Indolo[2,3-*a*]quinolizidines and derivatives: Bioactivity and asymmetric synthesis

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Abstract

Corynantheine alkaloids with a tetracyclic indole[2,3-*a*]-quinolizidine motif are an important issue in academia and in the life science industries due to their broad bioactivity profile ranging from antiarthritic, analgesic, anti-inflammatory, antiallergic, antibacterial, to antiviral activities. For that reason, in the last decades, numerous efforts have been invested in the development of novel synthetic strategies to obtain the indole[2,3-*a*]-quinolizidine system. This review focuses on the synthetic methodologies developed to target the most important alkaloids of this family, and highlights the potential use of these alkaloids or analogs to treat several diseases, ranging from cancer to neurodegenerative disorders.

Keywords: Indoloquinolizidines; Corynantheine alkaloids; Indole alkaloids; Natural products; Bioactivity

Introduction

Corynantheine alkaloids with a tetracyclic indole[2,3-*a*]-quinolizidine motif are of great interest for academia and pharmaceutical companies due to their broad bioactivity profile. In fact, this type of indole alkaloids have been described with different biological activities, ranging from antiarthritic, analgesic, anti-inflammatory, to anti-cancer activities. For this reason, in the last decades, numerous efforts have been invested in the development of novel synthetic strategies to obtain the indolo[2,3-*a*]quinolizidine system present in numerous monoterpenoid-derived alkaloids.[1-3] Since the chirality of the corynantheine alkaloids is crucial for the expression of bioactivity, there is a huge interest in the development of new enantioselective synthesis to obtain indolo[2,3-*a*]quinolizidine alkaloids. In particular, several research studies (development of novel synthetic strategies and biological evaluation) have been conducted with corynantheine alkaloids, such as dihydrocorynantheine (**1**), corynantheine (**2**), dihydrocorynantheol (**3**), hirsutine (**4**), hirsuteine (**5**), and geissoschizine methyl ether (**6**) (Figure 1). This review focus on the pharmacological and therapeutic interest of indolo[2,3-*a*]quinolizidines and the most recent advances in asymmetric synthetic strategies to obtain the main skeleton of these indole alkaloids. All the papers described in this review were found using Scifinder, PubMed, and Web of Science databases.

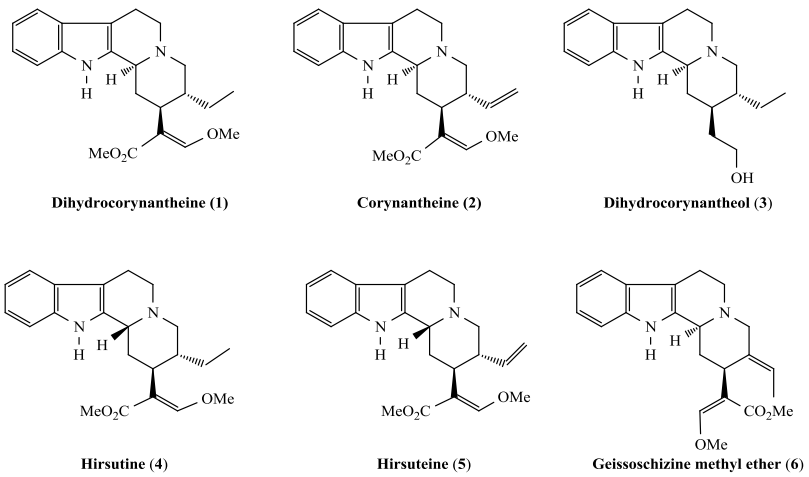


Figure 1 – Examples of corynantheine alkaloids.

1. Biological activities of indolo[2,3-*a*]quinolizidine alkaloids

1.1 Arborescidine A and desbromoarborescidine A

In 1966, it was described the isolation of 1,2,3,4,6,7-hexahydro-12*H*-indolo[2,3-*a*]quinolizine alkaloid (latter called desbromoarborescidine A) from *Dracontomelum mangiferum*.[4] The cardiovascular activities of desbromoarborescidine A (**7**) and five natural product analogs **8**-**12** (Figure 2) were evaluated by studying the effect of these alkaloids in blocking Alpha-1 and Alpha-2 adrenoceptors. Desbromoarborescidine A (**7**) showed a strong blocking activity of the adrenoceptors compared with the other 5 alkaloids. In fact, the presence of a hydroxyl group at position 1 led to loss of activity.[5]

In 1993, it was described the isolation of the brominated indole alkaloid arborescidine A (**13**) from the marine tunicate *Pseudodistoma arborescens*.[6] The antiproliferative activity of desbromoarborescidine A (**7**) and arborescidine A (**13**) (Figure 2) was evaluated *in vitro* against several tumor cell lines (lung fibroblasts, gastric adenocarcinoma, leukemia and others). Arborescidine A (**13**) showed an IC_{50} value of 34.5 μM for leukemia, while desbromoarborescidine A (**7**) was weakly active in all tumor cell lines tested (IC_{50} higher than 50 μM).[7]

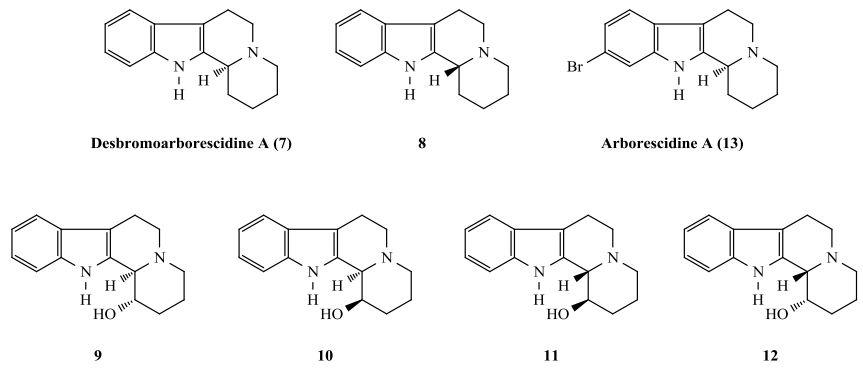


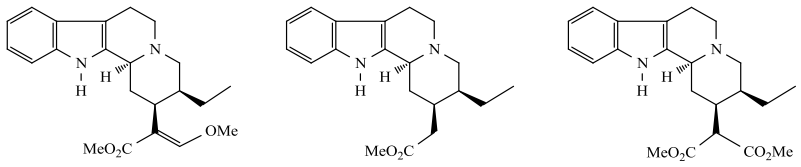
Figure 2 – Chemical structure of desbromoarborescidine A (**7**), indoloquinolizidines **8**-**12**, and arborescidine A (**13**).

1.2 Dihydrocorynantheine (1), corynantheine (2), and derivatives

In the late 80's Chang *et al.* reported the effects of dihydrocorynantheine (**1**) (see Figure 1) in arterial pressure. The alkaloid was extracted from the dried leaves and stems of *Uncaria Callophylla* and the studies demonstrated that dihydrocorynantheine (**1**) can effectively lower the arterial pressure in both anaesthetized and conscious normotensive rats.[8]

Later, Masumiya *et al.* described that dihydrocorynantheine (**1**) showed direct effects on the potential action of cardiac muscle through inhibition of multiple ion channels, which could explain their negative chronotropic and antiarrhythmic activity.[9]

In 2000, dihydrocorynantheine (**1**), corynantheine (**2**), and corynantheidine (**14**) were isolated from bark of *Corynanthe pachyceras* K. Schum. (Rubiaceae). These alkaloids, and two corynantheidine racemic synthetic derivatives **15**-**16** (Figure 3), were tested against Leishmania major promastigotes. All compounds were active for Leishmania, presenting IC_{50} values between 0.7 and 2.8 μM. The three alkaloids were also evaluated for antiplasmodial and cytotoxic activities but revealed to be inactive.[10]



Corynantheidine (14) **15** **16**

Figure 3 – Chemical structure of corynantheidine (**14**) and two synthetic derivatives **15**-**16**.

1.3 Dihydrocorynantheol (3) and derivatives

In 2011, Fröde's research group reported for the first time the anti-inflammatory effects of dihydrocorynantheol (**3**) (see Figure 1), an alkaloid isolated from *Esenbeckia leiocarpa*. Dihydrocorynantheol (DHC) (**3**) was shown to play a pivotal role in the anti-inflammatory effect exercised by this herb by preventing the IκB α ubiquitination and consequent degradation, inhibiting thus the NF-κB cascade and, consequently, the production of several pro-inflammatory mediators, such as IL-1β and TNF-α.[11]

A series of ester dihydrocorynantheol derivatives (DHC-acetyl **17**, DHC-*p*-methylbenzoyl **18**, DHC-benzoyl **19**, DHC-*p*-methoxybenzoyl **20** and DHC-*p*-chlorobenzoyl **21**) (Figure 4) were also tested as anti-inflammatory agents. It was observed that protection of the hydroxyl group resulted in a decrease of activity, which indicates that the presence of a hydroxyl group in the chemical structure of dihydrocorynantheol (**3**) is important for the activity of this alkaloid against inflammation.[12]

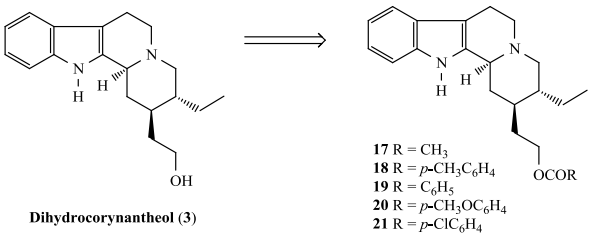


Figure 4 - Chemical structure of dihydrocorynantheol (**3**) and indoloquinolizidines **17**-**21**.

1.4 Hirsutine (4), hirsuteine (5), geissoschizine methyl ether (6) and derivatives

Hirsutine (**4**), hirsuteine (**5**) and geissoschizine methyl ether (**6**) (see Figure 1) are the primary constituents of *Uncaria* sp. Hirsutine (**4**), isolated from *Uncaria rhynchophylla* (traditional Chinese herb medicine), was described to possess antihypertensive and antiarrhythmic activities through modulation of the intracellular Ca^{2+} levels in rat thoracic aorta[13] and action potential in cardiac muscle[9]. Moreover, hirsutine (**4**) was shown to be effective in the protection of rat cardiomyocytes from hypoxia-induced cell death.[14] Moreover, the effects of hirsutine (**4**), hirsuteine (**5**) and geissoschizine methyl ether (**6**) (Figure 1), extracted from *Uncariae Ramulus et Uncus*, were evaluated on vascular responses. Geissoschizine methyl ether (**6**) proved to be 14 times more active (EC_{50} = 0.744μM) than hirsutine (**4**), in norepinephrine-induced vasocontractive response. Also, geissoschizine methyl ether (**6**) was shown to have two different mechanisms of action: endothelium dependency with nitric oxide and endothelium independency with voltage-dependent Ca^{2+} - channel blocking. Therefore, geissoschizine methyl ether (**6**) might be a candidate for vasodilative or antihypertensive medicines.[15]

In 2011, villocarine A (Figure 5) was isolated from the leaves of *Uncaria villosa* (Rubiaceae). In that report, the authors describe villocarine A as a new indole alkaloid, however the structure

is identical to the indole alkaloid 3-epi-geissoschizine methyl ether (**22**). Villocarine A showed potent vasorelaxant effects at 30 μM in rat aortic ring assays, revealed some inhibition effect on vasocontraction of depolarized aorta with high concentration potassium, and showed inhibition effect on phenylephrine (PE)-induced contraction in the presence of nicardipine in a Ca^{2+} concentration-dependent manner.[16, 17]

In 2011, T. Ueda *et al.* demonstrated that geissoschizine methyl ether (**6**) is a partial agonist at the serotonin 5-HT_{1A} receptor, a partial agonist/antagonist at the dopamine D_{2L} receptor and an antagonist at the serotonin 5-HT_{2A}, 5-HT_{2C} and 5-HT_7 receptors. The pharmacological profiles of geissoschizine methyl ether (**6**) were similar to aripiprazole (commercial drug used for the treatment of schizophrenia and related disorders), however, geissoschizine methyl ether (**6**) was less potent than aripiprazole at dopamine D_{2L} receptors (EC_{50}=4.4 μM for geissoschizine methyl ether (**6**) vs. EC_{50}=56 nM for aripiprazole).[18] Moreover, in 2012, gissoschizine methyl ether (**6**) was described as a potential acetylcholinesterase inhibitor. In this study, hirsutine (**4**), hirsuteine (**5**), and vallesiachotamine (**23**) (Figure 5), extracted from the hooks of *Uncaria Rhynchophylla*, were also tested. The results showed an inhibition of 50% of acetylcholinesterase activity at concentrations of 3.7±0.3 μg mL^{-1} for geissoschizine methyl ether (**6**). Hirsutine (**4**), hirsuteine (**5**), and vallesiachotamine (**23**) were weakly active against acetylcholinesterase.[19] Moreover, turbinatine (**24**) (Figure 5),[20] a corynanthean-type indole alkaloid, with a similar structure with geissoschizine methyl ether (**6**), inhibited acetylcholinesterase with an IC_{50} of 0.99 μg mL^{-1}.[19]

The efficacy of hirsutine (**4**) on neuroinflammation control was also explored. It was shown that hirsutine (**4**) reduces the production of several neurotoxic factors in activated microglial cells and possesses neuroprotective activity in a model of inflammation-induced neurotoxicity. In particular, in organotypic hippocampal slice cultures, hirsutine (**4**) blocked lipopolysaccharide-related hippocampal cell death and production of nitric oxide, prostaglandin E_2 and interleukin-1β.[21]

In 2014, a new alkaloid, 4-geissoschizine *N*-oxide methyl (**25**) (Figure 5), was isolated from the hook-bearing branch of *Uncaria rhynchophylla*. The neuroprotective effects of this compound,

and 5 other alkaloids [hirsutine (**4**), hirsuteine (**5**), 4-hirsuteine *N*-oxide (**26**), geissoschizine methyl ether (**6**), 3-epi-geissoschizine methyl ether (**22**)] were evaluated against 3mM glutamate-induced HT22 cell death. The 4-geissoschizine *N*-oxide methyl ether (**25**) and 4-hirsuteine *N*-oxide (2**6**) compounds revealed to be weak neuroprotective agents. On the other hand, the remaining compounds showed potent neuroprotective effects against glutamate induced HT22 cell death.[22]

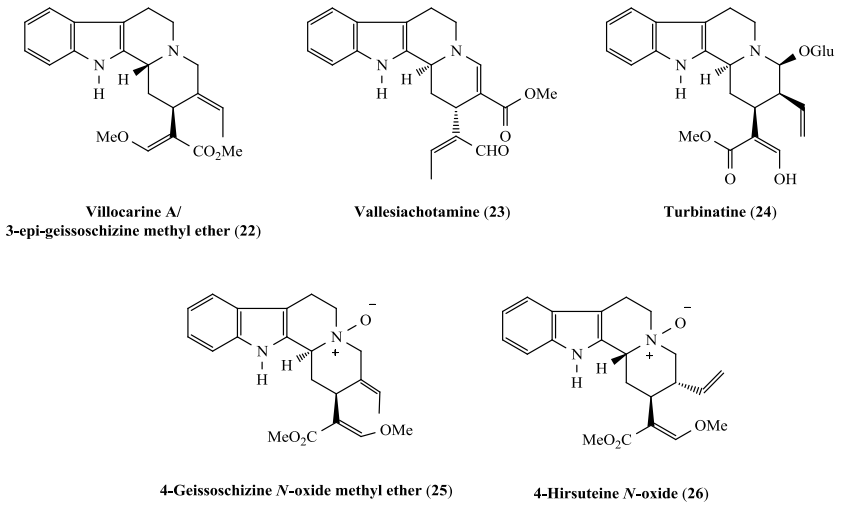


Figure 5 – Chemical structure of 3-epi-geissoschizine methyl ether (**22**), vallesiachotamine (**23**), turbinatine (**24**), 4-geissoschizine *N*-oxide methyl ether (**25**), 4-hirsuteine *N*-oxide (**26**).

Hirsutine (**4**) was also identified as an anti-metastatic by targeting nuclear factor-kB activation from a screening of 56 natural product derivatives. In particular, hirsutine (**4**) strongly suppressed NF-kB activity in murine 4T1 breast cancer cells, reducing the metastatic potential of 4T1 cells. Moreover, hirsutine (**4**) reduced the *in vivo* lung metastatic potential of 4T1 cells. These results indicate that hirsutine (**4**) can be an attractive lead compound for reducing the metastasis potential of cancer cells.[23]

1.5 Arboricinine and arboricine

Arboricinine (**27**) and arboricine (**28**) (Figure 6) were isolated from stem-bark extract of the *Malayan* Kopsia *arborea*. These indoloquinolizidines revealed moderate cytotoxicity against KB/VJ300 cell lines, a vincristine-resistant human oral epidermoid carcinoma, with IC_{50} values around 30 µM.[24]

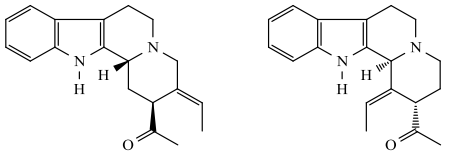


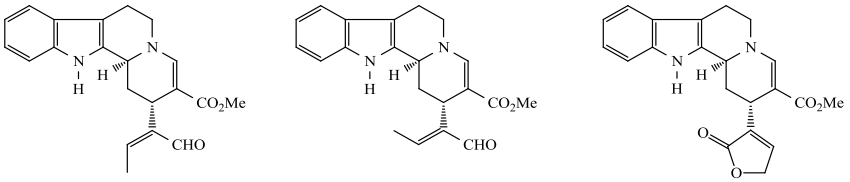
Figure 6 – Chemical structure of arboricinine (**27**) and arboricine (**28**).

1.6 Vallesiachotamine

In 1981, *Z*-vallesiachotamine (**29**) (Figure 7), a monoterpene indole alkaloid, isolated from *Rhaza stricta*, was reported to have anticancer properties on a carcinoma cell line.[25] Latter, the *in vitro* antiproliferative activity of vallesiachotamine isolated from the leaves of *Policourea rigida* was investigated on human melanoma cells. The compound presented an IC_{50} value of 14.7 µM in SK-MEL-37 melanoma cells (two times more active than doxorubicin), induced accumulation of melanoma cells in the G0/G1 growth phase and increased the proportion of sub-G1 hypodiploid cells (at 11 µM and 22 µM). Moreover, at 50 µM, vallesiachotamine caused extensive cytotoxicity and necrosis.[26]

Vallesiachotamine was also tested for therapeutic targets involved in neurodegeneration. In particular, extracts obtained from *Psychotria laciniata* containing *Z*-vallesiachotamine (**29**), and *E*-vallesiachotamine (**30**) (Figure 7) as major compounds, showed high potency against monoamine oxidase A (MAO-A) and only moderate potency against monoamine oxidase B (MAO-B).[27] Moreover, *Z*-vallesiachotamine (**29**), *E*-vallesiachotamine (**30**), and vallesiachotamine lactone (**31**) (Figure 7) were shown to inhibit butyrylcholinesterase (BChE) and MAO-A with IC_{50} values ranging from 7.08 to 14 µM for BChE inhibition and from 0.85 to 2.14 µM for MAO-A inhibition.[28] Finally, using a computational structure-based approach, it was investigated if these three alkaloids bind sirtuin 1 and sirtuin 2. The compounds

demonstrated a SIRT1 inhibitory profile comparable to that of sirtinol (nonspecific SIRT inhibitor). Opposite to *Z*-vallesiachotamine (**29**) and *E*-vallesiachotamine (**30**), vallesiachotamine lactone (**31**) demonstrated no apparent toxicity on Hek 293 and on rat astrocyte primary cells.[29] These findings are in line with the study of *Z*-vallesiachotamine (**29**) on human melanoma cells.[26]



***Z*-Vallesiachotamine (29)** **E-Vallesiachotamine (30)** **Vallesiachotamine lactone (31)**

Figure 7 – Chemical structure of *Z*-vallesiachotamine (**29**), *E*-vallesiachotamine (**30**), and vallesiachotamine lactone (**31**).

1.7 Mitragynine and derivatives

In 2005, Matsumoto *et al*. have studied the effect of mitragynine (**32**) (Figure 8), a major indole-alkaloid founded in Thai medicinal herb *Mitragyna speciosa*, on neurogenic contraction of smooth muscle. The results demonstrated that mitragynine (**32**) inhibited the contraction of guinea-pig vas deferens produced by electrical transmural stimulation. More precisely, mitragynine (**32**) was found to block T- and L-type Ca^{2+} channel currents and reduced KCl-induced Ca^{2+} influx in N1E-115 neuroblastoma cells.[30]

One year later, 7-hydroxyspeciociliatine (**33**) (Figure 8) was isolated, for the first time, from the fruits of *Malaysian Mitragyna speciosa* Korth. The opioid agonistic activity of this alkaloid and 7-hydroxymitragynine (**34**) was investigated in guinea-pig ileum experiments. The results demonstrated that 7-hydroxyspeciociliatine (**33**) had a weak stimulatory effect on μ-opioid receptors,[31] while 7-hydroxymitragynine (**34**) had moderate opioid agonist activity, as reported previously.[32, 33]

Also, 9-demethyl analogue of mitragynine, 9-hydroxycorynantheidine (**35**) (Figure 8), synthesized from mitragynine, was reported as a partial agonist of opioid receptors. The

receptor binding assays revealed that 9-hydroxycorynantheidine (**35**) has affinity for three opioid receptor types. In particular, 9-hydroxycorynantheidine (**35**) (Figure 8) presented pK_i values of 7.92, 4.51 and 5.53, for μ-, δ- and κ-opioid receptors, respectively. The results show that 9-hydroxycorynantheidine (**35**) has a high affinity and selectivity for μ-opioid receptors.[34]

Also, recently Shamima *et al*. investigated the action of mitragynine (**32**) as antinociceptive agent. The goal of this study was to understand if mitragynine (**32**) acts on Cannabinoid receptor type 1. The results demonstrated that mitragynine (**32**) doesn't act on Cannabinoid receptor type 1 but through activation of opioid receptor system, more precisely on μ- and δ-opioid receptors.[35]

More recently, two derivatives of 7-hydroxymitragynine (compounds **36** and **37**, Figure 8), were synthesized in order to develop dual-acting μ- and δ-opioid agonists. Compound **37** was shown to be more potent, *in vitro* and *in vivo*, than compound **36** and 7-hydroxymitragynine (**34**). Compound **37** exhibited a high affinity for μ- and δ-opioid receptors, with K_i values of 2.1 and 7.0 nM, respectively, while compound **36** reveled K_i values of 6.4 nM (μ-opioid receptor) and 16.0 nM (δ-opioid receptor). Moreover, the antinociceptive effect of compound **37** was approximately 240 times more potent than that of morphine in a mouse tail-flick test and, for this reason compound **37** could be used as potential therapeutic agent for treating neuropathic pain.[36]

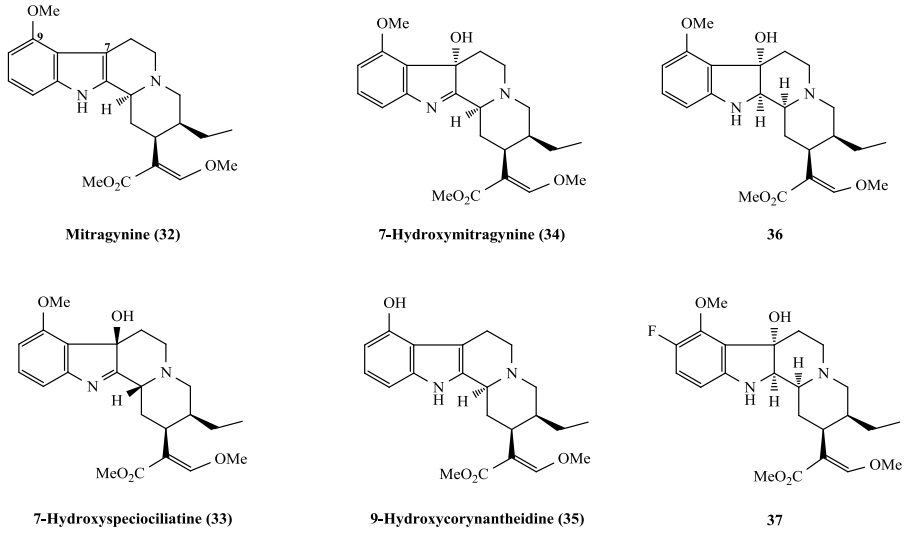


Figure 8 – Chemical structure of mitragynine (**32**), 7-hydroxyspeciociliatine (**33**), 7-hydroxymitragynine (**34**), 9-hydroxycorynantheidine (**35**) and indoloquinolizidines **36**-**37**.

1.8 Non-natural indolo[2,3-*a*]quinolizidine derivatives

Takanawa *et al.*, reported the synthesis of 10 mitragynine derivatives in order to perform a structure-activity relationship study. The rational was based on the fact that mitragynine (**32**) has analgesic activity. The effects of corynantheidine (**14**) (Figure 3), mitragynine (**32**) (Figure 8), synthetic derivatives **35**, **38**-**46**, and speciociliatine (**47**) (Figure 9) were evaluated on opioid receptors, using electrically stimulated contraction in isolated guinea pig ileum. Seven compounds (compounds **32**, **35**, **42**-**43**, and **45**-**47**) revealed an interesting potency against opioid receptors (Graph 1).

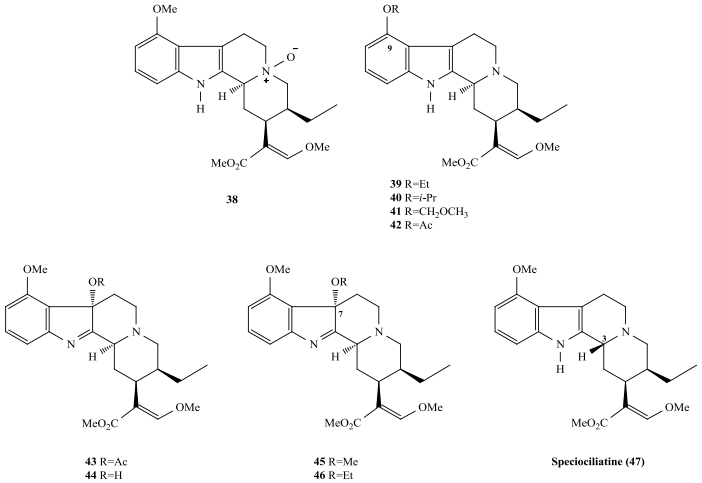
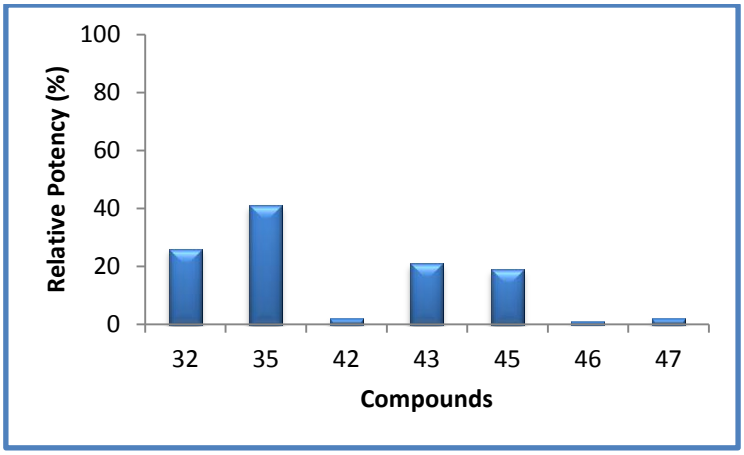


Figure 9 – Chemical structure of mitragynine derivatives **38**-**46** and speciociliatine (**47**).

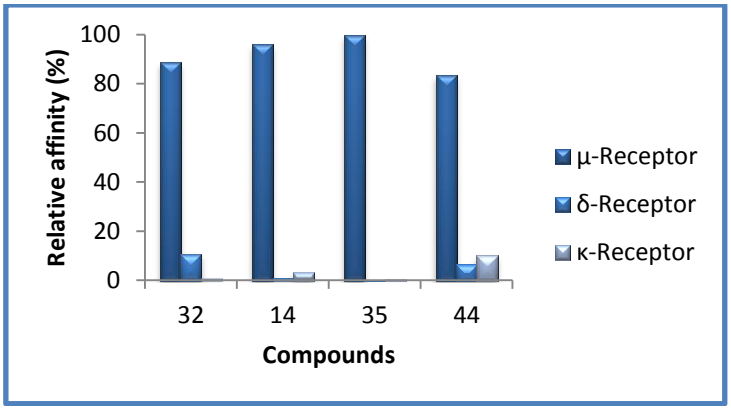
The potency of mitragynine (**32**) revealed to be one-fourth of morphine (standard compound that has a relative potency of 100%). The 9-demethoxy analogue of mitragynine, i.e. corynantheidine (**14**), did not show any opioid agonistic activity. However, analysis of its effects on twitch contraction inhibited by morphine, atropine, and verapamil in electrically stimulated guinea pig ileum, showed that corynantheidine (**14**) inhibits the effect of morphine via functional antagonism of opioid receptors. On the other hand, 9-hydroxycorynantheidine (**35**) inhibited electrically induced twitch contraction in guinea pig ileum and revealed relative potency higher than mitragynine (**32**). The introduction of the acetoxy group on the indole ring (compound **42**), led to marked reduction in both intrinsic activity and potency as compared with those of mitragynine (**32**) (Graph 1). Mitragynine derivative **41** did not show any opioid agonist activity, which indicates that the functional groups at the C9 position are very important for the activity of these compounds.

Speciociliatine (**47**), a C-3 stereoisomer of mitragynine (**32**), could be found as a minor constituent on *Mitragyna speciosa*. This compound reveled to be 14-fold weaker than mitragynine (**32**). The introduction of a methoxy or an ethoxy group at the C-7 position, respectively, compounds **45** and **46**, led to a dramatic reduction in potency for opioid receptors and, which indicates that the hydrogen atom at the C-7 position in mitragynine (**32**) has an important role for the activity. Finally, compound **44**, showed a relative potency 13- and 46-fold higher for opioid receptors than those of derivative **39** and mitragynine (**32**), respectively. Compound **44** demonstrated affinity also for δ- and κ-receptors.

The relative affinities of compounds **14**, **32**, **35** and **44**, for the three opioid receptors (μ, δ and κ), were determined using receptor binding assay (Graph 2) using morphine as comparison standard. The results show that these compounds have relatively high selectivity for μ-receptors. Moreover, mitragynine (**32**) revealed some affinity for δ-receptor, while compound **44** demonstrated affinity for both δ- and κ-receptors.[37]



Graph 1 - Relative potency of seven compounds with interesting activities for opioid receptor.



Graph 2 - Relative affinity of indoloquinolizidines **14**, **32**, **35**, **44** for μ, δ, and κ receptor types.

Waldmann *et al.* evaluated a collection of approximately 11000 natural-product derived and inspired compounds as apoptosis inducers. From that library, seven indoloquinolizidine derivatives **48**-**54** (Figure 10) were considered potential apoptosis inducers in three human tumor cell lines, presenting values of IC_{50} around 2 μmol L^{-1} in HeLa (cervix), MCF-7 (breast) cell lines and in HepG2 (liver, with slightly lower efficiency) cell lines.[38]

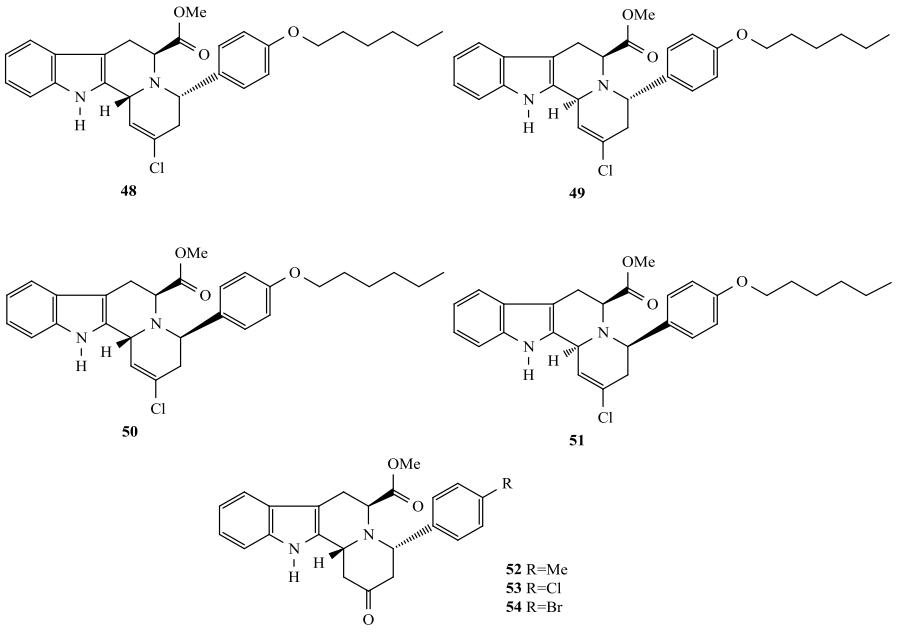


Figure 10 - Chemical structure of indoloquinolizidine derivatives **48**-**54**.

A series of 20 indolo[2,3-*a*]quinolizidine-peptide hybrids was synthesized and evaluated for D_1 dopamine receptors (D_1R) and D_2 dopamine receptors (D_2R). Two diastereomeric indolo[2,3-*a*]quinolizidines were coupled with tripeptides in order to enhance the affinity of the indoloquinolizidine moiety for the dopamine receptors. Several compounds presented higher affinities than dopamine. Furthermore, it was shown that *trans* (C-3 and C-12b) indoloquinolizidine derivatives had stronger effect in the interaction with the receptors than *cis* indoloquinolizidine derivatives (Figure 11).[39] The functional characterization of the hybrid compound **61** by means of kinetic assays and competition experiments in radioligand binding, demonstrated that indoloquinolizidine-peptide **61** behaves as an orthosteric ligand of dopamine D_2, D_3, D_4 and D_5 receptors, but as a negative allosteric modulator of agonist and antagonist binding to striatal dopamine D_1 receptors. In addition, compound **61** decreased receptor potency, while preserving agonist-induced maximal cAMP production.[40]

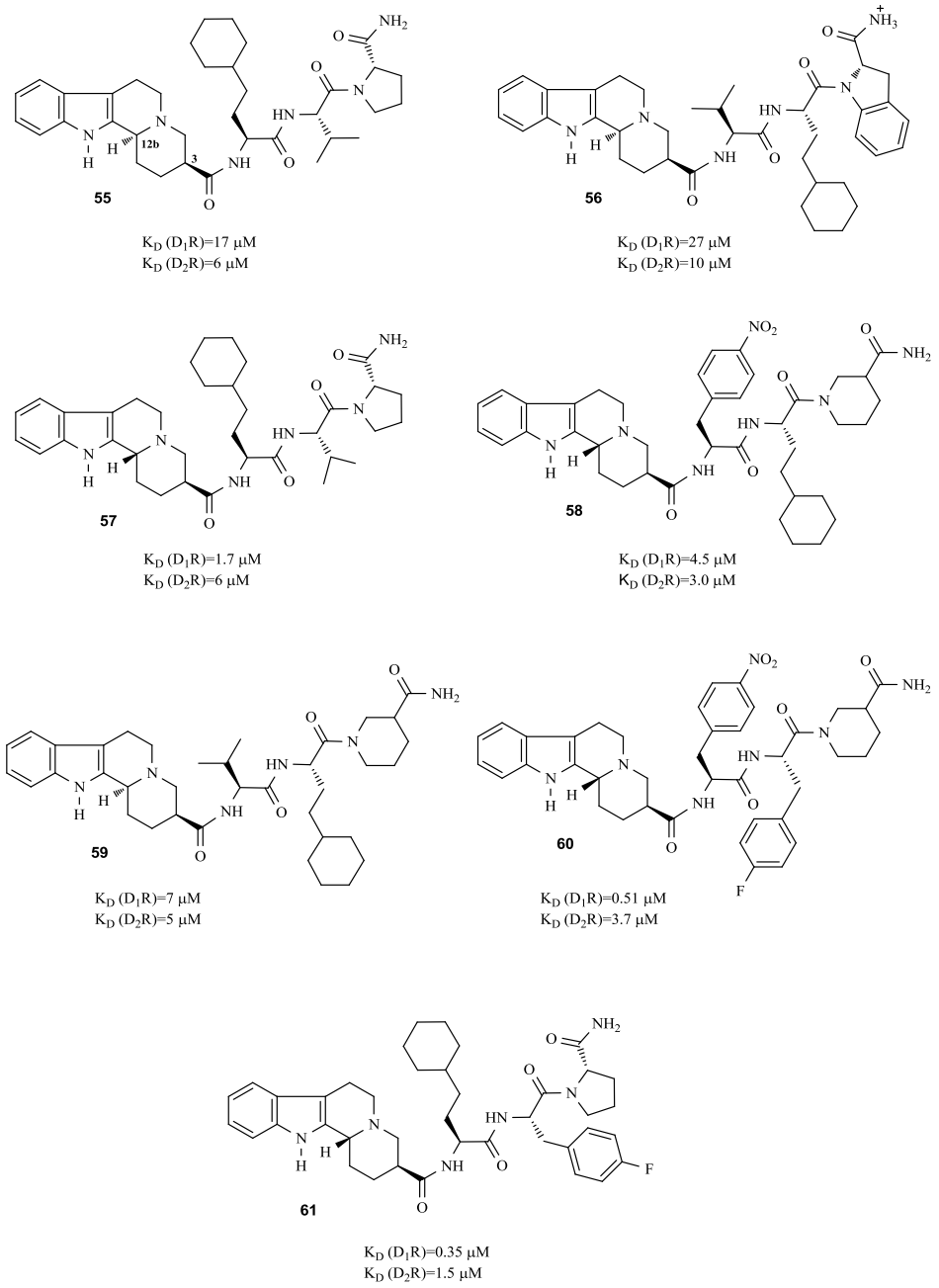


Figure 11 – Most active indoloquinolizidine-peptide hybrids.

In 2015, a novel indoloquinolizidine derivative **62** (Figure 12) was synthesized and evaluated as an anti-hypertension agent. The compound showed remarkable antihypertensive and dilating effect both in vitro and in vivo. Moreover, it was shown that compound **62** induced vasodilatation by both endothelium-dependent and-independent manners, blocked Ca^{2+} influx through L-type Ca^{2+} channels and inhibited intracellular Ca^{2+} release while not affecting K^+ channel.[41]

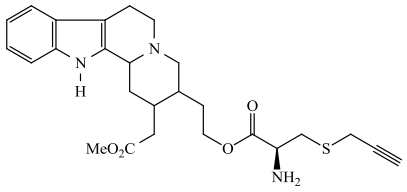


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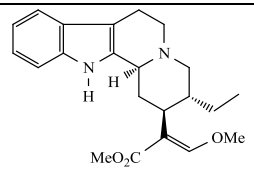
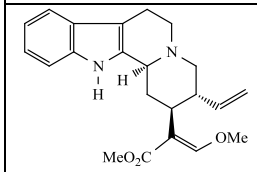
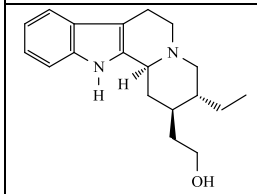
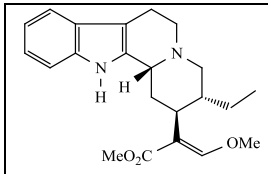
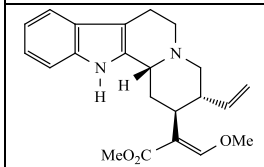
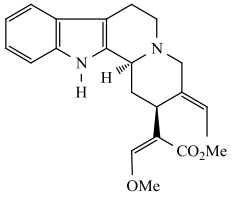
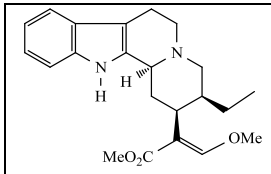
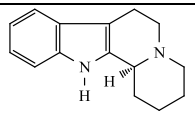
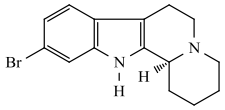
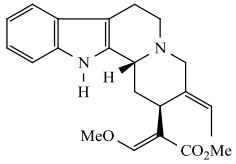
Figure 12 – Chemical structure of indoloquinolizidine derivative **62**.

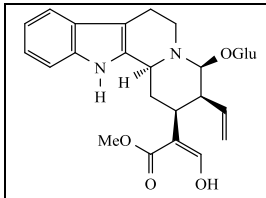
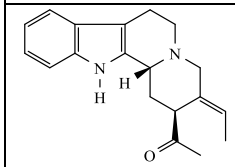
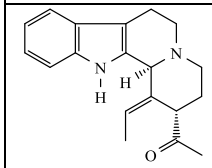
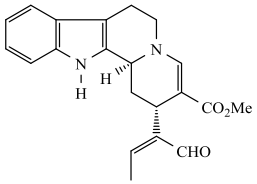
In tables 1 and 2 the reader can find a summary of the main biological properties described to date for Indolo[2,3-*a*]quinolizidines and derivatives.

Table 1 – Biological properties of Indolo[2,3-a]quinolizidines and derivatives.

Compound	Species isolated from	Effects	Refs
 **Dihydrocorynantheine (1)**	*UncariaCallophylla* *Corynanthepachyceras*	- lowers the arterial pressure in both anaesthetized and conscious normotensive rats - inhibition of multiple ion channels - active for Leishmania	[8-10]
 **Corynantheine (2)**	*Corynanthepachyceras*	- active for Leishmania	[10]
 **Dihydrocorynantheol (3)**	*Esenbeckialeiocarpa*	- anti-inflammatory effects	[11]

 **Hirsutine (4)**	*Uncaria rhynchophylla*	- antihypertensive and antiarrhythmic activities - reduces the production of several neurotoxic factors in activated microglial cells and possesses neuroprotective activity in a model of inflammation-induced neurotoxicity - potent neuroprotective effects against glutamate induced HT22 cell death anti-metastatic	[9, 13-14, 21-23]
 **Hirsuteine (5)**		- potent neuroprotective effects against glutamate induced HT22 cell death	[22]
 **Geissoschizine methyl ether (6)**	*Uncariae Ramulus et Uncus*	- Active in norepinephrine-induced vasocontractive response partial agonist at the serotonin 5-HT1A receptor, a partial agonist/antagonist at the dopamine D2L receptor and an antagonist at the serotonin 5-HT2A, 5-HT2C and 5-HT7 receptors - potential acetylcholinesterase inhibitor - potent neuroprotective effects against glutamate induced HT22 cell death	[15, 18-19, 22]

 **Corynantheidine (14)**	*Corynanthepachyceras*	- active for Leishmania - affinity for opioid receptors	[10, 37]
 **Desbromoarborescidine A (7)**	*Dracontomelum mangiferum*	- blocking of Alpha-1 and Alpha-2 adrenoceptors	[5]
 **Arborescidine A (13)**	*Pseudodistoma arborescens*	- IC_{50} value of 34.5 µM for leukemia	[6-7]
 **Villocarine A/** **3-epi-geissoschizine methyl ether (22)**	*Uncaria villosa*	- potent vasorelaxant effects at 30 µM in rat aortic ring assays - potent neuroprotective effects against glutamate induced HT22 cell death	[16-17, 22]

 **Turbinatine (24)**	*Uncaria rhynchophylla*	- acetylcholinesterase inhibitor	[19]
 **Arboricinine (27)**	*Malayan Kopsiaarborea*	- moderate cytotoxicity against KB/VJ300 cell lines (IC_{50} values around 30 µM)	[24]
 **Arboricine (28)**	*Malayan Kopsiaarborea*	- moderate cytotoxicity against KB/VJ300 cell lines (IC_{50} values around 30 µM)	[24]
 ***Z*-Vallesiachotamine (29)**	*Rhazastricta* *Policourearigida*	- anticancer properties on a carcinoma cell line - inhibit butyrylcholinesterase (BChE) Mixture of isomers *Z* and *E*: - IC_{50} value of 14.7 µM in SK-MEL-37 melanoma cells - high potency againstmonoamine oxidase A (MAO-A)	[25, 28] [26-27-28]

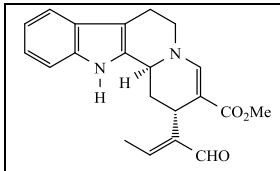
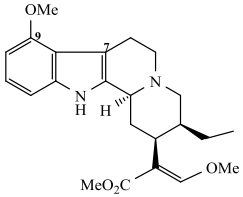
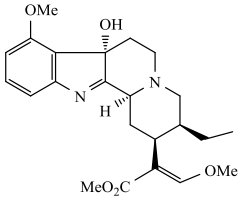
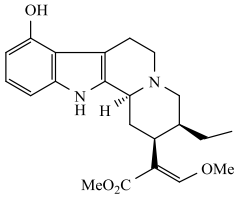
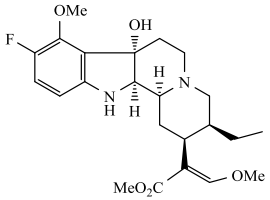
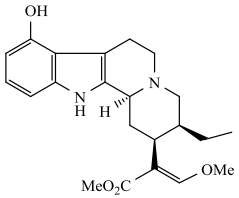
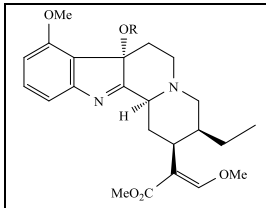
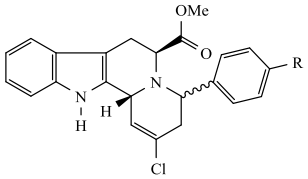
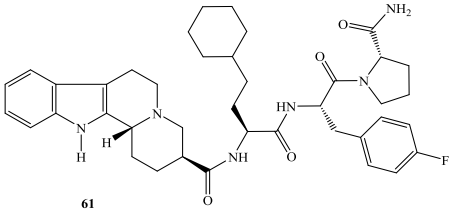
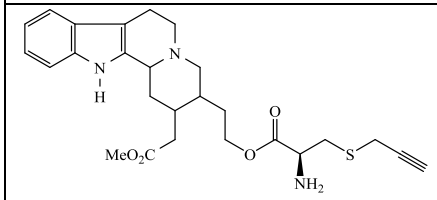
 ***E*-Vallesiachotamine (30)**	*Psychotrialaciniata*	- inhibit butyrylcholinesterase (BChE)	[28]
 **Mitragynine (32)**	*Mitragynaspeciosa*	- analgesic activity in N1E-115 neuroblastoma cells	[30, 37]
 **7-Hydroxymitragynine (34)**	*Mitragynaspeciosa*	- moderate opioid agonist activity	[32, 33]

Table 2 – Biological properties of Indolo[2,3-*a*]quinolizidine derivatives.

Compound	Effects	Refs
 **9-Hydroxycorynantheidine (35)**	- partial agonist of opioid receptors, high affinity and selectivity for μ-opioid receptors	[34]
 **37**	- high affinity for μ- and δ-opioid receptors	[36]
 **9-Hydroxycorynantheidine (35)**	- affinity for opioid receptors	[37]

 **43-45**	- affinity for opioid receptors	[37]
 **48-51**	- potential apoptosis inducers in three human tumor cell lines (HeLa, MCF-7 and HepG2 cell lines)	[38]
 **61**	- orthosteric ligand of dopamine D_2, D_3, D_4 and D_5 receptors; negative allosteric modulator of agonist and antagonist binding to striatal dopamine D_1 receptors.	[39-40]
 **62**	- blocked Ca^{2+} influx through L-type Ca^{2+} channels and inhibited intracellular Ca^{2+} release	[41]

2 Synthesis of indolo[2,3-*a*]quinolizidine alkaloids

The aim of this part of the review is to present the state of the art of the different strategies developed in enantioselective indolo[2,3-*a*]quinolizidine alkaloid synthesis, illustrated with representative examples. It is divided in three sections, namely, use of chiral pool resources, non-catalytic cascade/tandem sequences; and asymmetric metalcatalysis/organocatalysis approaches. From a synthetic point of view, construction of the fused-ring system of the indolo[2,3-*a*]quinolizidine alkaloids with control of the relative and absolute stereochemistry of the quinolizidine core represents a significant challenge that makes these natural products attractive synthetic targets. Traditionally, the majority of reported strategies for the asymmetric total synthesis of indolo[2,3-*a*]quinolizidine alkaloids have required a multistep synthesis that relies on starting materials from the chiral pool. These strategies often include several functional group transformations and tedious protection/deprotection steps, often providing a low overall yield of the target alkaloid. In the last decades cascade reactions have been applied in indoloquinolozidine alkaloids synthesis. Although extremely demanding, the well stablished advantages of these reactions include atom economy, as well as economies of time, labor, resources management, and waste generation. In this section we have include a significant racemic synthesis. Most recently there have been a few reports of efficient syntheses of optically active indoloquinolizidine natural products based on asymmetric catalysis. This approach is highly efficient and productive. However, the majority of the developed synthetic strategies is target-specific with respect to the relative configuration of the quinolizidine stereocenters and only allows for selective formation of one specific epimer of the alkaloid.

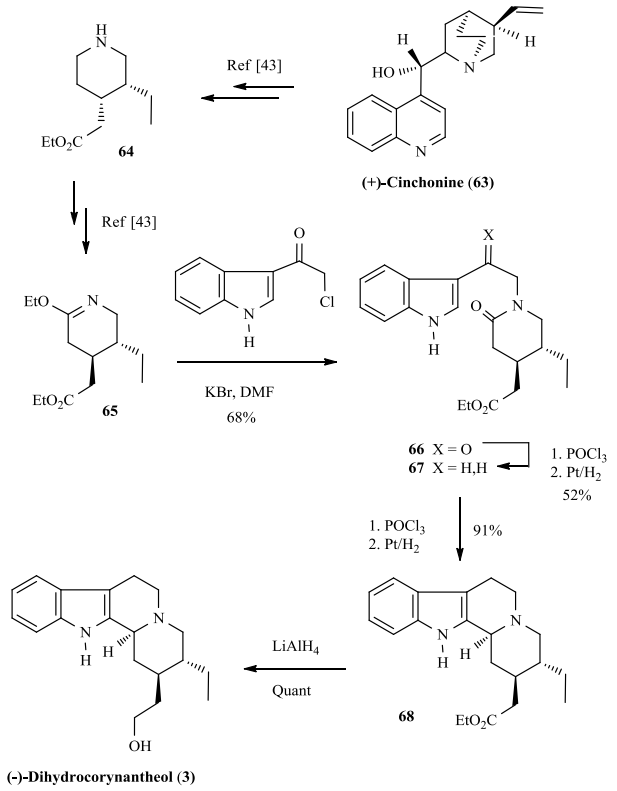
2.1. Use of chiral pool resources

Chiral pool synthesis makes use of chiral natural products by incorporating part of them into the target structure. As either enantiomer of the desired final product can be potentially generated, compounds from the chiral pool are extremely valuable and versatile in asymmetric synthesis. For many decades, it was the only source of enantiomerically pure compounds, but nowadays

many of the most effective chiral agents described in the literature have been designed and synthesized by organic chemists.

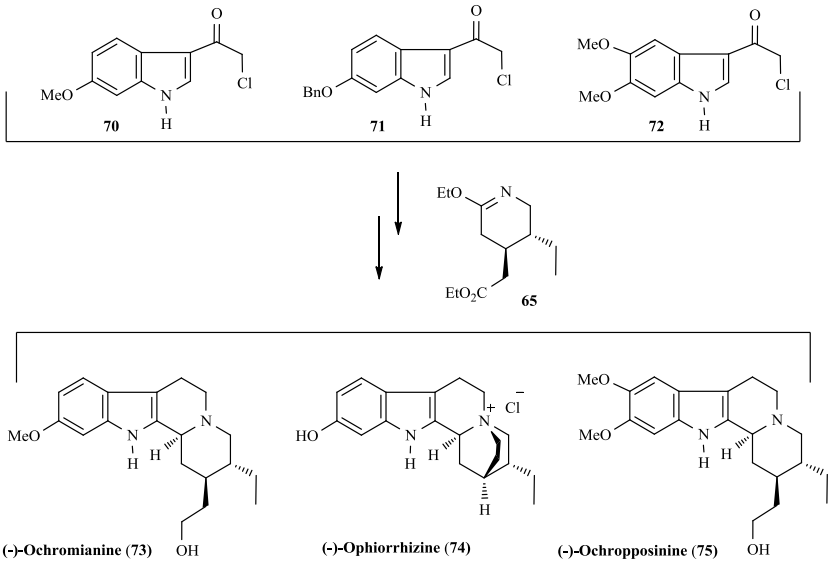
2.1.1. Lactim ether route: Enantioselective synthesis of (–)-dihydrocorynantheol (3)

Prof. Tozo Fujii has published several papers on fused quinolizidine ring systems, including the total synthesis of (–)-dihydrocorynantheine (**1**) in 1991.[42] The "lactim ether route" requires the coupling of the 3-(chloroacetyl)indole with the lactim ether **65**, prepared from cincholoipon ethyl ester (**64**, obtainable from commercially available (+)-cinchonine (**63**) by the classical degradation procedure[43]). Subsequent treatment of the resulting keto derivative **66** with $POC1_3$ afforded the corresponding oxazolium chloride, which was then reduced by catalytic hydrogenation to furnish the lactam **67**. The conversion into the tetracyclic ester **68** was carried out in 91% overall yield by means of Bischler-Napieralski cyclization followed by catalytic hydrogenation. Final $LiAlH_4$-reduction of **68** afforded (–)-dihydrocorynantheol (**3**) in quantitative yield (Scheme 1).



Scheme 1 – Enantioselective synthesis of (–)-dihydrocorynantheol (**3**).

The usefulness of the "lactim ether route" in the asymmetric synthesis of *Corynanthe*-type indoloquinolizidine alkaloids is demonstrated by the application of this methodology to the synthesis of (–)-ochromianine (**73**), (–)-ophiorrhizine (**74**), and (–)-ochropposinine (**75**), employing the lactim ether **65** as starting material (Scheme 2).



Scheme 2 – Enantioselective synthesis of of (–)-ochromianine (**73**), (–)-ophiorrhizine (**74**), and (–)-ochropposinine (**75**).

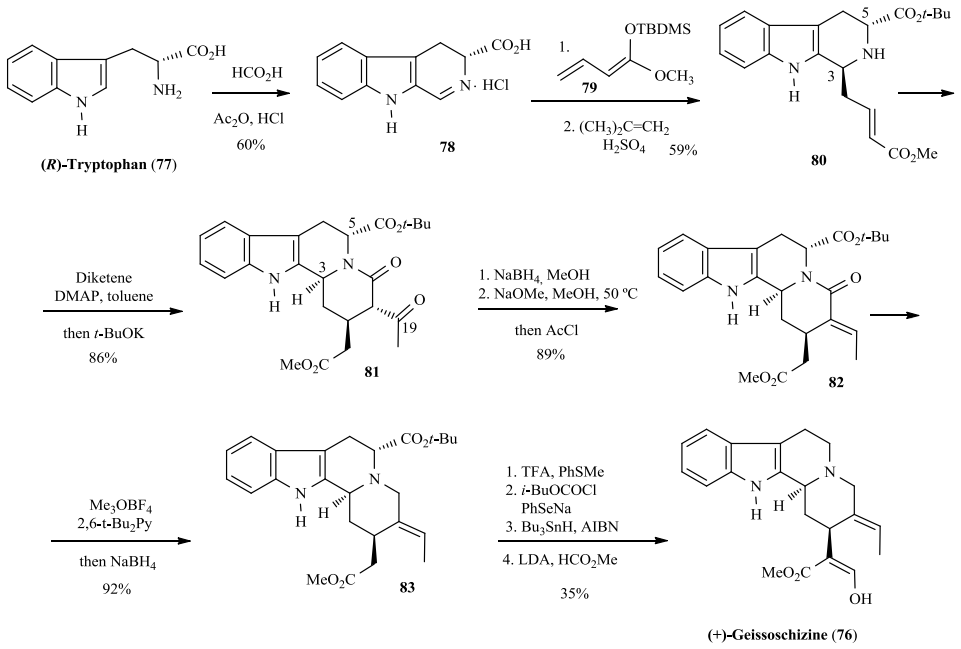
2.1.2. Stereoselective Mannich reaction from a (*R*)-tryptophan derivative: Enantioselective synthesis of (+)-geissoschizine (76)

A concise synthesis of (+)-geissoschizine (**76**) (Scheme 3), a biosynthetic precursor of a variety of monoterpenoid indole alkaloids,[1] from (*R*)-tryptophan was performed by Stephen F. Martin in 2003.[44]

The synthesis started with a vinylogous Mannich reaction involving the iminium ion **78**, which was prepared from (*R*)-tryptophan (**77**). The corresponding adduct was then treated directly with isobutylene in the presence of sulfuric acid to give **80** as the only isolable product. The nucleophilic attack of the vinyl ketene **79** on **78** occurred with high diastereoselectivity from the *si* face, establishing the correct absolute stereochemistry at C-3 of geissoschizine. N_b-Acylation

of **80** with diketene furnished an intermediate β-keto amide that underwent facile cyclization via an intramolecular Michael reaction upon addition of potassium *tert*-butoxide to give **81**. This reaction, which presumably proceeded under thermodynamic control to establish the correct relative stereochemistry at C-3 and C-5, completed the assembly of the corynantheane framework.

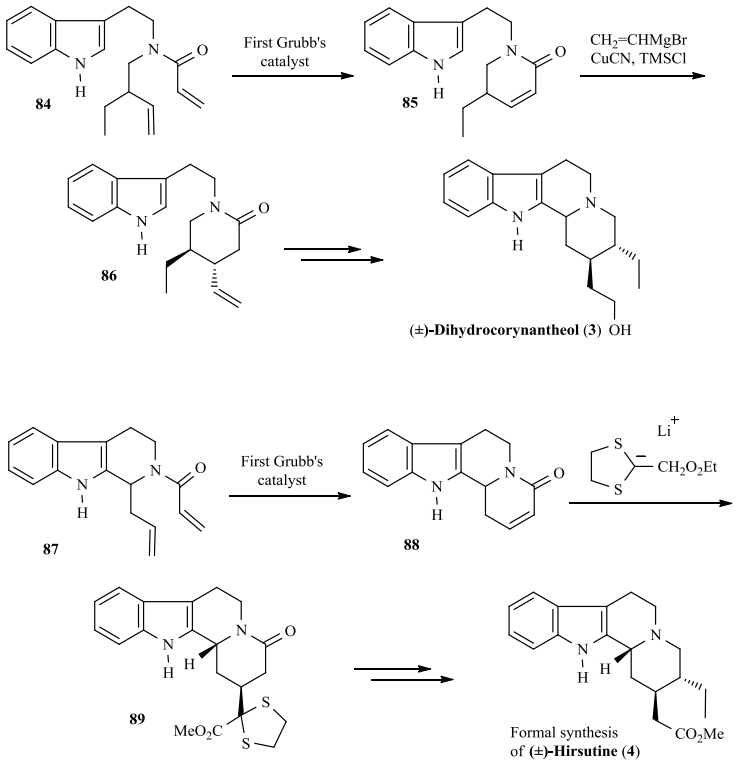
Toward the introduction of the *E*-ethylidene side chain, hydride reduction of the C-19 carbonyl function in **81**, followed by a stereoselective dehydration, led to the stereoselective elimination to give the ester **82**. The subsequent selective reduction of the lactam function according to the Borch protocol[45] furnished **83** in 92% yield. Cleavage of the *tert*-butyl ester moiety was achieved using trifluoroacetic acid in the presence of thioanisole, as an essential cation scavenger. The cleavage of the carboxyl group at C-5 was accomplished by a radical decarbonylation of an acyl selenide intermediate. A final formylation by Winterfeldt's procedure[46] afforded (+)-geissoschizine (**76**) in 48% yield.



Scheme 3 – Enantioselective synthesis of (+)-geissoschizine (**76**).

Three years later, this author described the total synthesis of the corynanthe alkaloid (±)-dihydrocorynantheol (**3**) and the formal synthesis of (±)-hirsutine (**4**).[47] Two different

strategies for assembling the indoloquinolizidine system involving the use of the ring-closing metathesis for the construction of the piperidines D ring, followed by a 1,4-addition to introduce the requisite side chain at C-15, are the key steps of this new racemic approach (Scheme 4).



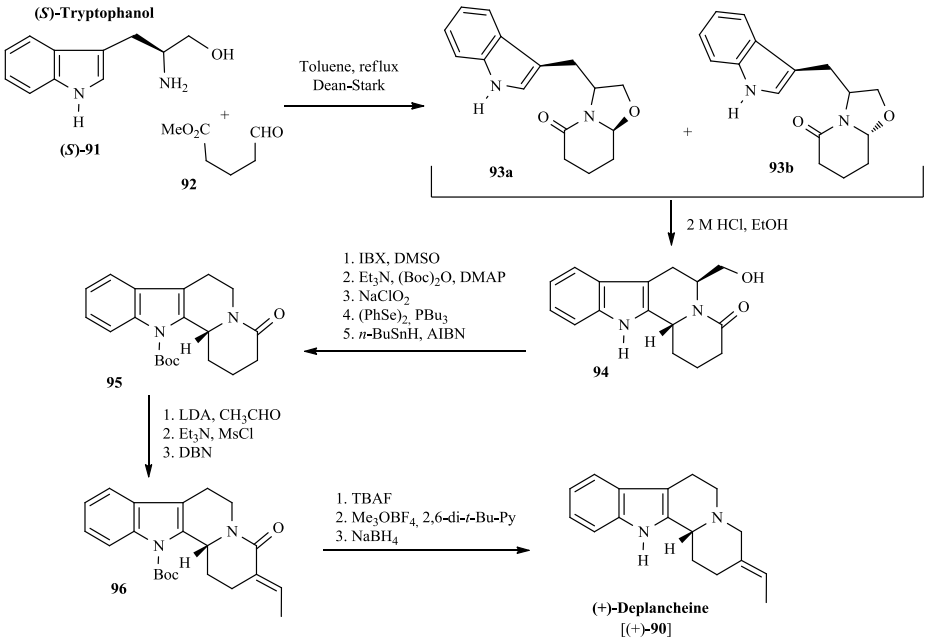
Scheme 4 – Total synthesis of the corynanthe alkaloid (±)-dihydrocorynantheol (**3**) and the formal synthesis of (±)-hirsutine (**4**).

2.1.3. Pictet-Spengler cyclization from a (*S*)-tryptophanol-derived lactam: Asymmetric synthesis of both enantiomers of (+)-deplancheine (90)

(+)-Deplancheine (**90**), an alkaloid with an unusual Corynantheine-type structure, was isolated from the New Caledonian plant *Alstonia deplanchei*. After its structure elucidation,[48] a number of total syntheses were reported for this alkaloid.[49-52]

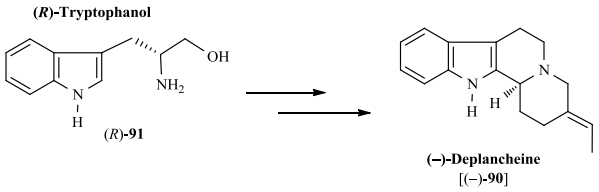
In 2005, Steven M. Allin,[51] reported the asymmetric synthesis of both enantiomers of the indole alkaloid deplancheine (Scheme 5) in an approach involving as the key intermediates the tryptophanol-derived lactams **93**, which are easily accessible from (*S*)-tryptophanol (*S*-**91**) by a cyclocondensation process with the aldehyde-ester **92**. Treatment of the mixture of bicyclic lactams with 2 M HCl in ethanol led to the formation of the indolo[2,3-*a*]quinolizine system by

Pictet-Spengler cyclization, affording **94** as a single compound. The hydroxymethyl chain underwent cleavage by oxidation to a carboxylic acid derivative through the corresponding aldehyde, followed by the generation of an acyl selenide and subsequent tin-mediated deacylation. The construction of the ethylidene moiety was achieved through a three-step procedure involving generation of the lithium enolate from **95** and a subsequent aldol reaction with acetaldehyde, activation of the hydroxyl group by mesylation, and finally, DBN-induced elimination to give the target **96**. Deprotection of the indole nitrogen atom with TBAF, followed by the reduction of the lactam carbonyl group, as described by Martin and co-workers,[53] satisfactorily afforded (+)-deplanchine (**90**).



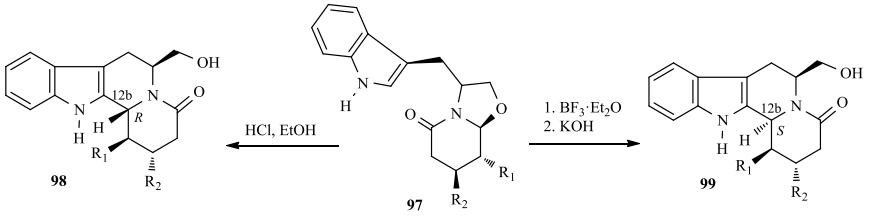
Scheme 5 – Asymmetric synthesis of (+)-deplancheine [(+)-**90**].

To demonstrate the potential synthetic utility of the methodology, Allin and co-workers have also undertaken an asymmetric synthesis of the enantiomer of the natural product using (*R*)-tryptophanol as the starting material (Scheme 6).



Scheme 6 – Access to (–)-deplancheine [(–)-**90**].

The stereochemical outcome of the Pictet Spengler cyclizations of tryptophanol-derived lactams was later thoroughly investigated by Amat-Bosch's research group, describing the stereocontrolled generation of C-12b epimeric indolo[2,3-*a*]quinolizidine derivatives using the appropriated reactions conditions (Scheme 7).[54-56]



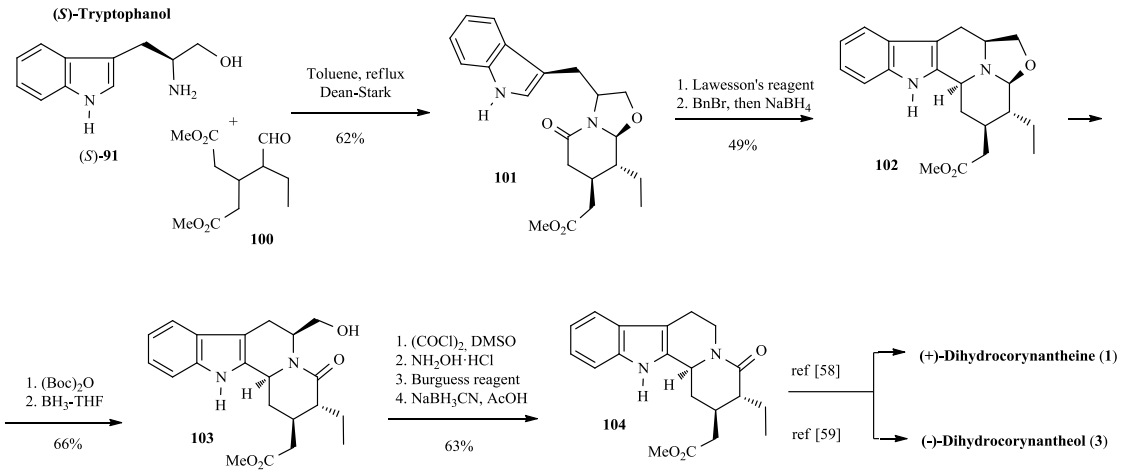
Scheme 7 – Stereocontrolled cyclizations from (*S*)-tryptophanol-derived oxazolopiperidone lactams.

2.1.4. Modified Bischler-Napieralski reaction from a (*S*)-tryptophanol-derived lactam: Enantioselective formal synthesis of (+)-dihydrocorynantheine (**1**) and (–)-dihydrocorynantheol (**3**)

Starting from an appropriately substituted tryptophanol-derived lactam bearing an ethyl substituent and an acetate chain at piperidine 3 and 4-positions,[54] respectively, an enantioselective access to indolo[2,3-*a*]quinolizidine alkaloids (+)-dihydrocorynantheine (**1**) and (–)-dihydrocorynantheol (**3**) (Scheme 8) was developed by the Amat/Bosch research group in 2009.[57] The synthesis requires the cyclization at the indole 2-position to take place regioselectively from the lactam carbonyl moiety, which is accomplished using a modified Bischler-Napieralski reaction.

The initial lactam **101** was prepared in 62% yield by cyclocondensation of (*S*)-tryptophanol (**91**) with racemic *δ*-oxo diester **100** in a process that involves a dynamic kinetic resolution and the

differentiation of diastereotopic ester chains, with generation of three stereogenic centers with a well-defined configuration in a single synthetic step. The regio- and stereoselective cyclization on the lactam carbonyl group, leading to an indolo[2,3-*a*]quinolizidine derivative, took place under modified Bischler-Napieralski conditions. Thus, alkylation of thiolactam (obtained by treatment of lactam **101** with Lawesson's reagent) using benzyl bromide generated a (benzylsulfanyl)-substituted iminium ion, which can be considered as a sulphur analogue of a Bischeler-Napieralski chloro-substituted iminium salt. Sodium borohydride reduction of the iminium intermediate, arising from the subsequent cyclization on the indole 2-position, afforded pentacyclic compound **102** as a single isomer. The indole nitrogen was protected as an *N*-Boc derivative and the oxazolidine ring of the resulting pentacyclic compound was subjected to reductive ring-opening with borane to give **103**. The synthesis of the target alkaloids was completed by cleavage of the hydroxymethyl appendage, which was satisfactorily accomplished by reductive decyanation of an α-amino nitrile intermediate. Finally, deprotection of the indole nitrogen led to the tetracyclic ester **104**,[58, 59] a known synthetic precursor of the alkaloids (+)-dihydrocorynantheine (**1**) and (–)-dihydrocorynantheol (**3**).



Scheme 8 – Enantioselective formal synthesis of (+)-dihydrocorynantheine (**1**) and (–)-dihydrocorynantheol (**3**).

2.1.5. Access to 9-methoxyindole alkaloids: Total synthesis of 9-methoxygeissoschizol (105), 9-methoxy-N_b-methylgeissoschizol (106) and (–)-mitragynine (32).

Cook, in 2007, described an enantiospecific method for the synthesis of (*R*)-4-methoxytryptophan (**107**) via a regiospecific Larock heteroannulation. This was a key reaction for the total synthesis of 9-methoxygeissoschizol (**105**), 9-metroxy-N_b-methylgeissoschizol (**106**), and mitragynine (**32**) using a asymmetric Pictet-Spengler strategy (Scheme 9).[60]

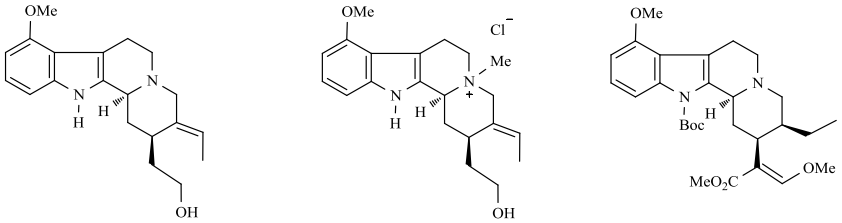
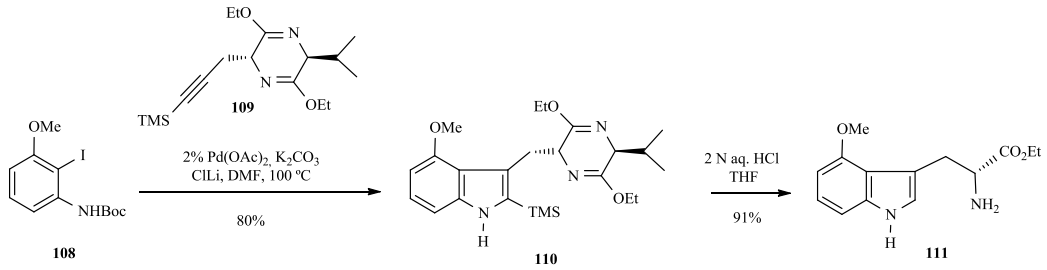


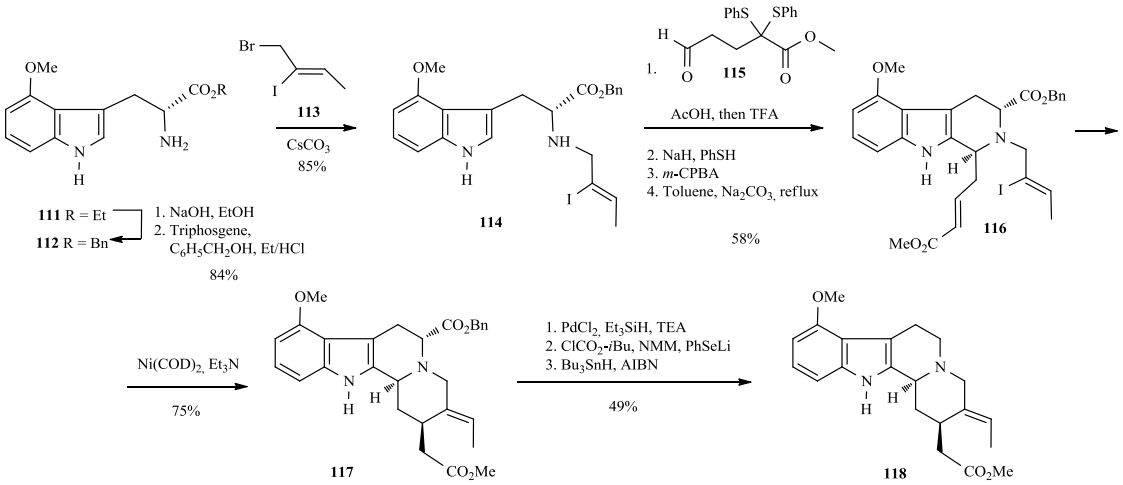
Figure 13 – Chemical structure of 9-methoxygeissoschizol (**105**), 9-methoxy-N_b-methylgeissoschizol (**106**) and (–)-mitragynine (**32**).

Before Cook's synthesis, the preparation of these alkaloids was hampered by the unavailability of 4-methoxytryptophan (**107**), which could only be obtained in high optical purity using the enzymatic kinetic resolution reported by Ley.[61, 62] The Larock heteroannulation,[63, 64] a palladium-catalysed heteroannulation reaction of substituted *o*-iodoanilines with internal alkynes, is a powerful method for the synthesis of substituted indole derivatives and has been satisfactorily employed for the regiospecific synthesis of both 11- and 12-methoxy-substituted indole alkaloids.[65-68] The strength of the Larock process stems from the regioselectivity that can be achieved when a bulky silyl-substituted alkyne is employed as a substrate. The internal alkyne chosen in this example (**109**) can be easily prepared by alkylation of Schöllkopf's auxiliary, which in turn is available from L-valine.[69, 70] The heteroannulation between 2-iodo-3-methoxy-*N*-Boc-aniline **108** and TMS-alkyne **109** gave 4-methoxy-N_a-H indole **110** in 82% yield. The subsequent hydrolysis of the Schöllkopf chiral auxiliary was accomplished by concomitant loss of the silyl group of **110**, providing 4-methoxy-D-tryptophan ethyl ester **111** in a single step in 91% yield (Scheme 9).



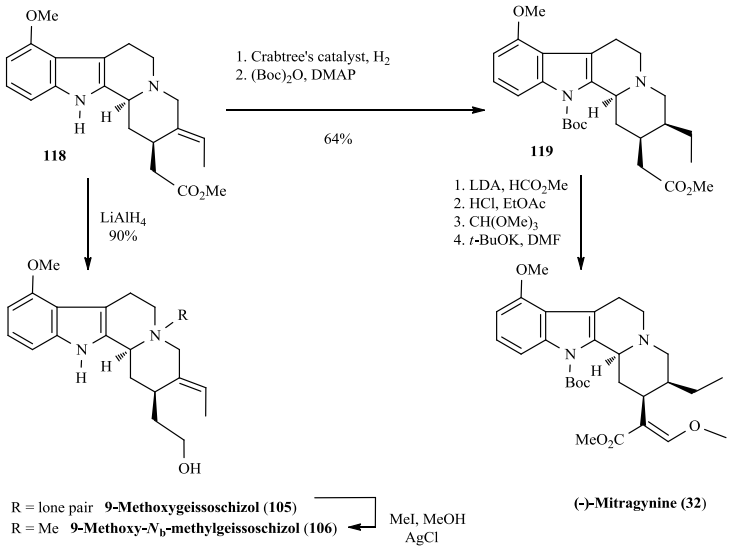
Scheme 9 – Preparation of the 4-methoxy-D-tryptophan ethyl ester **111**.

The monoalkylation of benzyl ester **112**, obtained by hydrolysis and esterification of **111**, with the allylic bromide **113** afforded the secondary amine **114** in 85% yield. The enantioselective construction of the stereocenter at C-3 was achieved by a modified asymmetric Pictet-Spengler reaction between **114** and the aldehyde **115** to furnish the tetrahydro-*β*-carboline system. The α,β-unsaturated ester moiety was generated via standard transformations, including removal of 1 equivalent of thiophenol, followed by an oxidation and sulfoxide elimination sequence, affording compound **116**. The α,β-unsaturated ester **116** was then subjected to the Ni-$(COD)_2$-mediated cyclization to provide the desired *Corynanthe* skeleton **117** in 75% yield. Removal of the benzyl group was achieved when **117** was treated with $PdCl_2$ in the presence of Et_3SiH and TEA, and the corresponding carboxylic acid was converted into tetracyclic ester **118** via the Barton-Crich decarboxylation process (Scheme 10).



Scheme 10 – Synthesis of the key intermediate **118**.

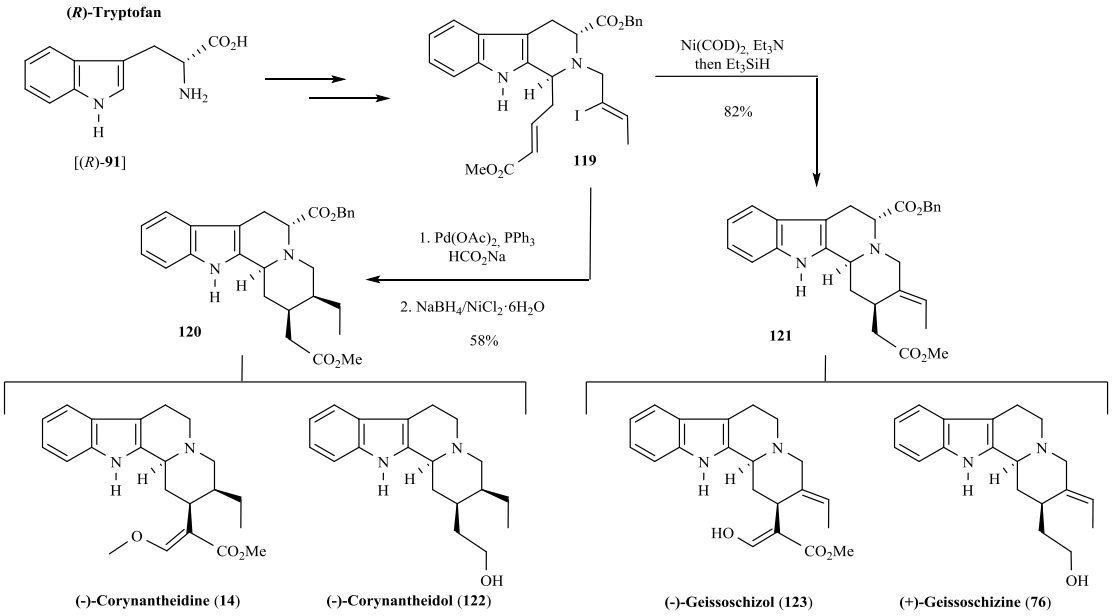
The ester **118** was envisaged as an advanced precursor for the synthesis of three 9-methoxy-substituted indole alkaloids. Thus, the ester carbonyl moiety present in **118** was reduced with $LiAlH_4$ to give 9-methoxygeissoschizol (**105**) in 90% yield, and 9-methoxy-N_b-methylgeissoschizol (**106**) was then synthesized via N_b methylation with methyl iodide, followed by an iodide exchange using AgCl. To prepare mitraginine (**32**), reduction of the olefin bond in **118** was required. The reduction of this double bond with Crabtree's catalyst, followed by treatment with $(Boc)_2O$ in the presence of a catalytic amount of DMAP, provided the Boc derivative **119** in 64% overall yield. The ester **119** was then subjected to formylation and Boc deprotection. The final acetal formation and *t*-BuOK-mediated elimination of MeOH, analogous to the final steps reported by Takayama,[71] provided (–)-mitragynine (**32**) (Scheme 11).



Scheme 11 – Total synthesis of 9-methoxygeissoschizol (**105**), 9-methoxy-N_b-methylgeissoschizol (**106**) and (–)-mitragynine (**32**).

Starting from (*R*)-tryptophan [(*R*)-**91**] as a chiral pool reagent, this methodology allows the enantiospecific total synthesis of (–)-corynantheidine (**14**), (–)-corynantheidol (**122**), (–)-geissoschizol (**123**), and (+)-geissoschizine (**76**) via the common key intermediate **119** (Scheme 12).[72] For the construction of the all-D-ring system present in corynantheidol and corynantheine, an intramolecular Heck coupling of α,β-unsaturated ester **119** and subsequent

$NaBH_4$-reduction in presence of a catalytic amount of $NiCl_2 \cdot 6H_2O$ was performed. In turn, to construct the molecular framework of geissoschizol and geissoschizine from **119**, a stereoselective Michael reaction consecutively using Ni[COD]$_2$-Et_3N and Et_3SiH was employed.



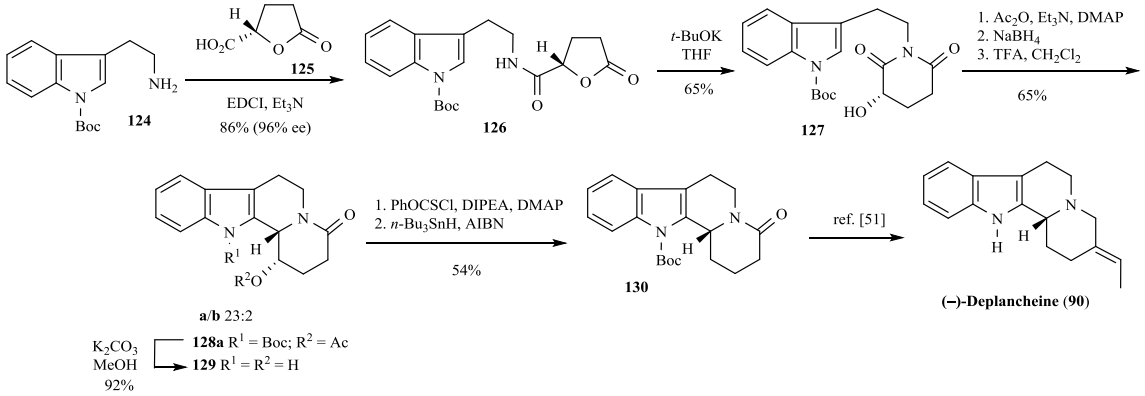
Scheme 12 - Enantiospecific total synthesis of (–)-corynantheidine (**14**), (–)-corynantheidol (**122**), (–)-geissoschizol (**123**), and (+)-geissoschizine (**76**).

2.1.6 Regioselective reduction of an imide carbonyl followed by an intramolecular stereoselective cyclization: Enantioselective formal synthesis of (–)-deplancheine (90).

The enantioselective formal synthesis of (–)-deplancheine (**90**), in a 9-step sequence from glutamic acid in good overall yields and high enantiomeric purity, was recently reported by Argade (Scheme 13).[52]

A carbodiimide-induced coupling reaction of Boc-protected tryptamine **124** with enantiomerically pure (*S*)-tetrahydro-5-oxo-2-furancarboxylic acid (**125**), prepared from (*S*)-glutamic acid furnished amidolactone **126** in 86% yield and 96% enantiomeric purity. Subsequent treatment with *t*-BuOK afforded the base-catalysed rearrangement of **126** to the hydroxyglutarimide **127** in 65% yield. The hydroxyl group in compound **127** was then transformed to the corresponding acetate using acetic anhydride and triethylamine. The

regioselective sodium borohydride reduction of the more reactive imide carbonyl group, followed by chemoselective trifluoroacetic acid-induced intramolecular cyclization, afforded indoloquinolicidine derivative **128** as a 23:2 mixture of isomers in very good yield. The diastereoisomers **128a/b** were quantitatively separated by flash column chromatography and the major isomer (**128a**) was treated with K_2CO_3/MeOH to undergo one-pot deacylation and *N*-Boc-deprotection to provide **129** in 92% yield. Subsequent chemoselective reaction with an excess of phenyl chlorothionoformate in the presence of diisopropylethylamine provided a xanthate intermediate, which was submitted to Barton−McCombie deoxygenation using tributyltin hydride in the presence of AIBN. The resulting lactam **130** was obtained in 54% yield and 94% ee (by HPLC) and it was transformed in (−)-deplancheine in a seven-step synthetic sequence.[51]



Scheme 13 – Enantioselective formal synthesis of (−)-deplancheine.

2.2. Non-catalytic cascade/tandem sequences

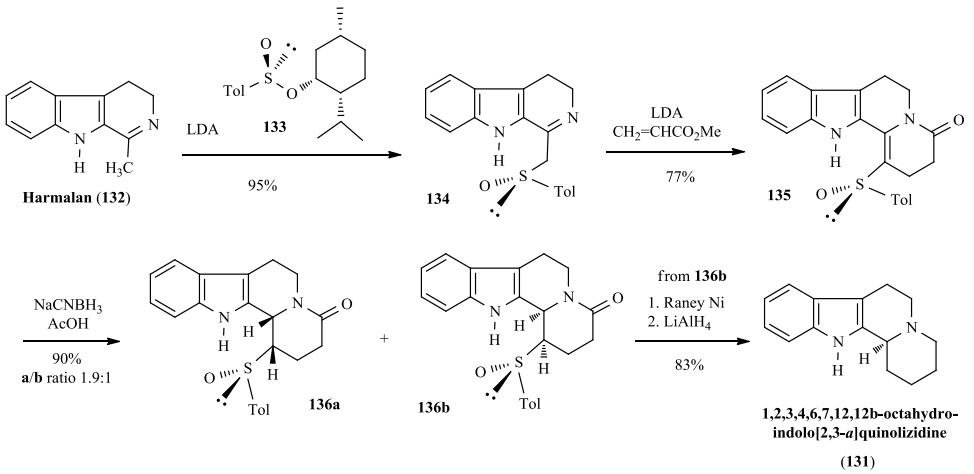
Cascade reactions have received considerable attention within organic chemistry, as reflected by the high number of reviews covering this field.[73-75] A variety of terms, including "cascade", "domino", "tandem" and "sequential", are used in the literature, often apparently interchangeably, although efforts have been made to restore order to this area of reaction terminology.[76] Nevertheless, we shall maintain the term used by each author in the original publication. This type of reaction in structurally complex molecule synthesis has several intrinsic advantages: multiple bond formation, time and cost efficiency, atom economy,

environmental sustainability as well as applicability to diversity-oriented high-throughput synthesis. Since the synthetic effort toward natural products and other interesting compounds usually requires the introduction of several stereogenic centers, the design of cascades to provide specific targeted molecules of structural and stereochemical complexity constitutes a significant intellectual challenge.

2.2.1 Stereoselective addition of a chiral α-sulfinyl ketamine anion to methyl acrylate: Asymmetric synthesis of 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizidine (131).

One of the first examples of enantioselective synthesis of indoloquinolizidine alkaloids using a tandem reaction was reported by Hua in 1991, and it was based on the asymmetric 1,4-addition/ring-closure procedure (Scheme 14).[77]

The chiral sulfinyl ketimine **134** was prepared from harmalan (**132**) and (–)-menthyl *p*-toluenesulfinate (**133**), and subsequently used in the stereoselective conjugate addition with methyl acrylate, followed by *in situ* cyclization. The resulting lactam **135**, formed in 77% yield, was then submitted to $NaCNBH_3$-reduction of the double bond. In contrast with previous results of this author, the reduction in this case was not stereoselective and a 1.9:1 mixture of diastereomers was formed. After separation in column chromatography, desulfuration of **136b** with Raney Nickel, followed by reduction with $LiAlH_4$, afforded 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizidine (**131**).

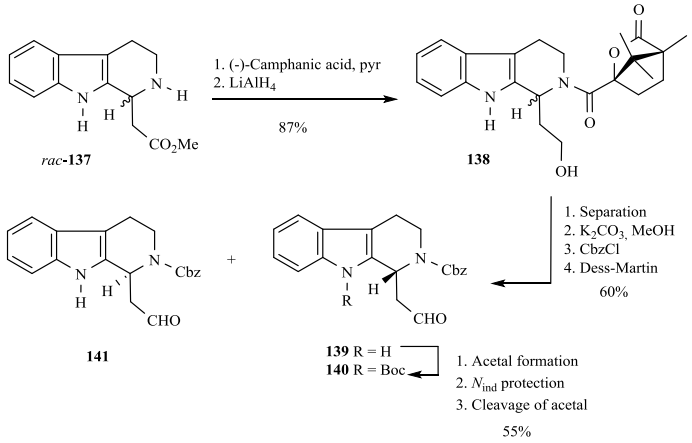


Scheme 14 – Asymmetric synthesis of 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizidine (**131**).

2.2.2 A domino Knoevenagel-hetero-Diels-Alder reaction strategy: Enantioselective total synthesis of (+)-hirsutine (**4**) and (+)-dihydrocorynantheine (**1**)

The enantioselective synthesis of corynanthe indole alkaloids (+)-hirsutine (**4**) and (+)-dihydrocorynantheine (**1**) by a domino Knoevenagel-hetero-Diels-Alder reaction, using enantiomerically pure tetrahydro-β-carboline carbaldehydes as starting material, was described in 1999 by Tietze.[78]

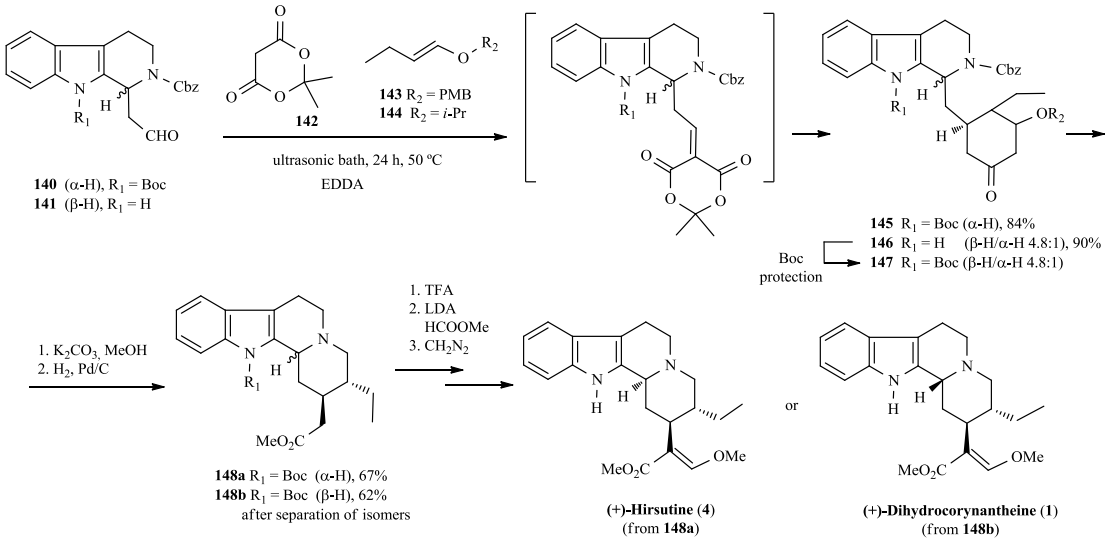
Aldehydes **140** (N_{ind}-Boc) and **141** (N_{ind}-H) were prepared on a large scale by separation of the diastereomeric amides **138**, which were prepared from *rac*-**137** and (–)-camphanic acid as shown in scheme 15.



Scheme 15 – Preparation of chiral non-racemic tetrahydro-β-carboline carbaldehydes **140** and **141**.

Condensation of the aldehyde **140** with Meldrum's acid (**142**) and 4-methoxybenzyl butenyl ether **143**, in an ultrasonic bath and in the presence of ethylenediamine diacetate (EDDA), led to cycloadduct **145** in 84% yield and with an asymmetric induction greater than 20:1. Direct solvolysis without further purification, followed by hydrogenation, afforded the tetracycle **148a** in 67% yield as a single product.

Similarly, the domino Knoevenagel-hetero-Diels-Alder reaction of **141** with **142** and the enol ether **144** gave the diastereomeric cycloadducts **146** in very good yield, although with somewhat lower asymmetric induction of 4.8:1. The mixture of cycloadducts was converted into the *tert*-butoxycarbonyl derivatives **147**, which were then treated with methanol/K_2CO_3 and hydrogenated. Chromatographic separation gave the enantiomerically pure diastereomer **148b** in 62% overall yield from **147**. Cleavage of the *tert*-butoxycarbonyl group in **148a** and **148b**, followed by condensation with methyl formate and treatment with diazomethane by known procedures,[71] gave the desired enantiomerically pure indole alkaloids (+)-hirsutine (**4**) and (+)-dihydrocorynantheine (**1**) (Scheme 16).



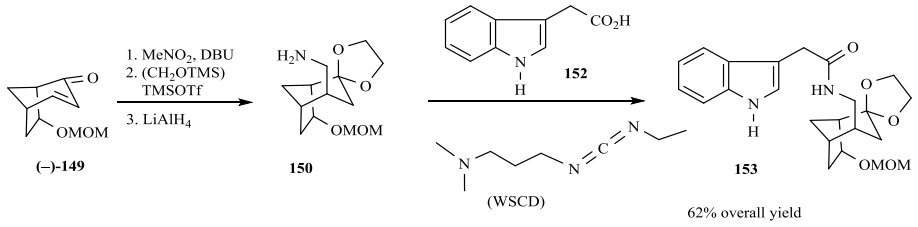
Scheme 16 – Enantioselective total synthesis of (+)-hirsutine (**4**) and (+)-dihydrocorynantheine (**1**).

2.2.3 Tandem retro-aldol-Pictet-Spengler: Total synthesis of (–)-dihydrocorynantheol (3)

The diastereocontrolled synthesis of the (–)-dihydrocorynantheol (**3**) alkaloid was accomplished by Ogasawara and Iwabuchi[79] employing a cascade sequence consisting of a Brønsted-acid-promoted retro-aldol reaction of the key intermediate **153** and a subsequent stereocontrolled Pictet-Spengler reaction.

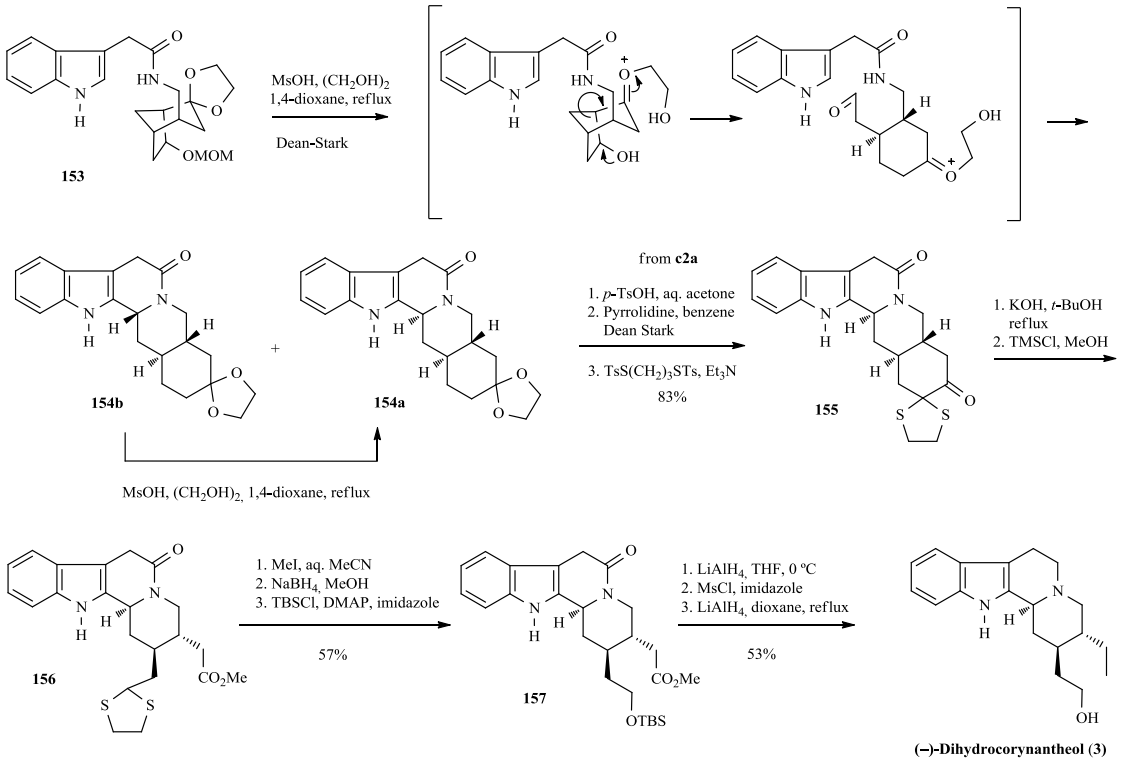
Amide **153** was prepared in 62% overall yield (Scheme 17) from the bicyclo[3.2.1]octenone chiral building block (–)-**149**[80] in a four-step sequence involving the regioselective and

convex-face selective introduction of a nitromethyl group, ketalization under Noyori's conditions,[81] reduction of the nitro group to the primary amine, and condensation with indole-3-acetic acid (**152**).



Scheme 17 – Preparation of the key intermediate **153**.

The treatment of amide **153** with methanesulfonic acid in boiling dioxane afforded a yohimbine-type derivative **154a** in 52% yield, together with pseudoyohimbane (**154b**) in 23% yield, by a tandem retro-aldol-Pictet-Spengler reaction and C-3 epimerization. The recovered **154b** was subjected to the above-mentioned acidic conditions to obtain **154a** in 59% yield and unreacted **154b** in 29% yield. For the transformation of the E-ring moiety to the seco form present in the dihydrocorynantheol (**3**) alkaloid, the ketal moiety was deprotected, and the resulting ketone was reacted with pyrrolidine to form an enamine, which was immediately treated with trimethylene dithiotosylate to generate **155**. Upon exposure to potassium hydroxide in boiling *tert*-butyl alcohol, the dithioketone moiety was cleaved and the resulting acid was esterified to obtain methyl ester **156**. Treatment of this compound with iodomethane in aqueous acetonitrile, followed by the reduction of the resulting aldehyde with sodium borohydride, afforded the corresponding alcohol, which was protected as TBS ether to give compound **157**. After subsequent treatment with lithium aluminium hydride and mesylation, the resulting mesylate was subjected to reduction using $LiAlH_4$ in boiling dioxane to furnish, with the concomitant reduction of the amide moiety, as well as deprotection of the TBS group, completed the synthesis of the target alkaloid (–)-dihydrocorynantheol (**3**) (Scheme 18).

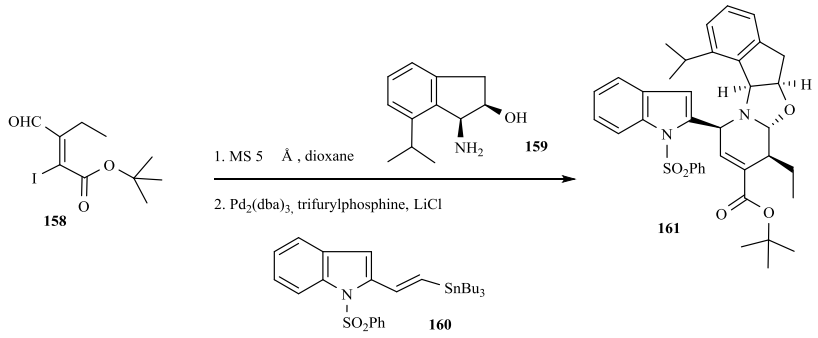


Scheme 18 – Total synthesis of (–)-dihydrocorynantheol (**3**).

2.2.4. One-pot asymmetric azaelectrocyclization: Enantioselective synthesis of (–)-corynantheidol (122) and formal synthesis of (–)-corynantheidine (14).

Soon after the publication of the one-pot asymmetric azaelectrocyclization procedure for the synthesis of chiral 2,4,5-trisubstituted tetrahydropyridines,[82] Katsumura demonstrated the usefulness of his methodology with an enantioselective synthesis of the indole alkaloids (–)-corynantheidol (**122**) and (–)-corynantheidine (**14**).[83]

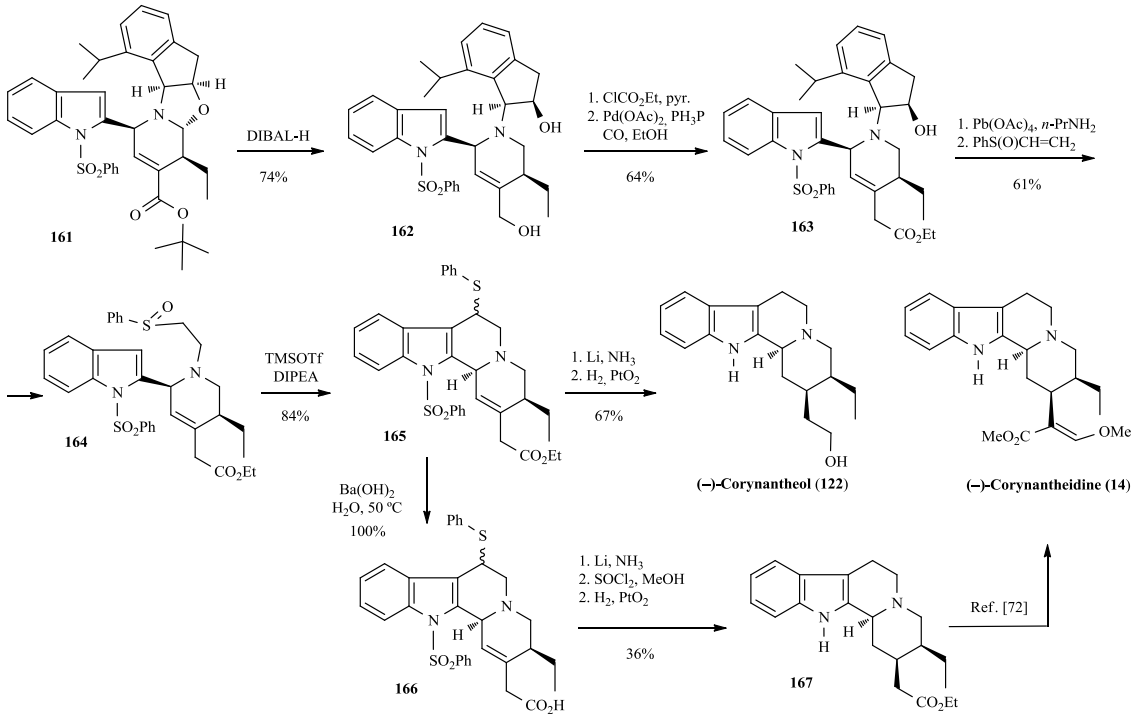
The one-pot azaelectrocyclization requires an initial mixture of the tetrasubstituted vinyl iodide **158** and the aminoindanol derivative **159**, and the subsequent addition of indolyl vinyl stannane **160**, and catalytic amounts of $Pd_2(dba)_3$, trifurylphosphine and LiCl. Four new bonds and three stereocenters were generated in a single operation, affording aminoacetal **161** as a single diastereomer in 77% yield (Scheme 19).



Scheme 19 – Preparation of the chiral non-racemic piperidine **161**.

The reduction of the ester group and aminoacetal moiety with DIBAL-H, followed by conversion of the resulting alcohol into a carbonate moiety, allowed the one-carbon elongation at the four position of the tetrahydropiridine ring by CO insertion, affording the ester **163**. Elimination of the indanol chiral auxiliary was accomplished by oxidation with lead tetraacetate in the presence of *n*-propylamine, leading to the corresponding secondary amine. The tetracyclic ring system was constructed from the amine intermediate by Bosch's Pummerer cyclization sequence,[84] via the generation of sulfoxide intermediate **164** and subsequent cyclization with trimethylsilyl triflate in the presence of diisopropylethylamine. The removal of the resulting thiophenyl substituent and the phenylsulfonyl group at the indole nitrogen in **165** was carried out using the Birch reduction, and the stereoselective reduction of the double bond in the tetrahydropyridine ring was accomplished by hydrogenation with platinum dioxide, affording (–)-corynantheidol (**122**) (Scheme 20).

The formal synthesis of (–)-corynantheidine (**14**) from the intermediate **165** was achieved by $Ba(OH)_2$ hydrolysis of the ester moiety to afford carboxylic acid **166**. The subsequent Birch reduction to remove the thiophenyl and benzenesulfonyl groups, esterification, and catalytic hydrogenation provided Cook's intermediate **167**, from which the synthesis of (–)-corynantheidine (**14**) could be completed in two steps (Scheme 20).[72]



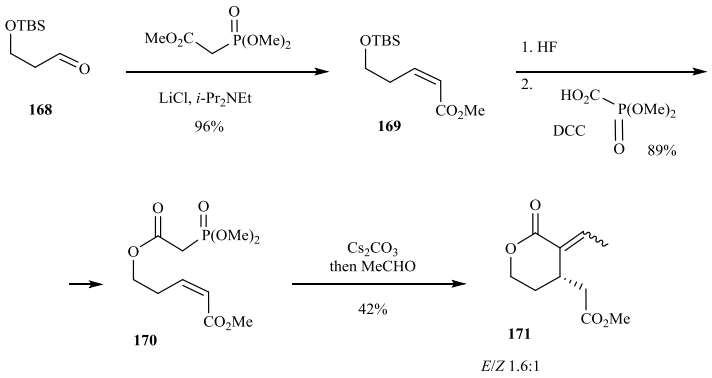
Scheme 20 – Enantioselective synthesis of (–)-corynantheidol (**122**) and formal synthesis of (–)-corynantheidine (**14**).

2.2.5 Stereodivergent synthesis of (±)-geissoschizol (123), (±)-corynantheidol (122), (±)-dihydrocorynantheol (3) from a single synthetic intermediate.

Traditionally, indoloquinolizidine alkaloids have been approached by individual strategies that have given access to a small number of structurally similar synthetic targets. In 2010, Robert M. Williams envisioned a approach based on a large-scale synthesis of a functionalized lactone intermediate **171**, via a tandem Michael cyclization and Horner-Wadsworth-Emmons olefination, which can be rapidly modified to obtain different alkaloids of this group, as well as secologanin dopamine alkaloids.[85]

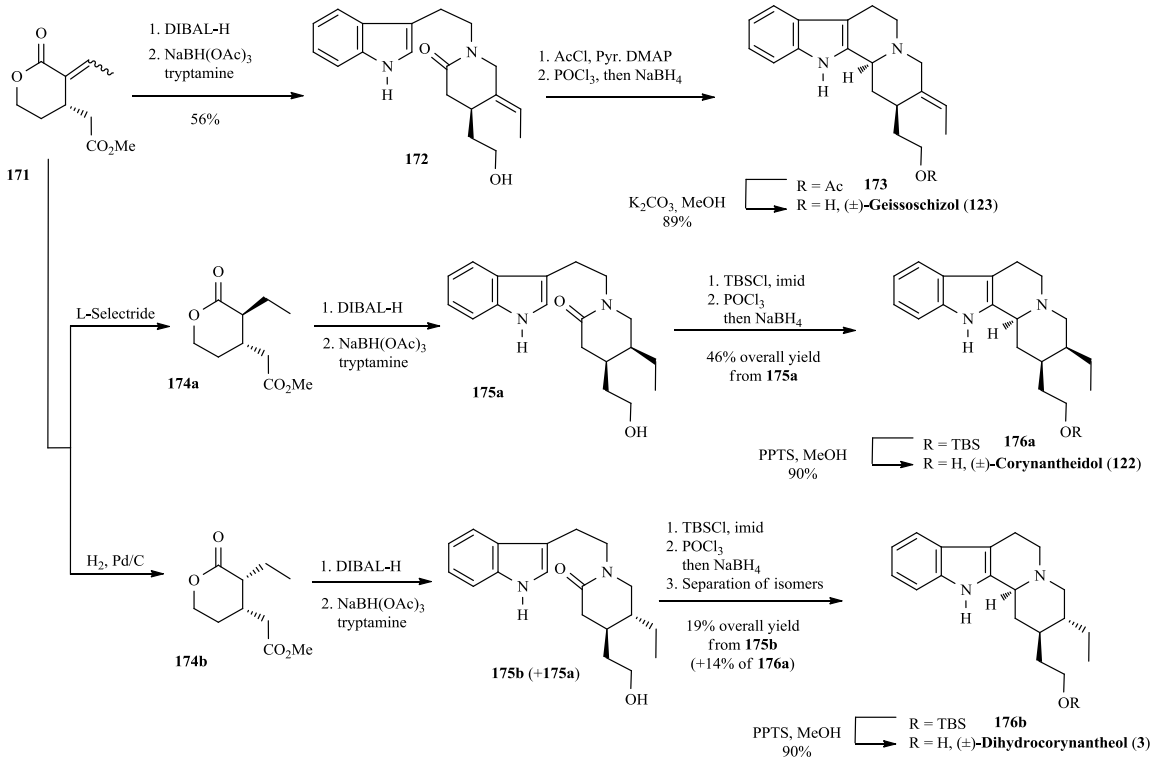
Assembly of lactone **171** (Scheme 21) [86] begins with the condensation of aldehyde **168** with commercially available trimethyl acetophosphonate under Masamune-Roush conditions, affording the unsaturated ester **169** as a single isomer in good yield. Deprotection and subsequent esterification gave the desired substrate **170**, which upon treatment with Cs_2CO_3 and

acetaldehyde underwent sequential intramolecular Michael cyclization and HWE-olefination to yield lactone **171** as a 1.6:1 mixture of *E*/*Z* isomers.



Scheme 21 – Preparation of the intermediate **171**.

Reduction of the lactone carbonyl of **171** with DIBAL-H, followed by a one-step reductive amination/lactam cyclization with tryptamine, afforded lactam intermediate **172**. Protection of the hydroxyl functionality as an acetate ester, followed by Bischler-Napieralski cyclization, gave acetate **173**, which was deprotected to yield (±)-geissoschizol in good yield (Scheme 22). Alternatively, catalytic hydrogenation of the olefin of lactone **171** exclusively generates the corresponding *cis*- lactone **174a**, presumably due to the delivery of hydrogen to the least sterically hindered face of the olefin. Conversely, conjugate reduction leads solely to the thermodynamically favored *trans*-isomer of the disubstituted lactone **174b**. Following a sequence similar to the above, corynantheidol and dihydrocorynantheol (**3**) were obtained from lactones **174a** and **174b**, respectively (Scheme 22). However, pure lactone **174b** led to a 1.3:1 mixture of isomers, which were separated by column chromatography after the formation of the indoloquinolizidine system.



Scheme 22 – Stereodivergent synthesis of (±)-geisssoschizol (**123**), (±)-corynantheidol (**122**), (±)-dihydrocorynantheol (**3**).

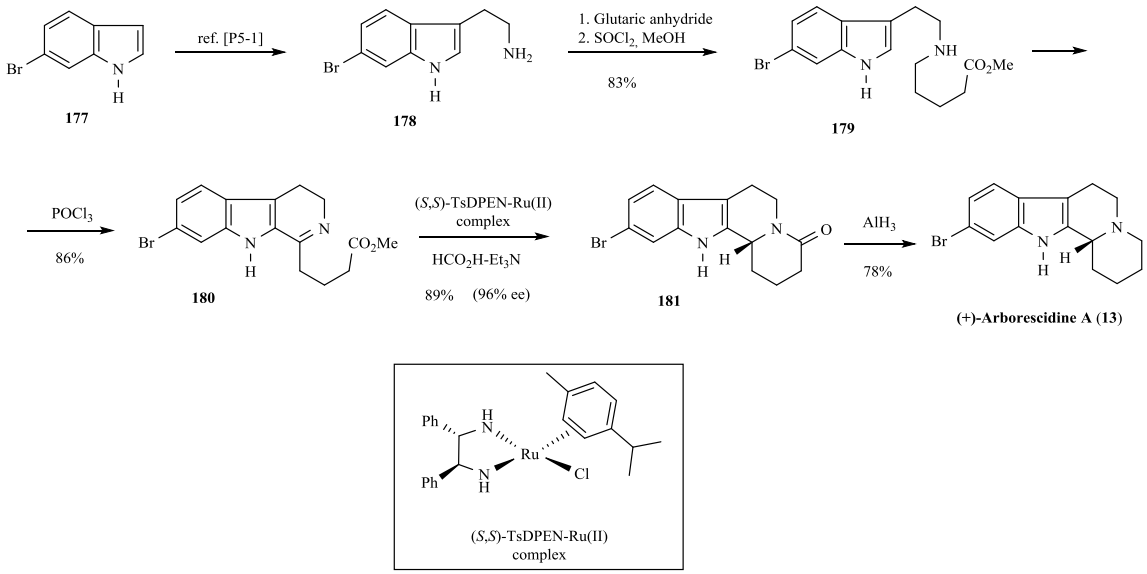
2.3. Asymmetric metalcatalysis/organocatalysis approaches

Catalysis has grown to play a prominent role in chemistry as it enables compounds to be prepared efficiently with atom economy. As well as producing far less waste is produced, new selective catalytic processes facilitate short-cuts in total synthesis. In recent years, asymmetric syntheses using organic compounds as catalysts have attracted considerable attention [87] as they are environmentally friendly compared with conventional transition metal catalysts. However, although this area is under intense study, there are still few reports [88, 89] on the application of this methodology for asymmetric total synthesis of natural products.

2.3.1 Asymmetric hydrogen-transfer reaction: Enantioselective Total synthesis of (+)-arborescidine A

A short enantiocontrolled syntheses of (+)-arborescidine A (**13**), by taking advantage of the Noyori asymmetric hydrogen-transfer reaction of appropriately functionalized β-carboline derivative, was described by Rawal in 2004 (Scheme 23).[90]

The 6-bromotryptamine (**178**), which was prepared from 6-bromoindole (**177**) following the Shumaker and Davidson method,[91] reacted with glutamic anhydride affording the corresponding amide carboxylic acid, which was then esterificated. Subsequent treatment with $POCl_3$ promoted the Bischler-Napieralsky cyclization to produce imine **180** in 86% yield. The Noyori reduction[92, 93] of imine **180**, to set the required asymmetry, was accomplished with preformed (*S*,*S*)-TsDPEN-Ru(II) complex, which afforded, after in situ cyclization, lactam **181** in 89% yield and 96% ee. Finally, alane reduction of the lactam carbonyl afforded (+)-arborescidine A (**13**).



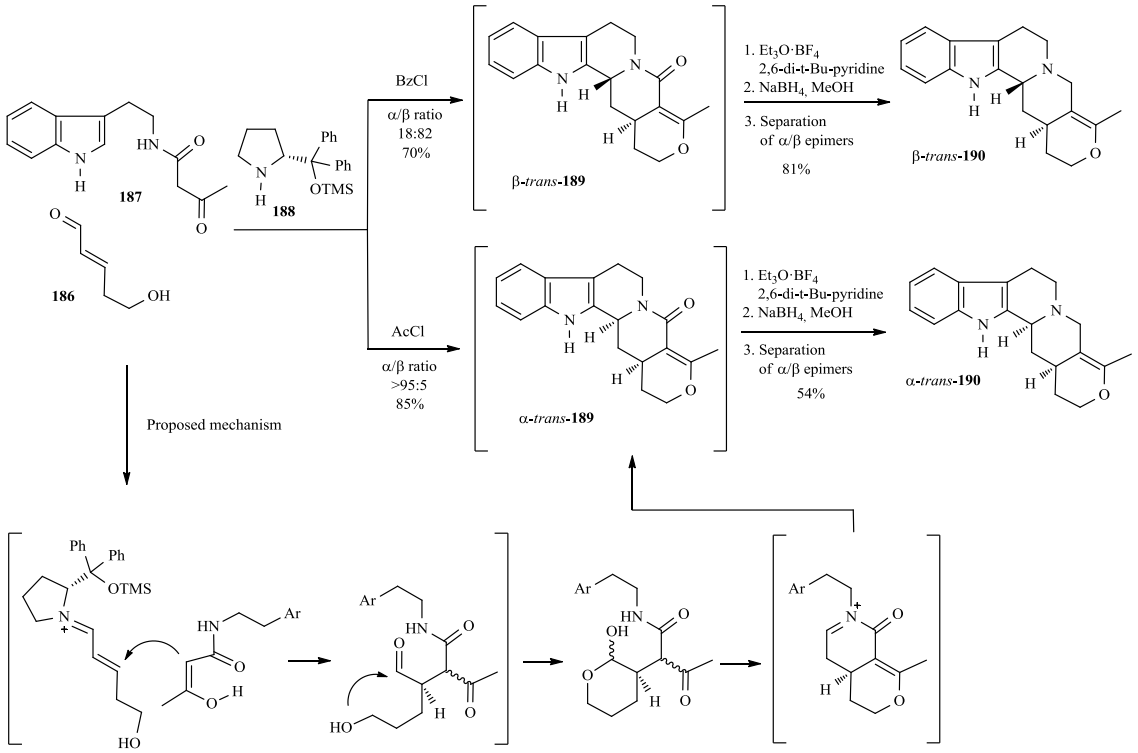
Scheme 23 – Enantioselective total synthesis of (+)-arborescidine A (**13**).

2.3.2 A Stereodivergent Strategy for the Preparation of Corynantheine alkaloids

A general and excellent catalytic asymmetric strategy for the total and formal synthesis of a broad number of optically active natural products from the corynantheine and ipecac alkaloid families, have been described by Franzén in 2011.[94] The construction of the core alkaloid skeletons, with the correct absolute and relative stereochemistry, relies on an enantioselective

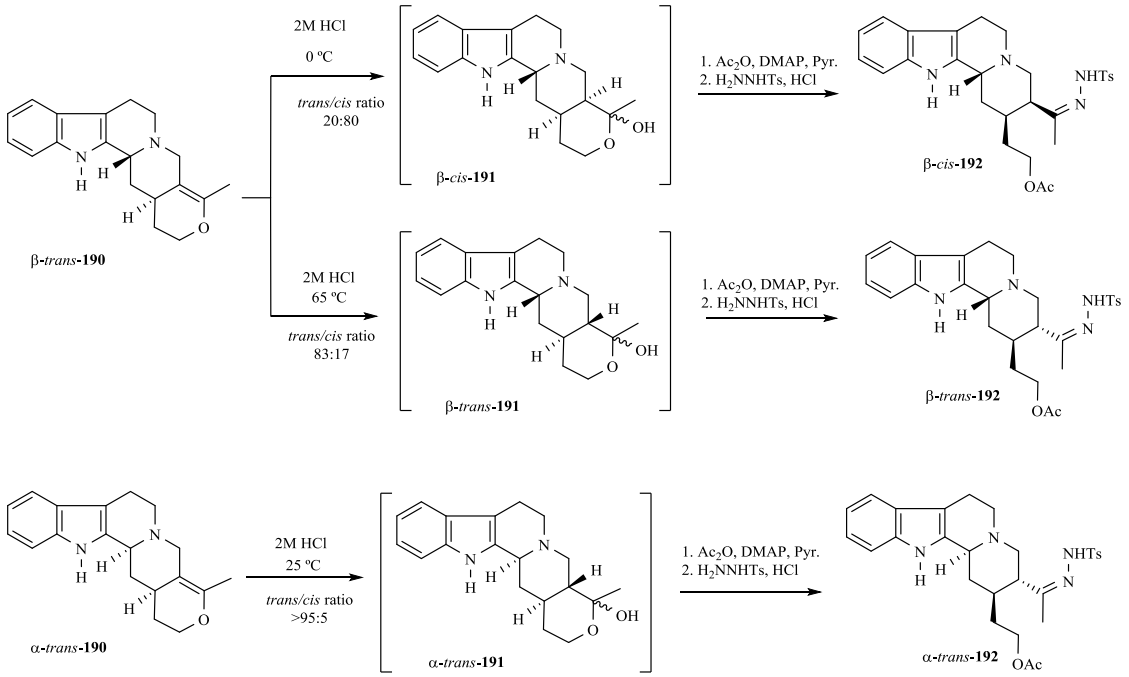
and diastereodivergent one-pot cascade sequence followed by an additional diastereodivergent reaction step. Starting from common and easily accessible starting materials and using a common synthetic route this approach gives access to the total synthesis of the indolo[2,3-a]quinolizidine alkaloids (−)-dihydrocorynantheol (**3**), (+)-hirsutinol (**182**), (−)-corynantheol (**183**), (−)-dihydrocorynantheal (**184**), and (−)-corynantheal (**185**).

The one-pot stereoselective construction of the quinolizidine carbon skeleton required the α,β-unsaturated aldehyde **186**, which was easily accessible through the cross-metathesis of acroleine and 3-butenol, and the β-ketoamides **187** which was obtained through the condensation of *tert*-butyl acetoacetate with the corresponding 2-arylethanamine. In the presence of catalyst **188**, β-ketoamides **187** smoothly reacted with the α,β-unsaturated aldehyde to give a diastereomeric mixture of lactols intermediates and then the reaction was quenched by addition of trifluoroacetic acid (TFA) giving a 1:1 mixture of the two ring-junction isomers α-**189** and β-**189**, which could be isolated in good yields and high enantioselectivity in a two-step one-pot process. Interestingly, when the reaction was quenched with acetyl chloride resulted in the formation of the thermodynamically favored indolo[2,3-*a*]quinolizidine α-**189** as the only observable isomer, whereas when using benzoyl chloride, a switch in diastereoselectivity it happened and the kinetically favored product β-**189** was obtained as the major isomer in 82:18 diastereoselectivity. It is also worth noting that the kinetically favored β-indolo[2,3-*a*]quinolizidine β-**189** could be epimerized to the thermodynamically favored α-**189** epimer by treatment with TFA heated at reflux to give a ratio of 85:15 in favor of the α-epimer. Subsequent reduction of the crude reaction mixture from the one-pot cascade was accomplished by initial alkylation with triethyloxonium tetrafluoroborate, followed by $NaBH_4$-reduction to give the corresponding amines **190** in high to moderate overall yields, and at this stage, the α- and β-epimers could be easily separated by flash column (Scheme 24).



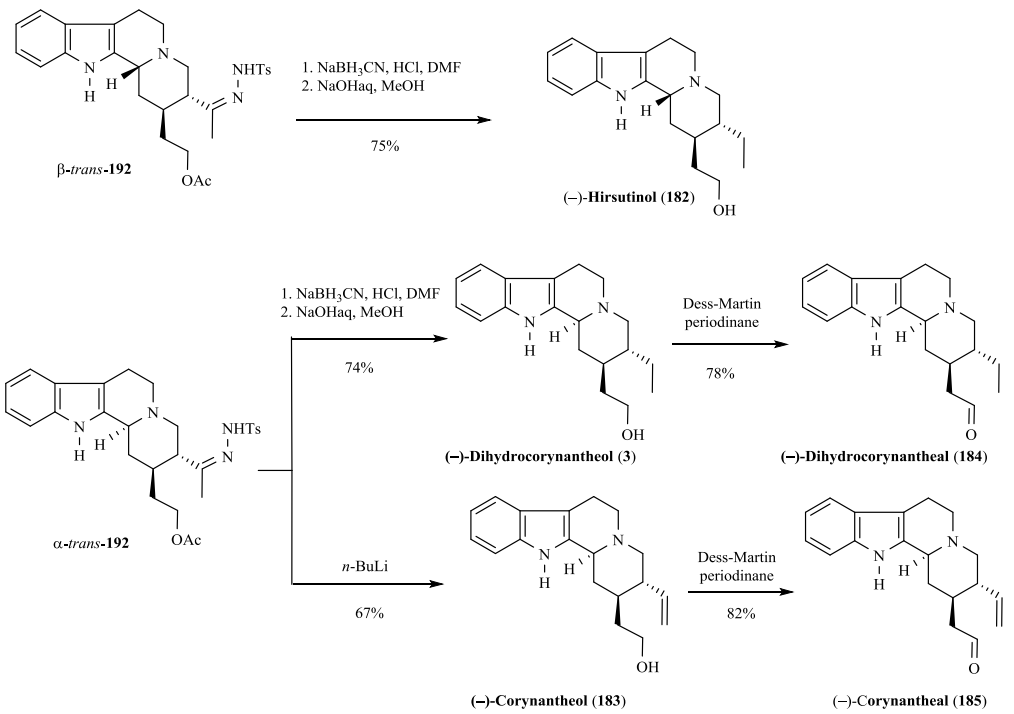
Scheme 24 – Preparation of the α- and β-epimers of the amine **190**.

Subsequent treatment of the α-epimer α-**190** with HCl in water/THF at room temperature gave exclusively the *trans* ring junction of the corresponding lactol α-*trans*-**191**. The selective formation of this stereocenter is due to the thermodynamic stability of the all-equatorial quinolizidine structure, and attempts to access the α-cis configuration have failed. However, in the β-series treatment of indolo[2,3-*a*]quinolizidine with HCl in water/THF at room temperature gave a 4:1 mixture of β-*cis*-**191** and β-*trans*-**191**. Interestingly, lactol formation at elevated temperatures (HCl in water/THF at 65 ºC) reversed the selectivity and β-*trans*-**191** was formed with a 5:1 diastereomeric ratio. The resulting lactols were successively treated with acetic anhydride to promote the ring opening of the lactol, and with tosyl hydrazide to give the corresponding hydrazones **192**, which were isolated as a single isomer in good to excellent overall yields from amine **190** without purification of synthetic intermediates (Scheme 25).



Scheme 25 – Preparation of the hydrazones **192**.

Hydrazones 12b-α-*trans*-**192** and 12b-β-*trans*-**192** were reduced with $NaBH_3CN$ in the presence of HCl. Final addition of KOH aq. in methanol gave the natural product (–)-dihydrocorynantheol (**3**) and (+)-hirsutinol (**182**). On the other hand, treatment of hydrazones α-*trans*-**192** and β-*trans*-**192** with *n*-BuLi resulted in the elimination of the hydrazone and deacetylation providing access to (–)-corynantheol (**183**), whereas the oxidation of the hydroxyquinolizidines gave (–)-dihydrocorynantheal (**184**) and (–)-corynantheal (**185**) (Scheme 26).



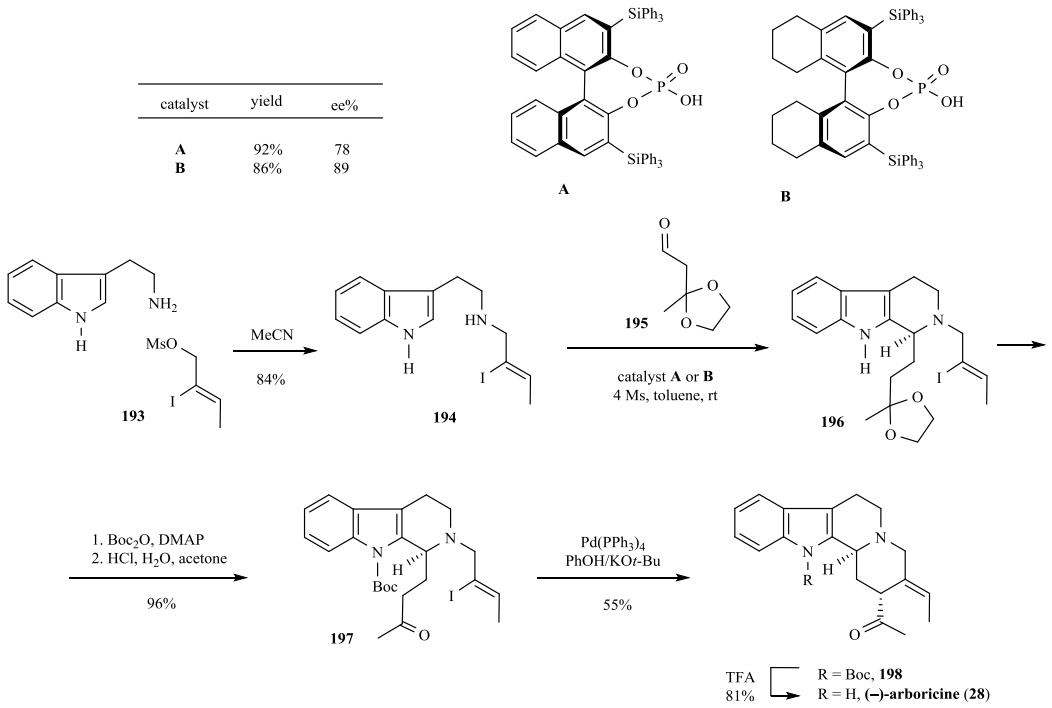
Scheme 26 – Preparation of Corynantheine alkaloids.

2.3.3. Organocatalytic Enantioselective total synthesis of (−)-arboricine (28).

A concise and scalable synthesis of (−)-arboricine (**28**) based on an asymmetric organocatalytic Pictet-Spengler reaction, followed by a Pd(0)-catalyzed enolate cyclization, was described by Maarseveen and Hiemstra in 2009 (Scheme 27).[95]

The synthesis started with the know tryptamine **194**,[96] which was prepared in one step by alkylation of tryptamine with *Z*-2-iodo-2-butene-1-ol mesylate (**193**) in 84% yield. Pictet-Spengler condensation of **194** with the dioxolane **195** using catalyst (*R*)-binol-PA (**A**), provided **196** in 92% yield and 78% ee. The acetal protecting group improves the ee of this reaction. The best ee was obtained using the sterically slightly more demanding catalyst (*R*)-H8-binol-PA (**B**) that gave **196** in 86% yield and 89% ee. Treatment of **196** with Boc_2O and DMAP followed by diluted HCl in acetone gave ketone **197** in 96% overall yield. The closure of the piperidine ring was accomplished by a Pd(0)-catalyzed vinyl iodide-enolate coupling using the procedure published by Sole and Bonjoch, in which potassium phenoxide avoids the migration of the isolated exocyclic double bond[97] affording keto amine **198** as a single diastereoisomer. A

single recrystallization from the EtOAc/PE mixture gave enantiometically pure **198**. (–)-arboricine was obtained in 81% yield after TFA-mediated removal of the Boc-protecting group of **198**.



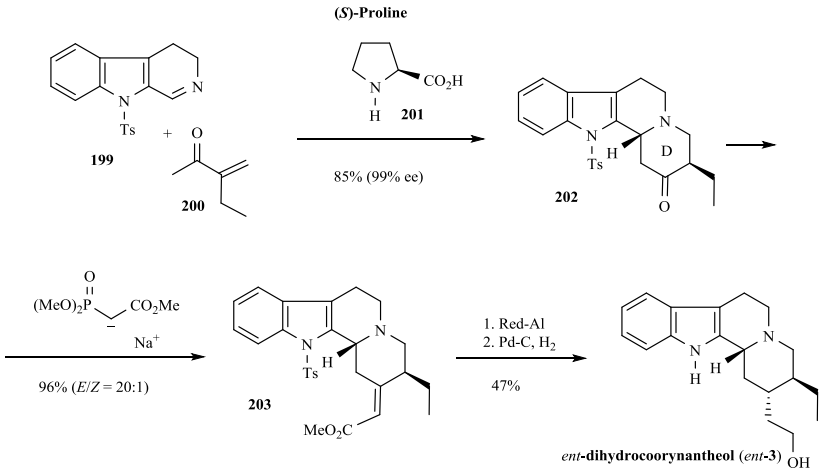
Scheme 27 – Organocatalytic enantioselective total synthesis of (–)-arboricine (**28**).

2.3.4. Proline-catalyzed asymmetric addition reaction: Total synthesis of *ent*-dihydrocorynantheol (3)

In the context of Itoh's research on the synthesis of chiral 1-substituted 1,2,3,4-tetrahydro-β-carboline derivatives, using the asymmetric addition of methyl ketones to the β-carboline system in the presence of (*S*)-proline,[98] this author envisaged that 3-ethyl-3-buten-2-one as a good substrate for the concise asymmetric synthesis of *ent*-dihydrocorynantheol (Scheme 28).[99]

The reaction of *N*-tosyl-3,4-dihydro-β-carboline (**199**) with 3-ethyl-3-buten-2-one (**200**)[100] in the presence of (*S*)-proline (**201**) led to the formation of the D ring of the target molecule with the correct configuration in a single step, affording the product **202** in a good yield of 85% with 99% ee. Since there were no intermediates observed in the reaction, it was not possible to

conclude whether the reaction proceeded via Mannich-Michael reaction or a Diels-Alder-type addition. Alkene **203** was then quantitatively obtained in the ratio of *E*/*Z* 1:20 from compound **202** by Wittig reaction. Subsequent treatment with Red-Al brought about the reductive elimination of the tosyl group and the reduction of the ester group to an alcohol. A final hydrogenation satisfactorily afforded *ent*-dihydrocorynantheol.



Scheme 28 – Total synthesis of *ent*-dihydrocorynantheol (*ent*-**3**).

Final Remarks

There has been much progress in the synthesis and biological evaluation of tetracyclic indole alkaloids containing an indolo[2,3-*a*]quinolizidine system. However, we can still find many reports describing the biological activity of extracts, instead of describing the activity of the pure indole alkaloids. Also, many reports do not describe correctly the stereochemistry of the indole alkaloids isolated and/or evaluated.

Herein, we have made a review about the potential pharmacological applications of indolo[2,3-*a*]quinolizidines and derivatives (see Table 1), as well as about the most important asymmetric approaches developed for the construction of the indolo[2,3-*a*]quinolizine ring system. Although, to our knowledge, there are no alkaloids in the market or in clinical assays containing an indolo[2,3-a]quinolizidine system, compounds containing a tetracyclic indole[2,3-*a*]-quinolizidine scaffold seem to be a potential starting point for the development of effective drugs.

Abbreviations

Ac, acetyl; Boc, *tert*-Butyloxycarbonyl; DHC, dihydrocorynantheol; Me, methyl; Nuclear factor-kB, NF-kB; OGlu, *O*-*β*-D-glucosyl; SIRT, sirtuin; DIBAL-H, diisobutylaluminium hydride; HWE, Horner-Wadsworth-Emmons; THF, tetrahydrofuran; DMAP, 4-dimethylaminopyridine; PPTS, Pyridinium *p*-toluenesulfonate; TBSCl, *tert*-Butyldimethylsilyl chloride;

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