SYNTHETIC APPROACHES FOR TOTAL SYNTHESIS OF HARMANE & BREVICOLLINE

A M.SC. DISSERTATION REPORT BY:

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DECLARATION

I hereby declare that the matter presented in this dissertation entitled "**Synthetic approaches for total synthesis of Harmane and Brevicolline**" is based on the results of the investigation carried out by me in the School of Chemical Sciences, Goa University, Goa, under the supervision of Dr. Vinod Mandrekar and the same has not been submitted elsewhere for the award of a degree or diploma.

Ms. Siddhi R. Manjrekar
M.Sc. Organic Chemistry

CERTIFICATE

This is to certify that the dissertation entitled "**Synthetic approaches for total synthesis of Harmane & Brevicolline**" is bonafide work carried out by Ms. Siddhi Ramchandra Manjrekar in the academic year 2021-2022 under my supervision in partial fulfilment of the requirement for the degree of Master of Science in Chemistry at the School of Chemical Sciences, Goa University.

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Project Guide

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Dean of School of Chemical Sciences, Goa University

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ABSTRACT

β-carboline and its saturated analogue are common structural motifs in nature and pharmaceuticals. Because of its biological value, the discovery of newer practical methods for the synthesis of this scaffold is of substantial interest. This report comprises primarily a literature review of numerous research papers, including isolation, characterization, and total synthesis of β-carboline alkaloids; Harmane and Brevicolline. Harmane is isolated from a variety of terrestrial plants and marine species. This article includes the isolation of harmane from tobacco and cigarette smoke reported in 1962 and its characterization carried out using infrared, ultraviolet, high-resolution mass spectrometry (HRMS), NMR, C-13 NMR, and X-Ray crystallography. Brevicolline is a major alkaloid of the plant Carex brevicollis DC, the β-carboline unit of this alkaloid has been confirmed to be derived from tryptophan and pyruvic acid, and it also includes reported characterization carried out using infrared, ultraviolet spectroscopy, NMR, and mass spectrometry. Particularly, synthetic approaches for the total synthesis of Harmane and Brevicolline reported till 2022 have been highlighted. An attempt has been made at retrosynthesis and forward synthesis of harmane. Information for the report is gathered from research articles from reputed journals.

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INTRODUCTION

β-Carbolines are a group of pharmacologically interesting compounds belonging to a class of indole alkaloids (non-isoprenoid) that contain a unique pyrido[3,4-b]indole structure with a well-documented neuroactivity[1]. Some are widely distributed in nature, including marine creatures, various plants, insects, foodstuffs, mammalians, human tissues, and body fluids. Molecules of the structurally diverse family of β-carbolines exhibit a wide range of biological activities, whose reported effects include antineoplastic (tubulin-binding), anticonvulsive, hypnotic, and anxiolytic (benzodiazepine receptor inhibitors), antiviral, antimicrobial, and topoisomerase II inhibition and inhibition of cGMP-dependent processes,[2]which has naturally attracted much attention from the synthetic community.

The β-carboline alkaloids were isolated originally from Peganum harmala[3,4] (Zygophyllaceae, Syrian Rue), a traditional herbal medicine used in the Middle East and North Africa as an emmenagogue and abortifacient[5]. The primary components of its extract are Harmane, harmine, harmaline, and harmalol. The plant seeds' extracts were traditionally used to treat syphilis, malaria, hysteria, neuralgia, Parkinson's disease, rheumatism, and alimentary tract cancers. Plants containing β-carbolines were commonly utilized as hallucinogenic beverages or snuffs in the Amazon basin.[6] Out of more than 750 species of local plants tested for alkaloid′s presence by the Laboratory of Chemistry of Natural Compounds of the Moldovan Branch of the Academy of Sciences of the USSR, the Parma buirush (Carex brevicollis) was found to contain high content of alkaloids. The overall extract obtained from this plant contained 7 alkaloids, four new ones were brevicolline, brevicarine, dehydrobrevicollin, and homobrevicollin.[7]Other important β-carbolines include Pinoline, Plakortamine D, Norharman[8], Eudistomin, Tetrahydroharmine,9-Methyl-βcarboline, Hyrtioerectine A, etc.

Harmane fig (1), a naturally occurring β-carboline alkaloid is found in a variety of foods including coffee[9], sauces, and cooked meat. It is also present in tobacco smoke[10]. It possesses antidepressant, antiplatelet, antioxidant, hypotensive, antidiabetic, antinociceptive, anti-parasite effects, and also acts as an inhibitor of acetylcholinesterase and myeloperoxidase.[4]

The effects of harmane and its two β-carbolinium synthetic derivative salts (N-methyl and N-ethyl) on cholinesterase inhibition were explored using a combination of kinetics and molecular modeling[11]. Harmane functions as a co-mutagen, causing non-mutagenic aromatic amines such as aniline or o-toluidine to become mutagenic.[12]Synthesis of Harmane fig(1) was carried out due to its various biological activities including good antiviral (anti-TMV, anti-HIV) and fungicidal activities. Harmane was also employed as a fluorescent molecular probe in stationary fluorimetry studies of transport proteins.

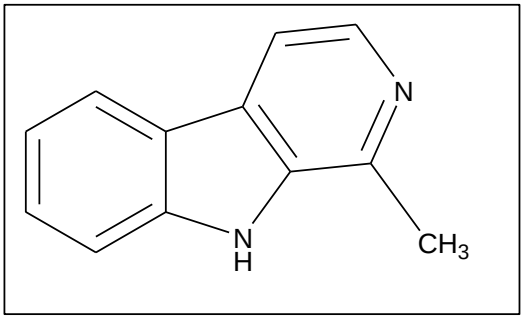


Fig (1): Harmane

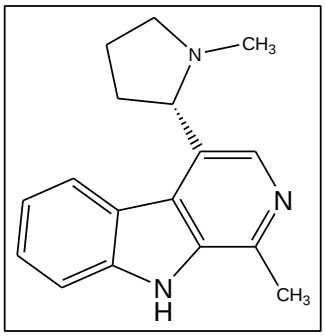


Fig (2): (S)-Brevicolline

The β-carboline alkaloid, Brevicolline is the major alkaloid of the plant Carex brevicollis DC (Cyperaceae), native to the southwestern part of the U.S.S.R.[13,14] is a derivative of harmane, first extracted in 1960. Later in 1977, B. Zsadon, and his co-workers, P. Kaposi & G. Kurti isolated 1.95 g of (S)-Brevicolline fig (2) from 1 Kg air-dried leaves of Carex brevicollis plant in Hungary.

The Pharmacologic State Committee of the Ministry of Health of the former USSR introduced Brevicolline onto medicinal practice as it was proven to be an excellent ganglion blocker, possessing hypotensive activity. Later, in 1977, brevicolline had been admitted for utilization in the field of veterinary.[7]The β-carboline unit of this alkaloid has been confirmed to be derived from tryptophan and pyruvic acid.[15]Synthesis of Brevicolline (fig 2), was carried out because of its known various biological effects, such as a phototoxic effect against bacteria and fungi, a photosensitizing effect, and its application against uterine inertia of pregnant women because of its oxytocic effect.[2] It also plays an organocatalytic role in the synthesis of Spirooxindole derivatives as shown in the 2011 publication.[16]Different nitro and Bromo derivatives of Brevicolline have also been synthesized.[17]

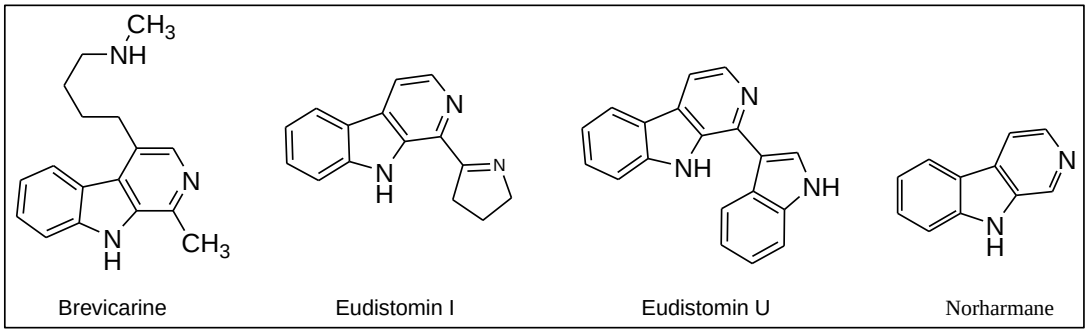


Fig (3): Other important β-carbolines

ISOLATION:

2.1 Isolation of Harmane:

Harmane was first isolated from a variety of terrestrial plants. Later, harmane was reported in marine species as a minor component in the marine dinoflagellate Noctiluca miliaris and the bryozoans Co-staticella hastata and Cribricellina cribraria.[18]

E. H. Poindexter et al. isolated harmane from tobacco and cigarette smoke.[1962][10]

On paper chromatograms, two extremely fluorescent chemicals were found during a study of the basic part of cigarette smoke. By using ultraviolet and infrared spectrophotometry, these were identified as harmane (fig 1) and norharmane (fig 3). Acidic extraction of smoke was used to isolate the alkaloid Harmane, which was followed by cellulose column chromatography of the free bases and resolution by paper chromatography. A quantitative approach was established to quantify the quantity of harmane alkaloids in smoke and tobacco. The quantities of harmane alkaloids found in the smoke of several types of cigarettes as well as in leaves are shown in Table (1).

Sr No.	Samples	Harmane concentration (ug/g)
1	Bright cigarette smoke	3.6*
2	Burley cigarette smoke	5.8*
3	A standard commercial blend	3.3*
4	Bright leaf	0.02
5	Burley leaf	0.02

Table (1): Concentration of Harmane alkaloid in the smoke and leaf of several types of cigarettes. *Based on wt. of cigarette: 1.0g

2.2 Isolation of Brevicolline:

Kompil, E. Grossmann, et al. biosynthesis of brevicolline.[1969][15]

Active Brevicolline was obtained when DL-[2-^{14}C] tryptophan, sodium[2-^{14}C] pyrotartrate, sodium [^{14}C]-formate, and universally labeled L-[^{14}C] glutamic acid were introduced through the root system into Carex brevicollis DC as shown in table (2).

SR.NO.	Preparation of nutrient solution	Specific incorporation %	Activity of Brevicolline counts/min/ mM $.10^5$
1	DL-[2-^{14}C] tryptophan	0.01	6.30
2	Sodium[2-^{14}C] pyrotartrate	0.017	6.78
3	L-[U-^{14}C] glutamic acid	0.0009	0.82
4	Sodium [^{14}C]-formate	0.012	0.59

Table (2): Introduction of preparations into Carex brevicollis resulting in brevicolline.

Radioactive brevicolline with specific incorporation of 0.01% was isolated from the plant Carex brevicollis DC grown in a nutrient solution containing DL-[2-^{14}C] tryptophan.

CHARACTERIZATION:

3.1 Characterization of Harmane:

The confirmed structural formula of Harmane is l-Methyl-9H-pyrido[3,4-b]indole. [19]

Melting Point = 244−245 °C.[20]

UV spectroscopy: λmax; 236, 291, 351 nm.[18]

IR Values (ν, cm^{-1}):

3131 (NH), 3064, 2971, 2883, 1625, 1568, 1504, 1322, 1236, 882, 820, 750.[4]

High resolution mass spectrometry (HRMS): MH+, 183.0917; Δmmu, -0.5.[18]

NMR Analysis of Harmane :

1H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H, NH), 8.37 (d, 3JHH = 5.2 Hz, 1H, Ar−H), 8.12 (d, 3JHH = 8.0 Hz, 1H, Ar−H), 7.83 (d, 3JHH = 5.2 Hz, 1H, Ar−H), 7.52−7.57 (m, 2H, Ar−H), 7.26− 7.32 (m, 1H, Ar−H), 2.84 (s, 3H, CH_3).[22]

13C NMR Values:

(CDCl3), d 142.9 (C-1), 140.7 (C-8a), 139.0 (C-3), 135.7 (C-9a), 128.5 (C-7), 128.3 (C-4a), 122.8 (C-4b), 122.0 (C-5), 120.4 (C-6), 113.0 (C-4), 111.9 (C-8), 20.0 (C-Me).[18] as shown in fig (4).

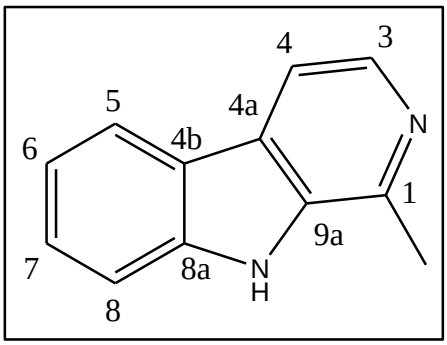


Fig: (4) Structure of Harmane

X-Ray Crystallography:

Crystals are orthorhombic, space group $P2_12_12_1$, and the unit cell dimensions are a =13.368(4), b = 15.537(3), and c = 9.535(3) Å, V = 1980.4(9) $Å^3$ with two molecules in the asymmetric unit. Diffraction data measured at room temperature with Cu-Kα radiation, λ(Cu-Kα) = 1.5418 Å. The structure was solved directly and refined using a full-matrix least-squares procedure (nonhydrogen atoms anisotropic, hydrogen atoms isotropic) to a final R = 0.046 for 1961 independent observed reflections. In the two molecules, the average out-of-plane distances for the 13 ring atoms are 0.022 and 0.029 A^0 respectively. Continuous spiral chains are formed through the structure by hydrogen bonding of each molecule to two others.[12]

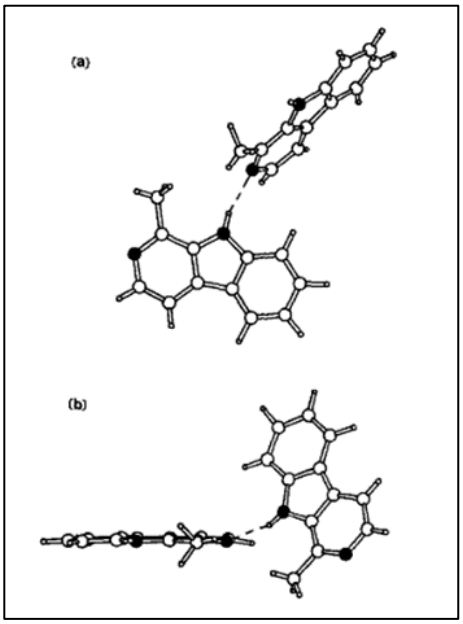


Fig (5): Hydrogen bonding of Harman viewed

(a) onto the molecular plane, and

(b) along the molecular plane.

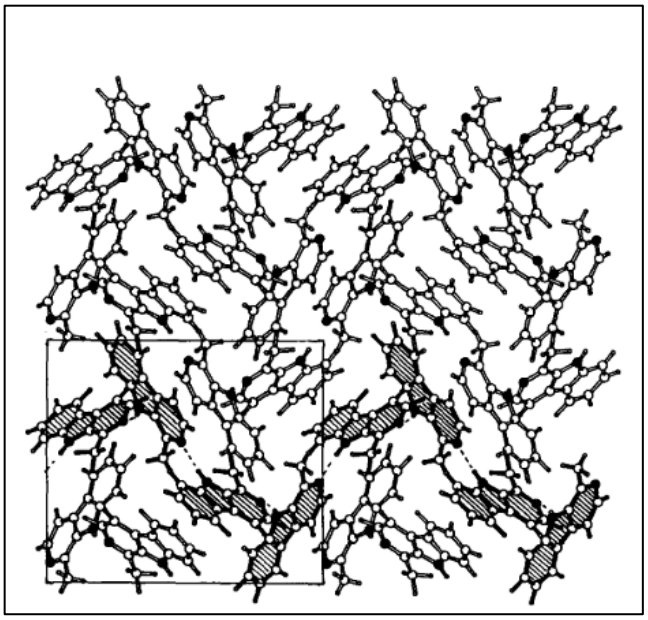


Fig (6): Packing of Harman molecules.

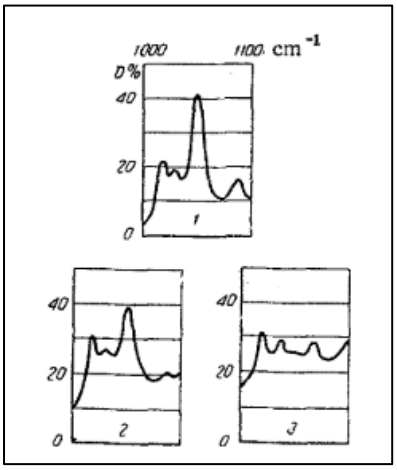
3.2 Characterization of Brevicolline:

A possible structure for brevicolline was proposed, making it a harmane derivative. To confirm the nature of the residue (-$C_5H_{10}N$) next to the β-carboline system and its attachment position, the oxidation of brevicolline was carried out. From the IR and UV spectroscopic analysis of the product formed, the structure of Brevicolline was proposed which was finally confirmed by Mass spectrometry and NMR.

The confirmed structural formula of Brevicolline is 1-methyl-4-(N-methyl-2′-pyrrolidyl)-β-carboline. [21]

Melting Point: 223-224^{0}C [2].

IR values : (KBr) 3422 (NH), 3147, 2089, 2873 (CH), 1684 (C=O) cm^{-1}.[2]Band at 1047 cm^{-1}(Aromatic ring vibration and C-H deformation frequency) is shown in Fig (7).

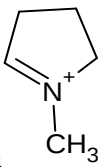


Fig(7): IR Absorption curves,1) Brevicolline; 2) a mixture containing 45% brevicollin;3) brevicarin.[22]

UV Spectroscopy:

(EtOH) λ_{max} (log ε) 351 (4.12), 337 (4.09), 287 (4.39), 279 (4.19), 232 (4.68), 213 (4.54) nm.[2]

Mass Spectrometry:

The alkaloid's mass spectrum (Fig.8) shows peaks for the molecular ion (M^+; m/e 265) and the ions M-1, M-29, and M-43 due to pyrrolidine ring fragmentation. The base peak with m\e 84 belongs to the ion  which is formed by the rupture of the C-C bond between the pyrrolidine nucleus and the β-carboline system.

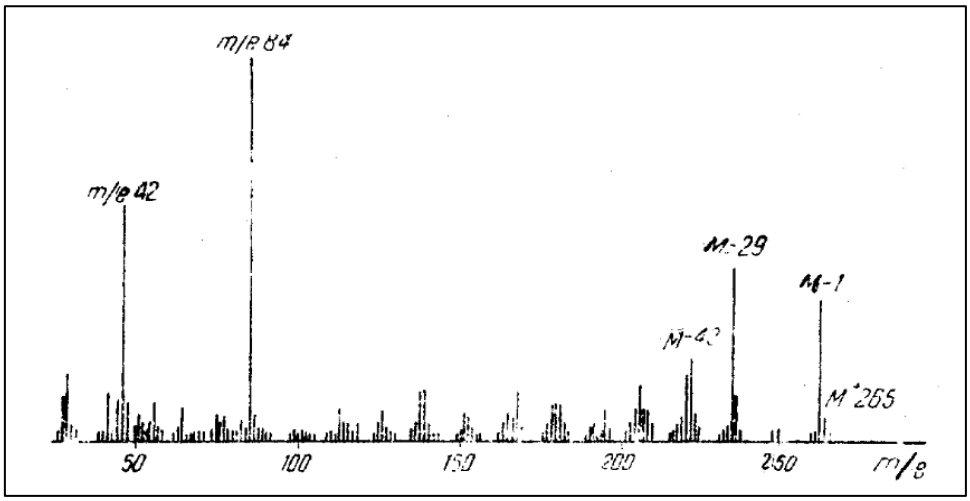
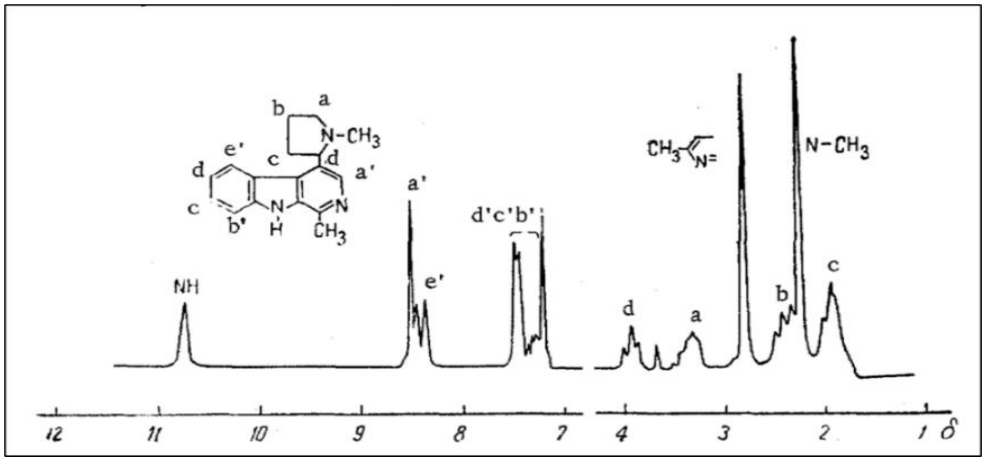


Fig (8): Mass spectrum of brevicolline.

This structure is also seen in nicotine fragmentation, where the ion with m/e 84 has the highest intensity in the mass spectrum.[21]

NMR Analysis of brevicolline:

The NMR spectrum's integral curve reveals the presence of 19 protons in the brevicolline molecule as seen in fig (9).



Fig(9): NMR spectrum of brevicolline (solvent $CDCl_3$; standard TMSO, instrument-JNM-4H-100,100 MHz.

The three-proton singlets at 2.26 and 2.80 ppm correspond to N-CH_3 and aromatic C-CH_3 groups, respectively. The peak at 10.70 ppm corresponds to an indole NH, while the peak at 8.50 ppm corresponds to the α-hydrogen of a pyridine ring. In the methylene group region, there are three two-proton signals and a one-proton triplet (2-4 ppm). The protons of the benzene ring are represented by a three-proton signal in the 7.50 ppm region and a one-proton doublet at 8.5 ppm. Such a shift to a weaker field appears to be caused by the action of currents from not only the aromatic ring itself, but also from a second (pyridine) ring, and the influence of the adjacent five-membered saturated ring.[21]

LITERATURE REVIEW:

Natural product scaffolds are involved in the majority of medicines that are presently in clinical use. The discovery of newer practical methods for the synthesis of this scaffold is of substantial interest because of its biological value.

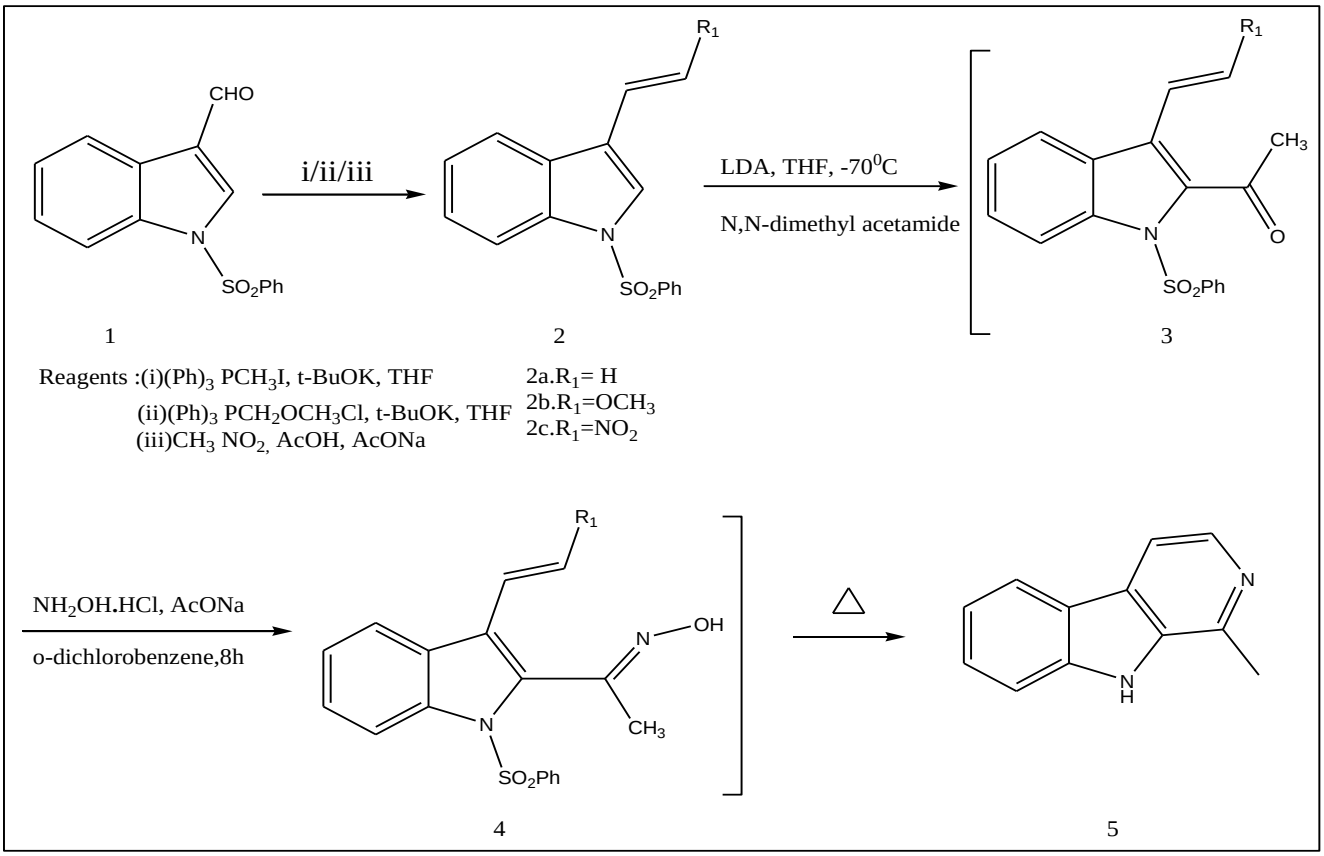
4.1 TOTAL SYNTHESIS OF HARMANE:

Harmane was reported to exhibit mutagenic, co-mutagenic properties and inhibit topoisomerase I, anti-HIV, anti-tumor, anti-tobacco mosaic virus (TMV), and fungicidal activities which have piqued the interest of scientists.

4.1.1 Radhika Kusurkar et al. synthesis of harmane, an anti-HIV and antitumor compound.[2003][23]

The Pictet–Spengler and Bischler–Napieralski condensations are the most extensively used among the variety of techniques available for synthesizing β-carboline alkaloids.

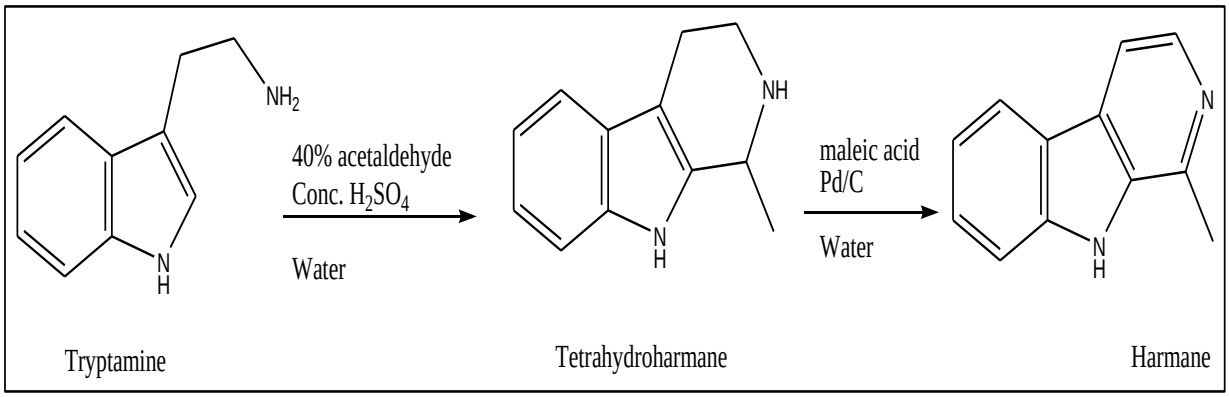
In this synthetic approach, the electrocyclization reaction of the monoazahexatriene system is used as a key step for Harmane synthesis. From scheme (1) Azatriene (4) is the key intermediate for the electrocyclization step. Initially, the Vilsmeier– Haack reaction was used to formylate indole, yielding 3-formyl indole. The reported approach was used to perform N-Protection utilizing benzene sulphonyl chloride. The protected aldehyde (1) was transformed using methylene-triphenyl phosphorane into 3-vinyl indole (2a) which was lithiated using LDA/THF at -70°C and then treated with N, N-dimethylacetamide to functionalize the indole ring at the 2-position (3). The reaction mixture was then treated with hydroxylamine hydrochloride and sodium acetate and refluxed in o-dichlorobenzene for 8 hours to yield Harmane (5) in 46% overall yield. The protected indole-3-aldehyde (1) on treatment with nitromethane and ammonium acetate was transformed to 3-vinylindole (2b) and 3-(β-nitro-vinyl) indole (2c). Treatment of (2b) and (2c) with LDA/THF at −70°C, followed by N, N-dimethylacetamide resulted in two oily liquids which on treated with hydroxylamine hydrochloride and sodium acetate and refluxed in o- dichlorobenzene furnished harmane (5) in 53% and 43% overall yield from 2b and 2c respectively. During the one-pot reaction sequence, the methoxy and the nitro groups were eliminated in all these reactions.



SCHEME (1): Efficient one-pot synthesis of anti-HIV and antitumor compound Harmane.

4.1.2 Hongjian Song et al. total synthesis of harmane [2014].[20]

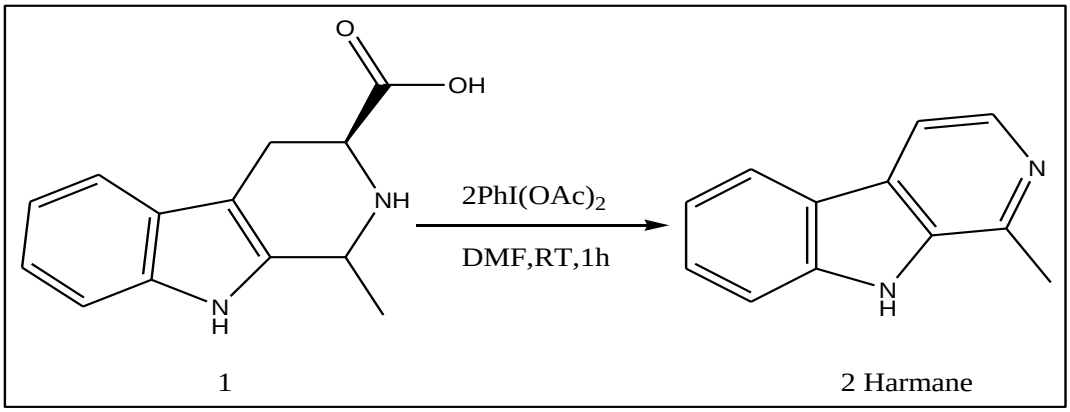
For Harman synthesis, tryptamine was used as a starting material as shown in scheme (2), in which on treatment with 40% aqueous solution of acetaldehyde in water and conc, H_2SO_4 undergoes Pictet−Spengler reaction to form tetrahydroharmane. The Pd/C-maleic acid system in water was used to oxidize tetrahydroharmane, yielding harmane in 60% overall yield.



SCHEME (2): Synthesis of Harmane.

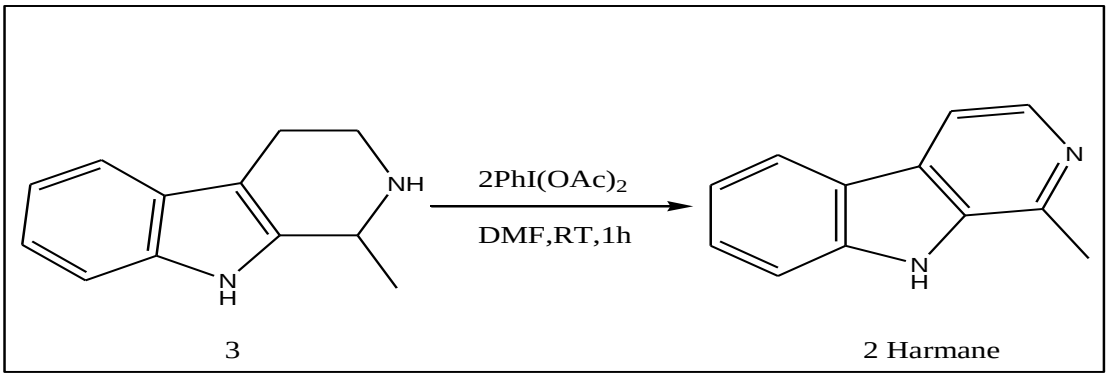
4.1.3 Ahmed Kamal et al. synthesis of harmane via a PhI(OAc)2-Mediated one-pot oxidative decarboxylation at ambient temperature [2015].[24]

This synthetic technique aims to create more environmentally friendly and practicable synthetic approaches for pharmaceutically relevant molecules. A hypervalent iodine reagent, iodobenzene diacetate which is a mild oxidant, was used for one-pot oxidative decarboxylation and aromatization of tetrahydro-β-carboline acid (1) from the scheme (3). After trying multiple solvents such as DMF, DMSO, DCM, and 1,4-dioxane, it was discovered that DMF provided the best yield. As a result, the best reaction conditions were 2 mmol of iodobenzene diacetate in DMF at room temperature for 1 hour. The overall yield of harmane was 76%.



SCHEME (3): Synthesis of Harmane via a $PhI(OAc)_2$-Mediated one-pot oxidative decarboxylation from tetrahydro-β-carboline acid.

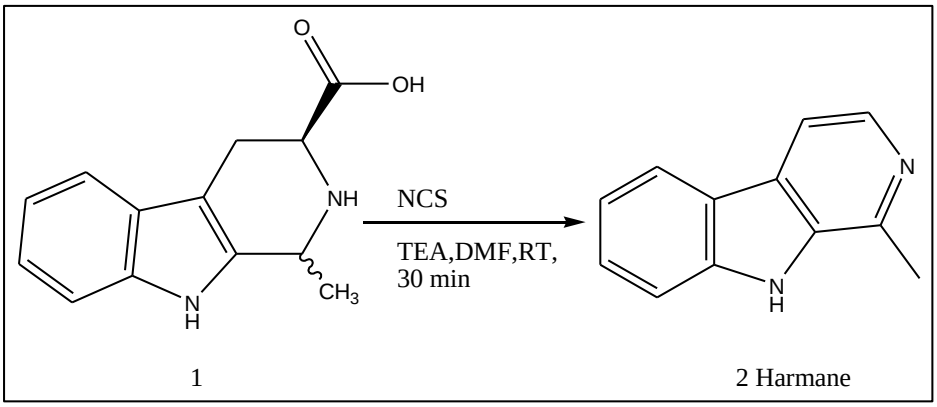
This approach can also be used for the dehydrogenation of tetrahydro-β-carbolines (3) which don't have any functionality at position 3 as shown in the scheme (4). The overall yield obtained is 84%.



SCHEME (4): Synthesis of Harmane via a $PhI(OAc)_2$-Mediated one-pot oxidative decarboxylation from tetrahydro-β-carboline.

4.1.4 Ahmed Kamal et al. total synthesis of harmane via an efficient one-pot decarboxylative aromatization of tetrahydro- β-carboline by using N-chlorosuccinimide.[2015][25]

This is an efficient and mild strategy for the synthesis of β-carboline, Harmane from the corresponding tetrahydro-β-carboline via one-pot decarboxylative aromatization and oxidative dehydrogenation utilizing N-chlorosuccinimide (NCS). Pictet-Spengler reaction of L-tryptophan and acetaldehyde efficiently generated the tetrahydro-β-carboline acid (1) scheme (5). N-chlorosuccinimide is a flexible and affordable reagent for moderate oxidation and halogenation, with lower toxicity than other oxidants. Furthermore, the by-product succinimide is highly soluble in water (1 g/3 mL at 25^0C), easy to remove from the reaction mixture during work-up, and in large-scale reactions, succinimide from the aqueous phase can be converted into the starting reagent N-chlorosuccinimide by treating with sodium hypochlorite, making the method sustainable. The overall yield obtained is 82%.

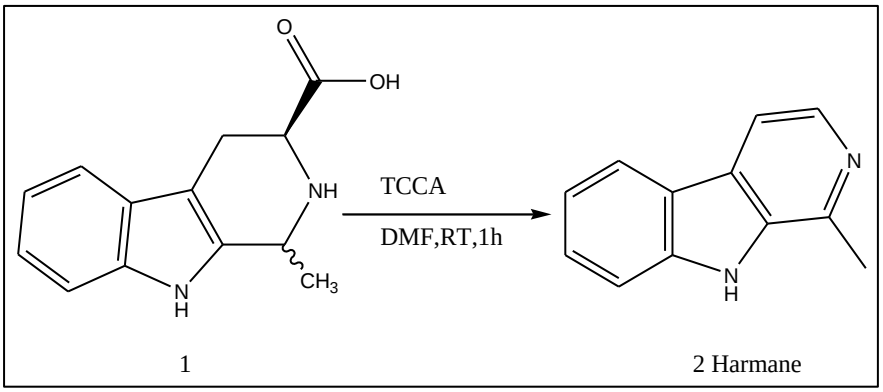


SCHEME (5): Total synthesis of harmane via an efficient one-pot decarboxylative aromatization of tetrahydro- β-carboline acid by using N-chlorosuccinimide.

4.1.5 Kesari Manasa et al. total synthesis of harmane via TCCA, a mild reagent for decarboxylative/Dehydrogenative Aromatisation of tetrahydro-β-carboline.[2017][26]

In this synthetic approach, Trichloro-isocyanuric acid (TCCA), an inexpensive mild oxidant is used for one-pot oxidative decarboxylation and aromatization of tetrahydro-β-carboline. A tetrahydro-β-carboline acid which was produced by Pictet-Spengler condensation of tryptophan with acetaldehyde was exposed to oxidative decarboxylation under optimized reaction conditions. DMF was found to be the preferred solvent for this transformation after screening it against toluene, CH_2Cl_2, 1,4-dioxane, THF, DMSO, and acetonitrile. As a result, the best reaction conditions were

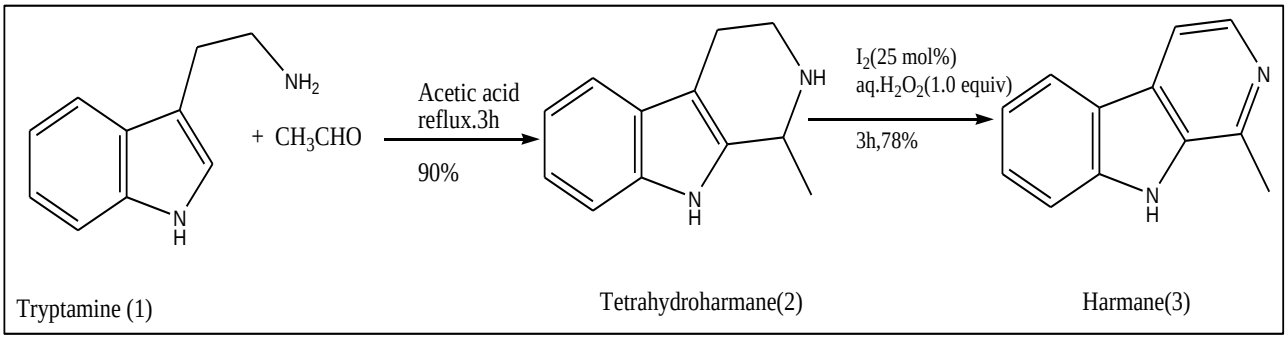
found to be 0.7 Equiv. of TCCA in DMF at room temperature for 1 hour as shown in scheme (6). The overall yield obtained is 82%.



SCHEME (6): Synthesis of Harmane via TCCA, for decarboxylative/Dehydrogenative Aromatisation of tetrahydro-β-carboline.

4.1.6 Sunil Gaikwad et al. synthesis of harmane via Iodine-catalysed chemo-selective dehydrogenation and aromatization of tetrahydro-β-carboline.[2018][27]

Pictet-Spengler condensation of tryptamine (1) & acetaldehyde yields 1-methyl-1,2,3,4-tetrahydro-β-carboline (2) 90% yield, scheme (7). Under optimal conditions such as molecular I_2 and H_2O_2, in DMSO solvent, dehydrogenation of (2) proceeded easily, affording Harmane with 78 % yield.



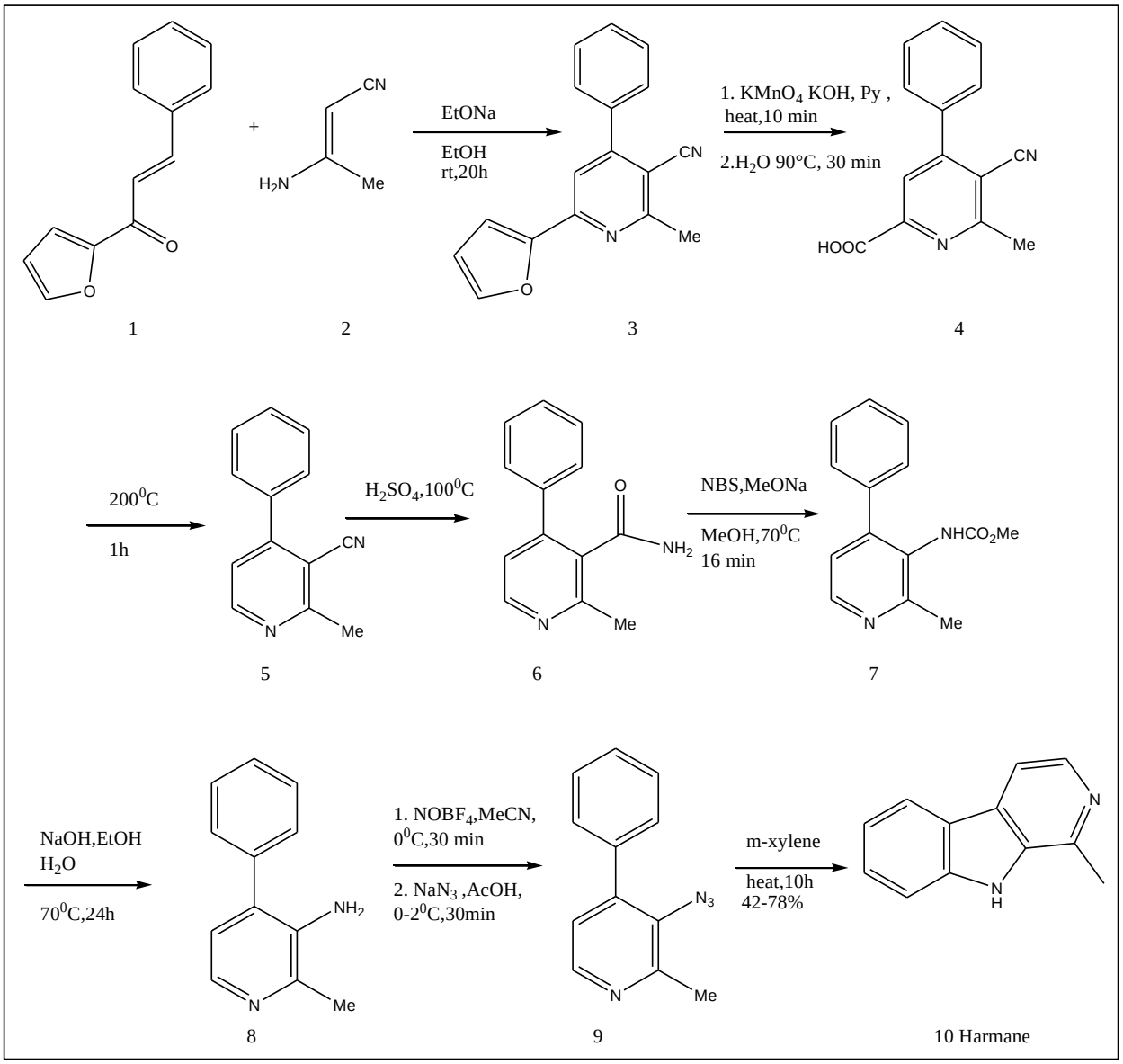
SCHEME (7): Synthesis of Harmane via Iodine-catalysed chemo-selective dehydrogenation and aromatization of tetrahydro-β-carboline.

4.1.7 Vladislav Shuvalov et al. synthesis of harmane by thermolysis of 4-aryl-3-azidopyridines. [2020][4]

In this synthetic approach, 3-cyano-2-methylpyridine (5) is used as a starting material. To increase the yield, the previously reported pyridine (4) synthesis was modified. Synthesis of pyridine (3) from

compound (1) was done using the single-step Hantzsch reaction which on further oxidation of the furyl substituent of pyridine gives (4) with high yield from the scheme (8).

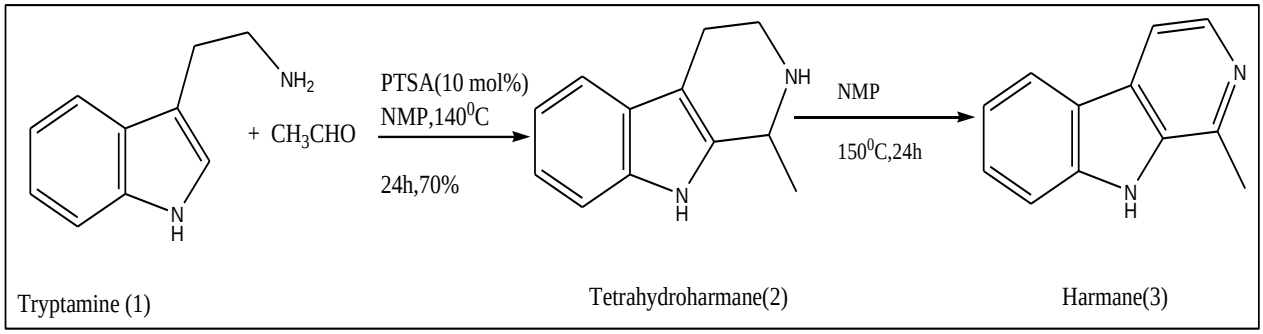
Decarboxylation of pyridine (4) by heating without solvent yielded 4-aryl-3-cyano-2-methylpyridine (5). The synthesis of amide (6) was carried out by heating pyridine (5) in concentrated H_2SO_4 by incomplete hydrolysis of the cyano group of pyridine (5). Hoffmann reactions were employed for the synthesis of 4-aryl- 2-methyl pyridine-3-ylcarbamate (7), from which 3-amino- pyridine (8) was synthesized. Harmane was synthesized by thermolysis of 4-aryl-3-azidopyridines (9) in xylene which in turn was obtained from diazonium salts of 3-aminopyridine (8). The overall yield of the reaction is 45%.



SCHEME (8): Synthesis of Harmane by thermolysis of 4-aryl-3-azidopyridines.

4.1.8 Srinath Santhanam et al. total Synthesis of harmane using metal-free aromatization.[2020][28]

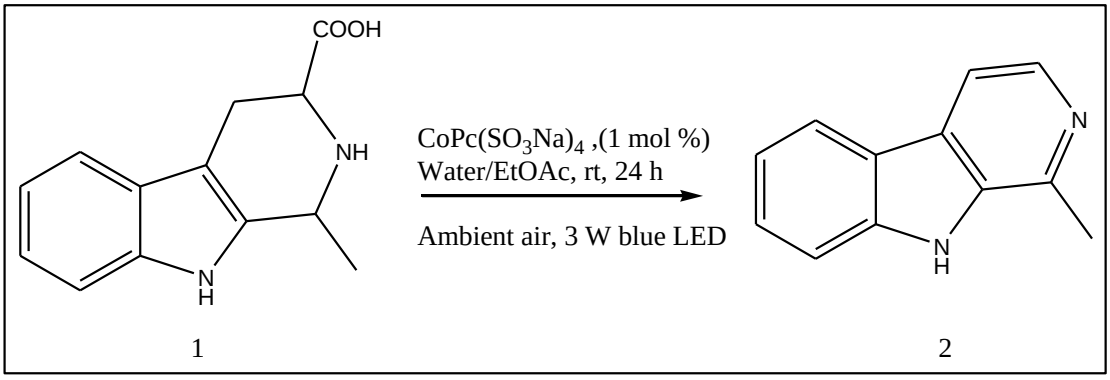
In this synthetic approach, tetrahydroharmane was synthesized from tryptamine (1) by the Pictet Spengler reaction in 85% yield and was then subjected to aromatization in presence of oxygen at 150^0C in N-methyl-2-pyrolidone (NMP) to obtain Harmane in 76% yield as shown in scheme (9).



SCHEME (9): Total Synthesis of Harmane using metal-free aromatization.

4.1.9 S. Srinath et al. synthesis of harmane via visible light-driven cobalt catalysed oxidative dehydrogenation in biphasic medium [2020].[29]

In this synthetic approach, Harmane (2) from scheme (10) is synthesized by using visible light-driven reusable, homogeneous water-soluble cobalt-phthalocyanine photo redox catalyst in the biphasic medium by oxidative dehydrogenation of tetrahydro-β-carboline acid (1). The advantages of a biphasic system include easy product separation and excellent reusability of the homogenous photo redox catalyst. In addition, this approach considerably aids in overcoming the substrate and catalyst solubility issue at room temperature. The overall yield obtained was 87%.



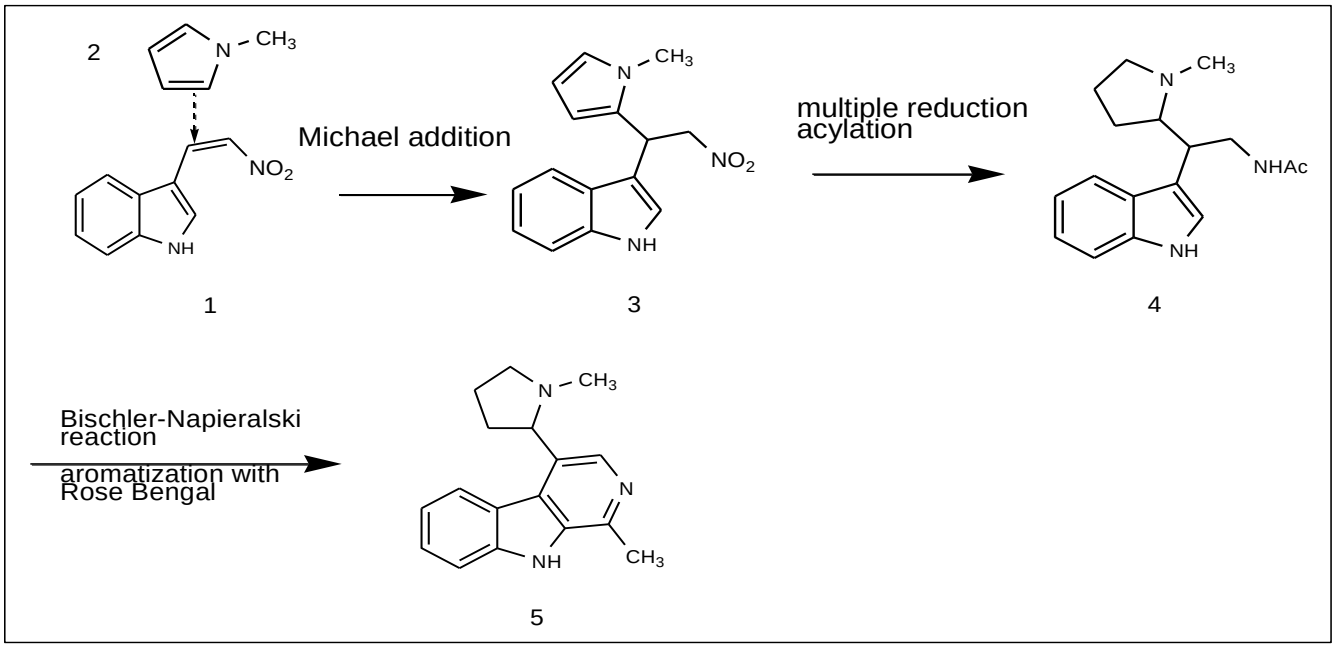
SCHEME (10): Synthesis of Harmane via visible light-driven cobalt catalysed oxidative dehydrogenation in the biphasic medium.

4.2 TOTAL SYNTHESIS OF BREVICOLLINE:

The remarkable pharmacological properties of Brevicolline including its photosensitizing ability and ability to induce abortion have attracted the attention of scientists.

4.2.1 Muller et al. synthesis of racemic [(±)- brevicolline] [1977].[30]

In this synthesis, starting materials used were Nitrovinyl indole (1) and N-methyl pyrrole (2), which were finally converted into [(±)- brevicolline] (5) in 6 steps using a sequence of Michael addition, reduction, acylation, Bischler–Napieralski reaction, and aromatization, resulting in total yield of 26% as shown in scheme (11).

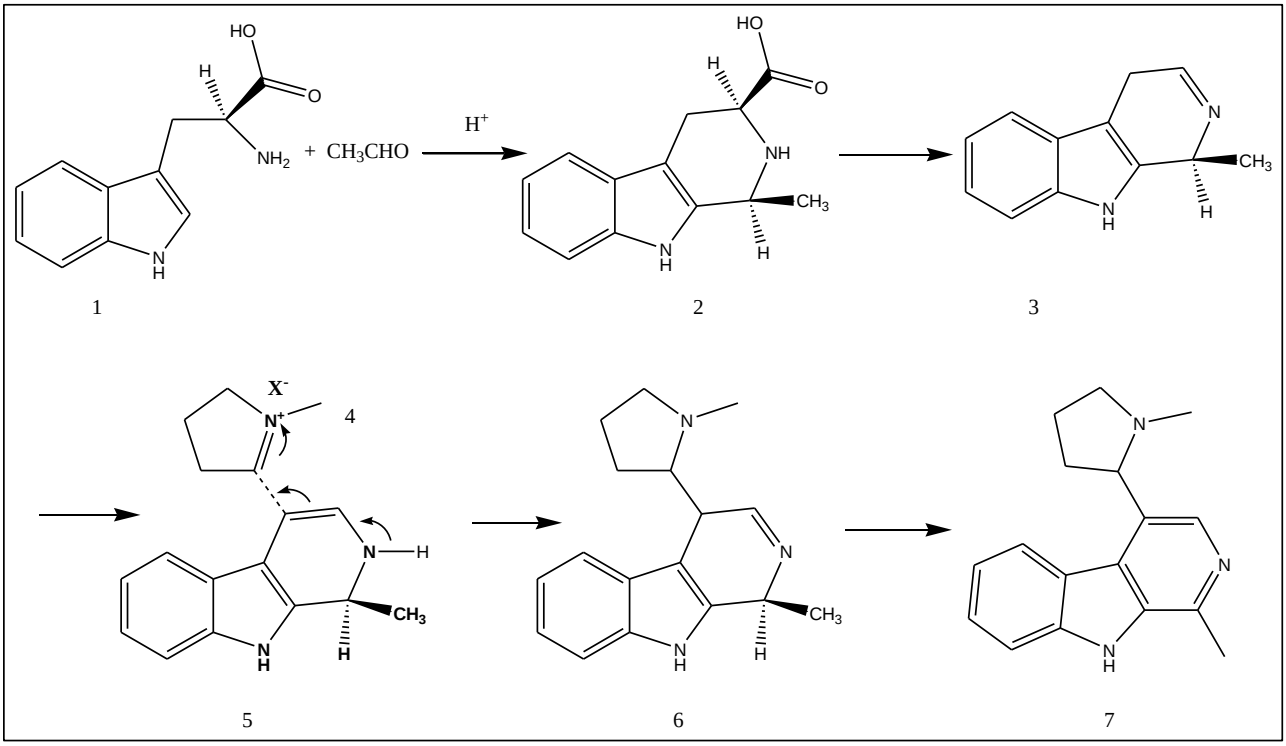


SCHEME (11): The synthesis of racemic [(±)- brevicolline]

4.2.2 Edward Leete synthesis of brevicolline from Tryptophan, Acetaldehyde, and N-Methyl- Δ1 -pyrrolinium Acetate[1979]. [14]

The scheme (12) illustrates a Mannich reaction between L-tryptophan (1) and acetaldehyde producing 1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid (2), with the (1S,3S)-isomer being the major product in vitro. (2) is oxidatively decarboxylated to give 1,4-dihydro-β-carboline (3). A tautomeric shift results in the formation of 1,2-dihydro-β-carboline (5). This enamine reacts with the N-methyl-Δ^1-pyrrolinium salt (4) which is formed from ornithine via putrescine and N-methylputrescine. The product (6) is then oxidized, yielding brevicolline (7).

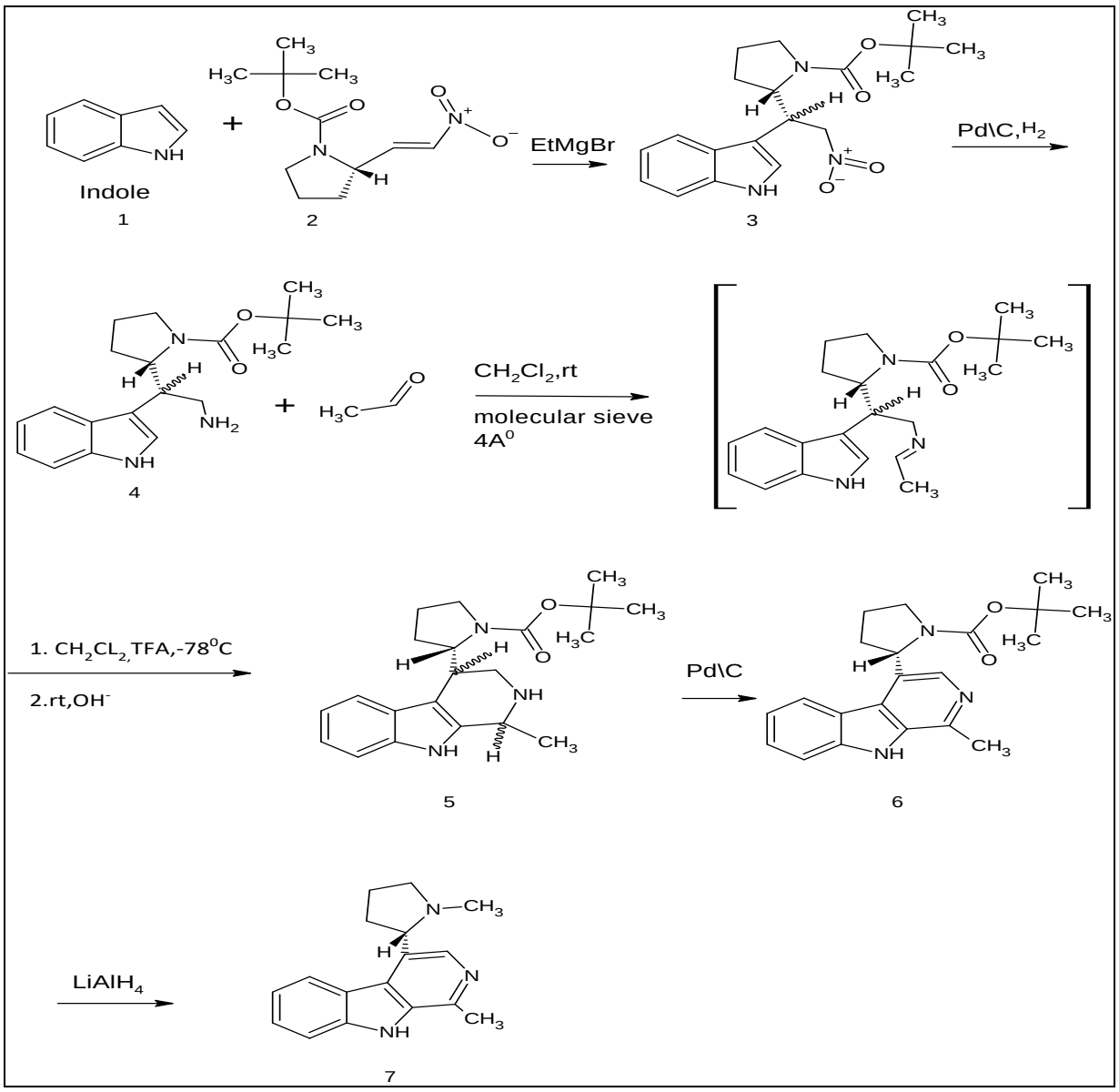
The overall yield of the racemic brevicolline was 1-2 %. It was identical to an authentic specimen of the natural alkaloid (u.v., high-resolution mass spectrum, t.l.c.)



SCHEME (12): Biomimetic synthesis of Brevicolline.

4.2.3 Siavosh Mahboobi et al. synthesis of enantiomerically Pure (-)-(S)-Brevicolline[1999]. [2]

The chiral Michael-acceptor synthon (2) from the scheme (13) was used in this synthetic approach. Precursor 3 was produced when the indole-anion, which can be obtained from indole and ethyl magnesium bromide, reacted with the nitroethene derivative (2). Catalytic hydrogenation over Pd/C transformed the nitro indole (3) into the amino indole (4). The β-carboline ring was then closed using acetaldehyde and trifluoroacetic acid by a Pictet-Spengler reaction. Pd in refluxing xylene provided aromatization of (5), resulting in the β-carboline system (6). The N-methyl group of the title compound (7) was obtained by reducing the Boc-protecting group with LiAlH4.This 7-step synthetic procedure resulted in an overall yield of 5%.

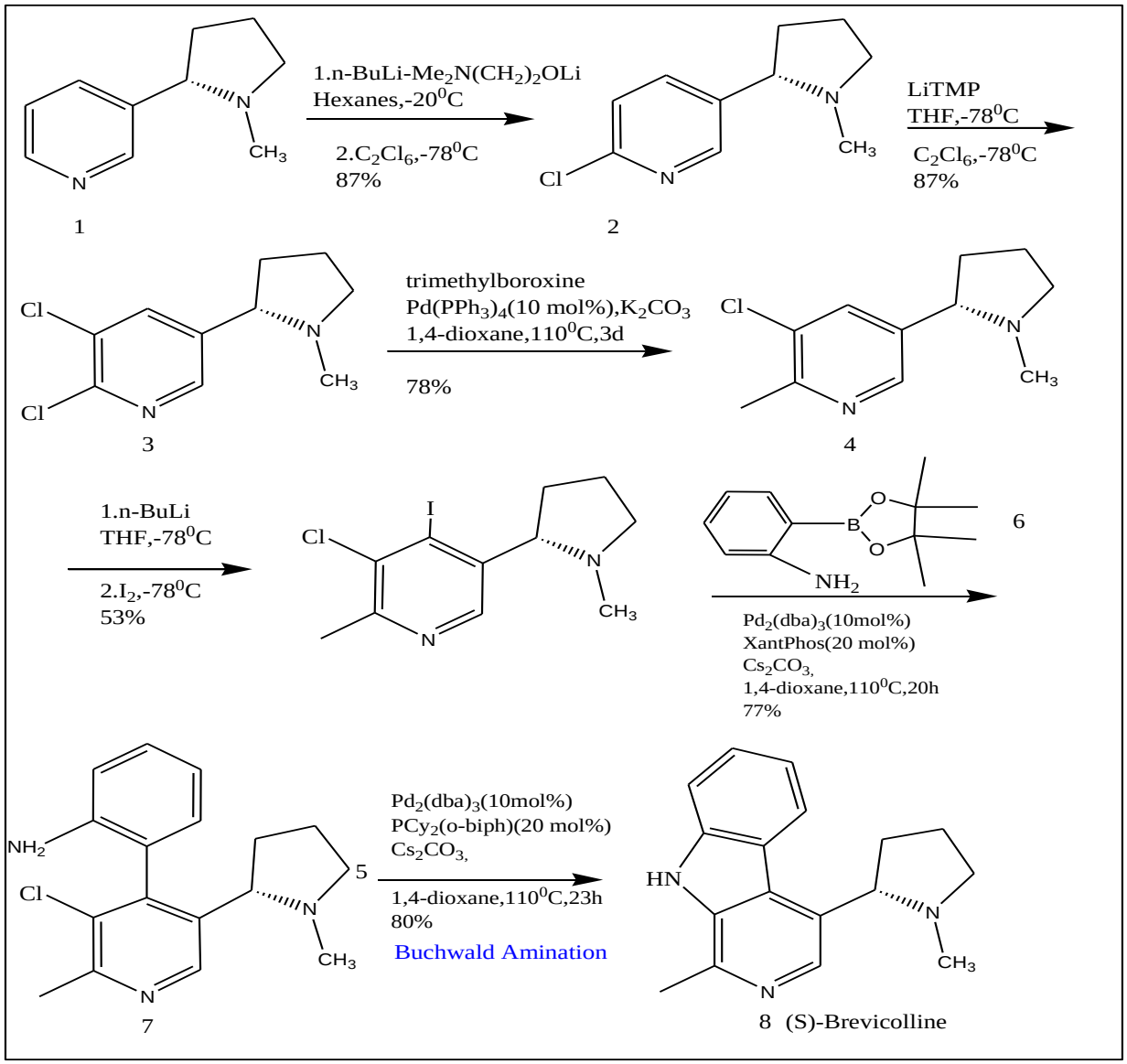


SCHEME (13): Synthesis of enantiomerically pure (-)-(S)-brevicolline.

4.2.4 Wagner and Comin's, six-step synthesis of (S)-Brevicolline from (S)-Nicotine[2006]. [31]

(S)- Nicotine (1) from the scheme (14) was used as a starting material as it was inexpensive. The enantiopure β-carboline alkaloid, brevicolline, was created through enantioselective trisubstituted of nicotine's pyridine ring, followed by Suzuki cross-coupling and Buchwald amination processes with an overall yield of 17%. (S)-6-chloronicotine (2) is obtained from (1) via an ortho-directed lithiation process. A regioselective lithiation-chlorination reaction of (2) using LiTMP as a base and hexachloroethane as an electrophile resulted in (S)-5,6-Dichloronicotine (3). Via a Suzuki cross-coupling reaction using trimethylboroxine, (S)-5-chloro-6-methylnicotine (4) was obtained in good

yield. Iodination at C-4 of (4) was done by the addition of n-BuLi to give the 4-iodo derivative (5). (7) was formed by a cross-coupling reaction between (5) and amino boronate ester (6). Finally in 1,4-dioxane, an intramolecular Buchwald amination with the use of Pd_2dba_3, Cs_2CO_3, and PCy_2(o-biph) as the ligand yielded (S)-brevicolline (8) in an isolated yield of 80%.



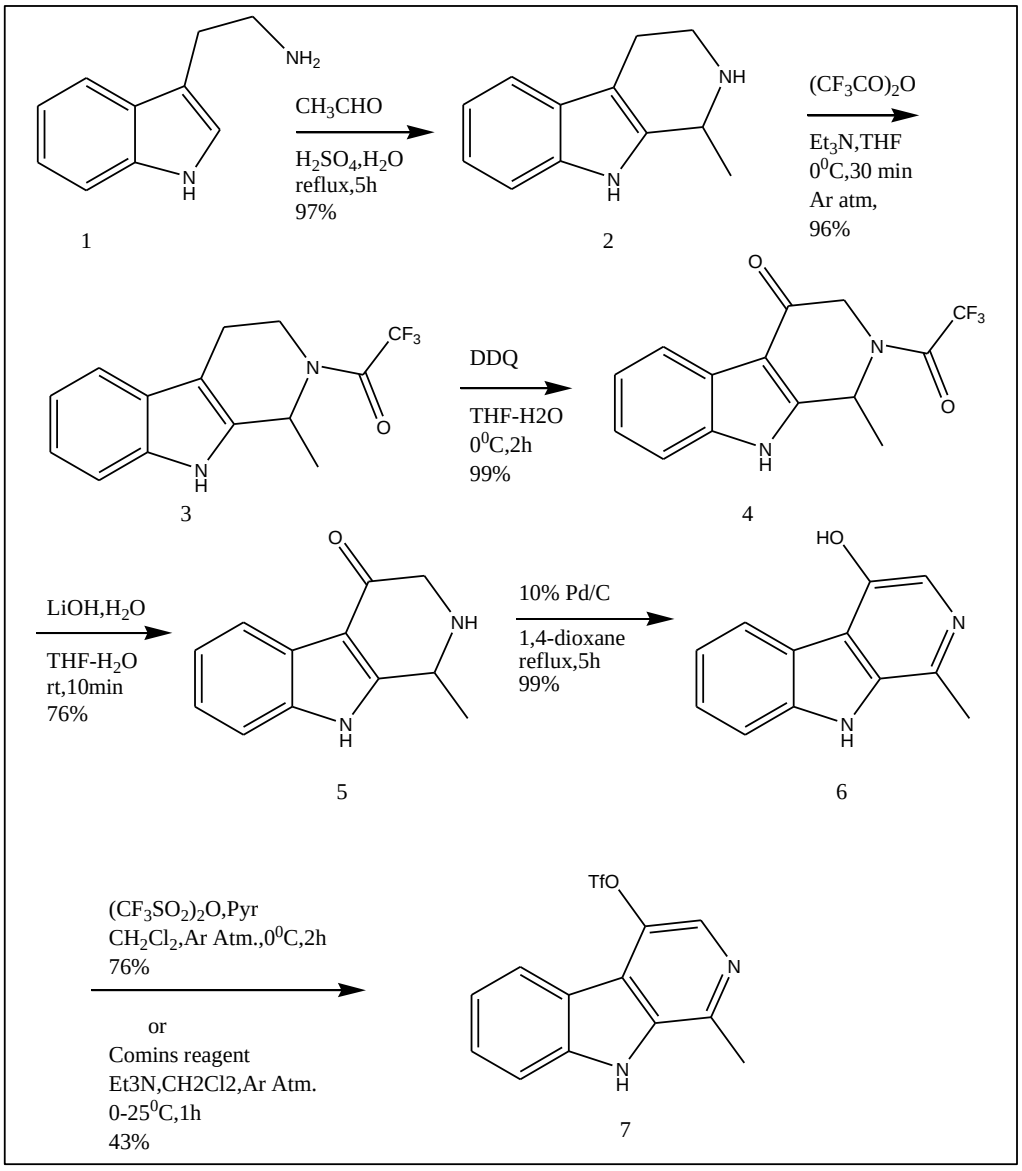
SCHEME: (14): Synthesis of (S)-Brevicolline from (S)-Nicotine.

4.2.5 T. Szabó et al. synthesis of racemic and enantiopure forms of β-Carboline Alkaloid Brevicolline[2022][32].

This synthetic approach uses Tryptamine (1) from the scheme (15) as a starting material which is easily available and is inexpensive. In comparison to previously reported approaches, the synthetic route described here was devised to enable sustainable access to the racemic brevicolline in 11 steps with an improved overall yield of 48%.

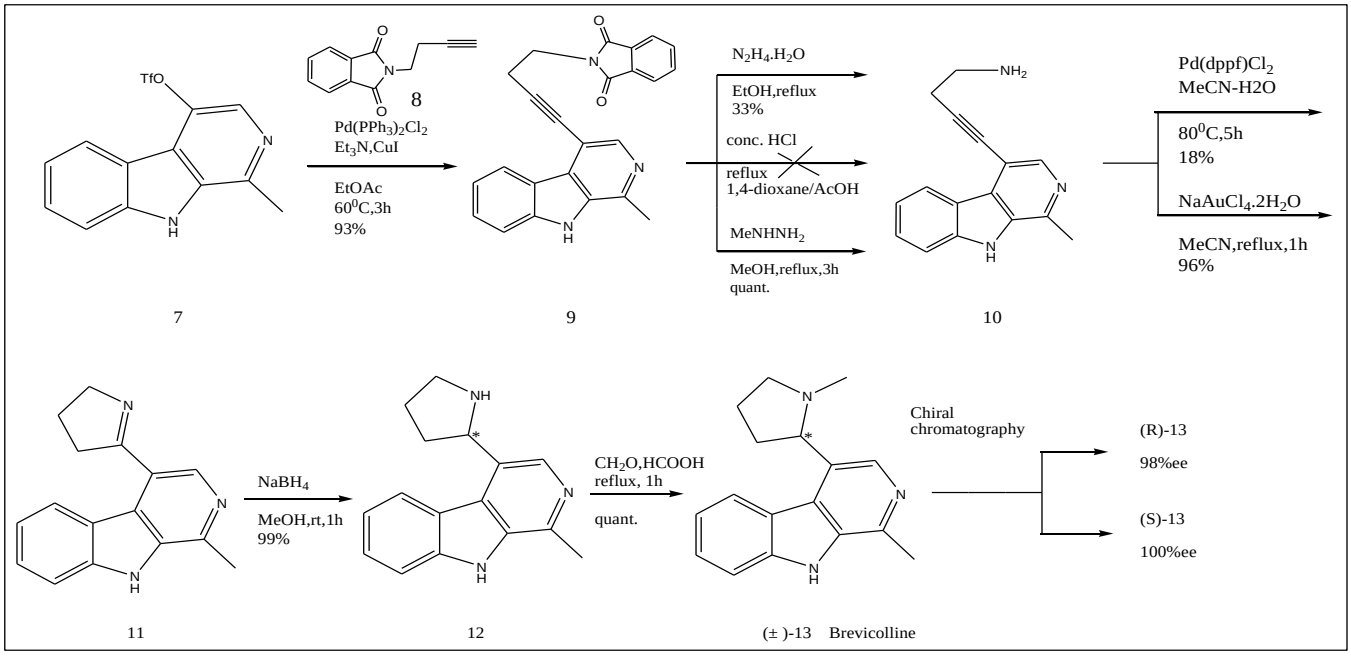
Initially, the construction of the β-carboline skeleton via Pictet–Spenger reaction with acetaldehyde was done yielding the β-carboline scaffold of (2) which was followed by the protection of the N atom by a trifluoroacetyl group to form intermediate (3). This step was followed by functionalization at the C4 location via hydride anion transfer using 2,3-dichloro-5,6-dicyano-1,4- benzoquinone (DDQ). The next step involves deprotection of (4) under alkaline conditions followed by aromatization of (5) using 10% Pd/C catalyst leading to the formation of intermediate (6) which contains a phenolic moiety.

In the presence of trifluoromethane sulfonic anhydride, sulfonylation of (6) was achieved, yielding the crucial intermediate (7). Comin's reagent was also used in the final stage in the hopes of getting a better yield, however, it was ineffective.



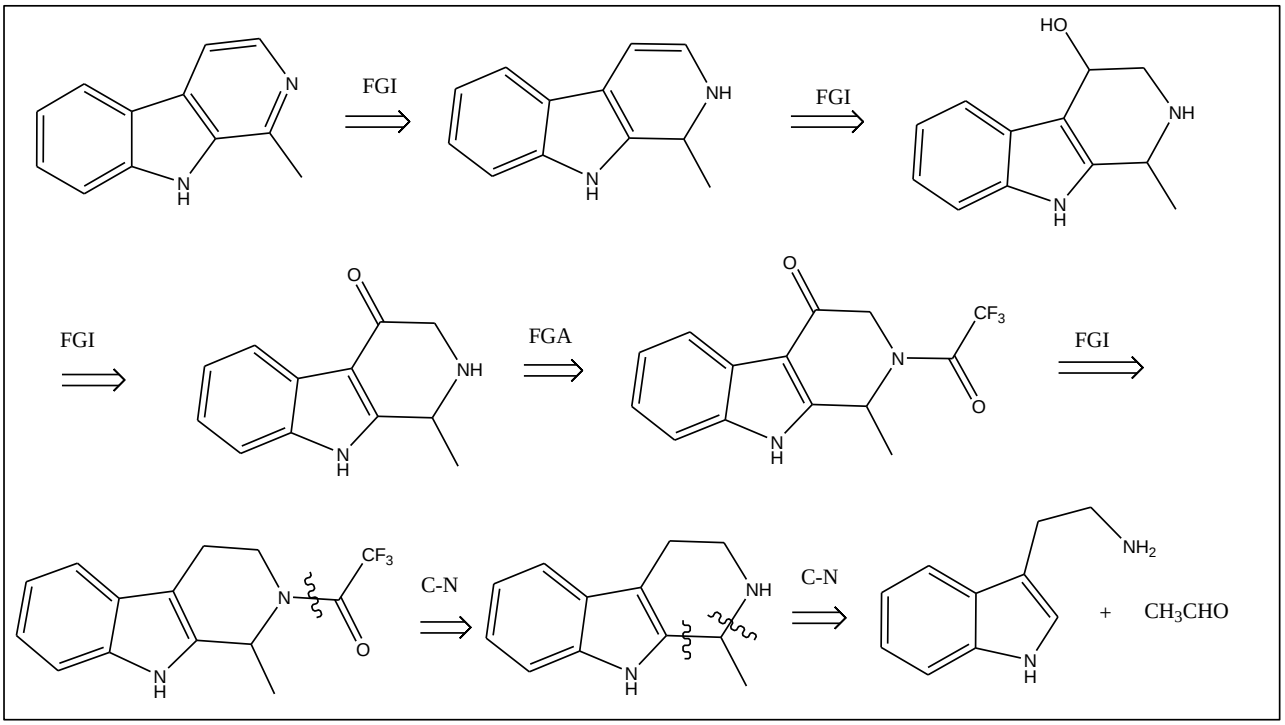
SCHEME (15): Synthesis of key intermediate 7. Functionalization at position C-(4) of the β-carboline framework.

The reaction of (7) with N-(3-butynyl) phthalimide (8) as shown in scheme (16) yields (9) via Sonogashira reaction. The intermediate (9) was first treated with hydrazine hydrate to remove the phthalimide moiety, but the expected amine (10) was formed along with many unidentified by-products, with only 33% yield. Treatment of (9) with concentrated hydrochloric acid in the presence of acetic acid in 1,4-dioxane solvent was also unsuccessful. Finally, it was treated with methyl hydrazine, resulting in a quantitative yield of (10) without any decomposition detected. As a result of an Au-catalyzed hydroamination reaction, a 3-dihydropyrrole structural unit was formed (11), followed by reduction to give a chiral intermediate (12). finally, the quantitative yield of racemic brevicolline ((±)13) was obtained by selective Eschweiler–Clarke methylation of ((±)12). Finally, chiral chromatography of (±)-13 was done to isolate the natural product (S)-brevicolline with 100% ee and its antipode (R)-Brevicolline with 98% ee.

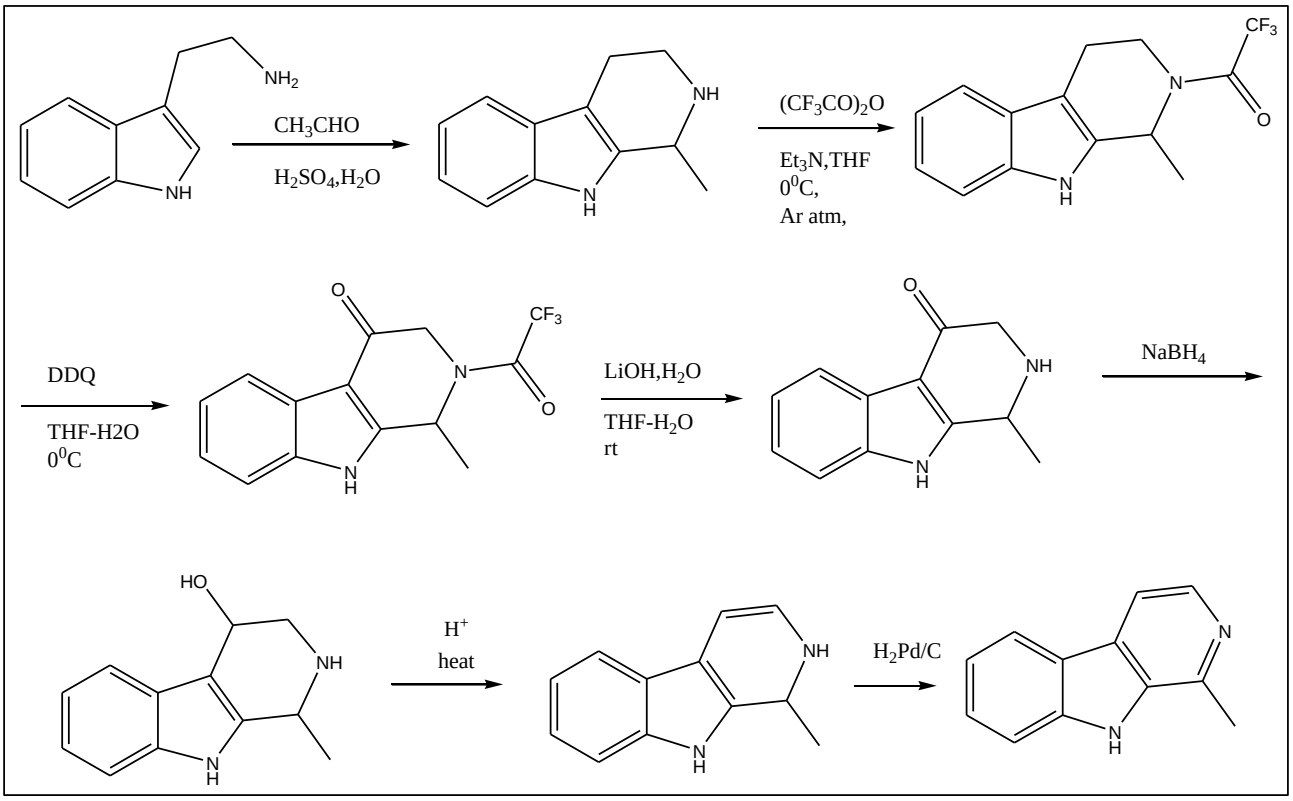


SCHEME (16): Final steps of the synthesis of (±)-13: synthesis of amine 10, formation of the dihydropyrrole ring, the establishment of a stereocenter, selective methylation, and chiral separation.

RETROSYNTHESIS AND FORWARD SYNTHESIS OF HARMANE:



SCHEME (17): Retrosynthesis of Harmane



SCHEME (18): Forward synthesis of Harmane

CONCLUSION:

In natural products and pharmaceuticals, β-carboline and its saturated analogue are common structural motifs. Newer practical methods for the synthesis of this scaffold have been discovered. The classic Pictet–Spengler and Bischler–Napieralski reactions are the most extensively used among the variety of techniques available for synthesizing β-carboline alkaloid

For the total synthesis of Harmane, aromatization of the tetrahydro- β-carboline ring constitutes a key step. From this literature review, it can be seen that the majority of the synthetic approaches reported involve decarboxylative/ dehydrogenative aromatization of tetrahydro-β-carbolines by using reagents such as Pd/C that either require harsh conditions or reagents such as trichloroisocyanuric acid, $PhI(OAc)_2$, I_2 with H_2O_2 and N-chloro-succinimide (NCS), which have their drawbacks, such as stoichiometric by-product generation, use of expensive reagents, low yields, or lack of general application. The synthetic approach by Srinath Santhnam uses oxygen as an oxidant which is a metal-free dehydrogenation reaction but the reaction requires high temperature. Therefore, the most suitable method for Harmane synthesis is via visible light-driven reusable, homogeneous water-soluble cobalt-phthalocyanine photo redox catalyst in the biphasic medium as it results in a high yield of 87% and visible light-based reactions are cheap and have environmentally benign reaction conditions.

From the literature review for the synthesis of Brevicolline, it can be concluded that Wagner and Comin's synthetic approach for (S)-Brevicolline from (S)-Nicotine was the shortest synthesis to date with an 80 % yield. However, the racemic form of the brevicolline alkaloid proposed by T. Szabó et al. in 2022 is the most suitable because although it was devised in 11 steps with an overall yield of 48 %, the essential intermediates were built using commercially accessible and inexpensive starting materials and reagents (triflate ester 7, acetylene-amine 10, and dihydropyrrole ring-containing derivative 11 from scheme (16)). Apart from the higher yield of this synthesis compared to other approaches, the gram-scale creation of intermediate 7 is a key characteristic that opens the door to more brevicolline analogues and additional C-(4) functionalized β-carbolines.

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