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A REVIEW ON INDOLO[2,3-*a*]QUINOLIZIDINE: THE SYNTHETIC APPROACHES TO THE DEVELOPMENT OF BIOACTIVE INDOLO[2,3-*a*]QUINOLIZIDINE SCAFFOLDS

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Abstract – Tetracyclic indolo[2,3-*a*]quinolizidine motifs are an important class of molecules in research and development due to their wide spectrum of biological activities, which include anti-allergic, antibacterial, antiviral, and other bioactive qualities. To develop the indolo[2,3-*a*]quinolizidine system, innovative synthetic methods have thus attracted tremendous attention during the past decades. This article describes the synthetic approaches developed to target the most important alkaloids of this family, with an emphasis on the possible use of these alkaloids or their analogues to treat a variety of illnesses, ranging from cancer to neurological disorders. In this review article, we have described several crucial synthetic methodologies leading to the indolo[2,3-*a*]quinolizidine scaffolds. Further, the biological activities and the structure-activity relationships (SAR) of such derivatives towards various diseases gives a better understanding of the significance of this moiety in medicinal chemistry.

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1. INTRODUCTION

The well-known alkaloids dihydrocorynantheine **1** and corynantheine **2**, have tetracyclic indolo[2,3-*a*]quinolizidine motif and show a wide spectrum of bioactivities, that's why they are of significant interest to both the pharmaceutical business and the academic community. The biological actions of this subclass of indole alkaloids, which include many properties have been connected to a range of biological processes.¹⁻⁴ Individually, the indole and quinoline are one of the most crucial heterocyclic compounds because they have several useful bioactivities.⁵⁻⁸ Over the past few decades, numerous novel synthetic techniques have been discovered to produce the indolo[2,3-*a*]quinolizidine system, which is present in many alkaloids derived from monoterpene molecules. It has been found that the stereochemistry of the corynantheine alkaloids is very important for the manifestation of bioactivity, and therefore discovery of a novel enantioselective methods to developed indolo[2,3-*a*]quinolizidine alkaloids. Corynantheine alkaloids,⁹ including dihydrocorynantheine **1**,¹⁰ corynantheine **2**,⁹ dihydrocorynantheol **3**,¹¹ hirsutine **4**,^{12,13} hirsuteine **5**,^{12,13} and geissoschizine methyl ether **6**,¹⁴ have been the subject of numerous research studies (**Figure 1**). In this review, we concentrate on the pharmacological as well as the therapeutic potential of indolo[2,3-*a*]quinolizidines as well as the most recent advances is asymmetric synthesis approaches to extract the essential structural elements of these indole alkaloids.^{15,16}

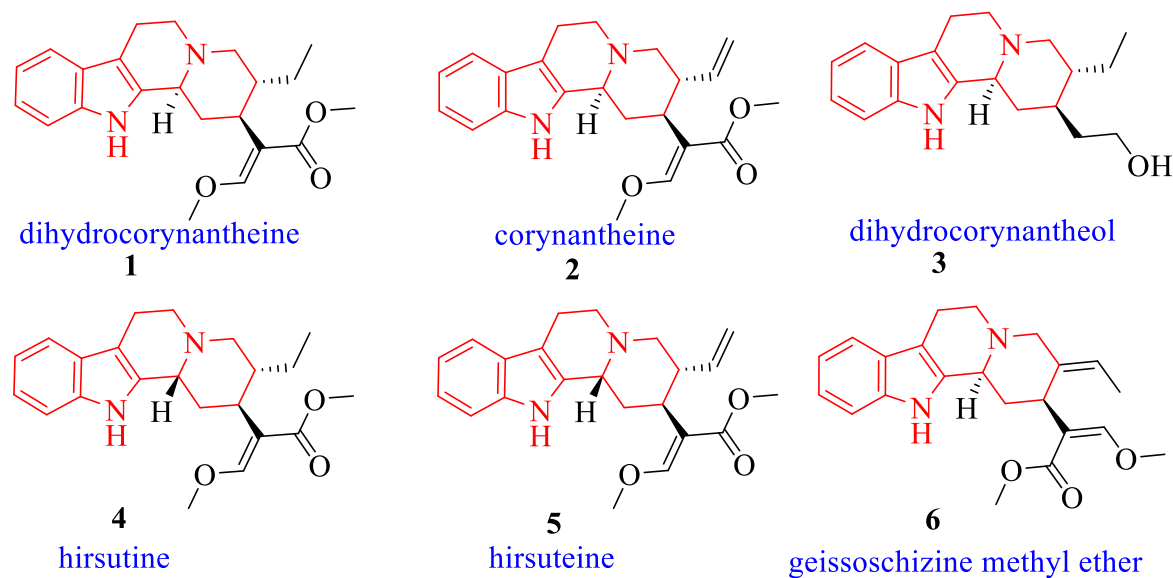


Figure 1. Structure of corynantheine alkaloids

Cryptolepine **7** is a naturally existing compound whose manufacture was recorded before it was separated from plants. Before it was initially synthesized in 1906 by Fichter and colleagues, first time it was isolated from *Cryptolepis triangularis* N.E.Br. by Clinquart in 1929. In addition to cryptolepine, these documented indoloquinolines from this plant also include neocryptolepine (cryptotackieine, **8**), isocryptolepine

(cryptosanguinolentine **9**), and many other isomeric indoloquinolines in **Figure 2**.¹⁷⁻²¹

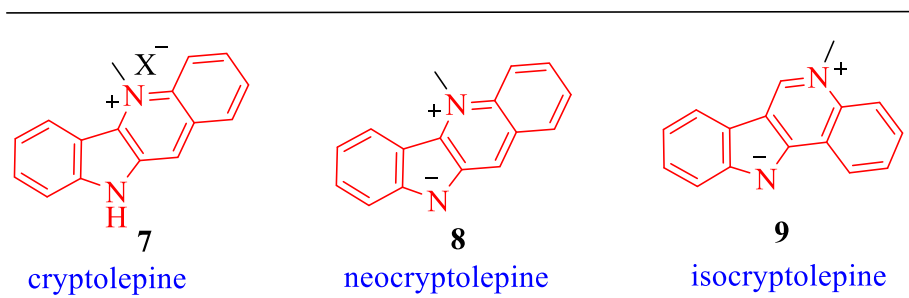


Figure 2. Different isomeric indoloquinolines

2. INDOLOQUINOLIZIDINE AND ITS DERIVATIVES HAVING POTENTIAL BIOLOGICAL ACTIVITIES

Desbromoarborescidine A, commonly known as indolo[2,3-*a*]quinolizine alkaloid, was discovered from *D. mangiferum* in 1966. The literature shows that the desbromoarborescidine A and their natural analogues (**Figure 3**) possess interesting cardiovascular properties, determining their efficiency to block alpha-1 and alpha-2 adrenoceptors. When compared to the other alkaloids, desbromoarborescidine A demonstrated a significant adrenoceptor blocking action. Arborescidine A, a brominated indole alkaloid derived from the marine tunicate *P. arborescens*, was described in 1993.^{16,22a}

Desbromoarborescidine A **10** & **11** and arborescidine A **12** were tested *in vitro* for their potential to decrease cell growth against several tumor cell lines (leukaemia). Desbromoarborescidine A was only modestly active (IC₅₀ greater than 50 μM) in all tumour cell lines tested, whereas arborescidine A showed a leukemia specific IC₅₀ value of 34.5 μM. Chang group revealed the studies on the effects of dihydrocorynantheine **1** (**Figure 1**) on arterial pressure.^{22b,23,24}

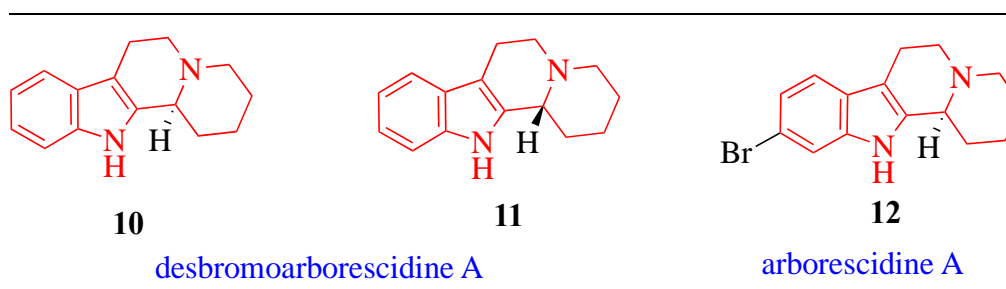


Figure 3. Framework present in indolo[2,3-*a*]quinolizine alkaloids

Dihydrocorynantheine **1**, an alkaloid isolated from the dried branches & leaves of *Uncaria callophylla*, has been demonstrated in studies to dramatically lower arterial pressure in both anaesthetized but also awake normotensive rats. Masumiya *et al.* later reported that dihydrocorynantheine **1** had negative chronotropic and antiarrhythmic effect because it directly altered cardiac muscle potential action by blocking a variety of ion channels. In 2000, dihydrocorynantheine **1**, corynantheine **2**, and corynantheidine **13** were isolated

from bark of *Corynanthe pachyceras* K. Schum. (Rubiaceae).^{9-11,24} These alkaloids were evaluated against *Leishmania major* promastigotes along with two synthetic corynantheidine racemic derivatives **14** & **15** (**Figure 4**). Each substance displayed IC₅₀ values for *Leishmania* ranging from 0.7 to 2.8 μM. Three alkaloids were tested for their ability to be cytotoxic as well as anti-malarial, but these tests came back negative.^{23,24}

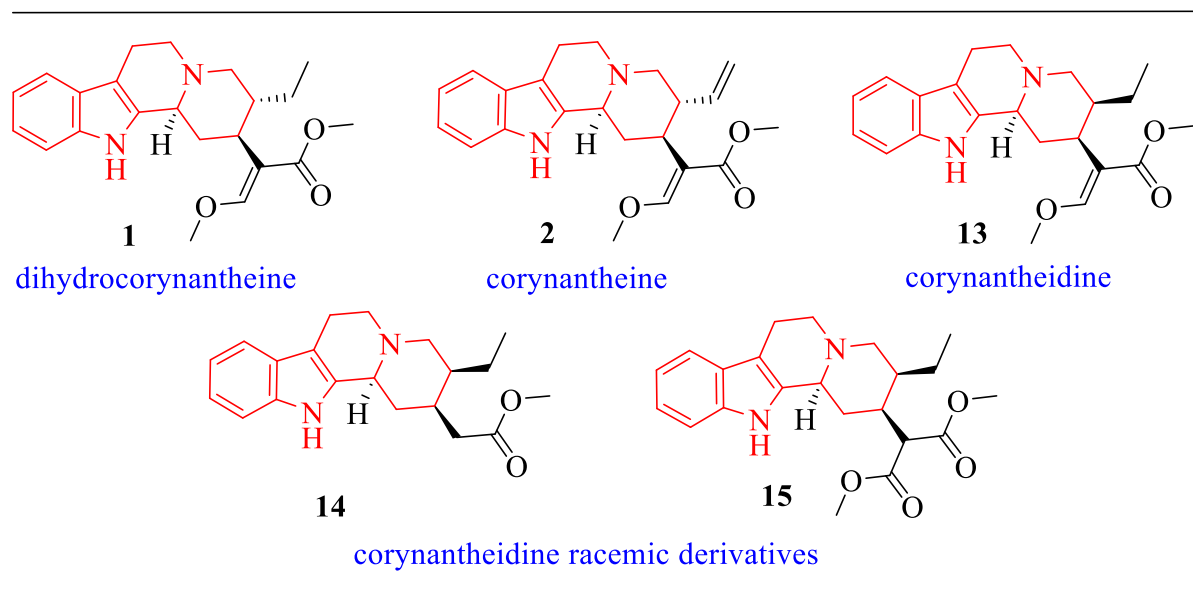


Figure 4. Some analogues of corynantheidine

Dihydrocorynantheol **3**²⁵ (**Figure 5**), an alkaloid discovered from *Esenbeckia leiocarpa*, was initially described as having anti-inflammatory activities by Fröde's group in the year 2011. Dihydrocorynantheol (DHC) has been found to have a critical role in the anti-inflammatory activity of this herb by inhibiting I-B ubiquitination and subsequent degradation. As a result, both the NF-κB cascade and the generation of many pro-inflammatory mediators, such as IL-1β and TNF-α, are inhibited. A variety of esters dihydrocorynantheol derivatives such as DHC-acetyl **16**, DHC-*p*-methylbenzoyl **17**, DHC-benzoyl **18**, DHC-*p*-methoxybenzoyl **19**, and DHC-*p*-chlorobenzoyl **20** (**Figure 5**), have anti-inflammatory properties. Dihydrocorynantheol's activity was seen it decreases when the hydroxyl group acts as a protection, that provides the hydroxyl group's role in the chemical structure of this alkaloid's anti-inflammatory effect is crucial.

The main chemical components of *Uncaria* sp. include hirsutine **4**, hirsuteine **5**, and geissoschizine methyl ether **6** (**Figure 6**).²⁵⁻²⁷ Hirsutine **4** was shown to have antihypertensive & antiarrhythmic activities *via* modifying the action potential in cardiac muscle as well as intracellular Ca²⁺ levels in the rat thoracic aorta (traditional Chinese herb medicine).²⁸ Additionally, hirsutine **4** was demonstrated to be successful in shielding rat cardiomyocytes from hypoxia-induced cell death.²⁹ Additionally, the effects of *Uncariae Ramulus* et *Uncus* extracts hirsutine **4**,^{30,31} hirsutein **5**, and geissoschizine methyl ether **6** (**Figure 6**)^{32,33} on

vascular responses were assessed.^{34,35} In the norepinephrine-induced vasocontractive response, geissoschizine methyl ether **6** proved that it is more effective ($EC_{50} = 0.744 \mu\text{M}$) than hirsutine **4**. Additionally, it was established that geissoschizine methyl ether **6** had two different modes of action: endothelium dependence with nitric oxide & endothelium independence with voltage dependent Ca^{2+} channel blockage. As a result, geissoschizine methyl ether **6**^{36,37} may be a candidate for medications that dilate blood vessels or lower blood pressure. With the help of *Uncaria villosa*'s leaves authors extracted the compound villocarine A **21** in 2011 (Rubiaceae).

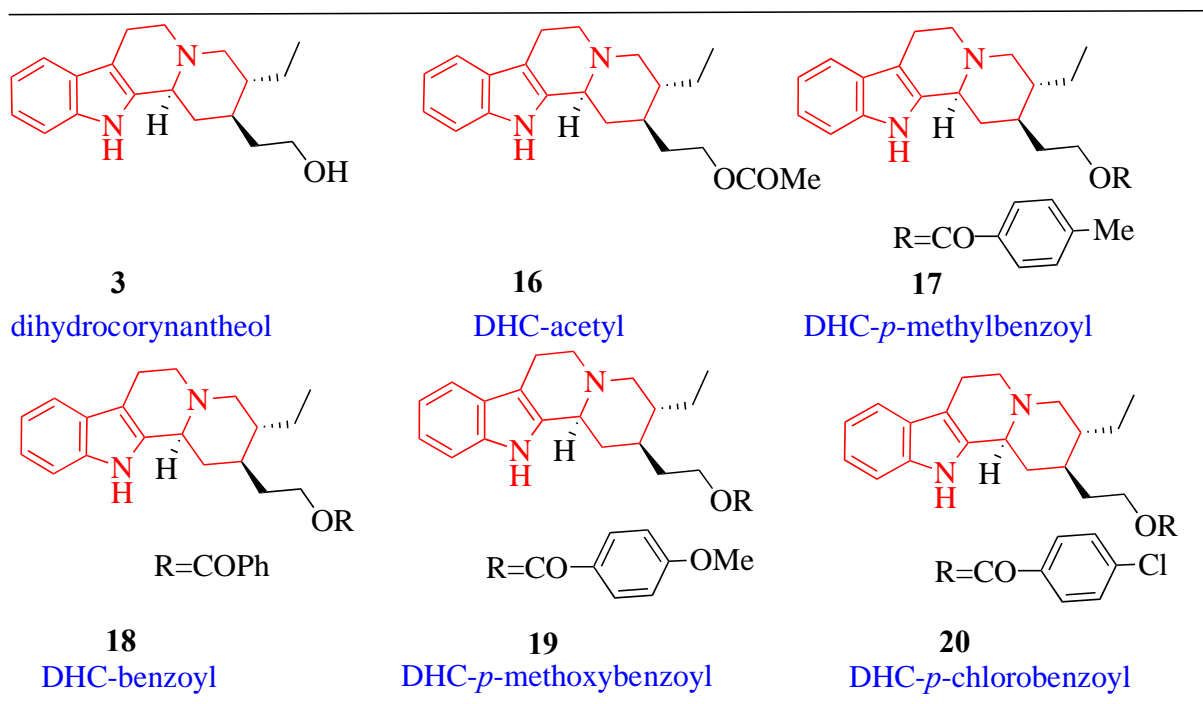


Figure 5. Analogues of dihydrocorynantheol

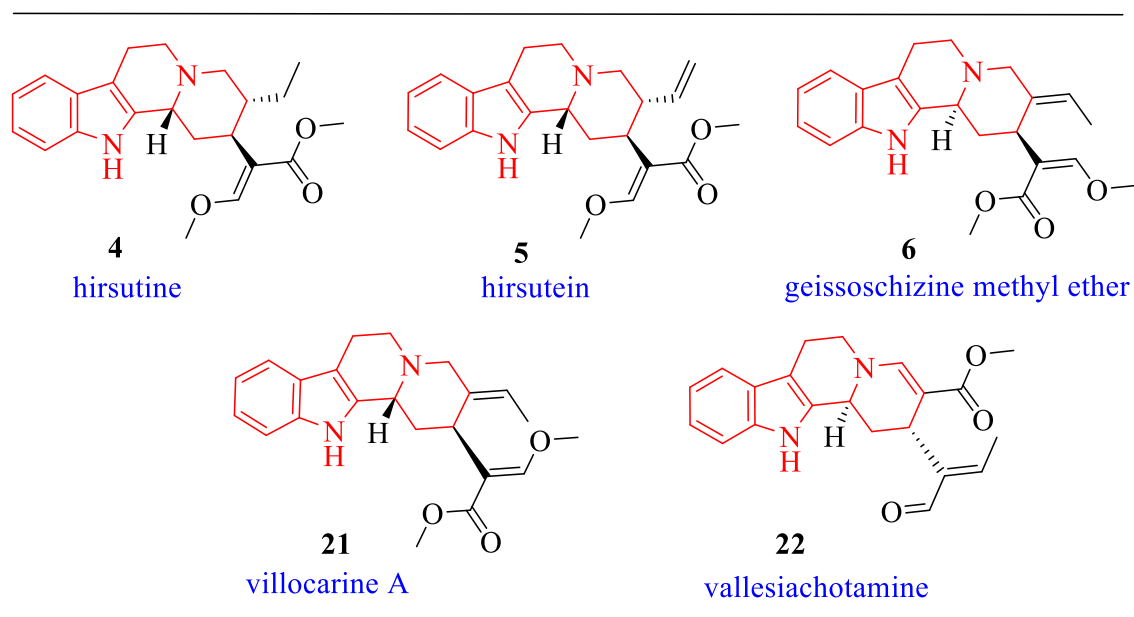


Figure 6. Possible acetylcholinesterase inhibitor

A potential acetylcholinesterase inhibitor that was mentioned in 2012 was geissoschizine methyl ether **6**. In this study were also examined the effects of hirsutine **4**, hirsuteine **5**, as well as vallesiachotamine **22** (**Figure 6**), which were taken from the hooks of *Uncaria rhynchophylla*. According to the findings, geissoschizine methyl ether **6** conc. of 3.7-0.3 $\mu\text{g mL}^{-1}$ inhibited acetylcholinesterase activity by 50%. vallesiachotamine **22**, hirsutine **4**, hirsuteine **5** had negligible inhibitory effects on acetylcholinesterase. Turbinatine, an indole alkaloid of the corynanthean type with structural similarities to geissoschizine methyl ether **6** (**Figure 6**),³⁸ also inhibited acetylcholinesterase with an IC_{50} value of 0.99 $\mu\text{g mL}^{-1}$.

A monoterpene indole alkaloid called *Z*-vallesiachotamine **23** (**Figure 7**), which was derived from the *Rhaza stricta* plant, was found to have anti-tumor activities on a carcinoma cell line in 1981. In contrast to *Z*- and *E*-vallesiachotamine **23** and **24** vallesiachotamine lactone **25** showed no obvious toxicity on HEK293 as well as the rat astrocyte primary cells. *E*-vallesiachotamine **24** also significantly increased cytotoxicity & necrosis at a concentration of 50 μM .³⁹⁻⁴³

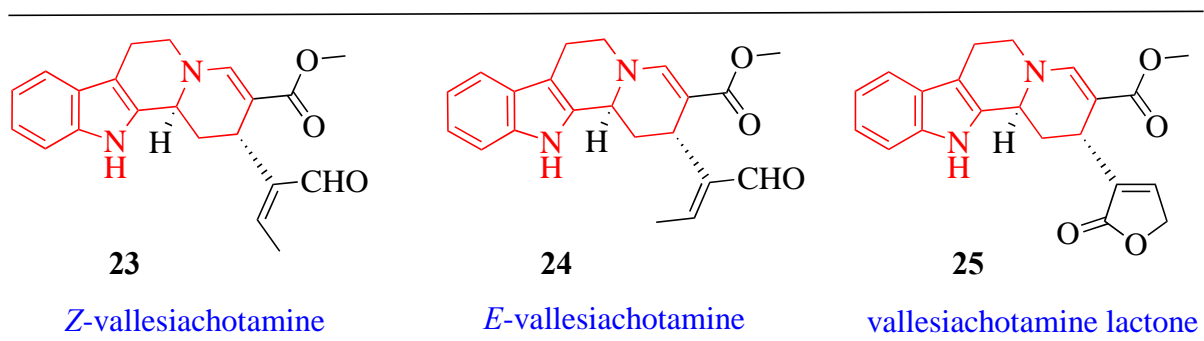


Figure 7. Vallesiachotamines and their analogue

In 2005, Matsumoto *et al.* investigated the effects of mitragynine **26** (**Figure 8**), from the Thai medicinal herb *Mitragyna speciosa*. The results demonstrated that mitragynine **26** inhibited the guinea-pig vas deferens' constriction because of electrical transmural stimulation. Takayama *et al.* described the synthesis of mitragynine derivative was examined on opioid receptors to undertake a SAR (structure-activity relationship) investigation. Several molecules have been identified that have intriguing potential against opioid receptors. The structure of mitragynine **26** and its derivatives such as, 7-hydroxyspeciociliatine **27**, 7-hydroxymitragynine **28**, 9-hydroxycorynantheidine **29** as well as indoloquinolizidines **30-31** are well documented.⁴⁴⁻⁵⁰ The presence of a hydroxyl group at 7-position really caused the decrease in activity.¹⁵ In addition, compounds associated with mitragynine also exhibit interesting opioid activities; in particular, pseudoindoxyl and 7-hydroxymitragynine **28** were found to have powerful antinociceptive activity.

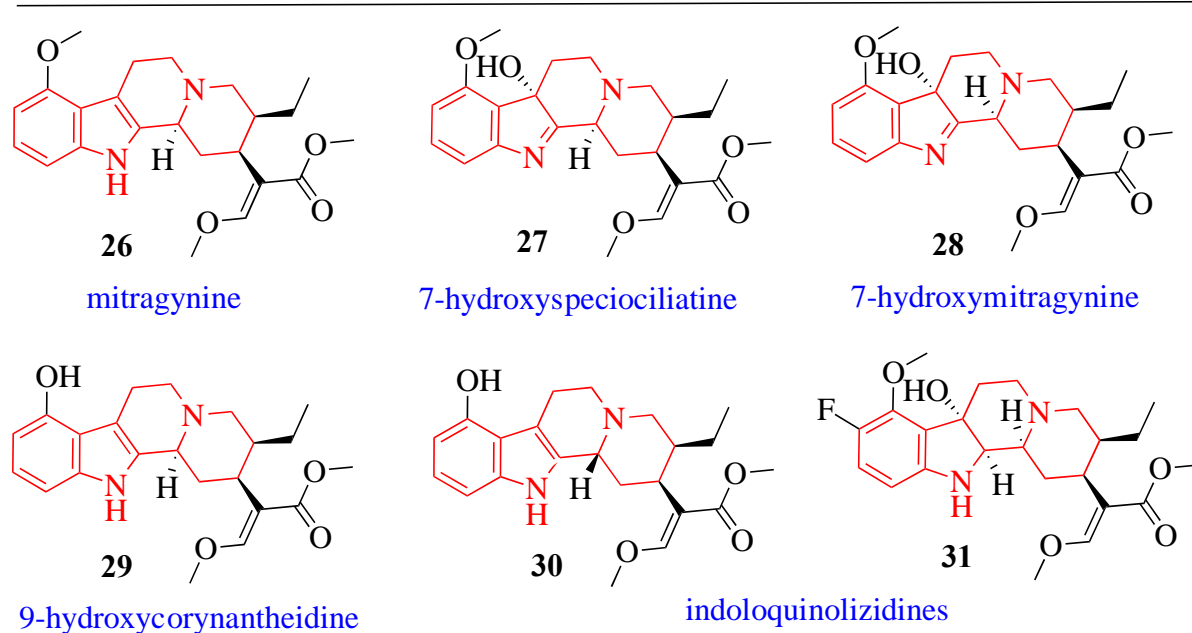


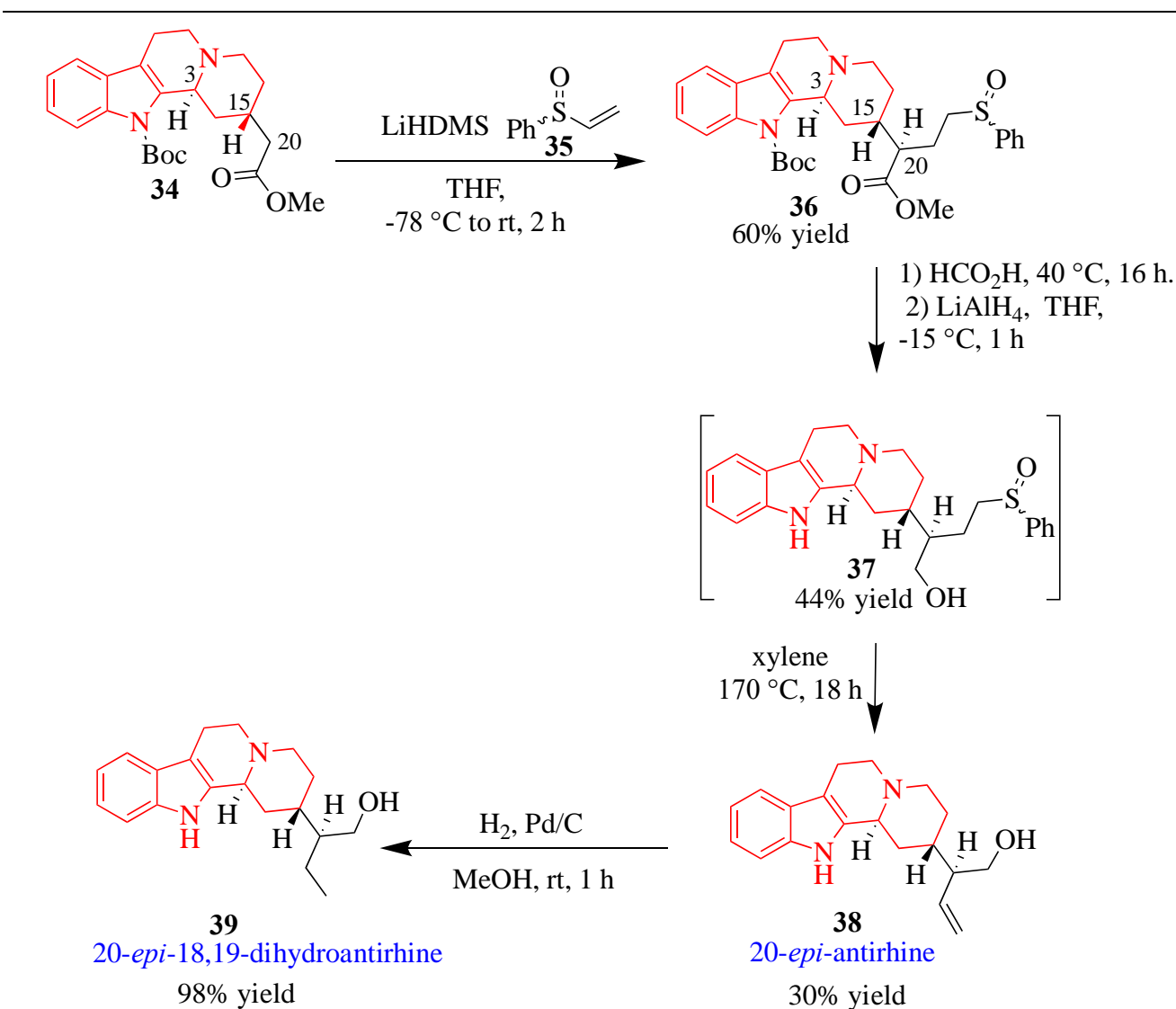
Figure 8. Mitragynine and its derivatives

3. SYNTHETIC ASPECTS OF INDOLOQUINOLIZIDINE AND ITS ANALOGUES

The aim of this section of the review is to present the most recent advancements in the various techniques used to synthesize enantioselective as well as the racemic indolo[2,3-*a*]quinolizidine alkaloids. The use of chiral pool resources, asymmetric metal catalysis, and non-catalytic cascade/tandem sequences or organocatalytic techniques to make up the indolo[2,3-*a*]quinolizidine based components. These organic molecules provide good synthetic targets since it can be difficult to produce the fused-ring system of the indolo[2,3-*a*]quinolizidine alkaloids while maintaining control over the quinolizidine core's relative and absolute stereochemistry. Cascade reactions have recently been employed in the synthesis of indoloquinolizidine alkaloids. While being extremely demanding, these reactions provide well-established advantages in resource management, waste production, time, and atom economies. Regarding the relative arrangement of the quinolizidine stereocenters, the bulk of the established synthetic techniques are target-specific and only permit the selective production of one epimer of the alkaloid.

When phenyl vinyl sulfoxide was combined with the ester **34**, which was produced *via* LiHMDS treatment at $-78\text{ }^{\circ}\text{C}$, the desired conjugate adducts **35** was produced in a reasonable amount of yield as a combination of just two diastereomers (**Scheme 1a**).⁵¹ It was unsure at this point that which stereogenic centre affected the diastereoselectivity because compound **36** can have four different diastereomers due to the presence of two potential stereogenic centres (C-20 and the sulphur atom). As a result, after converting sulfoxide **36** into the known natural product(s) and contrasting their spectroscopic data, the author decided to investigate their stereochemistry. To do this, the indole *N*-Boc group in compound **36** was removed with formic acid at $40\text{ }^{\circ}\text{C}$, and the methyl ester was reduced with LiAlH_4 to produce alcohol **37** as a mixture of two

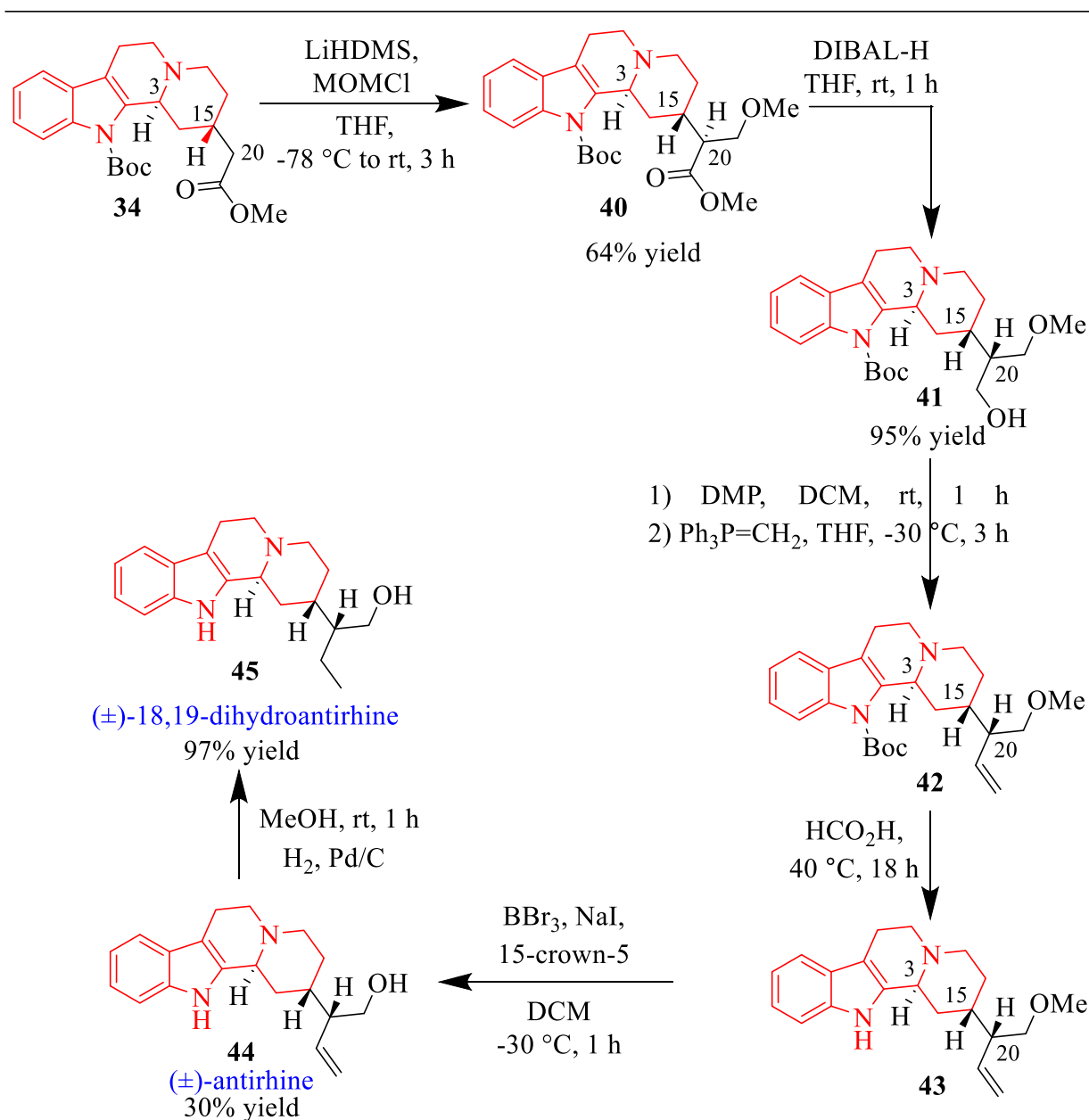
diastereomers with a similar diastereomeric ratio as compound **37**. Surprisingly, the product was produced as a single entity after the final heat removal of the sulfoxide group in alcohol **37**. Since the resulting homoallylic alcohol's spectroscopic results matched those of (\pm)-20-*epi*-antirhine **38**, it was determined that ester **36** had the α -H configuration at C-20. By contrasting the spectroscopic results for the hydrogenation product of the resultant homoallylic alcohol **38** with those of the previously described (\pm)-20-*epi*-18,19-dihydroantirhine **39**. It should be observed that the enolate alkylation process can regulate the diastereoselectivity, and the chirality of the sulphur atom in ester **36** is responsible for the diastereomeric connection. Additionally, the enolate is approached by the electrophile from the *Si* face, mostly resulting in the formation of the α -H isomer.



Scheme 1 (a). Synthesis of 20-*epi*-antirhine **38** & 20-*epi*-18,19-dihydroantirhine **39**

The synthesis of (\pm)-antirhine **44** and (\pm)-18,19-dihydroantirhine **45**, which calls for the installation of the vinyl (or ethyl) group at C-20 in ester **34**, was continued after getting the 20-*epimers* **38** and **39**. Different alkylating partners and reaction settings were investigated in light of this. All attempts, however, to reverse

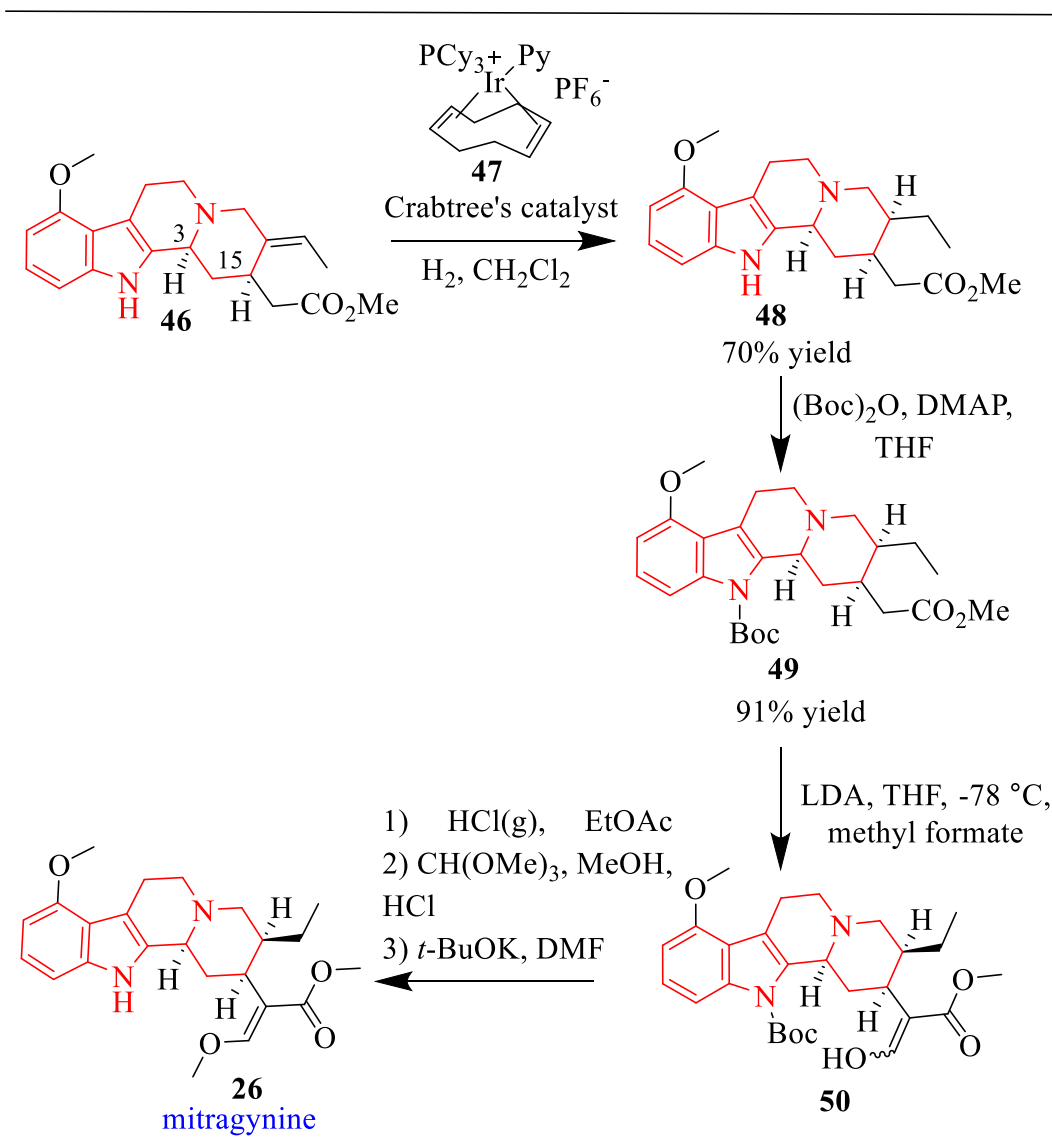
the stereochemical result of the alkylation reaction were ineffective. The majority of these reactions produced the 20- α -H structure as the main byproduct because the electrophiles entered via the *Si* face of the enolate. At this point, rather than attempting to reverse the strong *Si* face selectivity seen in the C-20 alkylation reactions, we decided to take advantage of it. We reasoned that the addition of a hydroxymethyl group at C-20 and the transformation of the ester group into the vinyl group would result in the formation of (\pm)-antirhine **44** and (\pm)-18,19-dihydroantirhine **45** (Scheme 1b).⁵¹



Scheme 1 (b). Synthesis of (\pm)-antirhine **44** and (\pm)-18,19-dihydroantirhine **45**

To synthesize mitragynine, the optically active 4-methoxytryptophan ethyl ester **47** was first treated with Crabtree's catalyst to afford **48** under dichloromethane solvent. The nitrogen of intermediate **48** was further protected with Boc using Boc-anhydride and DMAP, which is then treated with methyl formate and LDA

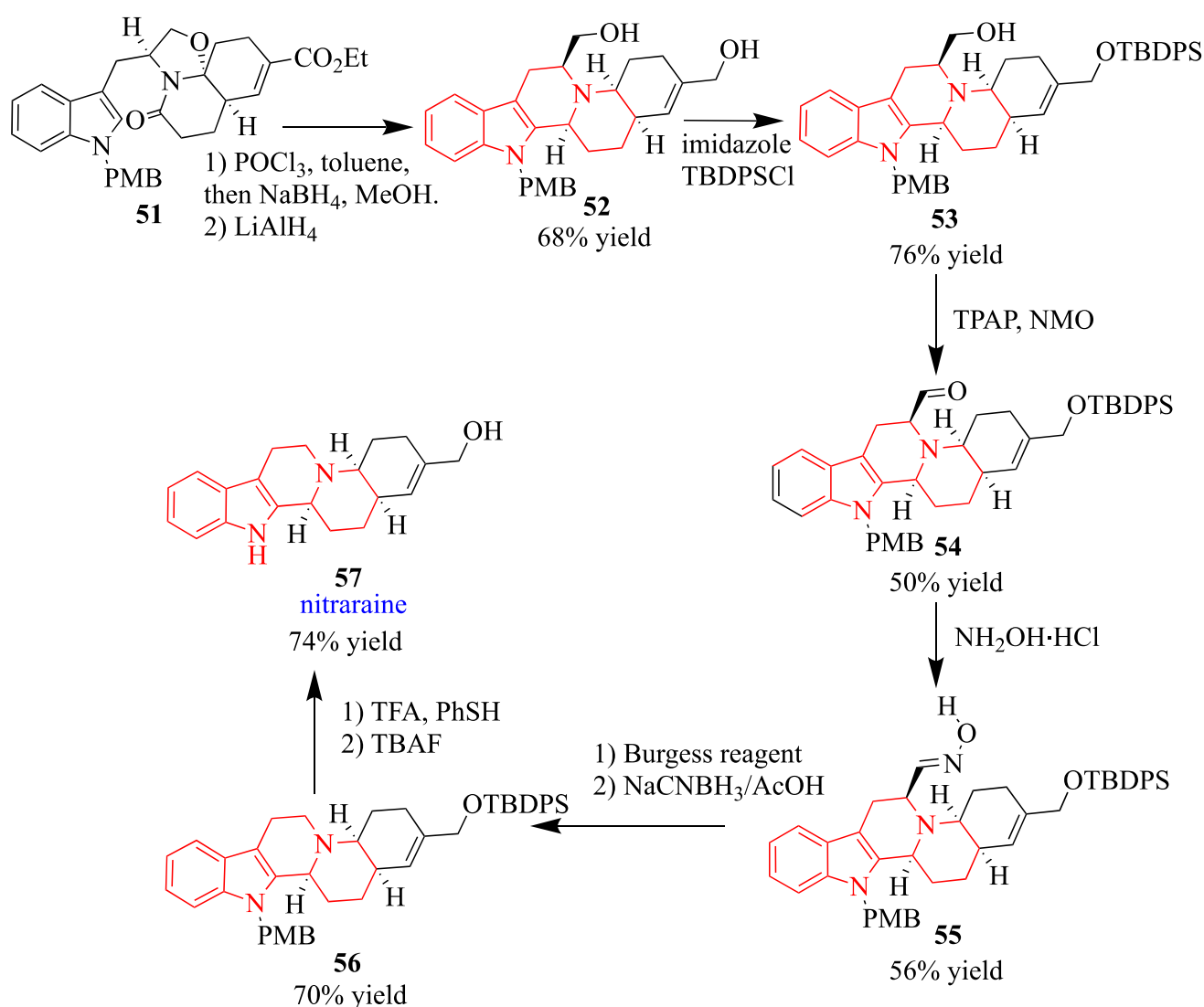
to afford intermediate **50** i.e. α,β -unsaturated ester using the Pictet-Spengler reaction. In the last crucial step, the opioid-agonistic indole alkaloid mitragynine **26** was completely synthesized in quantitative yield (Scheme 2).⁵²



Scheme 2. Synthesis of mitragynine **26**

The hydroxymethyl substituent is derived from tryptophanol required special preservation of the allylic hydroxy group, but diol's insolubility prevented its modification. As a result, the lactam **51** was converted to **52** in 68% overall yield using the Bischler-Napieralski cyclization and LiAlH_4 reduction process described above. Once the allylic hydroxyl group was selectively protected with the bulky *tert*-butyldiphenylsilyl group, the removal of the hydroxymethyl substituent of **53** was performed in four steps: oxidation to aldehyde **54** using tetrapropylammonium perruthenate in the presence of *N*-methylmorpholine *N*-oxide as the co-oxidant (TPAP/NMO), subsequent dehydration of the corresponding oxime **55** with Burgess reagent, and reductive decyanation of the resulting α -amino nitrile. Finally, the target pentacyclic

alcohol **57** was obtained by deprotecting the indole nitrogen of pentacycle **56** with TFA in the presence of PhSH as a carbocation scavenger, followed by desilylation of the alcohol function (Scheme 3).⁵³

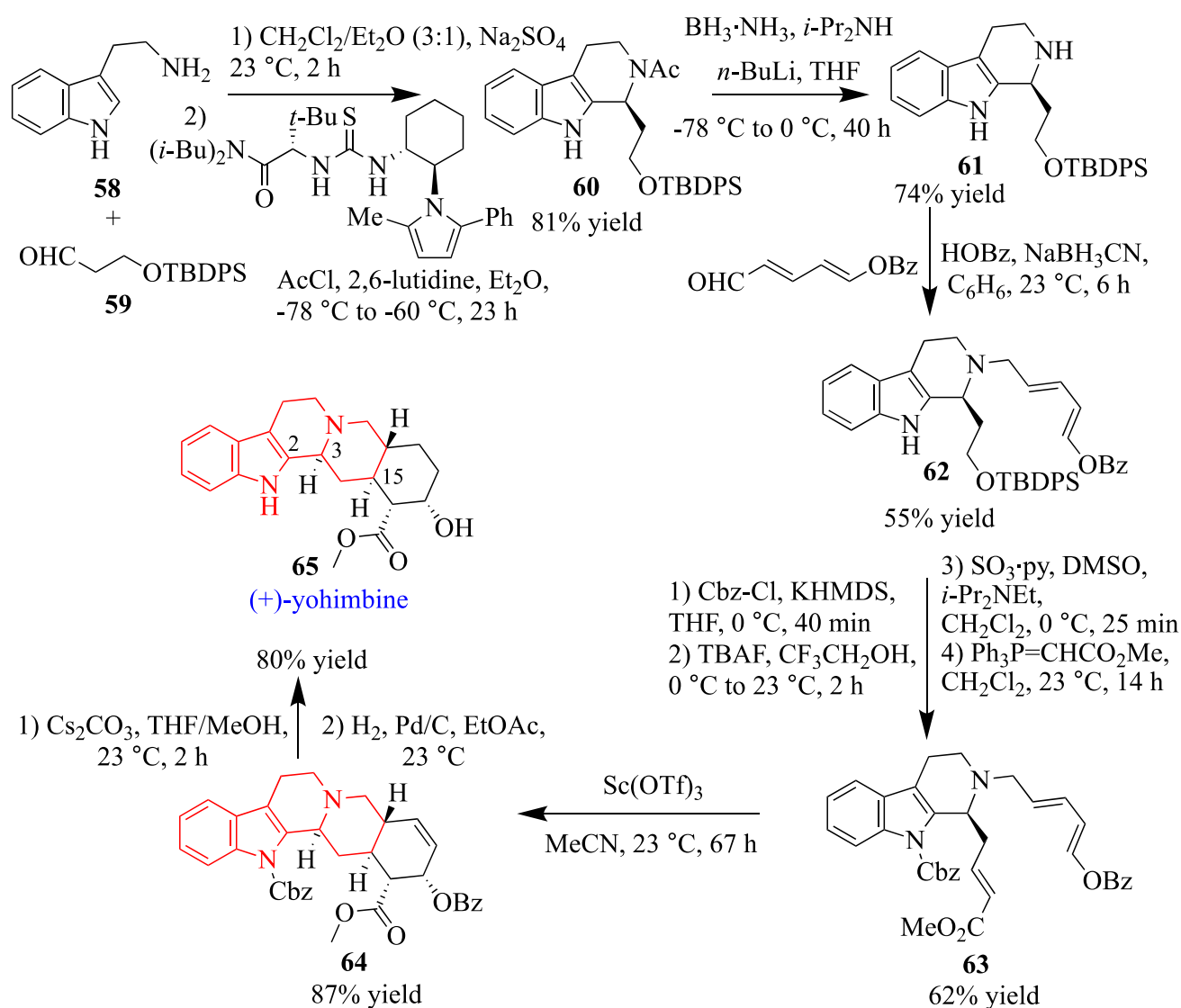


Scheme 3. Synthesis of the putative structure of nitrarine **57**

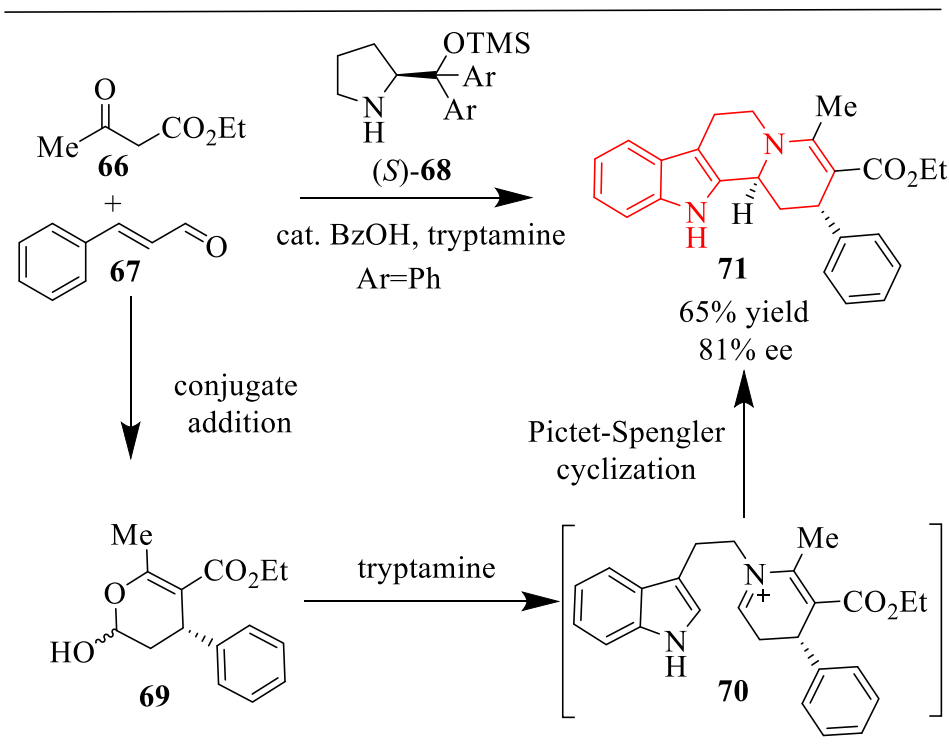
(+)-Yohimbine **65** was synthesized in its entirety over the course of several processes. The absolute configuration was established using a highly enantioselective thiourea-catalyzed acyl-Pictet-Spengler reaction, and the remaining stereocenters were set concurrently using a substrate-controlled intramolecular Diels-Alder reaction (Scheme 4).⁵⁴ The method represents a concise and stereoselective synthesis of (+)-yohimbine **65** via a reductive amination to install the diene side chain, and an exceptionally diastereoselective IMDA reaction. The most crucial finding of this approach is its efficient enantioenriched synthesis in 11 steps with 14% overall yield via asymmetric catalysis.

Using (*S*)-**68** as a catalyst, benzoic acid as an additive, and toluene as a solvent, the organocatalytic

conjugate addition of β -ketoester **66** and cinnamic aldehyde **67** was carried out at 10 °C. After 100% conversion of β -ketoester **66** was confirmed by TLC, the reaction liquid was diluted with toluene before tryptamine and a stoichiometric amount of benzoic acid were added. The mixture was heated at 50 °C for 24 hours. With high enantioselectivity and yield, the desired indoloquinolizidine **71** was isolated as a single diastereomer (Scheme 5).⁵⁵



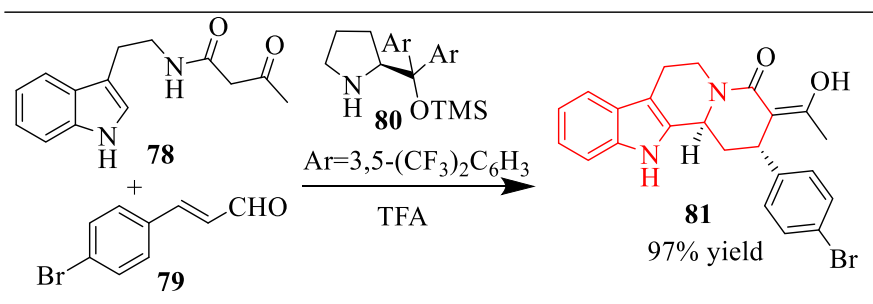
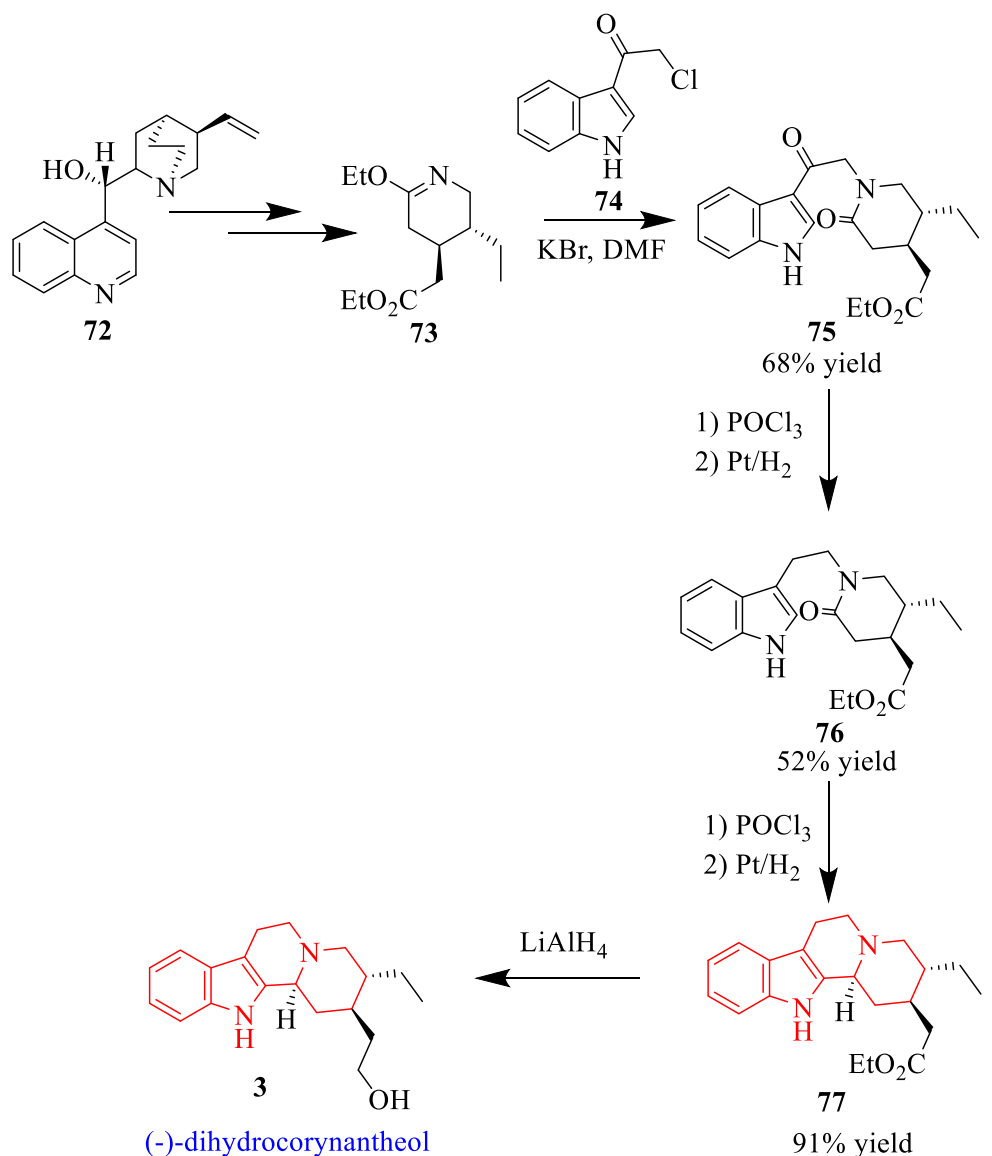
Scheme 4. Synthesis of (+)-yohimbine **65**



Scheme 5. Synthesis of indoloquinolizidine by Michael as well as the Pictet-Spengler reactions

Fujii has a number of studies on fused quinolizidine ring systems, including the entire synthesis of dihydrocorynantheine **1** in 1991. The "lactim ether route" needs the coupling of 3-(chloroacetyl)indole **74** with lactim ether **73**, which is generated from (+)-cinchonine **72** by the conventional degradation procedure. Following treatment of the resultant keto derivative **75** with POCl_3 , the matching oxazolium chloride was obtained, which was subsequently reduced by catalytic hydrogenation to provide lactam **76**. Bischler-Napieralski cyclization followed by catalytic hydrogenation resulted in a 91% total yield for the conversion into the tetracyclic ester **77**. In quantitative yield, the final LiAlH_4 -reduction of **77** produced dihydrocorynantheol **3** (**Scheme 6**).⁵⁶⁻⁵⁸

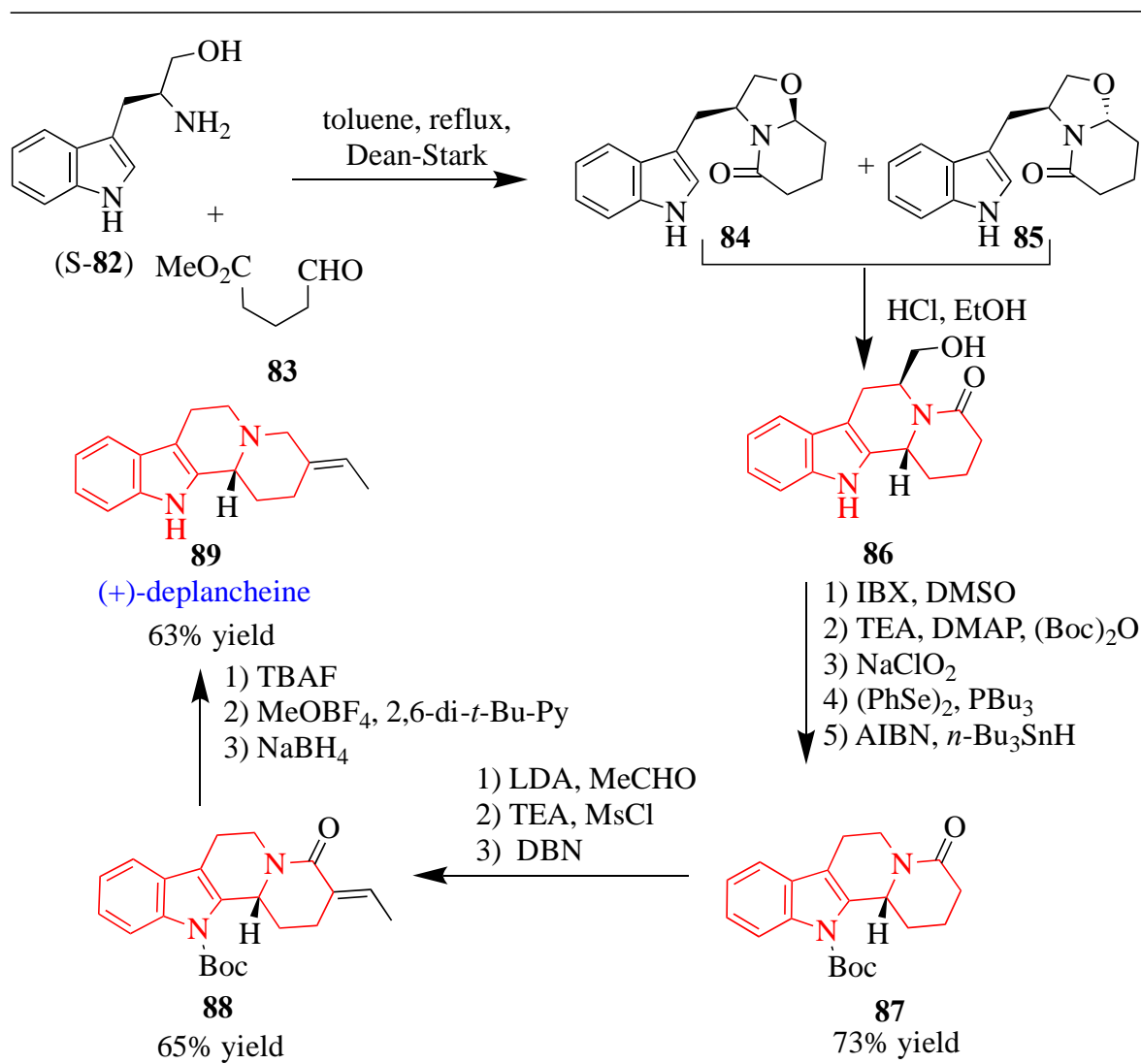
It was possible to obtain highly substituted indolo[2,3-*a*]quinolizidines and benzo[*a*]quinolizidines by an organocatalyzed one-pot Michael addition-Pictet-Spengler sequence of β -ketoamides and α,β -unsaturated aldehydes with moderate to good yields and good to exceptional enantioselectivities. The Michael addition-Pictet-Spengler sequence of compound **78** with aromatic α,β -unsaturated aldehydes **79** afforded the corresponding indoloquinolizidine **81** which had a stable enol structure (**Scheme 7**).⁵⁹



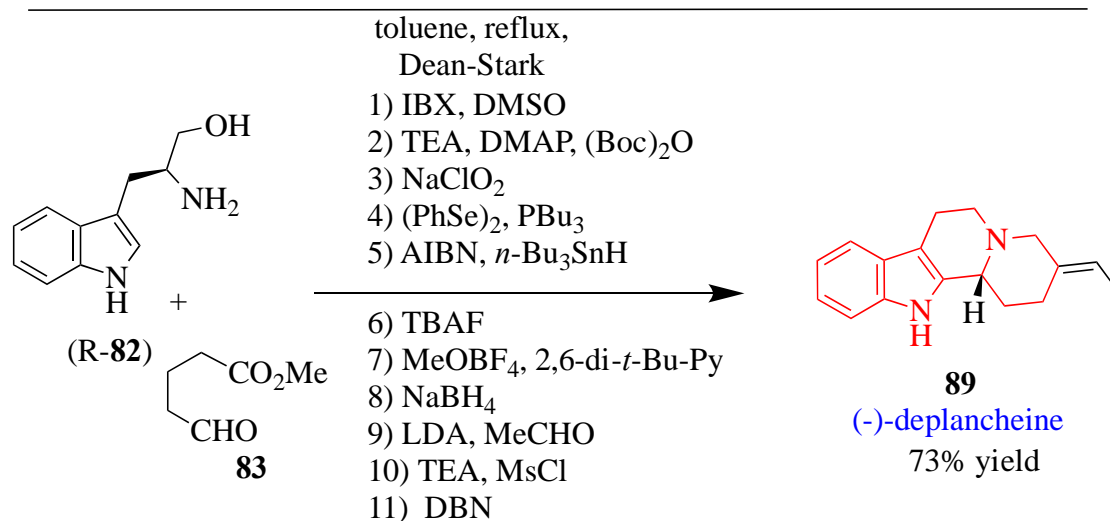
Allin reported the asymmetric synthesis of both enantiomers of the indole alkaloid deplancheine in 2005, using tryptophan-derived lactams **84** and **86** as key intermediates, which are easily accessible from (*S*)-tryptophan (*S*-**82**) and (*R*)-tryptophan (*R*-**82**) via a cyclocondensation process with the aldehyde-ester

83. Pictet-Spengler cyclization of a mixture of bicyclic lactams with HCl in ethanol resulted in the development of the indolo[2,3-*a*]quinolizidine system, yielding **86** as a single molecule. The hydroxymethyl chain was cleaved by oxidation to a carboxylic acid derivative *via* the appropriate aldehyde, followed by acyl selenide formation and subsequent tin-mediated deacylation. The ethylidene moiety was developed in three steps: production of the lithium enolate from **87** and a subsequent aldol reaction with acetaldehyde, activation of the hydroxyl group by mesylation, and finally DBN-induced elimination to yield the target **88**. According to Martin and colleagues, deprotection of the indole nitrogen atom using TBAF, followed by reduction of the lactam carbonyl group, yielded both enantiomers of (+)-deplancheine **89** and (-)-deplancheine **89** (Scheme 8 and 9).⁶⁰⁻⁶⁴

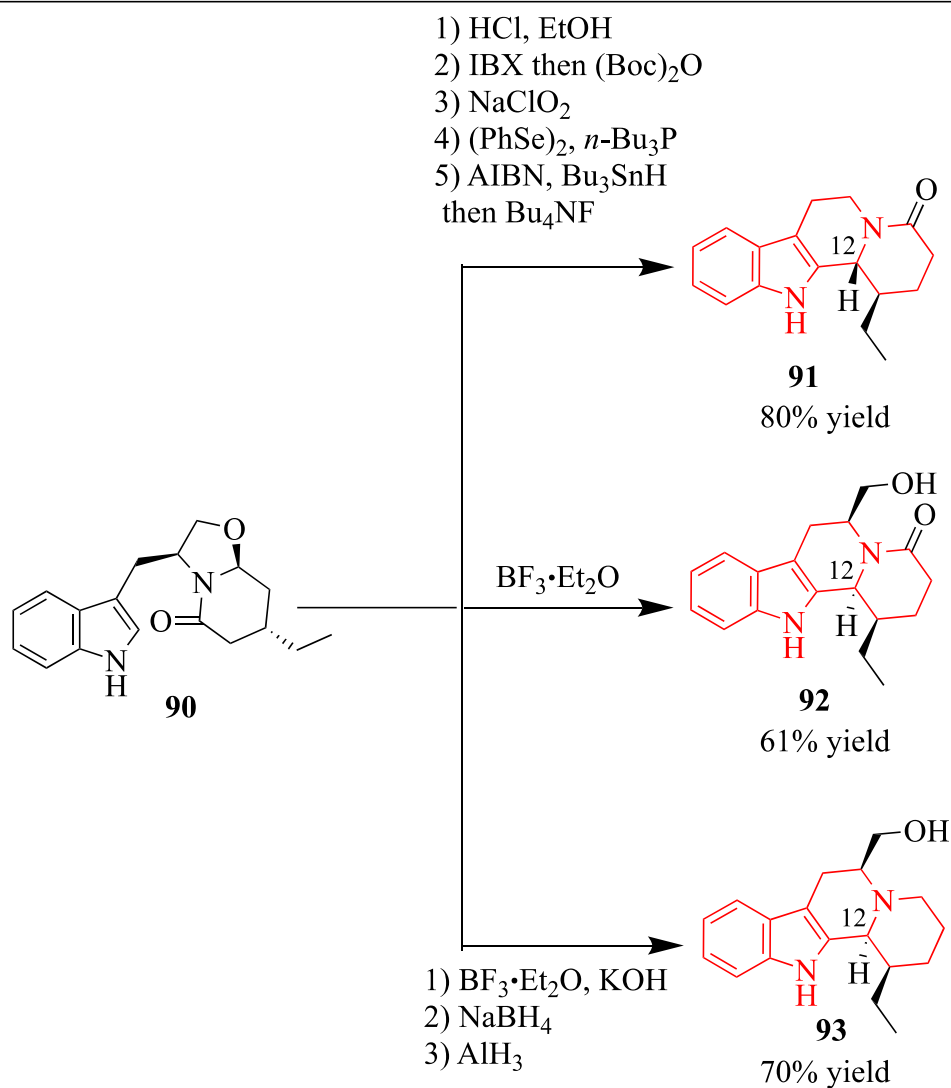
Bosch's research group later thoroughly investigated the stereochemical outcome of Pictet-Spengler cyclizations of tryptophan-derived lactams, describing the stereocontrolled generation of C-12 epimeric indolo[2,3-*a*]quinolizidine derivatives using the appropriated reaction conditions (Scheme 10).⁶⁵⁻⁶⁷



Scheme 8. Asymmetric synthesis of (+)-deplancheine **89**

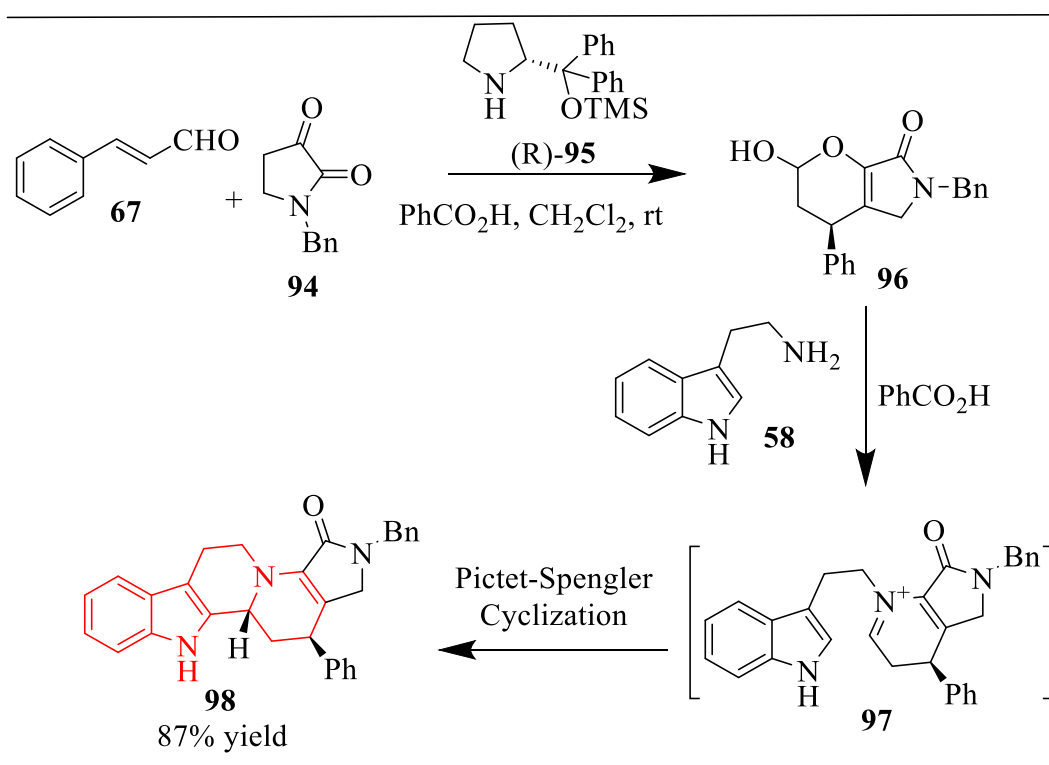


Scheme 9. Access to (-)-deplancheine **89**



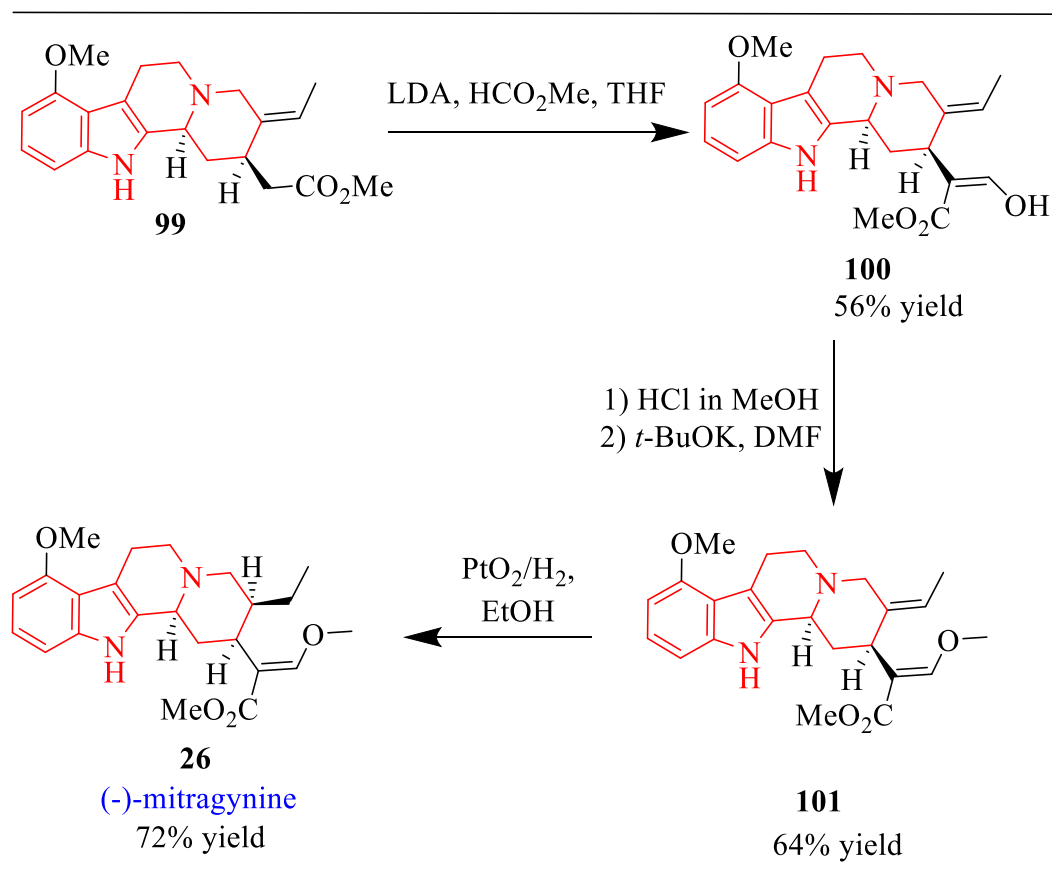
Scheme 10. Cyclizations from (*S*)-tryptophanol-derived oxazolopiperidone lactams

The widely available *N*-containing pronucleophile α -oxo- γ -butyrolactam **95** could be used, and the novel butyrolactam-fused indoloquinolizidine could be synthesized by an organocatalyzed three-component coupling process using **94**, α,β -unsaturated aldehyde **67**, and tryptamine. According to the iminium ion activation method, a secondary amine catalyzed Michael addition of **94** to **67** would start the reaction chain that would result in the chiral hemiacetal A **96**. Under acidic circumstances, activated hemiacetal A **96** interacts with tryptamine to form iminium ion B **97**, which then undergoes a diastereoselective Pictet-Spengler reaction to provide the expected butyrolactam-fused indoloquinolizidine **98** (Scheme 11).⁶⁸



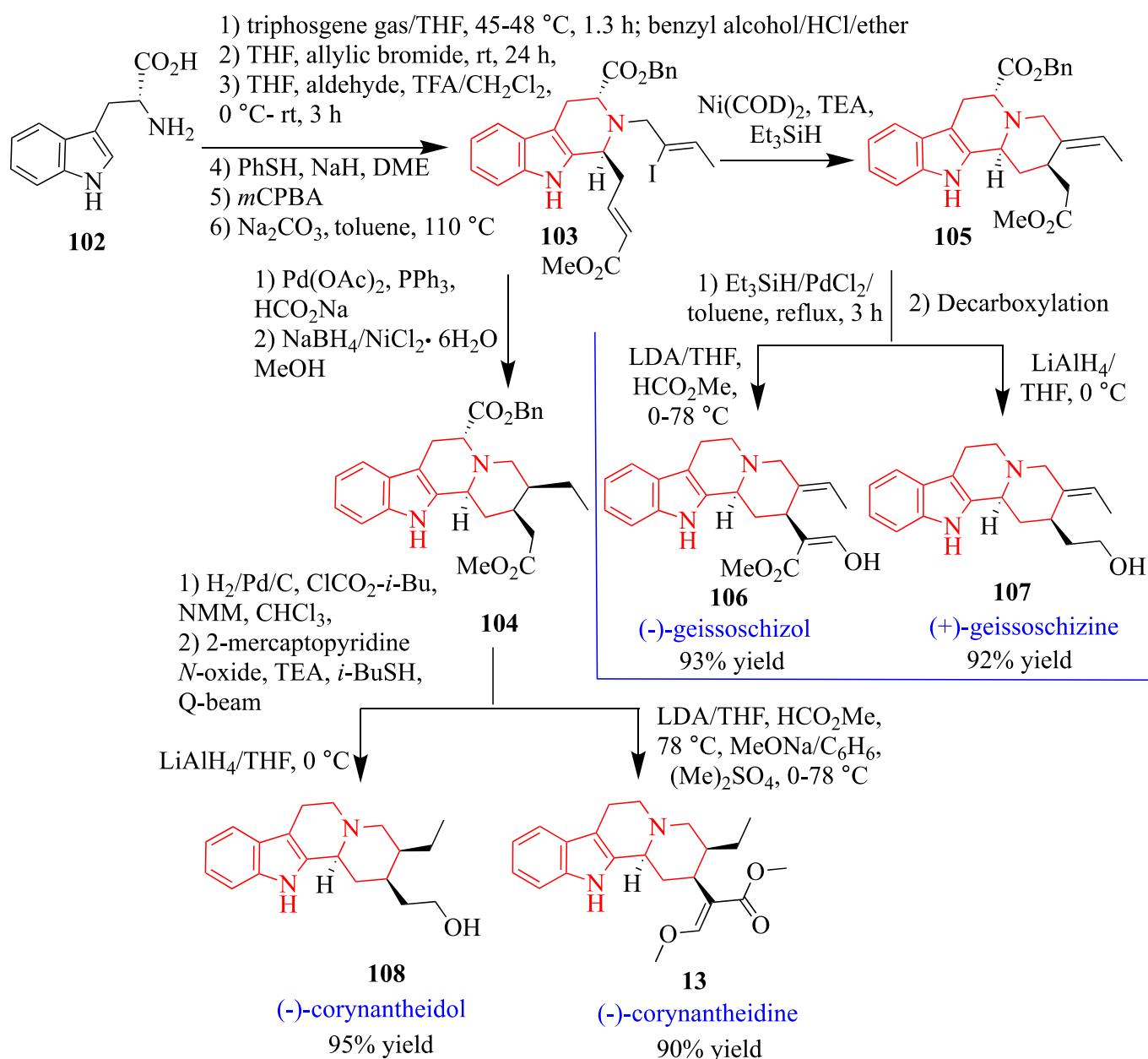
Scheme 11. One-pot synthesis of indoloquinolizidine scaffold

According to the conventional method a formyl group is introduced in the **99**. Since, the attempt of *O*-methylation gives the enol system by the using of common reagent. The formyl group in **100** was first converted in the dimethyl acetal which was treated with *t*-BuOK to give methyl enol ether **101** in 64% yield. In the last step, the reduction of methyl enol ether **101** to give (-)-mitragynine **26** (Scheme 12).⁶⁹



Scheme 12. Access of (-)-mitragynine **26**

Using (*R*)-tryptophan **102** as a chiral reagent, enantiospecific total synthesis of (-)-corynantheidine **13**, (-)-corynantheidol **108**, (-)-geissoschizol **106**, and (+)-geissoschizine **107** was achieved *via* the common critical intermediate **103**. An intramolecular Heck coupling of α,β -unsaturated ester **103** and subsequent NaBH_4 -reduction in the presence of a catalytic quantity of $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ was done to build the **104** ring system, which is found in corynantheidol and corynantheine. Further, stereoselective Michael reaction of **103** employing $\text{Ni}[\text{COD}]_2\text{-Et}_3\text{N}$ and Et_3SiH generated **105** in an efficient manner, which was further used to generate the molecular framework of geissoschizol and geissoschizine (**Scheme 13**).⁷⁰

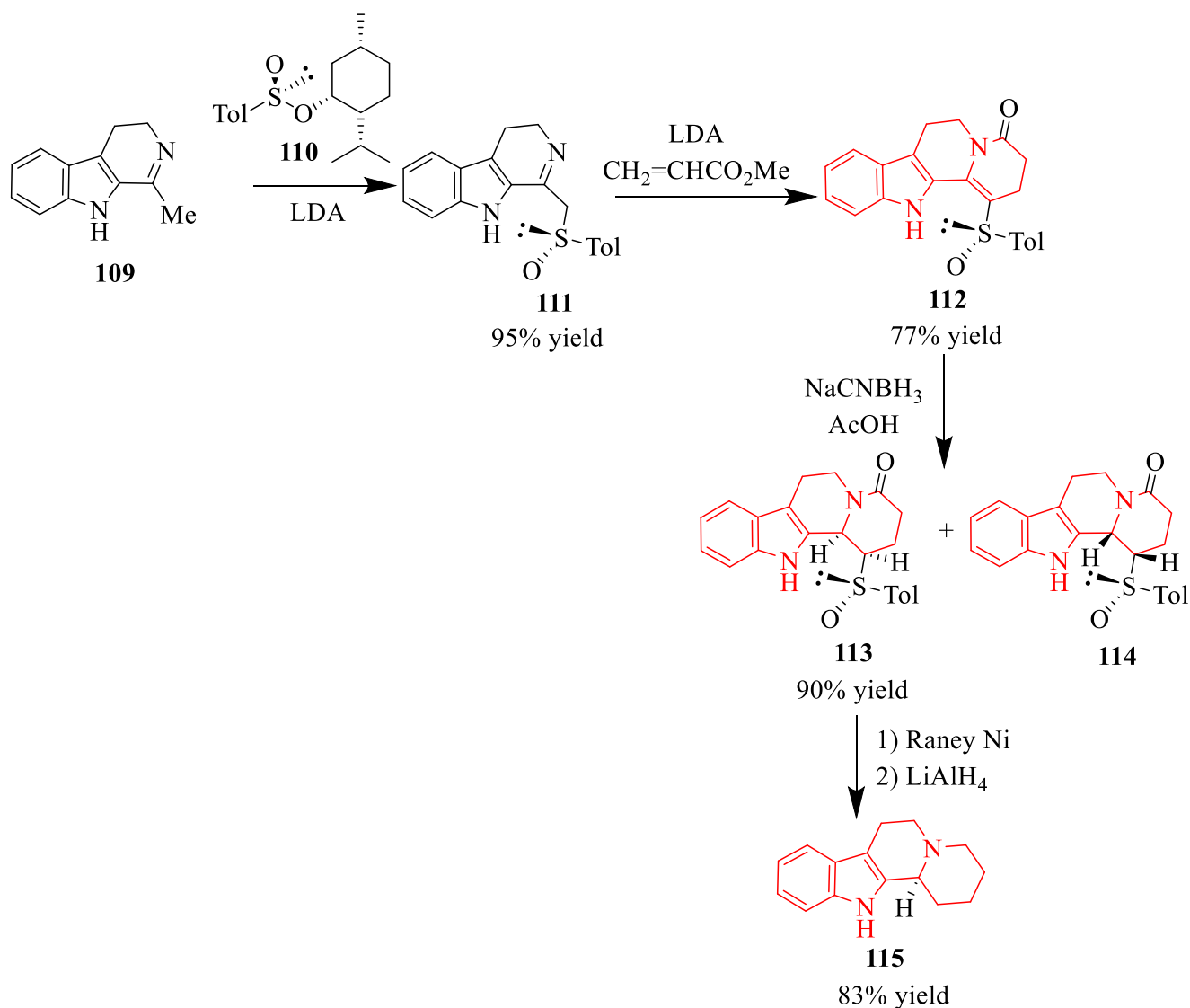


Scheme 13. Synthesis of (-)-corynantheidine **13**, (-)-corynantheidol **108**, (-)-geissoschizol **106**, and (+)-geissoschizine **107**

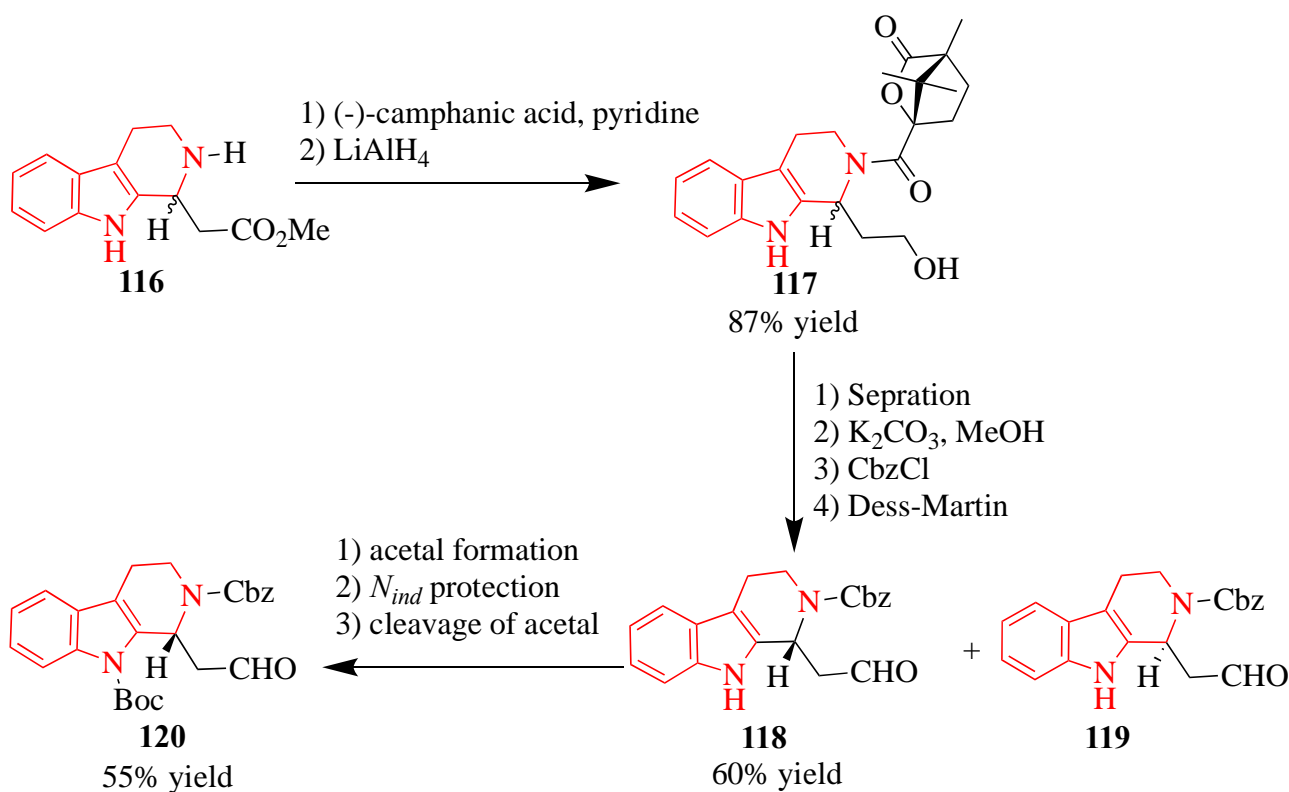
Hua reported one of the important examples of enantioselective synthesis of indoloquinolizidine alkaloids utilizing a tandem process in 1991, employing the asymmetric 1,4-addition/ring-closure technique. Harmal sulfinyl ketimine **111** was synthesized from harmalan **109** and (-)-menthyl *p*-toluenesulfinate **110**, and then employed in stereoselective conjugate addition with methyl acrylate, followed by *in situ* cyclization to generate lactam **112** in 77% yield. The resultant lactam **112** was then subjected to NaCNBH₃-reduction of the double bond to give the mixture of **113** and **114** in 90% yield. In contrast to previous results by this author, the reduction in this case was not stereoselective, resulting in a 1.9:1 mixture of diastereomers. Desulfuration of **113** with Raney Ni and subsequent LiAlH₄ reduction of the amide moiety produced

octahydroindolo[2,3-*a*]quinolizidine **115**. (Scheme 14).⁷¹

Tietze revealed the enantioselective synthesis of corynanthe indole alkaloids (+)-hirsutine **4** and (+)-dihydrocorynantheine **1** by a domino Knoevenagel-hetero-Diels-Alder reaction, employing enantiomerically pure tetrahydrocarboline carbaldehydes. Further, on a large scale, aldehydes **120** (N_{ind}-Boc) and **119** (N_{ind}-H) were synthesized by separating the diastereomeric amides **117** using Dess-Martin assembly, which were synthesized from *rac*-**116** and camphanic acid (Scheme 15).⁷²

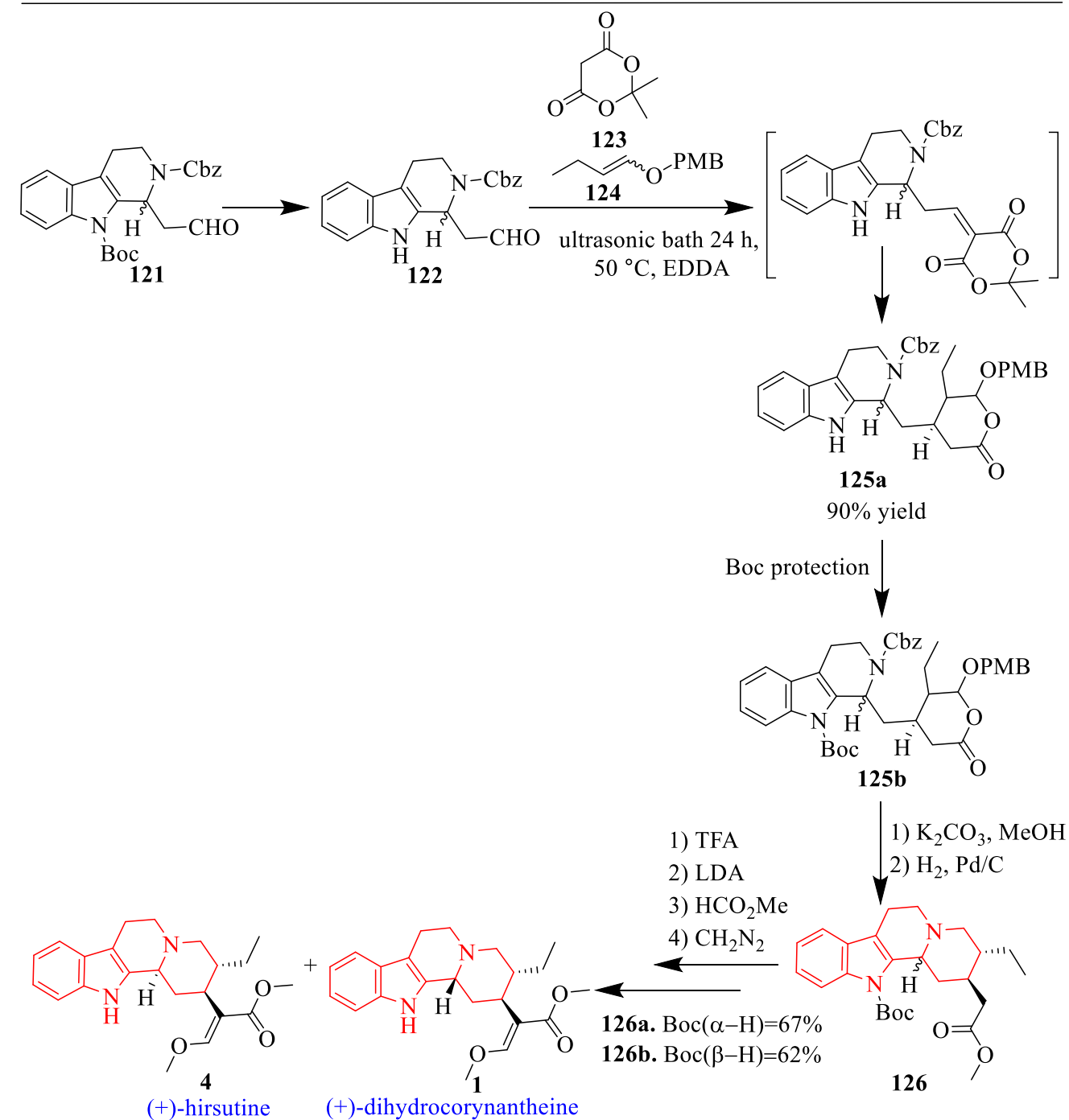


Scheme 14. Asymmetric synthesis of octahydroindolo[2,3-*a*]quinolizidine



Scheme 15. Synthesis of analogues of tetrahydro- β -carboline carbaldehydes

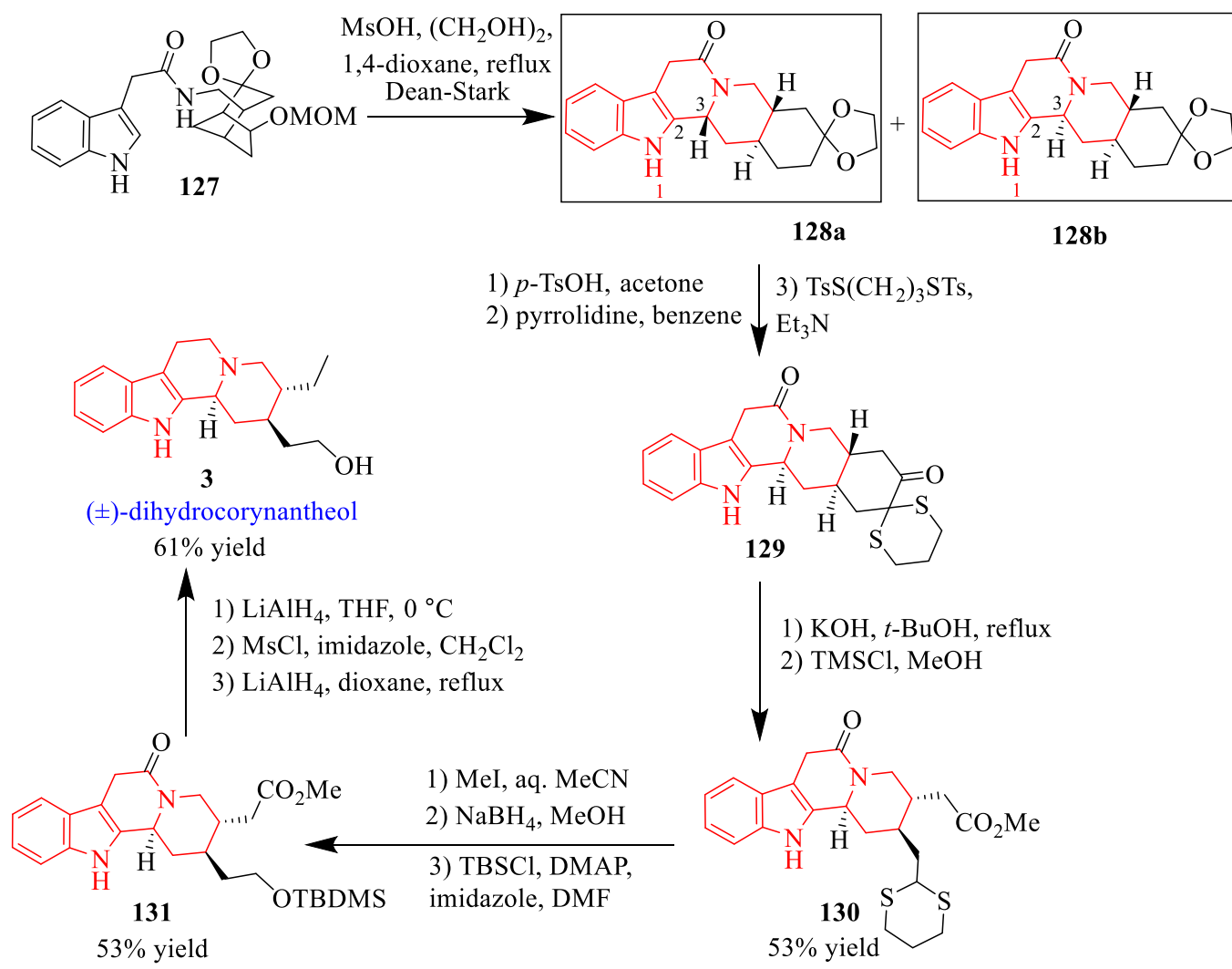
In an ultrasonic bath, the presence of ethylenediamine diacetate (EDDA), the aldehyde **122** was condensed with Meldrum's acid **123** as well as 4-methoxybenzyl butenyl ether **124** to yield the diastereomeric cycloadducts **125a** with a slightly lower asymmetric induction of 4.8:1. The cycloadduct mixture was transformed into *tert*-butoxycarbonyl derivatives **125b**, which were then hydrogenated with methanol/K₂CO₃. From **125b**, chromatographic separation yielded the enantiomerically pure diastereomer **126b** in 62% total yield. The enantiomerically pure indole alkaloids (+)-hirsutine **4** and (+)-dihydrocorynantheine **1** were obtained *via* cleavage of the *tert*-butoxycarbonyl group in **126a** and **126b**, followed by condensation with methyl formate & treatment with diazomethane (Scheme 16).^{69,72}



Scheme 16. Synthesis of (+)-hirsutine **4** and (+)-dihydrocorynantheine **1**

A tandem retro-Aldol-Pictet-Spengler reaction and C-3 epimerization of amide **127** with methanesulfonic acid in boiling dioxane resulted 52% yield of yohimbine type derivative **128a** and 23% yield of pseudoyohimbane **128b**. The recovered **128b** was treated to the aforementioned acidic conditions, yielding 59% **128a** and 29% unreacted **128b**. The ketal moiety was deprotected for the transition of the *E*-ring moiety to the seco form present in the dihydrocorynantheol **3** alkaloid, and the resultant ketone was reacted with pyrrolidine to form an enamine, which was promptly treated with trimethylene dithiosylate to generate **129**. The dithio ketone was further cleaved by using KOH in *tert*-butyl alcohol under boiling

conditions, and the resultant acid was esterified to yield methyl ester **130**. The corresponding alcohol was then obtained by treating this molecule with the iodomethane in aqueous acetonitrile, followed by the reduction of the resultant aldehyde with sodium borohydride to generate **131**. The resulting mesylate was also 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, completing the synthesis of the (-)-dihydrocorynantheol **3** (Scheme 17).⁷³⁻⁷⁵

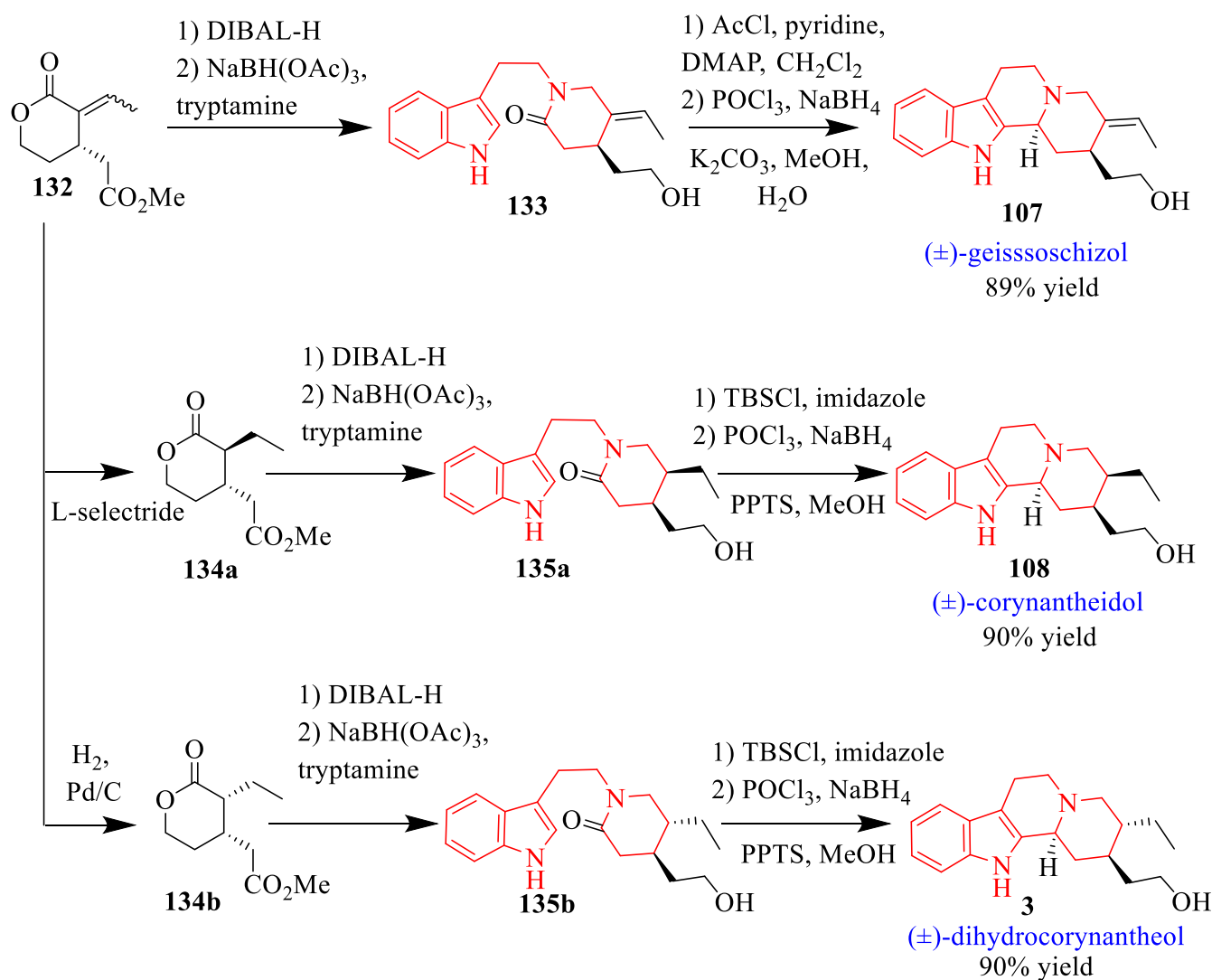


Scheme 17. Synthesis of (±)-dihydrocorynantheol **3**

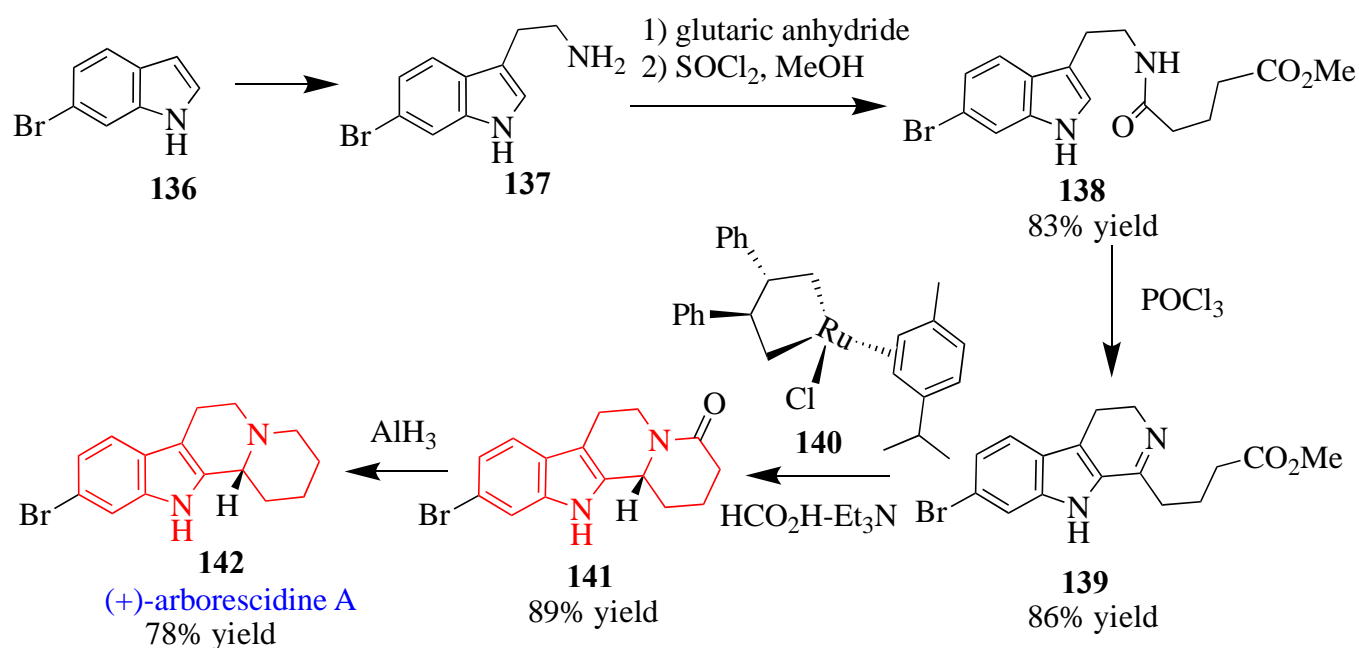
Lactam intermediate **133** was obtained by reducing the lactone carbonyl **132** with DIBAL, followed by a reductive amination/lactam cyclization with tryptamine. The hydroxyl functionality was protected as an acetate ester, followed by Bischler-Napieralski cyclization and alkaline hydrolysis, yielding racemic mixture of geissoschizol **107**. Alternatively, conjugate reduction of **132** produces only the thermodynamically preferred *trans*-isomer of the disubstituted lactone **134a**. On the other hand, catalytic hydrogenation of the olefin **132** yields just the matching *cis*-lactone **134a**, owing to hydrogen delivery to

the least sterically hindered face of the olefin. Corynantheidol (+)-**108** and dihydrocorynantheol (+)-**3** were synthesized from lactones **134a** and **134b** in a similar manner. Pure lactone **134b**, on the other hand, resulted in a 1.3:1 mixture of isomers, which were separated by column chromatography after the synthesis of the indoloquinolizidine system (**Scheme 18**).^{76,77}

The 6-bromotryptamine **137** is synthesized from 6-bromoindole **136** using the Shumaker and Davidson approach. In this method glutamic anhydride yielded the equivalent amide carboxylic acid, which was subsequently esterified. Following treatment with POCl₃, the Bischler-Napieralsky cyclization was accelerated, yielding imine **139** in 86% yield. To achieve the necessary asymmetry, imine **139** was reduced under Noyori asymmetric hydrogen-transfer reaction using a pre-made (*S,S*)-TsDPEN-Ru(II) complex **140**, yielding lactam **141** in 89% yield and 96% ee after *in situ* cyclization. Finally, the lactam carbonyl was reduced with alane to provide (+)- arborescidine A **142**. (**Scheme 19**).⁷⁸⁻⁸¹



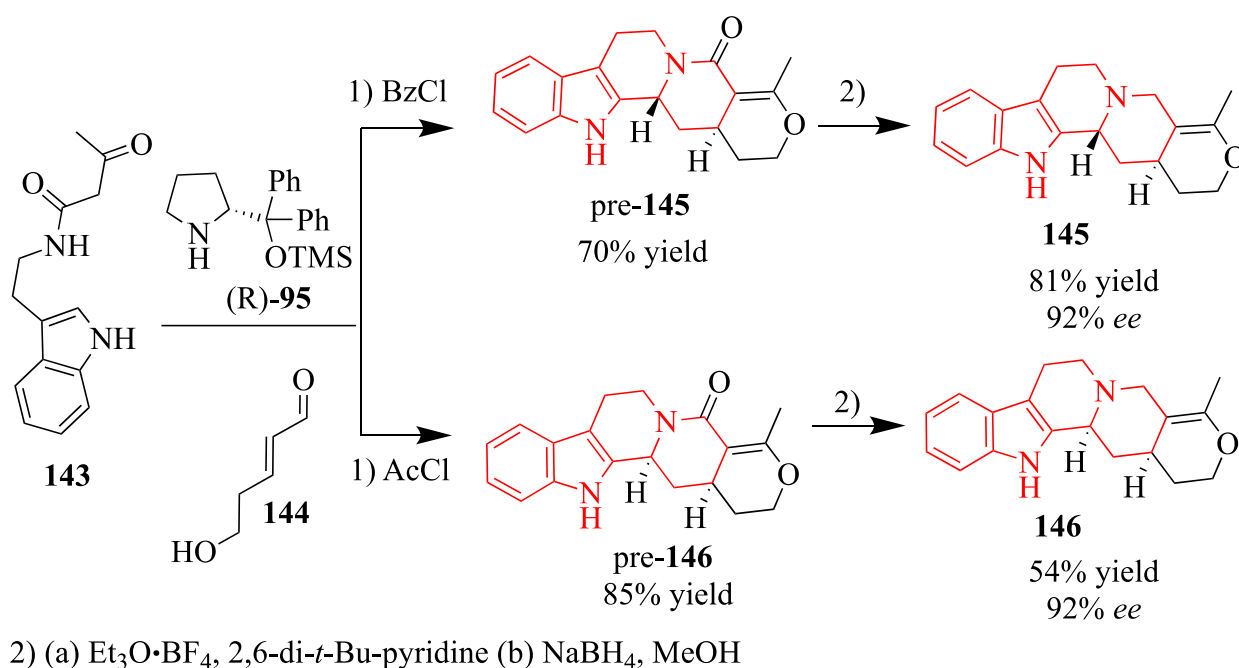
Scheme 18. Synthesis of (+)-geissoschizol **107**, (+)-corynantheidol **108** & (+)-dihydrocorynantheol **3**



Scheme 19. Synthesis of (+)-arborescicine A **142**

Franzén described a universal and good asymmetric approach for the synthesis of a wide range of optically active natural compounds from the corynantheine and ipecac alkaloids. The α,β -unsaturated aldehyde **144**, which was obtained through the cross-metathesis of acroleine and 3-butenol, and the β -ketoamides **143**, which were obtained through the condensation of *tert*-butyl acetoacetate with the corresponding 2-arylethanamine, were required for the stereoselective synthesis of the quinolizidine skeleton. In the presence of catalyst (*R*)-**95**, β -ketoamides **143** smoothly reacted with the α,β -unsaturated aldehyde to generate diastereomeric mixture of lactols and then the reaction was further quenched by adding trifluoroacetic acid (TFA) giving a 1:1 mixture of the two ring-junction isomers pre-**145** and pre-**146**. It has been also found that when the reaction is quenched with acetyl chloride, the only observable isomer was the indolo[2,3-*a*]quinolizidine pre-**146**, whereas when benzoyl chloride was used, diastereoselectivity switched to product pre-**145**. It is also worth mentioning that by treatment with TFA, the kinetically favoured β -indolo[2,3-*a*]quinolizidine pre-**145** could be epimerized to the thermodynamically favored pre-**146** epimer, yielding an 85:15 ratio. Following reduction of the crude reaction mixture from the one-pot cascade, the corresponding amines **145** and **146** were obtained in high to moderate overall yields by initial alkylation with triethylxonium tetrafluoroborate, followed by NaBH₄-reduction (**Scheme 20**).⁸² In addition, Zhang et al. also described the total synthesis of several natural products such as (-)-dihydrocorynantheol, (-)-hirsutinol, (-)-corynantheol, (-)-protoemetinol, (-)-dihydrocorynantheol, (-)-corynantheol, (-)-protoemetine, and (-)-(15*S*)-hydroxydihydrocorynantheol, and their epimers in quantitative yields. Further, it has been also well documented that the indole⁸³⁻⁸⁵ and its analogues possess

several useful bioactivities such as antibacterial,⁸⁶⁻⁹⁰ antifungal,⁹¹⁻⁹³ antimalarial,⁹⁴⁻⁹⁶ anticancer,⁹⁷⁻¹⁰⁰ analgesic,¹⁰¹⁻¹⁰³ etc.



Scheme 20. Synthetic approach for pre-145 and pre-146 of indolo[2,3-*a*]quinolizidines

4. CONCLUSION

Indolo[2,3-*a*]quinolizidine serves as the main scaffold for the formation of several class of drugs and therefore many bioactive indolo[2,3-*a*]quinolizidines have already been synthesized, allowing the flexible addition of various functional groups to the ring system. These functional structures possess a range of bioactivities such as anticancer, antihyperglycemic, antiplatelet aggregation, antiviral and vasodilation. Studies of the relationship between structure and activity have shown the potential role of these frameworks in the drug discovery and medicinal chemistry. In this article, we have discussed many synthetic methodologies for the preparation of indolo[2,3-*a*]quinolizidine scaffolds under different conditions. In addition, we have also described the existing biological activities of these frameworks and the role of different substituents on such derivatives towards better understanding the significance of this moiety in drug discovery. The tetracyclic ring is involved in various biological processes, although no clear explanation of how this occurs has yet been identified. However, the data shows that these frameworks are undoubtedly a future focus area and will play a crucial role in the field of drug discovery.

Abbreviation

SAR- Structure-activity relationship

DHC- Dihydrocorynantheol

TFA- Trifluoroacetic acid
DBN- 1,5-Diazabicyclo[4.3.0]non-5-ene
TBAF- Tetra-*n*-butylammonium fluoride
Boc- *tert*-Butoxycarbonyl
DMAP- 4-(Dimethylamino)pyridine
TEA- Triethylamine
TBS- Tris-buffered saline
EDDA- Ethylenediamine diacetate
DIBAL-H- Di-isobutylaluminium hydride
THF- Tetrahydrofuran

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