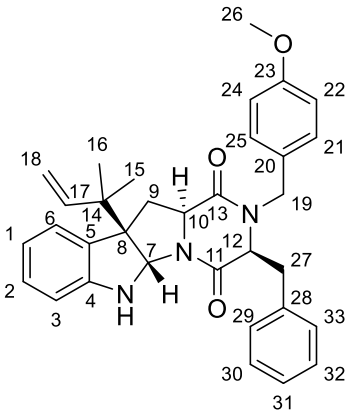
ESI-MS [*m/z*]: calc.: 552.2862 $[M]+H^+$.

found: 552.2849 $[M]+H^+$.

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3375.94, 2958.81, 2934.06, 2872.97, 2835.14, 2633.10, 2417.01, 1770.84, 1656.93, 1603.77, 1585.93, 1510.83, 1489.24, 1439.98, 1382.00, 1353.35, 1301.22, 1274.98, 1242.76, 1174.21, 1140.04, 1103.88, 1079.80, 1031.63, 977.17, 959.22, 918.59, 844.51, 817.83, 775.81, 742.96, 712.40, 865.71, 630.26, 570.46, 502.77, 469.90, 433.72, 419.81, 392.65.

Rotation value (*c* 0.70, $CHCl_3$) $[\alpha]_D^{20}$**:** -188°.

5.5.8 Synthesis of (3*S*,10b*R*,11a*S*)-3-benzyl-2-(4-methoxybenzyl)-10b-(2-methylbut-3-en-2-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (86a)



86a

$C_{33}H_{35}N_3O_3$

[521.65]

76.6 mg (0.178 mmol, 1.0 eq.) of (10b*R*,11a*S*)-2-(4-methoxybenzyl)-10b-(2-methylbut-3-en-2-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (**73a**) were dissolved in 5 mL of dry THF and stirred for ten minutes under a nitrogen atmosphere. After the solution was cooled to -78 °C 0.20 mL (0.033 g, 0.20 mmol, 1.1 eq.) of LHMDS (1 M in THF) were slowly added and the reaction mixture was again stirred for ten minutes. Then 0.042 mL (0.061 g, 0.36 mmol, 2.0 eq.) of benzyl bromide (**89**) were added and the mixture was stirred for two days, during which the solution was allowed to reach room temperature. After dilution with methanol the solvent was removed under reduced pressure.

The residue was purified by column chromatography (PE/EtOAc = 2:1) to afford the desired product **86a** (56.2 mg, 0.108 mmol, 57%) as a colourless solid.

The synthesis of (3*S*,10b*R*,11a*S*)-3-benzyl-2-(4-methoxybenzyl)-10b-(2-methylbut-3-en-2-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo [2,3-b]indole-1,4(5a*H*)-dione (**86a**) was performed according to the procedure of Davies *et al*.[77]

R_f value (PE/EtOAc 1:1 (v/v)): 0.81.

^{1}H-NMR (500 MHz, $CDCl_3$): *δ* [ppm] 7.20 (d, *J* = 8.6 Hz, 2H, C22/24-H), 7.14 (dd, *J* = 8.1, 6.9 Hz, 1H, C2-H), 6.95 (d, *J* = 7.6 Hz, 1H, C3-H), 6.90 – 6.84 (m, 7H, C21/25/29-33-H), 6.72 (t, *J* = 7.4 Hz, 1H, C1-H), 6.64 (d, *J* = 7.8 Hz, 1H, C6-H), 5.88 (dd, *J* = 17.3, 10.8 Hz, 1H, C17-H), 5.35 (s, 1H, C7-H), 5.23 (d, *J* = 14.7 Hz, 1H, C19-H), 5.09 – 4.95 (m, 2H, C18-H), 4.90 (s, 1H, N-H), 4.10 (dd, *J* = 5.0, 3.5 Hz, 1H, C12-H), 3.93 (d, *J* = 14.7 Hz, 1H, C19-H), 3.81 (s, 3H, C26-H), 3.12 (dd, *J* = 13.8, 3.4 Hz, 1H, C27-H), 3.03 (dd, *J* = 14.0, 5.1 Hz, 1H, C27-H), 2.24 (dd, *J* = 12.0, 5.8 Hz, 1H, C9-H), 2.15 (t, *J* = 11.6 Hz, 1H, C10-H), 2.09 (dd, *J* = 11.1, 5.8 Hz, 1H, C9-H), 1.02 (s, 3H, C15/16-H), 0.92 (s, 3H, C15/16-H).

^{13}C-NMR (126 MHz, $CDCl_3$): *δ* [ppm] 168.01 (C-13), 165.80 (C-11), 159.64 (C-23), 150.13 (C-4), 143.65 (C-17), 134.26 (C-28), 130.15 (C-22/24), 129.54 (C-29/33), 128.85 (C-2), 128.78 (C-30/31/32), 127.83 (C-20), 127.35 (C-5), 125.06 (C-3), 118.80 (C-1), 114.51 (C-21/25), 114.38 (C-18), 109.12 (C-6), 77.72 (C-7), 61.56 (C-12), 61.35 (C-8), 57.67 (C-10), 55.46 (C-26), 46.63 (C-19), 40.77 (C-14), 36.57 (C-27), 36.48 (C-9), 22.95 (C-15/16), 22.53 (C-15/16).

ESI-MS [*m/z*]: calc.: 522.2757 $[M]+H^+$.

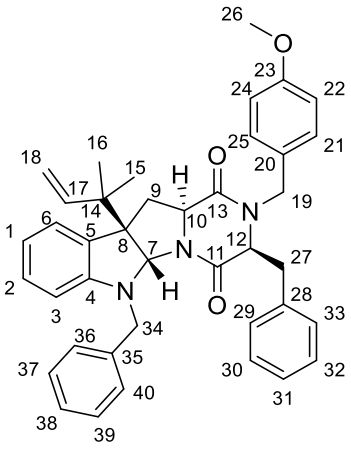
found: 522.2758 $[M]+H^+$.

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3329.474, 2961.17, 2931.42, 2873.08, 2835.86, 1711.29, 1651.07, 1607.33, 1511.92, 1482.09, 1441.84, 1418.95, 1382.56, 1361.31, 1295.69, 1274.33, 1244.90, 1215.12, 1205.00, 1174.79, 1144.26, 1106.25, 1081.69, 1062.04, 1031.30, 981.24, 918.32, 846.77, 818.27, 760.03, 741.20, 701.00, 631.70, 597.12, 561.07, 517.82, 498.26, 463.17, 431.74, 401.35, 382.19.

Rotation value (*c* 0.50, $CHCl_3$) $[\alpha]_D^{20}$**:** -191°.

Melting point: 71 °C.

5.5.9 Synthesis of (3*S*,10b*R*,11a*S*)-3,6-dibenzyl-2-(4-methoxybenzyl)-10b-(2-methylbut-3-en-2-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (87a)



87a

$C_{40}H_{41}N_3O_3$

[611.79]

76.6 mg (0.178 mmol, 1.0 eq.) of (10b*R*,11a*S*)-2-(4-methoxybenzyl)-10b-(2-methylbut-3-en-2-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (**73a**) were dissolved in 5 mL of dry THF and stirred for ten minutes under a nitrogen atmosphere. After the solution was cooled to -78 °C 0.20 mL (0.048 g, 0.29 mmol, 1.6 eq.) of LHMDS (1 M in THF) were slowly added and the reaction mixture was again stirred for ten minutes. Then 0.053 mL (0.076 g, 0.45 mmol, 2.5 eq.) of benzyl bromide (**89**) were added and the mixture was stirred for two days, during which the solution was allowed to reach room temperature. After dilution with methanol the solvent was removed under reduced pressure.

The residue was purified by column chromatography (PE/EtOAc = 2:1) to afford the compound **87a** (7.2 mg, 0.012 mmol, 6.6%) as a by-product in the synthesis of **86a** as a colourless solid.

The synthesis of (3*S*,10b*R*,11a*S*)-3,6-dibenzyl-2-(4-methoxybenzyl)-10b-(2-methylbut-3-en-2-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (**87a**) was performed according to the procedure of Davies *et al*.[77]

R_f value (PE/EtOAc 2:1 (v/v)): 0.65.

^{1}H-NMR (600 MHz, $CDCl_3$): *δ* [ppm] 7.41 (d, *J* = 7.2 Hz, 1H, C6-H), 7.29 (d, *J* = 3.8 Hz, 2H, C22/24-H), 7.16 (d, *J* = 8.4 Hz, 2H, C29/33-H), 7.15 – 7.12 (m, 3H, C1/2/3-H), 7.05 – 7.02 (m, 3H, C30/31/32-H), 6.88 – 6.85 (m, 2H, C36/40-H), 6.74 (d, *J* = 8.7 Hz, 2H, C21/25-H), 6.68 (dd, *J* = 8.1, 1.3 Hz, 3H, C37/38/39-H), 5.95 (s, 1H, C7-H), 5.78 – 5.70 (m, 1H, C17-H), 5.66 (s, 2H, C18-H), 4.82 (d, *J* = 15.0 Hz, 1H, C19-H), 4.57 (d, *J* = 8.3 Hz, 1H, C19-H), 3.89 (d, *J* = 14.3 Hz, 1H, C34-H), 3.81 (s, 3H, C26-H), 3.36 (d, *J* = 16.0 Hz, 1H, C34-H), 3.11 – 3.08 (m, 2H, C27-H), 2.37 – 2.32 (m, 1H, C9-H), 2.31 – 2.26 (m, 1H, C9-H), 1.02 (s, 3H, C15/16-H), 0.94 (s, 3H, C15/16-H).

^{13}C-NMR (151 MHz, $CDCl_3$): *δ* [ppm] 167.83 (C-13), 165.39 (C-11), 154.79 (C-23), 150.41 (C-4), 143.53 (C-17), 138.53 (C-35), 131.11 (C-22/24), 130.04 (C-37/38/39), 129.87 (C-30/31/32), 128.72 (C-2), 128.54 (C-3), 128.46 (C-29/33), 128.09 (C-36/40), 127.62 (C-5), 126.73 (C-1), 125.07 (C-6), 114.53 (C-18), 113.98 (C-21/25), 102.14 (C-20), 100.31 (C-28), 79.05 (C-7), 76.14 (C-12), 71.68 (C-8), 65.55 (C-9), 63.67 (C-26), 55.48 (C-19), 50.95 (C-27), 49.72 (C-34), 46.60 (C-10), 41.10 (C-14), 23.19 (C-15/16), 22.30 (C-15/16).

ESI-MS [*m/z*]: calc.: 612.3226 $[M]+H^+$.

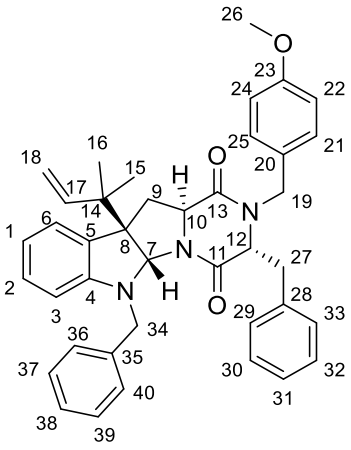
found: 612.3201 $[M]+H^+$.

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3350.19, 3061.88, 3028.18, 2956.91, 2928.46, 1732.05, 1657.36, 1609.79, 1512.04, 1438.84, 1416.29, 1360.76, 1302.28, 1276.45, 1244.50, 1204.42, 1175.27, 1144.07, 1106.73, 1080.93, 1030.39, 920.25, 845.70, 818.31, 749.05, 699.34, 666.04, 632.25, 596.13, 580.20, 500.30, 464.36, 433.08.

Rotation value (*c* 0.65, $CHCl_3$) $[\alpha]_D^{20}$**:** -29.4°.

Melting point: 67 °C.

5.5.10 Synthesis of (3*R*,10b*R*,11a*S*)-3,6-dibenzyl-2-(4-methoxybenzyl)-10b-(2-methylbut-3-en-2-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (87b)



87b

$C_{40}H_{41}N_3O_3$

[611.79]

76.6 mg (0.178 mmol, 1.0 eq.) of (10b*R*,11a*S*)-2-(4-methoxybenzyl)-10b-(2-methylbut-3-en-2-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (**73a**) were dissolved in 5 mL of dry THF and stirred for ten minutes under a nitrogen atmosphere. After the solution was cooled to -78 °C 0.20 mL (0.048 g, 0.29 mmol, 1.6 eq.) of LHMDS (1 M in THF) were slowly added and the reaction mixture was again stirred for ten minutes. Then 0.053 mL (76 mg, 0.45 mmol, 2.5 eq.) of benzyl bromide (**89**) were added and the mixture was stirred for two days, during which the solution was allowed to reach room temperature. After dilution with methanol the solvent was removed under reduced pressure.

The residue was purified by column chromatography (PE/EtOAc = 2:1) to afford the compound **87b** (3.7 mg, 0.0061 mmol, 3.4%) as a by-product in the synthesis of **86a** as a colourless solid.

The synthesis of (3*R*,10b*R*,11a*S*)-3,6-dibenzyl-2-(4-methoxybenzyl)-10b-(2-methylbut-3-en-2-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (**87b**) was performed according to the procedure of Davies *et al*.[77]

R_f value (PE/EtOAc 2:1 (v/v)): 0.77.

^{1}H-NMR (600 MHz, $CDCl_3$): *δ* [ppm] 7.39 (d, *J* = 4.2 Hz, 1H, C6-H), 7.31 (d, *J* = 3.6 Hz, 2H, C22/24-H), 7.17 (d, *J* = 5.7 Hz, 2H, C29/33-H), 7.08 – 7.04 (m, 3H, C-H1/2/3), 7.02 – 7.00 (m, 3H, C30/31/32-H), 6.83 (dd, *J* = 8.8, 2.7 Hz, 2H, C36/40-H), 6.76 (s, 2H, C21/25-H), 6.71 (d, *J* = 8.7 Hz, 3H, C37/38/39-H), 6.08 (s, 1H, C7-H), 5.73 (ddd, *J* = 20.2, 10.1, 7.3 Hz, 1H, C17-H), 4.83 – 4.77 (m, 2H, C18-H), 4.52 (d, *J* = 14.4 Hz, 1H, C19-H), 4.39 (d, *J* = 15.8 Hz, 1H, C19-H), 4.00 (d, *J* = 15.6 Hz, 1H, C34-H), 3.75 (s, 3H, C26-H), 3.46 (d, *J* = 6.7 Hz, 1H, C34-H), 3.04 (t, *J* = 5.8 Hz, 2H, C27-H), 2.39 (dd, *J* = 12.7, 6.3 Hz, 1H, C9-H), 2.33 (dd, *J* = 12.8, 6.2 Hz, 1H, C9-H), 1.17 (s, 3H, C15/16-H), 0.92 (s, 3H, C15/16-H).

^{13}C-NMR (151 MHz, $CDCl_3$): *δ* [ppm] 164.94 (C-13), 160.68 (C-11), 154.55 (C-23), 147.13 (C-4), 142.96 (C-17), 133.13 (C-35), 130.78 (C-22/24), 130.41 (C-37/38/39), 130.06 (C-30/31/32), 129.51 (C-2), 129.39 (C-3), 128.73 (C-29/33), 128.26 (C-36/40), 128.15 (C-5), 126.63 (C-1), 126.23 (C-6), 114.96 (C-18), 113.92 (C-21/25), 100.54 (C-20), 95.17 (C-28), 78.55 (C-7), 76.45 (C-12), 71.42 (C-8), 57.45 (C-9), 55.39 (C-26), 41.97 (C-19), 41.46 (C-27), 40.89 (C-34), 40.51 (C-10), 38.82 (C-14), 22.50 (C-15/16), 22.43 (C-15/16).

ESI-MS [*m/z*]: calc.: 612.3226 $[M]+H^+$.

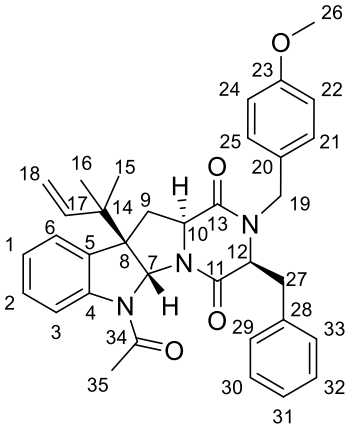
found: 612.3236 $[M]+H^+$.

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3369.10, 3062.15, 3027.91, 2928.23, 1734.96, 1656.77, 1610.31, 1511.54, 1495.20, 1476.56, 1454.01, 1436.27, 1410.20, 1354.41, 1303.05, 1243.68, 1176.31, 1140.31, 1106.89, 1080.89, 1031.20, 920.72, 847.70, 805.55, 750.65, 698.41, 666.54, 632.02, 606.04, 581.10, 499.03, 423.27.

Rotation value (*c* 0.43, $CHCl_3$) $[\alpha]_D^{20}$**:** -30.8°.

Melting point: 67 °C.

5.5.11 Synthesis of (3*S*,10b*R*,11a*S*)-3-benzyl-2-(4-methoxybenzyl)-10b-(2-methylbut-3-en-2-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (103)



103

$C_{35}H_{37}N_3O_4$

[563.69]

To a solution of 47.9 mg (0.0918 mmol, 1.0 eq.) of (3*S*,10b*R*,11a*S*)-3-benzyl-2-(4-methoxybenzyl)-10b-(2-methylbut-3-en-2-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo [2,3-b]indole-1,4(5a*H*)-dione (**86a**) in 2 mL of dichloromethane were added 0.032 mL (23 mg, 0.23 mmol, 2.5 eq.) of triethylamine and the reaction mixture was stirred for ten minutes. Then the mixture was cooled to 0 °C and 0.0079 mL (8.6 mg, 0.11 mmol, 1.2 eq.) of acetyl chloride were added and the reaction mixture was stirred overnight, during which it was allowed to reach room temperature. Afterwards, 0.1 mL of triethylamine and 1 mL of methanol were added to the solution and the solvent removed under reduced pressure.

The residue was purified by column chromatography (PE/EtOAc = 2:1) to afford the desired product **103** (48.7 mg, 0.0864 mmol, 94%) as a colourless solid.

R_f value (PE/EtOAc 1:1 (v/v)): 0.46.

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] 8.10 (d, *J* = 8.0 Hz, 1H, C31-H), 7.36 (ddd, *J* = 8.3, 6.5, 2.2 Hz, 1H, C2-H), 7.23 – 7.19 (m, 2H, C22/24-H), 7.08 (dd, *J* = 6.5, 1.4 Hz, 2H, C3/6-H), 6.93 - 6.83 (m, 5H, C1/21/25/30/32-H), 6.80 (dd, *J* = 7.6, 1.8 Hz, 2H, C29/33-H), 5.81 (s, 1H, C7-H), 5.68 (dd, *J* = 17.3, 10.8 Hz, 1H, C17-H), 5.22 (d, *J* = 14.5 Hz, 1H, C19-H), 5.10 – 4.97 (m, 2H, C18-H), 4.12 – 4.06 (m, 1H, C12-H), 3.97 (d, *J* = 14.5 Hz, 1H, C19-H), 3.81 (s, 3H, C26-H), 3.03 (t, *J* = 4.0 Hz, 2H, C27-H), 2.65 (s, 3H, C35-H), 2.42 – 2.28 (m, 1H, C10-H), 2.08 (t, *J* = 3.3 Hz, 2H, C9-H), 1.05 (s, 3H, C15/16-H), 0.89 (s, 3H, C15/16-H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ [ppm] 170.42 (C-34), 167.16 (C-13), 165.07 (C-11), 159.75 (C-23), 143.49 (C-4), 143.25 (C-17), 133.74 (C-28), 130.25 (C-22/24), 129.54 (C-29/33), 128.99 (C-2), 128.80 (C-30/32), 127.62 (C-20), 127.29 (C-1), 124.46 (C-5), 124.39 (C-3/6), 119.39 (C-31), 114.58 (C-21/25), 114.50 (C-18), 79.48 (C-7), 61.66 (C-12), 60.63 (C-8), 58.00 (C-9), 55.48 (C-26), 46.67 (C-19), 40.38 (C-14), 36.69 (C-27), 36.36 (C-10), 23.81 (C-35), 23.29 (C-15/16), 22.42 (C-15/16).

ESI-MS [*m/z*]: calc.: 564.2784 $[M]+H^+$.

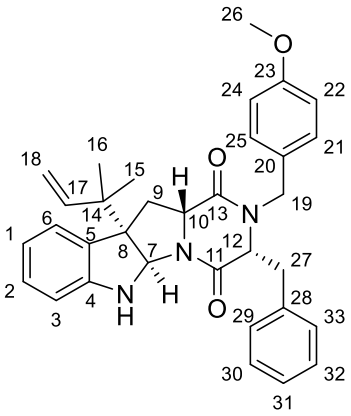
found: 564.2772 $[M]+H^+$.

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 2963.26, 2931.10, 2835.42, 1666.45, 1611.10, 1512.00, 1476.02, 1435.88, 1385.79, 1342.05, 1303.61, 1281.27, 1244.77, 1202.87, 1175.11, 1144.53, 1107.04, 1080.77, 1029.56, 981.05, 923.39, 846.53, 819.94, 802.56, 776.41, 754.10, 734.79, 718.94, 700.42, 655.39, 594.75, 578.12, 565.15, 498.65, 464.16, 400.48.

Rotation value (*c* 0.40, $CHCl_3$) $[\alpha]_D^{20}$**:** -45.3°.

Melting point: 68 °C.

5.5.12 Synthesis of (3*R*,10b*S*,11a*R*)-3-benzyl-2-(4-methoxybenzyl)-10b-(2-methylbut-3-en-2-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (86c)



86c

$C_{33}H_{35}N_3O_3$

[521.65]

76.8 mg (0.178 mmol, 1.0 eq.) of (10b*S*,11a*S*)-2-(4-methoxybenzyl)-10b-(2-methylbut-3-en-2-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (**73b**) were dissolved in 5 mL of dry THF and stirred for ten minutes under a nitrogen atmosphere. After the solution was cooled to -78 °C 0.20 mL (0.033 g, 0.20 mmol, 1.1 eq.) of LHMDS (1 M in THF) were slowly added and the reaction mixture was again stirred for ten minutes. Then 0.042 mL (61 mg, 0.36 mmol, 2.0 eq.) of benzyl bromide (**89**) were added and the mixture was stirred overnight, during which the solution was allowed to reach room temperature. After dilution with methanol the solvent was removed under reduced pressure.

The residue was purified by column chromatography (PE/EtOAc = 2:1) to afford the desired product **86c** (40.3 mg, 0.0773 mmol, 43%) as a colourless solid.

The synthesis of (3*R*,10b*S*,11a*R*)-3-benzyl-2-(4-methoxybenzyl)-10b-(2-methylbut-3-en-2-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (**86c**) was performed according to the procedure of Davies *et al*.[77]

R_f value (PE/EtOAc 1:1 (v/v)): 0.75.

^{1}H-NMR (500 MHz, $CDCl_3$): *δ* [ppm] 7.21 – 7.18 (m, 2H, C22/24-H), 7.15 (t, *J* = 7.7 Hz, 1H, C2-H), 6.95 (d, *J* = 7.5 Hz, 1H, C3-H), 6.92 – 6.82 (m, 7H, C21/25/29-33-H), 6.72 (t, *J* = 7.5 Hz, 1H, C1-H), 6.64 (d, *J* = 7.7 Hz, 1H, C6-H), 5.88 (dd, *J* = 17.4, 10.8 Hz, 1H, C17-H), 5.35 (s, 1H, C7-H), 5.23 (d, *J* = 14.6 Hz, 1H, C19-H), 5.09 – 4.97 (m, 2H, C18-H), 4.89 (s, 1H, N-H), 4.10 (dd, *J* = 5.4, 3.7 Hz, 1H, C12-H), 3.93 (d, *J* = 14.6 Hz, 1H, C19-H), 3.81 (d, *J* = 1.8 Hz, 3H, C26-H), 3.12 (dd, *J* = 13.8, 3.5 Hz, 1H, C27-H), 3.03 (dd, *J* = 13.9, 5.0 Hz, 1H, C27-H), 2.24 (dd, *J* = 12.1, 5.9 Hz, 1H, C9-H), 2.14 (t, *J* = 11.7 Hz, 1H, C10-H), 2.11 – 2.05 (m, 1H, C9-H), 1.02 (s, 3H, C15/16-H), 0.92 (s, 3H, C15/16-H).

^{13}C-NMR (126 MHz, $CDCl_3$): *δ* [ppm] 168.03 (C-13), 165.83 (C-11), 159.64 (C-23), 150.13 (C-4), 143.65 (C-17), 134.26 (C-28), 130.17 (C-22/24), 129.55 (C-29/33), 128.87 (C-2), 128.79 (C-30/31/32), 127.83 (C-20), 127.36 (C-5), 125.08 (C-3), 118.82 (C-1), 114.52 (C-21/25), 114.41 (C-18), 109.13 (C-6), 77.74 (C-7), 61.56 (C-12), 61.36 (C-8), 57.68 (C-10), 55.48 (C-26), 47.13 (C-19), 40.78 (C-14), 22.96 (C-27), 22.54 (C-9), 14.80 (C-15/16), 14.35 (C-15/16).

ESI-MS [*m/z*]: calc.: 522.2757 $[M]+H^+$.

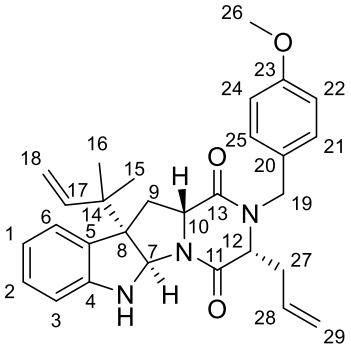
found: 522.2776 $[M]+H^+$.

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3346.96, 2961.76, 2930.52, 2836.39, 1650.95, 1607.61, 1511.92, 1482.46, 1441.21, 1362.76, 1296.41, 1245.53, 1214.81, 1174.74, 1145.66, 1106.45, 1081.92, 1061.98, 1032.29, 919.19, 741.55, 701.17, 597.09, 497.65, 465.73.

Rotation value (*c* 0.50, $CHCl_3$) $[\alpha]_D^{20}$**:** +198°.

Melting point: 69 °C.

5.5.13 Synthesis of (3*R*,10b*S*,11a*R*)-3-allyl-2-(4-methoxybenzyl)-10b-(2-methylbut-3-en-2-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (138)



138

$C_{29}H_{33}N_3O_3$

[471.59]

34.6 mg (0.0802 mmol, 1.0 eq.) of (10b*S*,11a*S*)-2-(4-methoxybenzyl)-10b-(2-methylbut-3-en-2-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (**73b**) were dissolved in 5 mL of dry THF and stirred for ten minutes under a nitrogen atmosphere. After the solution was cooled to -78 °C 0.088 mL (15 mg, 0.088 mmol, 1.1 eq.) of LHMDS (1 M in THF) were slowly added and the reaction mixture was again stirred for ten minutes. Then 0.014 mL (0.020 g, 0.016 mmol, 2.0 eq.) of allyl bromide (**99**) were added and the mixture was stirred overnight, during which the solution was allowed to reach room temperature. After dilution with methanol the solvent was removed under reduced pressure.

The residue was purified by column chromatography (PE/EtOAc = 2:1) to afford the desired product **138** (13.2 mg, 0.0280 mmol, 35%) as a colourless solid.

The synthesis of (3*R*,10b*S*,11a*R*)-3-allyl-2-(4-methoxybenzyl)-10b-(2-methylbut-3-en-2-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (**138**) was performed according to the procedure of Davies *et al*.[77]

R_f value (PE/EtOAc 1:1 (v/v)): 0.77.

^{1}H-NMR (500 MHz, $CDCl_3$): *δ* [ppm] 7.16 (dd, *J* = 7.9, 4.2 Hz, 3H, C3/22/24-H), 7.09 (t, *J* = 7.7 Hz, 1H, C2-H), 6.87 – 6.83 (m, 2H, C21/25-H), 6.76 (t, *J* = 7.5 Hz, 1H, C1-H), 6.56 (d, *J* = 7.8 Hz, 1H, C6-H), 5.97 (dd, *J* = 17.3, 10.8 Hz, 1H, C17-H), 5.62 – 5.52 (m, 1H, C28-H), 5.50 (s, 1H, C7-H), 5.14 – 5.04 (m, 2H, C18-H), 5.00 – 4.93 (m, 2H, C19/N-H), 4.92 – 4.85 (m, 2H, C29-H), 4.13 (d, *J* = 14.6 Hz, 1H, C19-H), 3.96 (dd, *J* = 11.3, 6.1 Hz, 1H, C12-H), 3.89 (t, *J* = 5.2 Hz, 1H, C10-H), 3.79 (s, 3H, C26-H), 2.57 (dd, *J* = 12.6, 6.0 Hz, 1H, C27-H), 2.48 (ddd, *J* = 12.6, 7.4, 4.5 Hz, 1H, C9-H), 2.43 – 2.37 (m, 2H, C9/27-H), 1.12 (s, 3H, C15/16-H), 1.01 (s, 3H, C15/16-H).

^{13}C-NMR (126 MHz, $CDCl_3$): *δ* [ppm] 167.55 (C-13), 165.81 (C-11), 159.58 (C-23), 150.11 (C-4), 143.71 (C-17), 131.87 (C-28), 129.93 (C-22/24), 129.06 (C-5), 129.00 (C-2), 128.07 (C-20), 125.23 (C-3), 120.73 (C-29), 119.02 (C-1), 114.54 (C-18), 114.45 (C-21/25), 109.08 (C-6), 77.71 (C-7), 61.60 (C-8), 61.14 (C-10), 58.69 (C-12), 55.45 (C-26), 47.34 (C-19), 40.94 (C-14), 37.07 (C-27), 36.13 (C-9), 23.09 (C-15/16), 22.64 (C-15/16).

ESI-MS [*m/z*]: calc.: 472.2600 $[M]+H^+$.

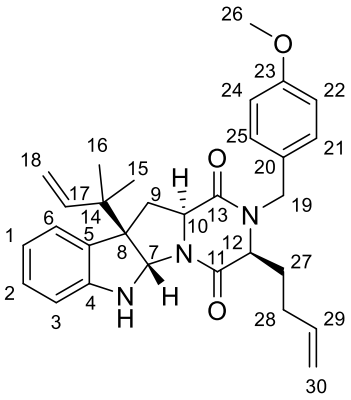
found: 472.2579 $[M]+H^+$.

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3349.63, 3080.18, 2966.82, 2931.50, 2836.62, 1653.84, 1607.66, 1511.95, 1482.25, 1442.23, 1356.18, 1302.77, 1273.07, 1245.51, 1210.50, 1175.50, 1147.74, 1106.81, 1081.96, 1060.91, 1033.31, 919.63, 745.78, 665.30, 508.41, 465.02, 435.32.

Rotation value (*c* 0.55, $CHCl_3$) $[\alpha]_D^{20}$**:** +249°.

Melting point: 62 °C.

5.5.14 Synthesis of (3*S*,10b*R*,11a*S*)-3-(but-3-en-1-yl)-2-(4-methoxybenzyl)-10b-(2-methylbut-3-en-2-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo [2,3-b]indole-1,4(5a*H*)-dione (139)



139

$C_{30}H_{35}N_3O_3$

[485.62]

43.2 mg (0.100 mmol, 1.0 eq.) of (10b*R*,11a*S*)-2-(4-methoxybenzyl)-10b-(2-methylbut-3-en-2-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (**73a**) were dissolved in 3 mL of dry THF and stirred for ten minutes under a nitrogen atmosphere. After the solution was cooled to -78 °C 0.11 mL (0.018 g, 0.11 mmol, 1.1 eq.) of LHMDS (1 M in THF) were slowly added and the reaction mixture was again stirred for ten minutes. Then 0.051 mL (68 mg, 0.50 mmol, 5.0 eq.) of 4-bromo-1-butene (**100**) were added and the mixture was stirred overnight, during which the solution was allowed to reach room temperature. After dilution with methanol the solvent was removed under reduced pressure.

The residue was purified by column chromatography (PE/EtOAc = 2:1) to afford the desired product **139** (3.0 mg, 0.0062 mmol, 6.2%) as a colourless solid.

The synthesis of (3*S*,10b*R*,11a*S*)-3-(but-3-en-1-yl)-2-(4-methoxybenzyl)-10b-(2-methylbut-3-en-2-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (**139**) was performed according to the procedure of Davies *et al*.[77]

R_f value (PE/EtOAc 1:1 (v/v)): 0.52.

^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] 7.17 (dd, *J* = 7.4, 0.6 Hz, 1H, C3-H), 7.14 (d, 2H, C21/25-H), 7.10 (dt, *J* = 7.6, 1.2 Hz, 1H, C1-H), 6.86 – 6.79 (m, 2H, H-23, C24-H), 6.76 (dt, *J* = 7.5, 0.9 Hz, 1H, C2-H), 6.58 (d, *J* = 7.7 Hz, 1H, C6-H), 5.97 (dd, *J* = 17.4, 10.8 Hz, 1H, C17-H), 5.62 (ddt, *J* = 16.9, 10.4, 6.5 Hz, 1H, C29-H), 5.52 (s, 1H, C7-H), 5.11 – 5.06 (m, 2H, C18-H), 5.01 (d, *J* = 14.8 Hz, 1H, C19-H), 4.92 (dq, *J* = 10.4, 1.5 Hz, 1H, C30-H), 4.90 (s, 1H, C30-H), 4.85 (s, 1H, N-H), 4.01 (d, *J* = 14.7 Hz, 1H, C19-H), 3.96 (dd, *J* = 11.1, 6.2 Hz, 1H, C10-H), 3.83 (dd, *J* = 7.5, 4.6 Hz, 1H, C12-H), 3.80 (s, 3H, C26-H), 2.62 (dd, *J* = 12.7, 6.2 Hz, 1H, C9-H), 2.46 (dd, *J* = 12.7, 11.2 Hz, 1H, C9-H), 2.04-1.91 (m, 2H, C28-H), 1.85 - 1.69 (m, 2H, C27-H), 1.12 (s, 3H, C15/16-H), 1.01 (s, 3H, C15/16-H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ [ppm] 166.06 (C-11), 164.21 (C-13), 159.74 (C-23), 143.67 (C-17), 136.49 (C-29), 129.96 (C-5), 129.82 (C-21/25), 129.73 (C-4), 129.07 (C-1), 127.93 (C-20), 125.26 (C-3), 119.05 (C-2), 116.32 (C-30), 114.60 (C-22/24), 114.45 (C-18), 109.12 (C-6), 77.71 (C-7), 61.57 (C-12), 60,91 (C-8), 58.41 (C-10), 55.47 (C-26), 47.26 (C-19), 41.23 (C-14), 37.26 (C-9), 30.90 (C-27), 28.91 (C-28), 23.08 (C-15/16), 22.60 (C-15/16).

ESI-MS [*m/z*]: calc.: 486.2757 $[M]+H^+$.

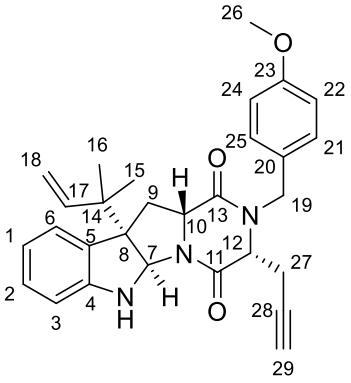
found: 486.2742 $[M]+H^+$.

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3339.80, 3078.71, 2958.16, 2925.79, 2871.17, 1654.40, 1607.32, 1511.94, 1482.23, 1440.31, 1380.68, 1362.53, 1302.07, 1274.12, 1245.35, 1211.56, 1275.37, 1147.74, 1106.76, 1082.03, 1061.37, 1032.91, 916.16, 846.30, 819.03, 786.39, 743.47, 629.71, 602.92, 567.46, 508.37, 464.98, 433.60.

Rotation value (*c* 0.24, $CHCl_3$) $[\alpha]_D^{20}$**:** -264°.

Melting point: 67 °C.

5.5.15 Synthesis of (3*R*,10b*S*,11a*R*)-2-(4-methoxybenzyl)-10b-(2-methylbut-3-en-2-yl)-3-(prop-2-yn-1-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (140)



140

$C_{29}H_{31}N_3O_3$

[469.57]

43.2 mg (0.100 mmol, 1.0 eq.) of (10b*S*,11a*S*)-2-(4-methoxybenzyl)-10b-(2-methylbut-3-en-2-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (**73b**) were dissolved in 3 mL of dry THF and stirred for ten minutes under a nitrogen atmosphere. After the solution was cooled to -78 °C 0.11 mL (0.018 g, 0.11 mmol, 1.1 eq.) of LHMDS (1 M in THF) were slowly added and the reaction mixture was again stirred for ten minutes. Then 0.043 mL (60 mg, 0.50 mmol, 5.0 eq.) of propargyl bromide (**101**) were added and the mixture was stirred overnight, during which the solution was allowed to reach room temperature. After dilution with methanol the solvent was removed under reduced pressure.

The residue was purified by column chromatography (PE/EtOAc = 2:1) to afford the desired product **140** (11.6 mg, 0.0247 mmol, 25%) as a colourless solid.

The synthesis of (3*R*,10b*S*,11a*R*)-2-(4-methoxybenzyl)-10b-(2-methylbut-3-en-2-yl)-3-(prop-2-yn-1-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (**140**) was performed according to the procedure of Davies *et al*.[77]

R_f value (PE/EtOAc 1:1 (v/v)): 0.65.

^{1}H-NMR (500 MHz, $CDCl_3$): *δ* [ppm] 7.18 (d, *J* = 7.6 Hz, 1H, C3-H), 7.16 – 7.12 (m, 2H, C21/25-H), 6.85 – 6.81 (m, 2H, 22/24-H), 6.74 (t, *J* = 7.6 Hz, 1H, C1-H), 6.59 (t, *J* = 7.8 Hz, 1H, C2-H), 6.51 (d, *J* = 8.1 Hz, 1H, C6-H), 5.95 (dd, *J* = 17.5, 10.9 Hz, 1H, C17-H), 5.81 (s, 1H, NH), 5.12 – 5.02 (m, 2H, C18-H), 4.76 (d, *J* = 14.4 Hz, 1H, C19-H), 4.24 (d, *J* = 14.4 Hz, 1H, C19-H), 4.01 (ddd, *J* = 11.7, 6.0, 0.8 Hz, 1H, C29-H), 3.90 (t, *J* = 3.7 Hz, 1H, C10-H), 3.78 (s, 3H, C26-H), 2.60 (dd, *J* = 12.5, 5.7 Hz, 1H, C9-H), 2.37 (dt, *J* = 11.9, 5.0 Hz, 1H, C9-H), 2.01 (t, *J* = 2.2 Hz, 1H, C12-H), 1.11 (s, 3H, C15/16-H), 1.02 (d, *J* = 4.9 Hz, 2H, C27-H), 0.99 (s, 3H, C15/16-H).

^{13}C-NMR (126 MHz, $CDCl_3$): *δ* [ppm] 166.19 (C-11), 164.79 (C-13), 159.61 (C-23), 143.74 (C-17), 129.96 (C-5), 129.79 (C-4), 128.98 (C-21/25), 127.32 (C-20), 125.73 (C-3), 125.19 (C-1), 118.62 (C-2), 114.88 (C-18), 114.51 (C-22/24), 114.40 (C-28), 107.03 (C-6), 77.85 (C-7), 60.85 (C-8), 58.66 (C-10), 55.44 (C-26), 50.31 (C-12), 48.89 (C-19), 41.26 (C-14), 40.97 (C-27), 39.55 (C-9), 35.12 (C-29), 23.24 (C-15/16), 23.10 (C-15/16).

ESI-MS [*m/z*]: calc.: 470.2444 $[M]+H^+$.

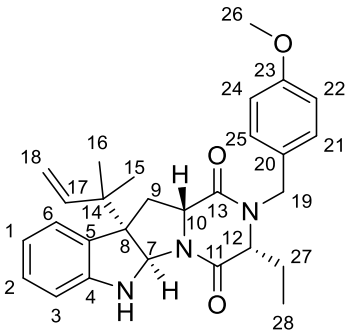
found: 470.2430 $[M]+H^+$.

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3294.35, 2965.33, 2932.70, 2836.76, 1655.90, 1605.55, 1512.05, 1485.04, 1442.07, 1382.69, 1340.00, 1302.80, 1274.13, 1244.77, 1219.38, 1174.59, 1145.25, 1106.45, 1082.01, 1032.04, 980.26, 918.70, 845.69, 819.04, 746.53, 664.49, 572.68, 503.14, 465.89, 433.51, 416.03.

Rotation value (*c* 0.85, $CHCl_3$) $[\alpha]_D^{20}$**:** +247°.

Melting point: 59 °C.

5.5.16 Synthesis of (3*R*,10b*S*,11a*R*)-3-ethyl-2-(4-methoxybenzyl)-10b-(2-methylbut-3-en-2-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (92)



92

$C_{28}H_{33}N_3O_3$

[459.58]

43.2 mg (0.100 mmol, 1.0 eq.) of (10b*S*,11a*S*)-2-(4-methoxybenzyl)-10b-(2-methylbut-3-en-2-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (**73b**) were dissolved in 3 mL of dry THF and stirred for ten minutes under a nitrogen atmosphere. After the solution was cooled to -78 °C 0.11 mL (0.018 g, 0.11 mmol, 1.1 eq.) of LHMDS (1 M in THF) were slowly added and the reaction mixture was again stirred for ten minutes. Then 0.040 mL (78 mg, 0.50 mmol, 5.0 eq.) of ethyl iodide (**91**) were added and the mixture was stirred overnight, during which the solution was allowed to reach room temperature. After dilution with methanol the solvent was removed under reduced pressure.

The residue was purified by column chromatography (PE/EtOAc = 2:1) to afford the desired product **92** (8.1 mg, 0.018 mmol, 17%) as a colourless solid.

The synthesis of (3*R*,10b*S*,11a*R*)-3-ethyl-2-(4-methoxybenzyl)-10b-(2-methylbut-3-en-2-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (**92**) was performed according to the procedure of Davies *et al*.[77]

R_f value (PE/EtOAc 1:1 (v/v)): 0.53.

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] 7.21 (d, *J* = 7.4 Hz, 1H, C3-H), 7.19 – 7.11 (m, 2H, C21/25-H), 7.09 (dt, *J* = 7.7, 1.0 Hz, 1H, C1-H), 6.87 – 6.81 (m, 2H, C22/24-H), 6.78 (dt, *J* = 7.4, 0.8 Hz, 1H, C2-H), 6.57 (d, *J* = 7.5 Hz, 1H, C6-H), 5.97 (dd, *J* = 17.1, 10.7 Hz, 1H, C17-H), 5.53 (s, 1H, N-H), 5.13 - 5.07 (m, *2*H, C18-H), 5.05 (dt, *J* = 7.5, 0.8 Hz, 1H, C7-H), 5.01 (d, *J* = 14.8 Hz, 1H, C19-H), 4.09 (t, *J* = 7.6 Hz, 1H, C10-H), 4.01 (d, *J* = 14.9 Hz, 1H, C19-H), 3.79 (s, 3H, C26-H), 2.61 (dd, *J* = 12.5, 6.1 Hz, 1H, C9-H), 2.43 (t, *J* = 11.3 Hz, 1H, C9-H), 2.01 – 1.97 (m, 1H, C12-H), 1.60 - 1.49 (m, 2H, C27-H), 1.11 (s, 3H, C15/16-H), 1.00 (s, 3H, C15/16-H), 0.79 (t, *J* = 7.4 Hz, 3H, C28-H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ [ppm] 167.50 (C-11), 166.17 (C-13), 150.06 (C-5), 143.66 (C-17), 130.09 (C-23), 129.79 (C-4), 129.04 (C-2), 125.25 (C-20), 119.28 (C-1), 118.96 (C-21/25), 114.77 (C-18), 109.32 (C-6), 109.05 (C-3), 62.02 (C-8), 61.54 (C-22/24), 60.55 (C-12), 57.23 (C-10), 55.43 (C-26), 47.19 (C-19), 41.03 (C-14), 40.99 (C-27), 37.26 (C-9), 22.67 (C-15/16), 22.57 (C-15/16), 20.94 (C-7), 9.37 (C-28).

ESI-MS [*m/z*]: calc.: 460.2600 $[M]+H^+$.

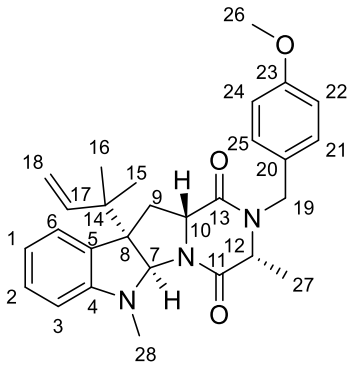
found: 460.2619 $[M]+H^+$.

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3366.14, 2966.52, 2933.80, 2875.13, 2836.80, 1731.90, 1655.02, 1608.03, 1511.82, 1482.81, 1462.68, 1440.61, 1417.01, 1382.40, 1361.91, 1302.55, 1244.65, 1212.20, 1173.92, 1150.37, 1107.02, 1082.55, 1062.77, 1032.79, 918.06, 845.37, 820.00, 789.09, 744.14, 666.32, 628.32, 554.25, 511.23, 464.34, 432.53.

Rotation value (*c* 0.88, $CHCl_3$) $[\alpha]_D^{20}$**:** +225°.

Melting point: 61 °C.

5.5.17 Synthesis of (3*R*,10b*S*,11a*R*)-2-(4-methoxybenzyl)-3,6-dimethyl-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (141a)



141a

$C_{28}H_{33}N_3O_3$

[459.58]

43.2 mg (0.100 mmol, 1.0 eq.) of (10b*S*,11a*S*)-2-(4-methoxybenzyl)-10b-(2-methylbut-3-en-2-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (**73b**) were dissolved in 3 mL of dry THF and stirred for ten minutes under a nitrogen atmosphere. After the solution was cooled to -78 °C 0.11 mL (0.018 g, 0.11 mmol, 1.1 eq.) of LHMDS (1 M in THF) were slowly added and the reaction mixture was again stirred for ten minutes. Then 0.031 mL (71 mg, 0.50 mmol, 5.0 eq.) of methyl iodide (**102**) were added and the mixture was stirred overnight, during which the solution was allowed to reach room temperature. After dilution with methanol the solvent was removed under reduced pressure.

The residue was purified by column chromatography (PE/EtOAc = 2:1) to afford the compound **141a** as a by-product as a colourless solid.

The synthesis of (3*R*,10b*S*,11a*R*)-2-(4-methoxybenzyl)-3,6-dimethyl-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (**141a**) was performed according to the procedure of Davies *et al*.[77]

R_f value (PE/EtOAc 2:1 (v/v)): 0.27.

^{1}H-NMR (500 MHz, $CDCl_3$): *δ* [ppm] 7.15 - 7.11 (m, 4H, C1/3/21/25), 6.85 – 6.79 (m, 2H, C22/24-H), 6.68 (dt, *J* = 7.4, 0.9 Hz, 1H, C2-H), 6.35 (d, *J* = 7.7 Hz, 1H, C6-H), 5.90 (dd, *J* = 17.4, 10.8 Hz, 1H, C17-H), 5.63 (s, 1H, C7-H), 5.40 (d, *J* = 14.9 Hz, 1H, C19-H), 5.11 - 5.01 (m, 1H, C18-H), 4.00 (ddd, *J* = 11.7, 5.6, 1.2 Hz, 1H, C12-H), 3.92 (dd, *J* = 6.8, 1.5 Hz, 1H, C10-H), 3.91 (d, *J* = 15.0 Hz, 1H, C19-H), 3.78 (s, 3H, C26-H), 2.96 (s, 3H, C28-H), 2.58 (dd, *J* = 12.2, 5.7 Hz, 1H, C9-H), 2.32 (t, *J* = 12.0 Hz, 1H, C9-H), 1.52 (d, *J* = 6.9 Hz, 3H, C27-H), 1.11 (s, 3H, C15/16-H), 0.97 (s, 3H, C15/16-H).

^{13}C-NMR (126 MHz, $CDCl_3$): *δ* [ppm] 166.59 (C-11), 165.66 (C-13), 159.40 (C-23), 152.07 (C-5), 143.70 (C-17), 129.53 (C-20), 129.38 (C-21/25), 129.15 (C-1), 127.66 (C-4), 125.21 (C-3), 117.50 (C-2), 114.65 (C-18), 114.38 (C-22/24), 105.62 (C-6), 83.51 (C-7), 58.71 (C-12), 55.44 (C-26), 54.37 (C-10), 45.55 (C-19), 41.13 (C-8), 40.97 (C-14), 39.58 (C-9), 32.42 (C-28), 23.36 (C-15/16), 22.32 (C-15/16), 17.95 (C-27).

ESI-MS [*m/z*]: calc.: 460.2592 $[M]+H^+$.

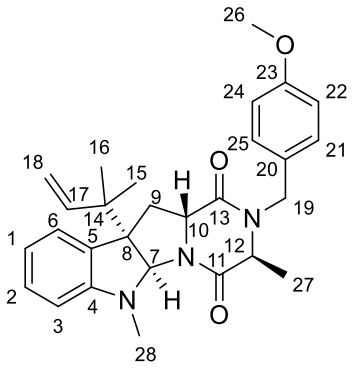
found: 460.2603 $[M]+H^+$.

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 2964.20, 2835.62, 1655.27, 1604.29, 1511.61, 1492.48, 1436.11, 1413.51, 1354.41, 1301.36, 1276.24, 1242.48, 1209.12, 1174.56, 1153.45, 1124.58, 1104.80, 1032.31, 1001.53, 969.76, 918.36, 844.11, 805.87, 747.68, 690.54, 665.63, 615.00, 575.11, 505.99, 472.10, 423.82.

Rotation value (*c* 0.40, $CHCl_3$) $[\alpha]_D^{20}$**:** +317°.

Melting point: 58 °C.

5.5.18 Synthesis of (3*S*,10b*S*,11a*R*)-2-(4-methoxybenzyl)-3,6-dimethyl-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (141b)



141b

$C_{28}H_{33}N_3O_3$

[459.58]

43.2 mg (0.100 mmol, 1.0 eq.) of (10b*S*,11a*S*)-2-(4-methoxybenzyl)-10b-(2-methylbut-3-en-2-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (**73b**) were dissolved in 3 mL of dry THF and stirred for ten minutes under a nitrogen atmosphere. After the solution was cooled to -78 °C 0.11 mL (0.018 g, 0.11 mmol, 1.1 eq.) of LHMDS (1 M in THF) were slowly added and the reaction mixture was again stirred for ten minutes. Then 0.031 mL (71 mg, 0.50 mmol, 5.0 eq.) of methyl iodide (**102**) were added and the mixture was stirred overnight, during which the solution was allowed to reach room temperature. After dilution with methanol the solvent was removed under reduced pressure.

The residue was purified by column chromatography (PE/EtOAc = 2:1) to afford compound **141b** as a by-product as a colourless solid.

The synthesis of (3*S*,10b*S*,11a*R*)-2-(4-methoxybenzyl)-3,6-dimethyl-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (**141b**) was performed according to the procedure of Davies *et al.*[77]

R_f value (PE/EtOAc 2:1 (v/v)): 0.24.

^{1}H-NMR (500 MHz, $CDCl_3$): *δ* [ppm] 7.16 (d, *J* = 7.7 Hz, 1H, C3-H), 7.15 (dt, *J* = 7.5, 1.2 Hz, 1H, C1-H), 7.12 – 7.05 (m, 2H, C21/25-H), 6.83 – 6.77 (m, 2H, C22/24-H), 6.73 (dt, *J* = 7.5, 0.9 Hz, 1H, C2-H), 6.48 (dd, *J* = 8.3, 0.9 Hz, 1H, C6-H), 5.79 (dd, *J* = 17.0, 10.8 Hz, 1H, C17-H), 5.12 (dd, *J* = 13.4, 0.8 Hz, 1H, C18-H), 5.11 (s, 1H, C7-H), 5.08 (dd, *J* = 17.5, 0.9 Hz, 1H, C18-H), 4.69 (d, *J* = 14.7 Hz, 1H, C19-H), 4.22 (d, *J* = 14.7 Hz, 1H, C19-H), 4.10 (dd, *J* = 10.4, 8.4 Hz, 1H, C12-H), 3.87 (q, *J* = 7.1 Hz, 1H, C10-H), 3.77 (s, 3H, C26-H), 3.15 (s, 3H, C28-H), 2.87 (dd, *J* = 14.0, 8.2 Hz, 1H, C9-H), 2.44 (dd, *J* = 14.0, 10.3 Hz, 1H, C9-H), 1.28 (d, *J* = 7.2 Hz, 3H, C27-H), 1.12 (s, 3H, C15/16-H), 0.96 (s, 3H, C15/16-H).

^{13}C-NMR (126 MHz, $CDCl_3$): *δ* [ppm] 169.22 (C-11), 167.41 (C-13), 159.45 (C-23), 150.96 (C-5), 144.03 (C-17), 129.94 (C-21/25), 128.54 (C-1), 128.11 (C-4), 127.81 (C-20), 124.87 (C-3), 118.34 (C-2), 114.52 (C-22/24), 114.38 (C-18), 108.23 (C-6), 87.20 (C-7), 57.86 (C-10), 57.50 (C-12), 55.40 (C-26), 47.37 (C-19), 41.24 (C-8), 40.95 (C-14), 36.89 (C-28), 36.12 (C-9), 23.36 (C-15/16), 22.39 (C-15/16), 15.97 (C-27).

ESI-MS [*m/z*]: calc.: 460.2592 $[M]+H^+$.

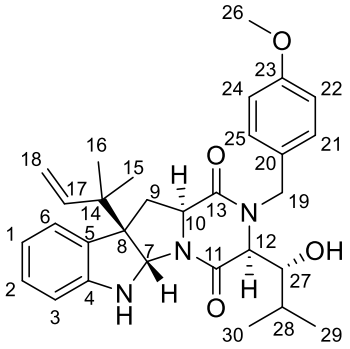
found: 460.2612 $[M]+H^+$.

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3338.98, 2964.42, 2931.00, 2873.67, 1662.37, 1604.88, 1512.05, 1492.12, 1449.81, 1415.73, 1365.48, 1336.37, 1301.78, 1273.55, 1243.76, 1196.29, 1173.09, 1155.49, 1126.97, 1106.79, 1031.13, 1009.61, 970.61, 918.48, 845.10, 814.17, 738.92, 690.63, 659.11, 619.71, 574.73, 511.66, 472.52, 438.85.

Rotation value (*c* 0.94, $CHCl_3$) $[\alpha]_D^{20}$**:** +133°.

Melting point: 57 °C.

5.5.19 Synthesis of (3*S*,10b*R*,11a*S*)-3-((*R*)-1-hydroxy-2-methylpropyl)-2-(4-methoxybenzyl)-10b-(2-methylbut-3-en-2-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (98)



98

$C_{30}H_{37}N_3O_4$

[503.63]

43.2 mg (0.100 mmol, 1.0 eq.) of (10b*R*,11a*S*)-2-(4-methoxybenzyl)-10b-(2-methylbut-3-en-2-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (**73a**) were dissolved in 3 mL of dry THF and stirred for ten minutes under a nitrogen atmosphere. After the solution was cooled to -78 °C 0.11 mL (0.018 g, 0.11 mmol, 1.1 eq.) of LHMDS (1 M in THF) were slowly added and the reaction mixture was again stirred for ten minutes. Then 0.018 mL (14 mg, 0.20 mmol, 2.0 eq.) of isobutyraldehyde (**97**) were added and the mixture was stirred overnight, during which the solution was allowed to reach room temperature. After dilution with methanol the solvent was removed under reduced pressure.

The residue was purified by column chromatography (PE/EtOAc = 2:1) to afford the desired product **98** (27.3 mg, 0.0542 mmol, 54%) as a colourless solid.

The synthesis of (3*S*,10b*R*,11a*S*)-3-((*R*)-1-hydroxy-2-methylpropyl)-2-(4-methoxybenzyl)-10b-(2-methylbut-3-en-2-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (**98**) was performed according to the procedure of Davies *et al*.[77]

R_f value (PE/EtOAc 1:1 (v/v)): 0.50.

^{1}H-NMR (400 MHz, $CDCl_3$): *δ* [ppm] 7.18 - 7.05 (m, 4H, C3/6/21/25-H), 6.86 – 6.81 (m, 2H, C22/24-H), 6.78-6.72 (m, 1H, C1-H), 6.56 (t, *J* = 7.8 Hz, 1H, C2-H), 5.97 (dd, *J* = 17.7, 11.0 Hz, 1H, C17-H), 5.52 (s, 1H, C7-H), 5.14-5.04 (m, 3H, C18/19-H), 4.92 (s, 1H, O-H), 4.24-4.10 (m, 1H, C10-H), 3.95 (d, *J* = 15.9 Hz, 1H, C12-H), 3.93 (d, *J* = 4.1 Hz, 1H, C19-H), 3.80 (s, 3H, C26-H), 2.58 (dd, *J* = 12.4, 6.2 Hz, 1H, C9-H), 2.45 - 2.35 (m, 1H, C9-H), 1.99 (s, 1H, C28-H), 1.73 (s, 1H, C27-H), 1.11 (s, 3H, C15/16-H), 1.00 (s, 3H, C15/16-H), 0.91 (s, 3H, C29/30-H), 0.89 (s, 3H, C29/30-H).

^{13}C-NMR (101 MHz, $CDCl_3$): *δ* [ppm] 166.25 (C-11), 164.04 (C-13), 159.54 (C-23), 149.66 (C-4), 143.71 (C-17), 129.70 (C-5), 129.16 (C-21/25), 127.95 (C-20), 125.23 (C-2), 125.20 (C-3), 114.61 (C-22/24), 114.50 (C-18), 114.49 (C-1), 109.23 (C-6), 78.67 (C-7), 63.26 (C-12), 61.63 (C-8), 58.83 (C-10), 55.44 (C-26), 46.76 (C-19), 41.12 (C-14), 37.78 (C-9), 30.83 (C-28), 30.50 (C-27), 23.10 (C-15/16), 22.52 (C-15/16), 19.52 (C-29/30), 17.42 (C-29/30).

ESI-MS [*m/z*]: calc.: 504.2862 $[M]+H^+$.

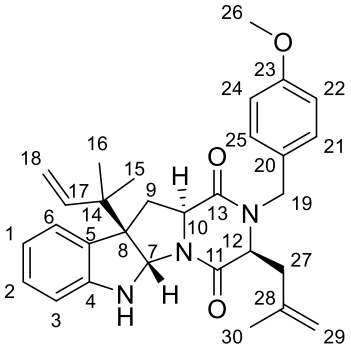
found: 504.2853 $[M]+H^+$.

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3352.76, 2962.95, 2930.95, 2871.78, 2837.66, 1650.68, 1609.11, 1512.38, 1481.83, 1442.44, 1418.47, 1382.33, 1363.88, 1302.63, 1245.67, 1211.72, 1174.16, 1147.54, 1106.30, 1082.32, 1062.04, 1032.64, 982.36, 916.39, 834.33, 743.41, 686.75, 653.06, 611.34, 544.64, 505.98, 489.61, 472.49, 457.39, 437.19, 415.02.

Rotation value (*c* 0.55, $CHCl_3$) $[\alpha]_D^{20}$**:** -248°.

Melting point: 63 °C.

5.5.20 Synthesis of (3*S*,10b*R*,11a*S*)-2-(4-methoxybenzyl)-3-(2-methylallyl)-10b-(2-methylbut-3-en-2-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (104)



104

$C_{30}H_{35}N_3O_3$

[485.62]

80.0 mg (0.183 mmol, 1.0 eq.) of (10b*R*,11a*S*)-2-(4-methoxybenzyl)-10b-(2-methylbut-3-en-2-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (**73a**) were dissolved in 5 mL of dry THF and stirred for ten minutes under a nitrogen atmosphere. After the solution was cooled to -78 °C 0.20 mL (0.34 g, 0.20 mmol, 1.1 eq.) of LHMDS (1 M in THF) were slowly added and the reaction mixture was again stirred for ten minutes. Then 0.037 mL (49 mg, 0.37 mmol, 2.0 eq.) of 3-bromo-2-methylpropene (**96**) were added and the mixture was stirred overnight, during which the solution was allowed to reach room temperature. After dilution with methanol the solvent was removed under reduced pressure.

The residue was purified by column chromatography (PE/EtOAc = 2:1) to afford the desired product **104** (57.8 mg, 0.119 mmol, 65%) as a colourless solid.

The synthesis of (3*S*,10b*R*,11a*S*)-2-(4-methoxybenzyl)-3-(2-methylallyl)-10b-(2-methylbut-3-en-2-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (**104**) was performed according to the procedure of Davies *et al*.[77]

R_f value (PE/EtOAc 1:1 (v/v)): 0.73.

^{1}H-NMR (500 MHz, $CDCl_3$): *δ* [ppm] 7.18 (d, *J* = 7.4 Hz, 1H, C3-H), 7.16 – 7.07 (m, 3H, C1/21/25-H), 6.88 – 6.83 (m, 2H, C22/24-H), 6.81 (t, *J* = 6.4, 2.5 Hz, 1H, C2-H), 6.60 (d, 1H, C6-H), 5.98 (dd, *J* = 17.3, 10.9 Hz, 1H, C17-H), 5.15 – 5.05 (m, 3H, C7/18-H), 4.72 (t, *J* = 1.7 Hz, 1H, C29-H), 4.62 (d, *J* = 2.6 Hz, 1H, C29-H), 3.99 – 3.89 (m, 3H, C10/19-H), 3.80 (s, 3H, C26-H), 3.78 – 3.75 (m, 1H, C12-H), 2.60 (dd, *J* = 12.7, 6.1 Hz, 1H, C9-H), 2.44 (dd, *J* = 12.8, 11.1 Hz, 1H, C27-H), 2.41 – 2.30 (m, 2H, C9/27-H), 1.64 (s, 3H, C30-H), 1.12 (s, 3H, C15/16-H), 1.02 (s, 3H, C15/16-H).

^{13}C-NMR (126 MHz, $CDCl_3$): *δ* [ppm] 167.80 (C-11), 165.98 (C-13), 159.59 (C-23), 149.78 (C-4), 143.60 (C-17), 139.92 (C-28), 129.84 (C-21/25), 129.14 (C-5), 127.94 (C-20), 125.24 (C-2), 123.09 (C-3), 118.21 (C-29), 116.32 (C-18), 114.70 (C-1), 114.51 (C-22/24), 109.10 (C-6), 77.61 (C-7), 72.75 (C-8), 61.75 (C-10), 60.17 (C-12), 58.62 (C-26), 55.46 (C-27), 47.31 (C-19), 40.98 (C-14), 37.01 (C-9), 23.16 (C-30), 22.73 (C-15/16), 22.68 (C-15/16).

ESI-MS [*m/z*]: calc.: 486.2757 $[M]+2H^+$.

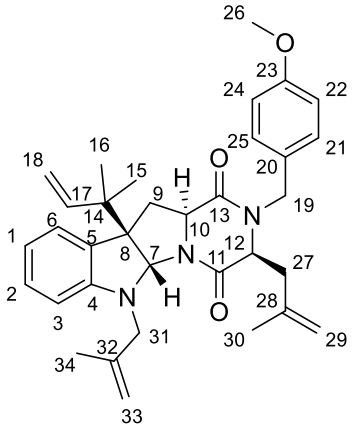
found: 486.2734 $[M]+2H^+$.

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3350.37, 3078.06, 2967.82, 2933.20, 2835.70, 1655.52, 1607.35, 1511.70, 1481.86, 1439.68, 1418.07, 1355.82, 1302.82, 1273.73, 1244.21, 1212.47, 1174.67, 1145.46, 1106.36, 1081.83, 1059.95, 1032.67, 982.34, 901.96, 846.44, 817.74, 787.10, 743.69, 691.82, 630.95, 587.18, 565.42, 516.10, 502.55, 464.94, 426.32, 382.88.

Rotation value (*c* 0.50, $CHCl_3$) $[\alpha]_D^{20}$**:** -267°.

Melting point: 60 °C.

5.5.21 Synthesis of (3*S*,10b*R*,11a*S*)-2-(4-methoxybenzyl)-3,6-bis(2-methylallyl)-10b-(2-methylbut-3-en-2-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (143a)



143a

$C_{34}H_{41}N_3O_3$

[539.71]

80.0 mg (0.183 mmol, 1.0 eq.) of (10b*R*,11a*S*)-2-(4-methoxybenzyl)-10b-(2-methylbut-3-en-2-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (**73a**) were dissolved in 5 mL of dry THF and stirred for ten minutes under a nitrogen atmosphere. After the solution was cooled to -78 °C 0.20 mL (0.34 g, 0.20 mmol, 1.1 eq.) of LHMDS (1 M in THF) were slowly added and the reaction mixture was again stirred for ten minutes. Then 0.037 mL (49 mg, 0.37 mmol, 2.0 eq.) of 3-bromo-2-methylpropene (**96**) were added and the mixture was stirred overnight, during which the solution was allowed to reach room temperature. After dilution with methanol the solvent was removed under reduced pressure.

The residue was purified by column chromatography (PE/EtOAc = 2:1) to afford the compound **143a** as a by-product in the synthesis of **104** as a colourless solid.

The synthesis of (3*S*,10b*R*,11a*S*)-2-(4-methoxybenzyl)-3,6-bis(2-methylallyl)-10b-(2-methylbut-3-en-2-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (**143a**) was performed according to the procedure of Davies *et al*.[77]

R_f value (PE/EtOAc 1:1 (v/v)): 0.88.

^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] 7.29 (d, *J* = 8.7 Hz, 2H, C21/25-H), 7.16 (dd, *J* = 7.6, 1.2 Hz, 1H, C3-H), 7.07 (td, *J* = 7.7, 1.2 Hz, 1H, C1-H), 6.77 (d, *J* = 8.7 Hz, 2H, C22/24-H), 6.74 (td, *J* = 7.4, 1.0 Hz, 1H, C2-H), 6.51 (d, *J* = 7.7 Hz, 1H, C6-H), 5.96 (dd, *J* = 17.4, 10.9 Hz, 1H, C17-H), 5.53 (s, 1H, C7-H), 5.12 – 5.04 (m, 2H, C18-H), 4.76 (d, *J* = 15.0 Hz, 1H, C19-H), 4.69 (s, 2H, C29-H), 4.57 (t, *J* = 1.6 Hz, 1H, C27-H), 4.47 (s, 2H, C33-H), 4.39 (d, *J* = 15.2 Hz, 1H, C19-H), 3.96 (dd, *J* = 11.5, 5.8 Hz, 1H, C10-H), 3.80 (d, *J* = 2.6 Hz, 1H, C12-H), 3.76 (s, 3H, C26-H), 3.05 (d, *J* = 17.2 Hz, 1H, C31-H), 2.60 (dd, *J* = 12.4, 5.8 Hz, 1H, C9-H), 2.47 (d, *J* = 17.2 Hz, 1H, C31-H), 2.41 (t, *J* = 12.0 Hz, 1H, C9-H), 1.56 (s, 3H, C30-H), 1.45 (s, 3H, C34-H), 1.12 (s, 3H, C15/16-H), 1.00 (s, 3H, C15/16-H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ [ppm] 168.99 (C-11), 166.82 (C-13), 159.06 (C-23), 150.35 (C-4), 143.70 (C-17), 140.26 (C-28), 139.17 (C-32), 130.91 (C-21/25), 130.20 (C-5), 129.01 (C-20), 128.90 (C-2), 125.42 (C-3), 118.86 (C-29), 117.58 (C-33), 114.52 (C-18), 113.73 (C-22/24), 112.36 (C-1), 108.63 (C-6), 78.17 (C-7), 69.15 (C-8), 61.47 (C-10), 58.56 (C-12), 55.39 (C-26), 46.45 (C-27), 46.02 (C-31), 43.22 (C-19), 41.03 (C-14), 38.14 (C-9), 24.19 (C-30), 23.92 (C-34), 23.01 (C-15/16), 22.57 (C-15/16).

ESI-MS [*m/z*]: calc.: 540.3226 $[M+2H]^+$.

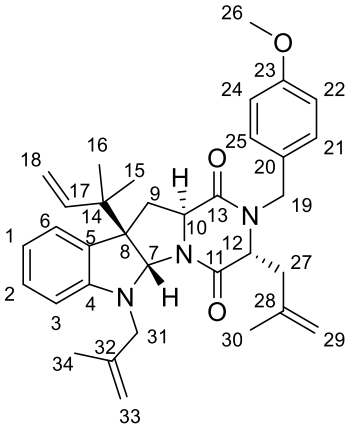
found: 540.3241 $[M+2H]^+$.

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3350.41, 3077.95, 2966.05, 2930.99, 1650.86, 1607.38, 1511.41, 1482.25, 1448.78, 1428.93, 1407.95, 1362.57, 1302.81, 1272.93, 1244.01, 1211.74, 1176.01, 1151.11, 1132.15, 1109.11, 1084.51, 1060.68, 1034.04, 907.69, 847.49, 815.92, 787.04, 756.73, 742.81, 703.88, 689.62, 605.86, 544.49, 505.00, 462.87, 423.44.

Rotation value (*c* 0.78, $CHCl_3$) $[\alpha]_D^{20}$**:** -183°.

Melting point: 48 °C.

5.5.22 Synthesis of (3*R*,10b*R*,11a*S*)-2-(4-methoxybenzyl)-3,6-bis(2-methylallyl)-10b-(2-methylbut-3-en-2-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (143b)



143b

$C_{34}H_{41}N_3O_3$

[539.71]

80.0 mg (0.183 mmol, 1.0 eq.) of (10b*R*,11a*S*)-2-(4-methoxybenzyl)-10b-(2-methylbut-3-en-2-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (**73a**) were dissolved in 5 mL of dry THF and stirred for ten minutes under a nitrogen atmosphere. After the solution was cooled to -78 °C 0.20 mL (0.34 g, 0.20 mmol, 1.1 eq.) of LHMDS (1 M in THF) were slowly added and the reaction mixture was again stirred for ten minutes. Then 0.037 mL (49 mg, 0.37 mmol, 2.0 eq.) of 3-bromo-2-methylpropene (**96**) were added and the mixture was stirred overnight, during which the solution was allowed to reach room temperature. After dilution with methanol the solvent was removed under reduced pressure.

The residue was purified by column chromatography (PE/EtOAc = 2:1) to afford the compound **143b** as a by-product in the synthesis of **104** as a colourless solid.

The synthesis of (3*R*,10b*R*,11a*S*)-2-(4-methoxybenzyl)-3,6-bis(2-methylallyl)-10b-(2-methylbut-3-en-2-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (**143b**) was performed according to the procedure of Davies *et al*.[77]

R_f value (PE/EtOAc 1:1 (v/v)): 0.81.

^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] 7.19 – 7.17 (m, 1H, C3-H), 7.16 – 7.14 (m, 1H, C1-H), 7.11 – 7.09 (m, 2H, C21/25-H), 6.86 – 6.84 (m, 1H, C2-H), 6.77 (d, *J* = 8.7 Hz, 2H, C22/24-H), 6.72 (s, 1H, C7-H), 6.59 – 6.54 (m, 1H, C6-H), 5.79 (dd, *J* = 17.4, 10.8 Hz, 1H, C17-H), 5.58 - 5.52 (m, 2H, C18-H), 5.12 (s, 1H, C29-H), 4.92 (t, *J* = 1.6 Hz, 1H, C27-H), 4.83 (d, *J* = 15.3 Hz, 1H, C31-H), 4.75 (s, 2H, C33-H), 4.52 (t, *J* = 1.7 Hz, 1H, C27-H), 4.44 (s, 1H, C29-H), 4.31 (d, *J* = 15.2 Hz, 1H, C31-H), 4.03 – 3.99 (m, 1H, C10-H), 3.82 (d, *J* = 4.7 Hz, 1H, C12-H), 3.77 (s, 3H, C26-H), 3.09 (d, *J* = 17.6 Hz, 1H, C19-H), 2.69 – 2.63 (m, 3H, C9/19-H), 1.59 (s, 3H, C30-H), 1.39 (s, 3H, C33-H), 1.21 (s, 3H, C15/16-H), 1.16 (s, 3H, C15/16-H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ [ppm] 166.60 (C-11), 166.05 (C-13), 159.17 (C-23), 149.93 (C-4), 143.37 (C-17), 140.34 (C-28), 140.25 (C-32), 130.94 (C-21/25), 130.63 (C-5), 129.59 (C-20), 129.15 (C-2), 124.73 (C-3), 114.61 (C-29), 114.50 (C-18), 114.42 (C-33), 113.81 (C-22/24), 112.36 (C-1), 109.51 (C-6), 77.80 (C-7), 68.97 (C-8), 59.07 (C-10), 57.61 (C-12), 55.45 (C-26), 46.12 (C-27), 45.26 (C-31), 42.80 (C-19), 40.57 (C-14), 38.15 (C-9), 23.43 (C-15/16), 23.04 (C-15/16), 17.64 (C-30), 17.44 (C-34).

ESI-MS [*m/z*]: calc.: 540.3226 $[M]+2H^+$.

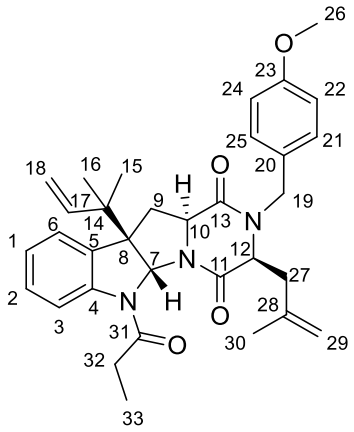
found: 540.3209 $[M]+2H^+$.

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3350.05, 3077.80, 2965.71, 2930.54, 1652.07, 1609.63, 1511.61, 1444.79, 1412.14, 1386.12, 1353.13, 1303.64, 1279.56, 1243.97, 1209.30, 1175.57, 1135.58, 1108.52, 1083.92, 1062.21, 1032.60, 904.75, 845.26, 817.25, 754.71, 688.54, 656.88, 601.56, 574.84, 510.09, 467.17, 423.69, 382.00.

Rotation value (*c* 0.48, $CHCl_3$) $[\alpha]_D^{20}$**:** -176°.

Melting point: 46 °C.

5.5.23 Synthesis of (3*S*,10b*R*,11a*S*)-2-(4-methoxybenzyl)-3-(2-methylallyl)-10b-(2-methylbut-3-en-2-yl)-6-propionyl-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (105)



105

$C_{33}H_{39}N_3O_4$

[541.68]

To a solution of 90.9 mg (0.187 mmol, 1.0 eq.) of (3*S*,10b*R*,11a*S*)-2-(4-methoxybenzyl)-3-(2-methylallyl)-10b-(2-methylbut-3-en-2-yl)-2,3,6,10b,11,11a-hexahydro-4*H*-pyrazino[1',2':1,5] pyrrolo[2,3-b]indole-1,4(5a*H*)-dione (**104**) in 2 mL of dichloromethane were added 0.065 mL (47 mg, 0.47 mmol, 2.5 eq.) of triethylamine and the reaction mixture was stirred for ten minutes. Then the mixture was cooled to 0 °C and 0.020 mL (21 mg, 0.23 mmol, 1.2 eq.) of propionyl chloride were added and the reaction mixture was stirred overnight, during which it was allowed to reach room temperature. The next day the reaction mixture was heated to 35 °C for eight hours. Afterwards, 0.1 mL of triethylamine and 1 mL of methanol were added to the solution and the solvent removed under reduced pressure.

The residue was purified by column chromatography (PE/EtOAc = 2:1) to afford the desired product **105** (93.6 mg, 0.173 mmol, 92%) as a colourless solid.

R_f value (PE/EtOAc 1:1 (v/v)): 0.77.

^{1}H-NMR (600 MHz, $CDCl_3$): *δ* [ppm] 7.36 – 7.27 (m, 3H, C1/3/6-H), 7.19 (td, *J* = 7.6, 1.1 Hz, 1H, C2-H), 7.16 – 7.14 (m, 2H, C21/25-H), 6.86 (dt, *J* = 8.4, 1.8 Hz, 2H, C22/24-H), 6.27 (s, 1H, C7-H), 5.88 (dd, *J* = 17.3, 10.8 Hz, 1H, C17-H), 5.03 – 4.96 (m, 1H, C18-H), 4.67 – 4.62 (m, 2H, C32-H), 4.50 (d, *J* = 17.5 Hz, 1H, C29-H), 4.06 (d, *J* = 14.6 Hz, 1H, C27-H), 4.03 (d, *J* = 14.7 Hz, 1H, C29-H), 3.91 (d, *J* = 6.7 Hz, 1H, C27-H), 3.89 – 3.87 (m, 1H, C10-H), 3.80 (s, 3H, C26-H), 3.78 – 3.76 (m, 1H, C12-H), 2.72 (dd, *J* = 12.8, 5.7 Hz, 1H, C9-H), 2.62 (dt, *J* = 14.5, 6.9 Hz, 3H, C33-H), 2.24 (m, 3H, C9/19-H), 1.07 (s, 3H, C30-H), 0.98 (d, *J* = 1.5 Hz, 1H, C15/16-H), 0.94 (s, 3H, C15/16-H).

^{13}C-NMR (151 MHz, $CDCl_3$): *δ* [ppm] 171.14 (C-31), 166.94 (C-11), 166.06 (C-13), 159.74 (C-23), 152.27 (C-4), 142.86 (C-17), 139.32 (C-27), 130.04 (C-21/25), 130.00 (C-5), 129.30 (C-20), 129.22 (C-2), 127.55 (C-3), 124.96 (C-29), 115.50 (C-18), 114.58 (C-22/24), 114.54 (C-1), 111.65 (C-6), 78.20 (C-7), 71.68 (C-8), 60.41 (C-10), 60.21 (C-12), 59.02 (C-32), 55.46 (C-26), 51.25 (C-27), 47.25 (C-19), 39.77 (C-14), 36.79 (C-9), 22.76 (C-15/16), 22.58 (C-15/16), 14.18 (C-30), 7.56 (C-33).

ESI-MS [*m/z*]: calc.: 542.2941 $[M]+H^+$.

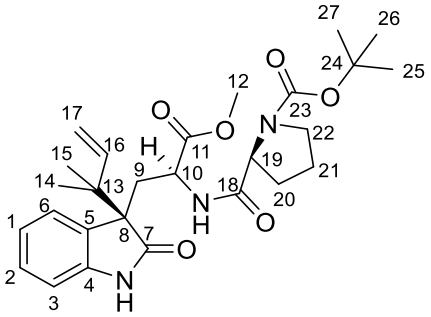
found: 542.2938 $[M]+H^+$.

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3075.01, 2974.41, 2938.02, 2837.20, 1657.95, 1612.16, 1512.34, 1476.25, 1418.47, 1383.42, 1326.92, 1303.54, 1284.44, 1242.79, 1175.09, 1144.74, 1109.04, 1074.86, 1030.82, 979.15, 955.23, 917.51, 902.69, 846.47, 819.33, 756.83, 691.69, 581.07, 508.36, 470.52, 422.98.

Rotation value (*c* 0.40, $CHCl_3$) $[\alpha]_D^{20}$**:** -86.1°.

Melting point: 44 °C.

5.5.24 Synthesis of *tert*-butyl (*S*)-2-(((*S*)-1-methoxy-3-((*R*)-3-(2-methylbut-3-en-2-yl)-2-oxoindolin-3-yl)-1-oxopropan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (137a)



137a

$C_{27}H_{37}N_3O_6$

[499.61]

A solution of 0.248 g (0.819 mmol, 1.0 eq.) of methyl-(*S*)-2-amino-3-((*R*)-3-(2-methylbut-3-en-2-yl)-2-oxoindolin-3-yl)propanoate (**135a**) in 10 mL of dimethylformamide was cooled to 0°C. Afterwards, 0.194 g (0.901 mmol, 1.1 eq.) of Boc-*L*-Pro-OH (**136**) were added and the reaction mixture was stirred for ten minutes. Then 1.4 mL (1.1 g, 8.2 mmol, 10 eq.) of DIPEA and 0.854 g (1.64 mmol, 2.0 eq.) of PyBOP were added and the reaction mixture was stirred for four hours, during which it was allowed to reach room temperature. Afterwards, the solvent was removed under reduced pressure.

The residue was purified by column chromatography using ethyl acetate as eluent to afford the desired product **137a** (66.1 mg, 0.132 mmol, 16%) as a colourless solid.

The synthesis of *tert*-butyl (*S*)-2-(((*S*)-1-methoxy-3-((*R*)-3-(2-methylbut-3-en-2-yl)-2-oxoindolin-3-yl)-1-oxopropan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (**137a**) was performed according to the procedure of Sénèque *et al*.[114]

R_f value (EtOAc): 0.65.

^{1}H-NMR (600 MHz, $CDCl_3$): δ [ppm] 9.27 (s, 1H, indole N-H), 7.22 – 7.10 (m, 2H, C2/3-H), 6.99 (t, *J* = 7.5 Hz, 1H, C1-H), 6.72 (d, *J* = 7.7 Hz, 1H, C6-H), 6.12 (dd, *J* = 17.5, 10.8 Hz, 1H, C16-H), 5.91 (d, *J* = 9.7 Hz, 1H, DP N-H), 5.14 – 4.97 (m, 2H, C17-H), 4.29 – 4.18 (m, 1H, C19-H), 4.01 (ddd, *J* = 12.4, 9.5, 2.7 Hz, 1H, C10-H), 3.64 (s, 3H, C12-H), 3.46 (ddd, *J* = 11.5, 8.4, 2.9 Hz, 1H, C21-H), 3.27 (q, *J* = 9.4 Hz, 1H, C21-H), 2.45 (dd, *J* = 14.0, 2.8 Hz, 1H, C9-H), 2.36 (dd, *J* = 14.0, 12.3 Hz, 1H, C9-H), 2.09 – 2.01 (m, 1H, C20-H), 1.85 (d, *J* = 9.2 Hz, 1H, C20-H), 1.90 – 1.73 (m, 2H, C22-H), 1.53 (s, 9H, C25-27-H), 1.15 (s, 3H, C14/15-H), 1.06 (s, 3H, C14/15-H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] 182.58 (C-7), 172.75 (C-11), 171.07 (C-18), 154.92 (C-23), 143.49 (C-16), 143.21 (C-4), 129.28 (C-5), 128.63 (C-3), 125.59 (C-2), 121.68 (C-1), 113.98 (C-17), 110.66 (C-6), 80.00 (C-24), 59.52 (C-19), 56.60 (C-8), 52.51 (C-12), 49.13 (C-10), 47.14 (C-21), 41.70 (C-13), 34.74 (C-9), 30.51 (C-20), 28.74 (C-25-27), 23.99 (C-22), 22.16 (C-14/15), 22.12 (C-14/15).

ESI-MS [*m/z*]: calc.: 500.2755 $[M]+H^+$.

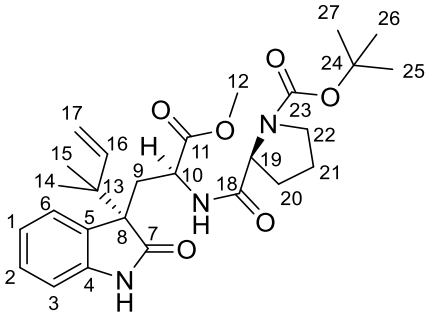
found: 500.2757 $[M]+H^+$.

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3313.34, 2972.17, 1703.42, 1668.16, 1636.40, 1618.38, 1593.82, 1537.88, 1471.31, 1432.79, 1392.53, 1365.21, 1327.64, 1295.14, 1258.91, 1160.14, 1112.33, 1088.24, 1051.31, 1009.63, 914.07, 857.11, 826.30, 728.12, 697.92, 643.62, 492.97.

Rotation value (*c* 0.40, $CHCl_3$) $[\alpha]_D^{20}$**:** -31.5°.

Melting point: 81 °C.

5.5.25 Synthesis of *tert*-butyl (*S*)-2-(((*S*)-1-methoxy-3-((*S*)-3-(2-methylbut-3-en-2-yl)-2-oxoindolin-3-yl)-1-oxopropan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (137b)



137b

$C_{27}H_{37}N_3O_6$

[499.61]

A solution of 0.158 g (0.523 mmol, 1.0 eq.) of methyl-(*S*)-2-amino-3-((*S*)-3-(2-methylbut-3-en-2-yl)-2-oxoindolin-3-yl)propanoate (**135b**) in 10 mL of dimethylformamide was cooled to 0°C. Afterwards, 0.124 g (0.576 mmol, 1.1 eq.) of Boc-*L*-Pro-OH (**136**) were added and the reaction mixture was stirred for ten minutes. Then 0.91 mL (0.68 g, 5.2 mmol, 10 eq.) of DIPEA and 0.544 g (1.05 mmol, 2.0 eq.) of PyBOP were added and the reaction mixture was stirred for four hours, during which it was allowed to reach room temperature. Afterwards, the solvent was removed under reduced pressure.

The residue was purified by column chromatography using ethyl acetate as eluent to afford the desired product **137b** (0.171 g, 0.342 mmol, 66%) as a colourless solid.

The synthesis of *tert*-butyl (*S*)-2-(((*S*)-1-methoxy-3-((*S*)-3-(2-methylbut-3-en-2-yl)-2-oxoindolin-3-yl)-1-oxopropan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (**137b**) was performed according to the procedure of Sénèque *et al.*[114]

R_f value (EtOAc): 0.62.

^{1}H-NMR (300 MHz, $CDCl_3$): *δ* [ppm] 8.07 (s, 1H, indole N-H), 7.24 – 7.15 (m, 2H, C2/3-H), 6.99 (t, *J* = 7.5 Hz, 1H, C1-H), 6.90 – 6.81 (m, 1H, C6-H), 6.59 (s, 1H, DP N-H), 6.03 (dd, *J* = 17.4, 10.9 Hz, 1H, C16-H), 5.14 – 4.91 (m, 2H, C17-H), 4.32 (m, 1H, C19-H), 4.05 (m, 1H, C10-H), 3.50 (m, 5H, C12/21-H), 2.57 (dd, *J* = 14.4, 6.7 Hz, 1H, C9-H), 2.47 – 2.26 (m, 1H, C9-H), 2.04 – 1.91 (m, 1H, C20-H), 1.87 – 1.73 (m, 3H, C20/22-H), 1.45 (m, 9H, C25-27-H), 1.07 (s, 3H, C14/15-H), 0.98 (s, 3H, C14/15-H).

^{13}C-NMR (76 MHz, $CDCl_3$): *δ* [ppm] 180.81 (C-7), 172.43 (C-11), 171.51 (C-18), 154.86 (C-23), 141.79 (C-16), 141.41 (C-4), 128.56 (C-5), 128.32 (C-3), 126.20 (C-2), 121.39 (C-1), 114.10 (C-17), 109.87 (C-6), 81.04 (C-24), 60.62 (C-19), 55.85 (C-8), 52.28 (C-12), 49.92 (C-10), 47.05 (C-21), 42.82 (C-13), 30.50 (C-9), 28.33 (C-20), 28.05 (C-25-27), 24.42 (C-22), 23.90 (C-14/15), 23.70 (C-14/15).

ESI-MS [*m/z*]: calc.: 500.2755 $[M]+H^+$.

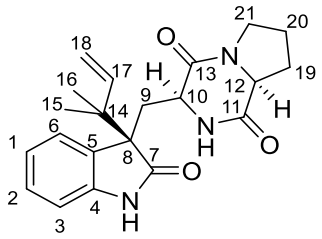
found: 500.2752 $[M]+H^+$.

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3258.12, 2971.70, 1666.71, 1618.05, 1518.61, 1471.81, 1391.46, 1364.97, 1159.67, 1113.60, 1018.57, 915.86, 727.36, 644.98, 493.01.

Rotation value (*c* 0.40, $CHCl_3$) $[\alpha]_D^{20}$**:** -12.5°.

Melting point: 80 °C.

5.5.26 Synthesis of (3*S*,8a*S*)-3-(((*R*)-3-(2-methylbut-3-en-2-yl)-2-oxoindolin-3-yl) methyl)hexahydropyrrolo[1,2-a]pyrazine-1,4-dione (128a)



128a

$C_{21}H_{25}N_3O_3$

[367.45]

To a solution of 53.4 mg (0.107 mmol, 1.0 eq.) of *tert*-butyl (*S*)-2-(((*S*)-1-methoxy-3-((*R*)-3-(2-methylbut-3-en-2-yl)-2-oxoindolin-3-yl)-1-oxopropan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (**137a**) in 1 mL of dichloromethane were added 0.085 mL (0.13 g, 1.1 mmol, 10 eq.) of trifluoroacetic acid and the reaction mixture was stirred overnight at room temperature. As the conversion was not complete the next day another 10 eq. of trifluoroacetic acid were added and the reaction mixture again stirred overnight. After no further conversion was visible 5 mL of 7 N ammonia solution in methanol were added and the reaction mixture was again stirred overnight. The next day the reaction mixture was heated to 80 °C for eight hours before it was stirred again overnight at room temperature. Then the conversion was complete so that the solvent could be removed under reduced pressure.

The residue was purified by column chromatography (dichloromethane/methanol = 50:1 plus 3% triethylamine) to afford the desired product **128a** (14.2 mg, 0.0386 mmol, 36%) as a colourless solid.

The synthesis of (3*S*,8a*S*)-3-(((*R*)-3-(2-methylbut-3-en-2-yl)-2-oxoindolin-3-yl)methyl)hexahydropyrrolo[1,2-a]pyrazine-1,4-dione (**128a**) was performed according to the procedure of Danishefsky *et al*.[8]

R_f value (EtOAc): 0.10.

^{1}H-NMR (600 MHz, $CDCl_3$): δ [ppm] 8.71 (s, 1H, indole N-H), 7.25 – 7.21 (m, 2H, C2/3-H), 7.02 (td, *J* = 7.6, 1.1 Hz, 1H, C1-H), 6.91 (dd, *J* = 7.7, 1.0 Hz, 1H, C6-H), 6.68 (s, 1H, DKP N-H), 6.08 (dd, *J* = 17.4, 10.8 Hz, 1H, C17-H), 5.18 – 4.95 (m, 2H, C18-H), 3.85 (ddd, *J* = 9.0, 7.1, 1.5 Hz, 1H, C12-H), 3.50 (dt, *J* = 11.9, 8.1 Hz, 1H, C21-H), 3.43 (ddd, *J* = 12.0, 8.7, 3.6 Hz, 1H, C21-H), 3.24 (dd, *J* = 15.1, 1.5 Hz, 1H, C9-H), 3.16 (d, *J* = 8.8 Hz, 1H, C10-H), 2.25 (dd, *J* = 15.1, 8.9 Hz, 1H, C9-H), 2.20 (ddt, *J* = 13.6, 7.1, 3.1 Hz, 1H, C19-H), 2.04 (dddd, *J* = 11.4, 9.5, 3.4, 2.1 Hz, 1H, C19-H), 1.98 – 1.90 (m, 1H, C20-H), 1.78 (ddtd, *J* = 12.9, 10.8, 8.8, 6.8 Hz, 1H, C20-H), 1.16 (s, 3H, C15/16-H), 1.09 (s, 3H, C15/16-H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] 181.98 (C-7), 170.05 (C-13), 165.39 (C-11), 142.63 (C-17), 141.77 (C-4), 129.63 (C-5), 128.70 (C-2), 126.27 (C-3), 122.45 (C-1), 114.58 (C-18), 109.79 (C-6), 58.94 (C-12), 58.01 (C-8), 52.81 (C-10), 45.80 (C-21), 42.48 (C-14), 31.25 (C-9), 28.13 (C-19), 22.87 (C-20), 22.53 (C-15/16), 21.73 (C-15/16).

ESI-MS [*m/z*]: calc.: 368.1969 $[M]+H^+$.

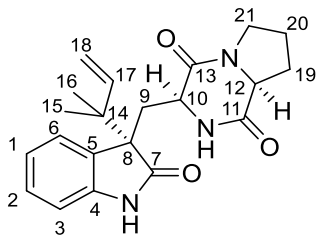
found: 368.1950 $[M]+H^+$.

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3203.81, 2972.05, 2880.63, 1663.73, 1616.27, 1470.56, 1415.32, 1383.16, 1336.85, 1303.07, 1260.39, 1230.04, 1194.94, 1157.07, 1112.36, 1009.31, 910.95, 861.43, 751.22, 727.18, 675.35, 644.73, 569.30, 491.61, 470.63, 440.90, 411.10.

Rotation value (*c* 0.53, $CHCl_3$) $[\alpha]_D^{20}$**:** -155°.

Melting point: 90 °C.

5.5.27 Synthesis of (3*S*,8a*S*)-3-(((*S*)-3-(2-methylbut-3-en-2-yl)-2-oxoindolin-3-yl) methyl)hexahydropyrrolo[1,2-a]pyrazine-1,4-dione (128b)



128b

$C_{21}H_{25}N_3O_3$

[367.45]

To a solution of 11.1 mg (0.220 mmol, 1.0 eq.) of *tert*-butyl (*S*)-2-(((*S*)-1-methoxy-3-((*S*)-3-(2-methylbut-3-en-2-yl)-2-oxoindolin-3-yl)-1-oxopropan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (**137b**) in 2 mL of dichloromethane were added 0.17 mL (0.25 g, 2.2 mmol, 10 eq.) of trifluoroacetic acid and the reaction mixture was stirred overnight at room temperature. Then 4 mL of 7 N ammonia solution in methanol were added and the reaction mixture was again stirred overnight. The next day the solvent was removed under reduced pressure.

The residue was purified by column chromatography (dichloromethane/methanol = 50:1 plus 3% triethylamine) to afford the desired product **128b** (74.0 mg, 0.201 mmol, 92%) as a colourless solid.

The synthesis of (3*S*,8a*S*)-3-(((*S*)-3-(2-methylbut-3-en-2-yl)-2-oxoindolin-3-yl)methyl)hexahydropyrrolo[1,2-a]pyrazine-1,4-dione (**128b**) was performed according to the procedure of Danishefsky *et al*.[8]

R_f value (EtOAc): 0.06.

^{1}H-NMR (600 MHz, $CDCl_3$): δ [ppm] 10.45 (s, 1H, indole N-H), 8.01 (s, 1H, DKP N-H), 7.23 (dd, *J* = 7.6, 1.1 Hz, 1H, C3-H), 7.15 (td, *J* = 7.6, 1.2 Hz, 1H, C2-H), 6.92 (dd, *J* = 7.7, 1.0 Hz, 1H, C6-H), 6.87 (td, *J* = 7.6, 1.1 Hz, 1H, C1-H), 6.10 (dd, *J* = 17.4, 10.8 Hz, 1H, C17-H), 5.13 - 4.89 (m, 2H, C18-H), 4.23 (d, *J* = 6.6 Hz, 1H, C10-H), 3.73 (ddd, *J* = 11.5, 5.9, 2.5 Hz, 1H, C12-H), 3.40 (dt, *J* = 12.0, 8.7 Hz, 1H, C21-H), 3.23 (ddd, *J* = 12.4, 9.5, 3.5 Hz, 1H, C21-H), 3.17 (dd, *J* = 14.9, 2.0 Hz, 1H, C9-H), 2.76 (dd, *J* = 14.9, 6.8 Hz, 1H, C9-H), 1.93 (dtd, *J* = 12.2, 6.7, 1.7 Hz, 1H, C19-H), 1.70 – 1.54 (m, 2H, C20-H), 1.09 (s, 3H, C15/16-H), 0.96 (s, 3H, C15/16-H), 0.68 (qd, *J* = 11.7, 8.5 Hz, 1H, C19-H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ [ppm] 182.63 (C-7), 168.13 (C-13), 163.92 (C-11), 142.91 (C-17), 142.69 (C-4), 129.10 (C-3), 128.34 (C-5), 127.77 (C-2), 120.10 (C-1), 113.90 (C-18), 109.87 (C-6), 58.49 (C-12), 56.04 (C-8), 54.25 (C-10), 44.75 (C-21), 42.79 (C-14), 32.69 (C-9), 28.66 (C-19), 22.19 (C-15/16), 21.38 (C-15/16), 21.01 (C-20).

ESI-MS [*m/z*]: calc.: 368.1969 $[M]+H^+$.

found: 368.1963 $[M]+H^+$.

IR (ATR) $\tilde{\nu}$ [cm^{-1}]: 3202.15, 3083.20, 2968.44, 2878.52, 1652.31, 1614.86, 1469.92, 1449.15, 1414.52, 1381.44, 1366.30, 1341.45, 1310.44, 1266.71, 1234.26, 1191.63, 1154.11, 1125.71, 1110.42, 1062.36, 1007.80, 915.69, 794.21, 752.49, 730.65, 690.76, 629.07, 491.79, 472.45, 440.48.

Rotation value (*c* 0.85, $CHCl_3$) $[\alpha]_D^{20}$**:** +66.4°.

Melting point: 134 °C.

6 Abbreviations

Table 6.1: List of abbreviations.

Abbreviation	Meaning
abs.	Absolute
Ac	Acetyl
aq.	Aqueous
ATR	Attenuated total reflectance
9-BBN	9-Borabicyclo[3.3.1]nonane
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyle
BopCl	Bis(2-oxo-3-oxazolidinyl)phosphinic chloride
n-BuLi	*n*-Butyllithium
c	concentration
calc.	Calculated
CAN	Ceric ammonium nitrate
conc.	Concentrated
COSY	Correlated spectroscopy
d	Doublet (NMR) / Days
δ	Chemical shift in the NMR-Spectrum [ppm]
DAP	Double alkylated product
9-DBBN	9-Decyl-9-borabicyclo[3.3.1]nonane
DBU	Diazabicycloundecen
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-*p*-benzoquinone
DIPEA	*N,N*-Diisopropylethylamine
DKP	Diketopiperazine
DMAP	4-Dimethylaminopyridine
DMAPP	Dimethylallyl pyrophosphate
DMAT	Dimethylallyltryptophan
DMB	Dimethoxybenzyl
DME	1,2-Dimethoxyethane
DMF	*N,N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
DP	Dipeptide
d.r.	Diastereomeric ratio

Abbreviation	Meaning
ee	Enantiomeric excess
e.g.	*exempli gratia*/for example
eq.	Equivalent
ESI	Electrospray ionisation
Et	Ethyl
et al.	*et alii/et alia*
EtOAc	Ethyl acetate
FG	Functional group
Fmoc	Fluorenylmethoxycarbonyl
FT-IR	Fourier-transform infrared spectroscopy
Gly	Glycine
h	hour
HATU	(1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluoro-phosphate
9-HBBN	9-Hexyl-9-borabicyclo[3.3.1]nonane
HBTU	*O*-(1*H*-benzotriazol-1-1yl),*N,N,N‘,N‘*-tetrame-thyluronium-hexafluorophosphat
HMBC	Heteronuclear multiple bond correlation
HSQC	Heteronuclear single quantum coherence
IR	Infra red
J	Coupling constant [Hz]
LHMDS	Lithium-bis(trimethylsilyl)amide
m	meta
M	Molar
m	Multiplet (NMR)
min	Minutes
Me	Methyl
mg	Milligram
MHz	Mega Hertz
mmol	Millimol
N	Normal
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide
NMO	*N*-methylmorpholine *N*-oxide
NMR	Nuclear magnetic resonance

Abbreviation	Meaning
NOESY	Nuclear overhauser enhancement and exchange spectroscopy
o	Ortho
9-OBBN	9-Octyl-9-borabicyclo[3.3.1]nonane
p	Para
p	Pentet (NMR)
PE	Petroleum ether
PG	Protective group
Ph	Phenyl
Phth	Phthalimide
PMB	*p*-Methoxybenzyl
ppm	Parts per million
prim.	Primary
PyBOP	Benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate
q	Quartet (NMR)
quant.	Quantitatively
quin	Quintet (NMR)
R	Rest
R_f	Retention factor
rt	Room temperature
s	Singlet (NMR)
sec.	Secondary
t	Triplet (NMR)
TBD	Triazabicyclodecene
tert.	Tertiary
TfO	Triflate
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TPAP	Tetrapropylammonium perruthenate
Trp	Tryptophan
UV	Ultraviolet
v/v	Volume ratio
$\tilde{\nu}$	Wave number

7 Literature

[1] H. Kato, T. Yoshida, T. Tokue, Y. Nojiri, H. Hirota, T. Ohta, R. M. Williams, S. Tsukamoto, *Angew. Chemie - Int. Ed.* **2007**, *46*, 2254–2256.

[2] M. Yamazaki, K. Sasago, K. Miyaki, *J. Chem. Soc. Chem. Commun.* **1974**, *33*, 408–409.

[3] K. Arai, K. Kimura, T. Mushiroda, Y. Yamamoto, *Chem. Pharm. Bull. (Tokyo).* **1989**, *37*, 2937–2939.

[4] J. M. Müller, C. B. W. Stark, *Angew. Chemie - Int. Ed.* **2016**, *55*, 4798–4802.

[5] X. Yu, G. Zocher, X. Xie, M. Liebhold, S. Schütz, T. Stehle, S.-M. Li, *Chem. Biol.* **2013**, *20*, 1492–1501.

[6] D. Pockrandt, L. Ludwig, A. Fan, G. M. König, S.-M. Li, *ChemBioChem* **2012**, *13*, 2764–2771.

[7] C. Almeida, N. Part, S. Bouhired, S. Kehraus, G. M. König, *J. Nat. Prod.* **2011**, *74*, 21–25.

[8] J. M. Schkeryantz, J. C. G. Woo, P. Siliphaivanh, K. M. Depew, S. J. Danishefsky, *J. Am. Chem. Soc.* **1999**, *121*, 11964–11975.

[9] J. M. Schkeryantz, J. C. G. Woo, S. J. Danishefsky, *J. Am. Chem. Soc.* **1995**, 7025–7026.

[10] S.-M. Li, *Nat. Prod. Rep.* **2010**, *27*, 57–78.

[11] P. Ruiz-Sanchis, S. A. Savina, F. Albericio, M. Alvarez, *Chem. - A Eur. J.* **2011**, *17*, 1388–1408.

[12] D. J. Faulkner, *Tetrahedron* **1977**, *33*, 1421–1443.

[13] M. F. Elsebai, V. Rempel, G. Schnakenburg, S. Kehraus, C. Müller, G. König, *ACS Med. Chem. Lett.* **2011**, *2*, 866–869.

[14] W. C. Chen, M. M. Joullie, *Tetrahedron Lett.* **1998**, *39*, 8401–8404.

[15] S. Takase, M. Iwami, T. Ando, M. Okamoto, K. Yoshida, H. Horiai, H. Imanaka, *J. Antibiot. (Tokyo).* **1984**, *37*, 1320–1323.

[16] K. M. Depew, S. P. Marsden, D. Zatorska, A. Zatorski, W. G. Bornmann, S. J. Danishefsky, *J. Am. Chem. Soc.* **1999**, *121*, 11953–11963.

[17] Y. Kimura, T. Hamasaki, H. Nakajima, A. Isogai, *Tetrahedron Lett.* **1982**, *23*, 225–228.

[18] S. Ohmomo, K. Oguma, T. Ohashi, M. Abe, *Agric. Biol. Chem.* **1978**, *12*, 2387–2389.

[19] L. Du, X. Yang, T. Zhu, F. Wang, X. Xiao, H. Park, Q. Gu, *Chem. Pharm. Bull.* **2009**, *57*, 873–876.

[20] S. Tsukamoto, H. Kato, M. Samizo, Y. Nojiri, H. Onuki, H. Hirota, T. Ohta, *J. Nat. Prod.* **2008**, *71*, 2064–2067.

[21] B. Bhat, D. M. Harrison, *Tetrahedron Lett.* **1986**, *27*, 5873–5874.

[22] B. Bhat, D. M. Harrison, *Tetrahedron* **1993**, *49*, 10655–10662.

[23] T. Hino, M. Nakagawa, *Alkaloids Chem. Pharmacol.* **1989**, *34*, 1–75.

[24] U. Anthoni, C. Christophersen, P. H. Nielsen, *Alkaloids* **1999**, *13*, 163–236.

[25] P. L. Julian, J. Pikl, *J. Am. Chem. Soc.* **1935**, *57*, 755–757.

[26] F. E. King, R. Robinson, *J. Chem. Soc.* **1933**, *111*, 270–273.

[27] H. F. Tsai, H. Wang, J. C. Gebler, C. D. Poulter, C. L. Schardl, *Biochem. Biophys. Res. Commun.* **1995**, *216*, 119–125.

[28] Y. Ding, R. M. Williams, D. H. Sherman, *J. Biol. Chem.* **2008**, *283*, 16068–16076.

[29] I. A. Unsöld, S. M. Li, *Microbiology* **2005**, *151*, 1499–1505.

[30] M. Shibuya, H. M. Chou, M. Fountoulakis, S. Hassam, S. U. Kim, K. Kobayashi, H. Otsuka, E. Rogalska, J. M. Cassady, H. G. Floss, *J. Am. Chem. Soc.* **1990**, *112*, 297–304.

[31] J. C. Gebler, A. B. Woodside, C. D. Poulter, *J. Am. Chem. Soc.* **1992**, *114*, 7354–7360.

[32] L. Y. P. Luk, M. E. Tanner, *J. Am. Chem. Soc.* **2009**, *131*, 13932–13933.

[33] U. Metzger, C. Schall, G. Zocher, I. Unsöld, E. Stec, S.-M. Li, L. Heide, T. Stehle, *Proc. Natl. Acad. Sci. U. S. A.* **2009**, *106*, 14309–14314.

[34] S. M. Li, *Phytochemistry* **2009**, *70*, 1746–1757.

[35] H. G. Floss, *Tetrahedron* **1976**, *32*, 873–912.

[36] E. Wenkert, H. Sliwa, *Bioorg. Chem.* **1977**, *6*, 443–452.

[37] M. Westermaier, H. Mayr, *Org. Lett.* **2006**, *8*, 4791–4794.

[38] N. Otero, M. Mandado, R. A. Mosquera, *J. Phys. Chem. A* **2007**, *111*, 5557–5562.

[39] D. D. Schwarzer, P. J. Gritsch, T. Gaich, *Angew. Chemie - Int. Ed.* **2012**, *51*, 11514–11516.

[40] W. B. Yin, H. L. Ruan, L. Westrich, A. Grundmann, S.-M. Li, *ChemBioChem* **2007**, *8*, 1154–1161.

[41] W. B. Yin, A. Grundmann, J. Cheng, S.-M. Li, *J. Biol. Chem.* **2009**, *284*, 100–109.

[42] W. B. Yin, X. Yu, X. L. Xie, S.-M. Li, *Org. Biomol. Chem.* **2010**, *8*, 2430–2438.

[43] B. M. Trost, S. Malhotra, W. H. Chan, *J. Am. Chem. Soc.* **2011**, *133*, 7328–7331.

[44] M. Kimura, M. Fukasaka, Y. Tamaru, *J. Am. Chem. Soc.* **2005**, *127*, 4592–4594.

[45] W. F. Billups, R. S. Erkes, L. E. Reed, *Synth. Commun.* **1980**, *10*, 147–154.

[46] B. M. Trost, G. A. Molander, *J. Am. Chem. Soc.* **1981**, *103*, 5969–5972.

[47] T. Lindel, L. Bräuchle, G. Golz, P. Böhrer, *Org. Lett.* **2007**, *9*, 283–286.

[48] B. M. Trost, W. J. Bai, C. Hohn, Y. Bai, J. J. Cregg, *J. Am. Chem. Soc.* **2018**, *140*, 6710–6717.

[49] J. Ruchti, E. M. Carreira, *J. Am. Chem. Soc.* **2014**, *136*, 16756–16759.

[50] X. Zhang, L. Han, S. L. You, *Chem. Sci.* **2014**, *5*, 1059–1063.

[51] X. Zhang, W. B. Liu, H. F. Tu, S. L. You, *Chem. Sci.* **2015**, *6*, 4525–4529.

[52] C. Defieber, M. A. Ariger, P. Moriel, E. M. Carreira, *Angew. Chemie - Int. Ed.* **2007**, *46*, 3139–3143.

[53] A. Borthwick, *Chem. Rev.* **2012**, *112*, 3641–3716.

[54] H. Moon, J.-H. Chang, *Biotechnlogy Bioprocess Eng.* **2004**, *9*, 59–61.

[55] S. Takiguchi, T. Iizuka, Y. S. Kumakura, K. Murasaki, N. Ban, K. Higuchi, T. Kawasaki, *J. Org. Chem.* **2010**, *75*, 1126–1131.

[56] A. Dömling, I. Ugi, *Angew. Chemie* **2000**, *39*, 3168–3210.

[57] H. Yu, Y. Zong, T. Xu, *Chem. Sci.* **2020**, *11*, 656–660.

[58] V. A. Ignatenko, P. Zhang, R. Viswanathan, *Tetrahedron Lett.* **2011**, *52*, 1269–1272.

[59] T. J. Greshock, A. W. Grubbs, S. Tsukamoto, R. M. Williams, *Angew. Chemie - Int. Ed.* **2007**, *46*, 2262–2265.

[60] S. Tsukamoto, H. Kato, T. J. Greshock, H. Hirota, T. Ohta, R. M. Williams, *Communication* **2009**, *131*, 3834–3835.

[61] N. S. Simpkins, I. Pavlakos, M. D. Weller, L. Male, *Org. Biomol. Chem.* **2013**, *11*, 4957–4970.

[62] E. V. Mercado-Marin, R. Sarpong, *Chem. Sci.* **2015**, *6*, 5048–5052.

[63] J. D. Sunderhaus, T. J. McAfoos, J. M. Finefield, H. Kato, S. Li, S. Tsukamoto, D. H. Sherman, R. M. Williams, *Org. Lett.* **2013**, *15*, 22–25.

[64] S. Li, J. M. Finefield, J. D. Sunderhaus, T. J. McAfoos, R. M. Williams, D. H. Sherman, *J. Am. Chem. Soc.* **2012**, *134*, 788–791.

[65] J. M. Finefield, R. M. Williams, *J. Org. Chem.* **2013**, *78*, 8214.

[66] J. M. Finefield, R. M. Williams, *J. Org. Chem.* **2010**, *75*, 2785–2789.

[67] A. D. Batcho, W. Leimgruber, in *Org. Synth.*, Wiley Online Library, **1985**, p. 214.

[68] B. T. Kametani, N. Kanaya, M. Ihara, *J. Chem. Soc., Perkin Trans 1* **1981**, 959–963.

[69] F. A. Davis, J. C. Towson, D. B. Vashi, R. ThimmaReddy, J. P. McCauley, J. P. McCauley, M. E. Harakal, D. J. Gosciniak, *J. Org. Chem.* **1990**, *55*, 1254–1261.

[70] B. B. Snider, H. Zeng, *J. Org. Chem.* **2003**, *68*, 545–563.

[71] A. W. Grubbs, G. D. Artman, S. Tsukamoto, R. M. Williams, *Angew. Chemie - Int. Ed.* **2007**, *46*, 2257–2261.

[72] J. Clayden, S. Warren, N. Greeves, P. Wothers, in *Org. Chem.*, Oxford, **2001**, p. 667f.

[73] U. Schöllkopf, U. Groth, C. Deng, *Angew. Chemie Int. Ed. English* **1981**, *20*, 798–799.

[74] U. Schöllkopf, T. Tiller, J. Bardenhagen, *Tetrahedron* **1988**, *44*, 5293–5305.

[75] J. Bülle, A. Hüttermann, in *Das Basiswissen Der Org. Chemie Die Wichtigsten Org. Reaktionen Im Labor Und Der Natur*, Wiley-VCH, **2000**, p. 310/311.

[76] S. D. Bull, S. G. Davies, S. W. Epstein, M. A. Leech, J. V. A. Ouzman, *J. Chem. Soc. - Perkin Trans. 1* **1998**, *15*, 2321–2330.

[77] S. D. Bull, S. G. Davies, S. W. Epstein, J. V. A. Ouzman, *Tetrahedron Asymmetry* **1998**, *9*, 2795–2798.

[78] M. Pichowicz, N. S. Simpkins, A. J. Blake, C. Wilson, *Tetrahedron* **2008**, *64*, 3713–3735.

[79] C. F. Dignam, C. J. Richards, J. J. Zopf, L. S. Wacker, T. J. Wenzel, *Org. Lett.* **2005**, *7*, 1773–1776.

[80] A. Speicher, T. Klaus, T. Eicher, *J. Prakt. Chem.* **1998**, *340*, 581–583.

[81] C. U. Hjørringgaard, A. Brust, P. F. Alewood, *J. Pept. Sci.* **2012**, *18*, 199–207.

[82] L. A. Carpino, *Acc. Chem. Res.* **1987**, *20*, 401–407.

[83] H. Takaku, K. Kamaike, H. Tsuchiya, *J. Org. Chem.* **1984**, *49*, 51–56.

[84] F. G. Bordwell, H. E. Fried, *J. Org. Chem.* **1991**, *56*, 4218–4223.

[85] F. Fini, *Dissertation* **2008**, University of Bologna.

[86] K. Suzuki, Y. Sasaki, N. Endo, Y. Mihara, *Chem. Pharm. Bull.* **1981**, *29*, 233–237.

[87] J. Budderus, B. Schmidt, in *Grundlagen Der Org. Chemie*, De Gruyter, **2014**, pp. 245–248.

[88] K. P. C. Vollhardt, N. E. Schore, in *Org. Chemie 4. Auflage*, Wiley-VCH, Weinheim, **2005**, p. 898.

[89] H. E. Zimmerman, M. D. Traxler, *J. Am. Chem. Soc.* **1957**, *79*, 1920–1923.

[90] J. Clayden, S. Warren, N. Greeves, P. Wothers, in *Org. Chem.*, Oxford, **2001**, p. 424.

[91] V. J. Shiner, J. S. Humphrey, *J. Am. Chem. Soc.* **1967**, *89*, 622–630.

[92] D. Schmelzer, *Bachelor Thesis* **2019**, University of Hamburg.

[93] J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.

[94] W. Steglich, G. Höfle, *Angew. Chemie* **1969**, *81*, 1001.

[95] C. Schotten, *Ber. Deut. Chem. Ges.* **1884**, *17*, 2544–2547.

[96] E. Baumann, *Berichte der Dtsch. Chem. Gesellschaft* **1886**, *19*, 3218–3222.

[97] Y. Oikawa, T. Yoshioka, O. Yonemitsu, *Tetrahedron Lett.* **1982**, *23*, 885–888.

[98] V. Nair, L. Balagopal, R. Rajan, J. Mathew, *Acc. Chem. Res.* **2004**, *37*, 21–30.

[99] D. J. Watson, E. D. Dowdy, W. Sen Li, J. Wang, R. Polniaszek, *Tetrahedron Lett.* **2001**, *42*, 1827–1830.

[100] M. E. Jung, P. Koch, *Tetrahedron Lett.* **2011**, *52*, 6051–6054.

[101] N. Iqbal, E. J. Cho, *Adv. Synth. Catal.* **2015**, *357*, 2187–2192.

[102] T. W. Greene, P. G. M. Wuts, *Protective Groups in Organic Synthesis, Third Edition*, Wiley-VCH, New York, **1999**.

[103] J. A. Soderquist, H. C. Brown, *J. Org. Chem.* **1981**, *46*, 4599–4600.

[104] Y. Zhang, P. Yang, C. J. Chou, C. Liu, X. Wang, W. Xu, *ACS Med. Chem. Lett.* **2013**, *4*, 235–238.

[105] D. Leow, C. H. Tan, *Chem. - An Asian J.* **2009**, *4*, 488–507.

[106] C. M. Cain, R. P. C. Cousins, G. Coumbarides, N. S. Simpkins, **1989**, *46*, 523–544.

[107] R. F. Borch, M. D. Bernstein, H. D. Durst, *J. Am. Chem. Soc.* **1971**, *93*, 2897–2904.

[108] O. I. Afanasyev, E. Kuchuk, D. L. Usanov, D. Chusov, *Chem. Rev.* **2019**, *119*, 11857–11911.

[109] A. L. Lane, R. Viswanathan, *Org. Biomol. Chem.* **2015**, *13*, 7177–7192.

[110] M. A. Mohamed, K. ichi Yamada, K. Tomioka, *Tetrahedron Lett.* **2009**, *50*, 3436–3438.

[111] L. Kürti, B. Czakó, *Strategic Applications of Named Reactions in Organic Synthesis: Background and Detailed Mechanisms*, Elsevier, **2005**.

[112] K. M. Depew, S. J. Danishefsky, N. Rosen, L. Sepp-Lorenzino, *J. Am. Chem. Soc.* **1996**, *118*, 12463–12464.

[113] S. E. Sen, S. L. Roach, *Synthesis (Stuttg).* **1995**, *7*, 756–758.

[114] A. Roux, M. Isaac, V. Chabert, S. A. Denisov, N. D. McClenaghan, O. Sénèque, *Org. Biomol. Chem.* **2018**, *16*, 5626–5634.

[115] P. Klán, T. Šolomek, C. G. Bochet, A. Blanc, R. Givens, M. Rubina, V. Popik, A. Kostikov, J. Wirz, *Chem. Rev.* **2013**, *113*, 119–191.

[116] A. Blanc, C. G. Bochet, *J. Org. Chem.* **2002**, *67*, 5567–5577.

[117] A. Patchornik, B. Amit, R. B. Woodward, *J. Am. Chem. Soc.* **1970**, 6333–6335.

[118] J. A. Soderquist, A. Negron, *Org. Synth.* **1992**, *70*, 169.

[119] M. Roggen, E. M. Carreira, *Angew. Chemie - Int. Ed.* **2012**, *51*, 8652–8655.

[120] W. Chang, D. Sanyal, J. Huang, K. Ittiamornkul, Q. Zhu, X. Liu, *Org Lett* **2017**, *19*, 17–20.

[121] G. Y. Qing, Y. B. He, F. Wang, H. J. Qin, C. G. Hu, X. Yang, *European J. Org. Chem.* **2007**, *11*, 1768–1778.

[122] R. Suhas, D. C. Gowda, *J. Pept. Sci.* **2012**, *18*, 535–540.

[123] “Sigma Aldrich,” can be found under http://sigmaaldrich.com, **2020**.

[124] “Alfa Aesar-Safety Data Sheets,” can be found under https://www.alfa.com/de, **2020**.

[125] “GESTIS Stoffdatenbank,” can be found under http://www.gestis.itrust.de, **2020**.

8 Appendix

8.1 Hazardous materials and safety instructions

Table 8.1: Hazardous materials and safety instructions.[123–125]

Substance	GHS	H/P-statements
Acetic acid	GHS02, GHS05	H226-H314; P280-P305+P351+P338-P310
Acetone	GHS02, GHS08	H225-H319-H336, P210-P240-P305+P351+P338-P403+P233
Acetonitrile	GHS02, GHS07	H225-H302+H312+H332-H319, P210-P280-P305+P351+P338
Acetyl chloride	GHS02, GHS05, GHS08	H225-H302-H314, P210-P280-P305+P351+P338-P310
Allyl bromide	GHS02, GHS05, GHS06, GHS07, GHS09	H225-H301-H331-H314-H340-H350-H400, P210-P280-P301+P330+P331-P303+P361+P353-P305+P351+P338-P310
Ammonia	GHS05, GHS06, GHS09	H221-H280-H314-H331-H400, P210-P261-P273-P280-P305+P351+P338-P310
Anisol	GHS02	H226; P210-P403+P233
Argon	GHS04	H280, P410+P403
Benzaldehyde	GHS07	H302+H312-H315,P264-P270-P280-P301+P312+P330-P302+P352+P312-P501
Benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate	GHS07	H315-H319-H335; P261+P264+P271+P280
Benzyl bromide	GHS08	H315-H319-H335, P261-P305+P351+P338
Benzyl chloride	GHS05, GHS06, GHS08	H302-H315-H317-H318-H331-H335-H340-H350-H373, P201-P260-P280-P304+P340+P312-P305+P351+P338+P310-P308+P313

Substance	GHS	H/P-statements
9-Borabicyclo[3.3.1]nonan-dimer, 9-BBN	GHS02, GHS08	H228-H261-H315-H319-H335, P210-P231+P232-P261-P305+P351+P338-P422
Borane dimethyl sulfide complex	GHS02, GHS05, GHS06	H225-H260-H301+H311-H315-H318-H335, P210-P231+P232-P280-P301+P310+P330-P305+P351+P338+P310-P370+P378
4-Bromo-1-butene	GHS02, GHS07, GHS08	H225-H319-H334-H335, P210-P261-P305+P351+P338-P342+P311
3-Bromo-2-methylpropene	GHS02, GHS05, GHS07, GHS09	H225-H302+H332-H314-H411, P210-P273-P280-P305+P351+P338-P310
n-Butyllithium (1.6 M in *n*-hexane)	GHS02, GHS05, GHS07, GHS08, GHS09	H225-H250-H261-H304-H314-H336-H361-H373-H411, P210-P222-P231+P232-P261-P273-P422
Ceric ammonium nitrate	GHS03, GHS05, GHS07, GHS09	H272-H290-H302-H314-H317-H410; P210-P220-P260-P280-P305+P351+P338-P370+P378
Chloroform	GHS07, GHS08	H302+H332-H315-H319-H336-H351-H361-H373, P261-P281-P305+P351+P338
Chloroform-d_1	GHS07, GHS08	H302-H315-H351-H373; P281
Citric acid	GHS07	H319, P264-P280-P305+P351+P338-P337+P313
1,5-Cyclooctadiene	GHS02, GHS07	H226-H304-H315-H317-H319-H334, P261-P280-P301+310, P305+351+338-P331-P342+311
1-Decene	GHS02, GHS07, GHS09	H226-H304-H410, P210-P273-P301-P330+P331
Diazabicycloundecen	GHS05, GHS06	H301-H314-H412-H290, P273-P280-P301+P310-P305+P351+P338-P310
2,3-Dichloro-5,6-dicyano-*p*-benzoquinone	GHS06	H301; P301+P310
Dichloromethane	GHS07, GHS08	H315-H319-H335-H336-H351-H373; P261-P281-P305+P351+P338
Diethyl ether	GHS02, GHS07	H224-H302-H336, P210-P261

Substance	GHS	H/P-statements
N,N-Diisopropylethylamine	GHS02, GHS05, GHS06	H225-H302-H331-H318-H335, P210-P261-P280-P305+P351+P338-P311
2,4-Dimethoxybenzylamine	GHS05	H314; P280-P305+P351+P338-P310
1,2-Dimethoxyethane	GHS02, GHS07, GHS08	H225-H332-H360, P201-P210-P240-P308+P313
N,N-Dimethylformamide	GHS02, GHS07, GHS08	H226-H312+H332-H319-H360, P201-P210-P261-P280-P308+P313-P370+P378
Di-*tert*-butyl dicarbonate	GHS02, GHS05, GHS06	H226-H330-H315-H317-H318-H335, P210-P260-P280-P304+P340+P310-P305+P351+P338+P310-P370+P378
Ethanol	GHS02, GHS07, GHS08	H225-H302-H371, P210-P260
Ethyl acetate	GHS02, GHS07	H225-H319-H336, P210-P261-P305+P351+P338
Ethyl bromoacetate	GHS02, GHS06	H226-H300+H310+H330, P210-P280-P302+P352+P310-P304+P340+P310-P370+P378
Ethyl bromide	GHS02, GHS07, GHS08	H225-H302+H332-H351-H420, P210-P261-P304+P340+P312-P370+P378-P403+P235-P502
Ethyl iodide	GHS07, GHS08	H302-H315-H317-H319-H334-H335, P261-P280-P284-P304+P340-P305+P351+P338-P342+P311
O-(1*H*-benzotriazol-1-1yl),*N,N,N',N'*-tetramethyluronium-hexafluorophosphat	GHS07, GHS08	H315-H317-H319-H334-H335, P261-P280-P284-P304-P305-P311-P338-P340-P342-P351
1-Hexene	GHS02, GHS07	H225-H304, P210-P243-P280-P301+P310-P331-P403+P233
Hydrazine hydrate	GHS05, GHS06, GHS08, GHS09	H301+H311+H331-H314-H317-H350-H410, P201-P261-P273-P280-P301+P310+P330-P305+P351+P338
Hydrochloric acid	GHS05, GHS08	H290-H314-H335, P260-P280-P303+P361+P353-P304+P340+P310-P305+P351+P338

Substance	GHS	H/P-statements
Bis(1,5-cyclooctadiene) diiridium(I) dichloride	GHS07	H315-H319-H335, P261-P305+P351+P338
Iminostilbene	GHS07, GHS09	H302-H411, P273
Isobutyraldehyde	GHS02, GHS07	H225-H319, P210-P233-P280-P303+P361+P353-P337+P313-P370+P378
Isopropyl iodide	GHS02, GHS07	H226-H302-H315-H319-H335, P210-P302+P352-P305+P351+P338
Lithium bis(trimethylsilyl)amide	GHS02, GHS05	H228-H314-H318, P210-P280-P305+P351+P338-P309-P310-P402
Methanol	GHS02, GHS06, GHS08	H225-H301+H311+H331-H370, P210-P260-P280-P301+P310-P311
Methanol-d_4	GHS02, GHS06, GHS08	H225-H301+H311+H331-H370, P210-P280-P302+P352+P312-P304+P340+P312-P370+P378-P403+P235
p-Methoxybenzyl amine	GHS05, GHS07	H302-H314, P280-P305+P351+P338-P310
p-Methoxybenzyl chloride	GHS05	H314, P280-P305+P351+P338-P310
2-Methyl-2-butene	GHS02, GHS07, GHS08, GHS09	H225-H302-H304-H336-H341-H411, P210-P273-P280-P301+P310-P331-P370+P378-P391
2-Methylbut-3-en-2-ol	GHS02, GHS08	H225-H302-H315-H319, P210-P280-P301+P312+P330-P305+P351+P338-P337+P313-P403+P235
Methyl iodide	GHS06, GHS08	H301-H312-H315-H331-H335-H351, P261-P280-P301-P311
N-Methyl-2-pyrrolidone	GHS07, GHS08	H315-H319-H335-H360, P201-P280-P305+P351+P338-P308+P313
1,1′-Bi-2-naphthol	GHS06	H301-H319, P301+P310-P305+P351+P338
Ninhydrin	GHS07	H302-H315-H319, P301+P312+P330-P305+P351+P338
1-Octene	GHS02, GHS07, GHS09	H225-H304-H410, P210-P273-P301+P310-P331-P501

Substance	GHS	H/P-statements
Petroleum ether	GHS02, GHS08	H225-H304-H340-H350-H361f-H373-H412, P201-P210-P273-P281-P301+P310-P308+P313
2,2'-Biphenyldiol	GHS05, GHS07	H315-H318-H335, P261-P280-P305+P351+P338
Phosphomolybdic acid	GHS03, GHS05	H272-H314, P220-P280-P305+P351+P338-P310
Phosphorous trichloride	GHS05, GHS06, GHS07	H300-H330-H373-H314, P260-P280-P301+P310-P330-P303+P361+P353-P304+P340-P310-P305+P351+P338-P403+P233
Phthaloyl chloride	GHS05	H314, P280-P305+P351+P338-P310
2-Propanol	GHS02, GHS07	H225-H319-H336, P210-P261-P305+P351+P338
Potassium carbonate	GHS08	H315-H319-H335, P302+P352-P305+P351+P338
Potassium hydroxide	GHS05, GHS07	H290-H314, P280-P305+P351+P338-P310
Potassium permanganate	GHS03, GHS05, GHS07, GHS09	H272-H302-H314-H410, P210-P220-P260-P273-P280-P303+P361+P353-P304+P340+P310-P305+P351+P338+P310-P370+P378-P391
Propargyl bromide	GHS02, GHS06, GHS08	H225-H301-H304-H315-H319-H335-H336-H361-H373, P210-P260-P280-P370+P378-P403+P235
Propionyl chloride	GHS02, GHS05, GHS06	H225-H302-H314-H331, P361+P353-P304+P340+P310-P305+P351+P338-P403+P233
Silver triflate	GHS07	H315-H319-H335, P305+P351+P338
Sodium	GHS02, GHS05	H260-H314, P280-P301+P330+P331-P305+P351+P338-P309-P310-P370+P378-P422

Substance	GHS	H/P-statements
Sodium chlorite	GHS03, GHS05, GHS06, GHS07, GHS09	H271-H301-H310-H314-H373-H410, P210-P280-P301+P330+P331-P310-P303+P361+P353-P305+P351+P338-P370+P378
Sodium cyanoborohydride	GHS02, GHS05, GHS06, GHS09	H228-H300+H310+H330-H314-H410, P210-P280-P303+P361+P353-P304+P340+P310-P305+P351+P338
Sodium hydride	GHS02, GHS05	H228-H260-H314, P210-P223-P231+P232-P280-P370+P378-P422
Sodium hydroxide	GHS05	H290-H314, P280-P305+P351+P338-P310
Sodium iodide	GHS07, GHS09	H315-H319-H400, P273-P305+P351+P338
Sulfuric acid	GHS05	H290-H314, P260-P280-P303+P361+P353-P304+P340+P310-P305+P351+P338
Tetrahydrofuran	GHS02, GHS07, GHS08	H225-H319-H335-H351, P210-P261-P281-P305+P351+P338
Thionyl chloride	GHS05, GHS06	H302-H331-H314-H335, P280-P301+P330+P331-P304+P340-P305+P351+P338-P309+P310
Toluene	GHS02, GHS07, GHS08	H225-H304-H315-H336-H361d-H373, P210-P261-P281-P301+P310-P331
Triazabicyclodecene	GHS05	H314, P280-P305+P351+P338-P310
Triethylamine	GHS02, GHS05, GHS07	H225-H302-H312-H314-H332, P210-P280-P305+P351+P338-P310
Triethylborane	GHS02, GHS05, GHS06	H250-H301-H330-H314, P210-P222-P231-P280-P301+P310-P422
Trifluoroacetic acid	GHS05, GHS07	H314-H332-H412; P261-P273-P280-P303+P361+P353-P304+P340+P310-P305+P351+P338
Triphenylborane	GHS02	H228, P210
Vanillin	GHS07	H319, P305+P351+P338

GHS01

GHS02

GHS03

GHS04

GHS05

GHS06

GHS07

GHS08

GHS09

8.2 Curriculum vitae

This page was omitted on the grounds of data protection.

This page was omitted on the grounds of data protection.

8.3 Statutory declaration

I hereby declare that the thesis submitted is my own work without making use of impermissible aids or use of any sources other than those cited in the text and acknowledgements. This applies also to all graphics, drawings and images included in the thesis. The submitted written version is equal to the one on the electronic storage device. I further declare that I have not submitted this nor a similar thesis at any other examination board in order to obtain a degree.

Hamburg, the 14th of August 2020

M.Sc. Carina Susanne Michaelis