Hexahydropyrrolo[2,3-b]indole alkaloids of biological relevance: proposed biosynthesis and synthetic approaches

Avishek Roy, a Arindam Maity, a Saina Shaheeda MK, a Rahul Giri, a and Alakesh Bisai* a,b

a Department of Chemistry, Indian Institute of Science Education and Research Bhopal, Bhauri, Bhopal – 462066, Madhya Pradesh, India
b Department of Chemical Sciences, Indian Institute of Science Education and Research Kolkata, Mohanpur, Nadia – 741 246, West Bengal, India

Email: alakesh@iiserkol.ac.in, alakeshb@gmail.com

Received 07-20-2020 Accepted 09-29-2020 Published on line 10-22-2020

Abstract

The hexahydropyrrolo[2,3-b]indole alkaloids represent a diverse family of structurally complex tryptamine derived alkaloids isolated from a widespread series of natural sources. A hexahydropyrrolo[2,3-b]indole ring having a carbon substituent at C-3a is the defining structural feature of a diverse collection of natural products. The structural complexity of the hexahydropyrrolo[2,3-b]indole alkaloids makes them a particularly elusive and at the same time, appealing target for total synthetic effort. In this review article, we discuss on the biosynthetic proposal as well as key efforts on the total syntheses of naturally occurring complex hexahydropyrrolo[2,3-b]indole alkaloids.

Keywords: Hexahydropyrrolo[2,3-b]indole alkaloids, natural products, total synthesis, biological activities

DOI: https://doi.org/10.24820/ark.5550190.p011.307
1. Introduction

Nitrogen containing heterocycles are omnipresent in bioactive compound of both natural and synthetic origin. In this regard, the hexahydropyrrolo[2,3-b]indole alkaloids are a subset of tryptamine derived tricyclic structures (also known as cyclotryptamine alkaloids) with an all-carbon stereogenic center at the pseudobenzylic position. These cyclotryptamine alkaloids are important building blocks in the total synthesis of natural products, as well as for the development of new drugs. Architecturally intriguing C-3 alkylated hexahydropyrrolo[2,3-b]indole alkaloids (1a-r, Figures 1 and 2) are an important class of indole alkaloids which are found in an array of natural products.1 A subset of methylated, prenylated and reverse-prenylated hexahydropyrrolo[2,3-b]indole natural products exhibit a broad spectrum of biological activities.2 The characteristic molecular architecture and promising medicinal value has prompted the development of a number of methods to access such motifs, with numerous studies particularly in the area of pyrrolidinoindoline syntheses.

2. Representatives of Hexahydropyrrolo[2,3-b]indole Alkaloids

The cyclic hexahydropyrrolo[2,3-b]indole alkaloids of type 1a-r (Figures 1 and 2) is the fundamental building block of cyclotryptamine alkaloids. One of the congener of this family, physostigmine (1d), isolated from the African Calabar bean seeds,3,4 of Physostigma venenosum.5 This is the oldest known acetylcholinesterase (AChE) inhibitor.6 Physostigmine (1d) drew much of attention from medicinal and synthetic groups due to its unique structural feature and potent biological activity.7 The analogues of naturally occurring hexahydropyrrolo[2,3-b]indole alkaloid 1d, i.e. (−)-eseroline (1b) and (−)-esermethole (1c) were synthesized by the hydrolysis of physostigmine (1d) (Figure 1). It is worthwhile to mention that, (−)-eseroline (1b) display potent morphine-like analgesic effects.8
Figure 1. Selected C-3 alkylated hexahydropyrrolo[2,3-b]indole alkaloids (1a-n).

Hexahydropyrrolo[2,3-b]indole alkaloids (Figures 1 and 2) having a prenyl and reverse prenyl moiety adjacent to the pseudobenzyl 3a-site, viz. flustramines (1f-k),9,10 ardeemin (1l-m),11,12 fructigenine A (1n)13 and pseudophrynamines (1o-r),14-17 have gained considerable attention owing to their potential biological activities. An array of brominated pyrroloindolines has yielded from marine cheilostome bryozoan Flustra foliacea collected in the North sea.18,19 The same species from Canadian waters has yielded five different but closely related indole alkaloids (-)-flustramine E (1i) and (-)-pseudophrynaminol (1o). It is interesting to note that the alkaloids from the Canadian waters showed strong activity against Bacillus subtilis, while those from the North Sea were devoid of such activity.20-22 The pioneering work of Carlé and Christophersen led to the isolation of two new metabolites from the Scandinavean bryozoan, Flustra foliacea, which were named (-)-flustramines A (1j) and B (1g).23,24 To date, several indole alkaloids and one quinoline have been isolated from Flustra foliacea collected in the North Sea,25-27 and from material collected in Canadian waters.28 Another type of hexahydropyrazino[2',1'-5,1]pyrrolo[2,3-b]indole ring system bearing a reverse-prenyl group at C10b is a widely distributed structural framework present in a number of biologically active alkaloids such as (-)-ardeemin (1l), (-)-N-acetylardeemin (1m) and (-)-fructigenine A (1n) have been isolated from a marine-derived fungal strain identified as Penicillium fructigenium (Figure 1,2).11-13
Hexahydropyrrolo[2,3-b]indole alkaloids 1a-k and 1o-q possess architecturally interesting structural motifs and share two contiguous stereocenters. Among these two stereocenters, one of them is all-carbon quaternary stereogenic center (Figure 1,2). A structural survey of alkaloids (1) reveals a central cis-fused pyrroloindoline core with a quaternary center at C-3a apparently because of the higher level of ring strain in the trans-stereoisomer. The absolute configuration assigned to the naturally occurring (−)-debromoflustramine B (1f), (−)-flustramines A (1j) and B (1g).

3. Biological Profile of Hexahydropyrrolo[2,3-b]indole Alkaloids

The history of (−)-physostigmine (1d) and pharmacological effects has been reviewed independently by Holmstedt, Somani and Triggle. (−)-Physostigmine (1d) alkaloids isolated from West African perennial shrub Physostigma venenosum. Initially naturally occurring (−)-physostigmine (1d) was utilized for ophthalmic treatment purposes. The general and dominant pharmacology of physostigmine is due to a short-acting inhibition of the enzymes AChE and butyrylcholinesterase (BuChE).

The role of physostigmine (1d) in the central cholinergic nervous system in memory processes was summarized by Deutsch in 1971 and in 1983. Many observations indicating that the role of (−)-physostigmine (1d) in the amelioration of the symptoms of Alzheimer's disease. Another new analgesic drug (-)-eseroline (1b) can be derived from (-)-physostigmine (1d), after hydrolysis of N-methyl carbamyl group. Eseroline (1b) as a free base is quite unstable and is easily oxidized, whereas its salts with acids like salicylic, fumaric, tartaric etc. are stable even in solution in presence of antioxidant agents. In this respect (−)-eseroline (1b) resembles (−)-physostigmine (1d) which also possesses antinociceptive activity in various purpose. Unlike the latter compound, however, eseroline (1b) is devoid of anticholinesterase activity and its analgesic effect is not antagonized by atropine. In agreement with the findings of Bartolini and Ireson, eseroline (1b), a physostigmine (1d) derivative, proved to be a potent analgesic as evidenced by the hot plate test with rats. It has about the same order of potency as morphine. Among these derivatives of physostigmine, the most attractive compound, (−)-phenserine (1e), is a dual AChE and β-amyloid precursor protein (β-APP) inhibitor being developed to treat mild to moderate Alzheimer’s disease. Therefore, phenserine may represent an important new catalog of compounds for treatment of AD, with the goal of developing potential Alzheimer’s pharmacotherapeutics (Figure 1).

Flustramines, isolated from the Bryozoa Flusta foliacea, are a family of marine alkaloids with characteristic prenylated or reverse prenylated hexahydropyrrolo[2,3-b]indole backbone. (−)-Flustramine B (1g) possesses skeletal and smooth-muscle relaxant activity and its analogue, (−)-debromoflustramine B (1f) was proven to
have significant butyrylcholinesterase inhibitory activity and antibacterial activity against vancomycin-resistant Enterococci and methicillin-resistant Staphylococcus aureus.

(--)Pseudophrynaminol (1o) was isolated from the skin of the Australian frog Pseudophryne coriacea and emerge as a potent inhibitor of ganglionic and neuromuscular nicotinic receptor-channels (Figure 2).

Another class of biologically active indole alkaloid like (--)ardeemin (1l), (--)N-acetylardeemin (1m) and (--)fructigenine A (1n) display promising bioactivities towards life-threatening diseases. Where as fructigenine A (1n) has growth-inhibitory activity against Avena coleoptile and leukemia L-5178Y cells and N-acetylardeemin (1m) is one of the most potent known agents for reversal of multiple drug resistance (MDR), as measured against KBV-1 (vinblastine resistant) tumor cell lines. Thus, 5-N-acetylardeemin would be termed a naturally occurring MDR reversal agent (Figure 1).

![Image](https://example.com/image.png)

Figure 3: Representatives of hexahydropyrrolo[2,3-b]indole alkaloids.

The biological activities of these compounds have been well studied, the results of which have shown several promising applications, including muscle relaxants, potassium channel-blockers and anti-cancer agents. For this reason, the total synthesis of these natural products has received considerable attention, and has been accomplished by several research groups.

4. Proposed Biosynthesis of Hexahydropyrrolo[2,3-b]indole Alkaloids

4.1 Biosynthesis of C-3 methylated hexahydropyrrolo[2,3-b]indole alkaloids

Biosynthetically, these alkaloids are believed to be originated from L-tryptophan, which is shown in Scheme 1. A reaction of L-tryptophan (3a) with nature’s methylating agent (SAM, S-Adenosyl Methionine, 2a) chemoselectively (a C-C bond formation) to furnish intermediate (3b), which could do iminium cyclization leading to the formation of intermediate (3c). Next, a decarboxylative reaction (probably catalysed by the decarboxylase enzyme) of hexahydropyrrolo[2,3-b]indoline (3c) could afford intermediate 3d (Scheme 1), which is considered to be the advanced intermediate for all C-3 methylated hexahydropyrrolo[2,3-b]indoline alkaloids. Intermediate 3d then reacts with methylating agent (SAM, S-Adenosyl Methionine, 2a) could lead to the formation of naturally occurring (--)deoxyeseroline (1a). Next, deoxyeseroline (1a) could be considered to be the advanced intermediate for all C-3 methylated hexahydropyrrolo[2,3-b]indoline alkaloids, such as (--)eseroline (1b) and (--)esermethole (1c) and (--)physostigmine (1d). Towards this, an electrophilic oxidation of aromatic ring of (--)deoxyeseroline (1a) could afford (--)eseroline (1b), where electrophilic substitution must take place at the p-position of N-Me group. Eseroline (1b) also could afford other hexahydropyrrolo[2,3-b]indole alkaloids such as (--)physostigmine (1d) and (--)phenserine (1e).
Scheme 1. Proposed biosynthetic proposal to C3-methylated hexahydropyrrolo[2,3-b]-indole alkaloids.

4.2 Biosynthesis of C-3 prenylated hexahydropyrrolo[2,3-b]indole alkaloids

Along similar line, biosynthetically, C-3 prenylated hexahydropyrrolo[2,3-b]indoline alkaloids are believed to be originated from L-tryptophan 3a, which is shown in Scheme 2. A reaction of L-tryptophan (3a) with a 3,3-dimethylallyl pyrophosphate (DMAPP, 2b) to craft the hexahydropyrrolo[2,3-b]indoline core (4b) via the intermediacy of iminium 4a.20 Next, a decarboxylative reaction (probably catalysed by the decarboxylase enzyme) of hexahydropyrrolo[2,3-b]indoline (4b) could afford intermediate 4c (Scheme 2), which is considered to be the advanced intermediate for all C-3 prenylated hexahydropyrrolo[2,3-b]indoline alkaloids. Intermediate 4c then reacts with methylating agent (SAM, S-Adenosyl Methionine) chemoselectively to furnish (−)-debromoflustramine E (1h). Further methylation using SAM could lead to the formation of N-methyl debromoflustramine E (4d). Later, a regioselective allylic oxidation of N-methyl debromoflustramine E (4d) could generate (−)-pseudophrynamine 272A (1p), which on further oxidation affords (−)-pseudophrynamine 270 (1q).
Scheme 2. Proposed biosynthetic proposal to C3-prenylated hexahydropyrrolo[2,3-b]-indole alkaloids.

Further, regioselective allylic oxidation of (−)-debromoflustramine E (1h) could complete the synthesis of (−)-pseudophrynaminol (1o). Because of their interesting architecture with a vicinal stereogenic center (out of which one of them is having an all-carbon quaternary stereogenic center), a number of efficient strategies for the construction of such quaternary stereogenic centers were developed.\(^{69-70}\)

5. Synthetic Approaches to the Hexahydropyrrolo[2,3-b]indole Alkaloids

5.1 Non-stereocontrolled synthesis of hexahydropyrrolo[2,3-b]indole alkaloids

The first synthesis of physostigmine was reported by Julian and Pikl in 1935,\(^{71}\) via a key reductive cyclization of 1,3-dimethyl-5-ethoxyindolylethyl-methylamine (5a) to eserethol (1s) (Scheme 3). Resolution of (±)-amine (5a) using (+)-camphorsulphonic acid and (+)-tartaric acid gave (−)-amine base (5a), which was reacted with sodium and ethanol to furnish (−)-eserethole (1s) with excellent yield. Later the transformation of (−)-eserethole (1s) to (−)-eseroline (1b) was conducted by gently boiling of (1s) in petroleum ether in presence of anhydrous AlCl\(_3\). Polonovski and Nitzberg have disclosed the conversion of (−)-eseroline (1b) to (−)-
physostigmine (1d) by treatment of (-)-eseroline (1b) with methyl isocyanate to complete the synthesis of (-)-physostigmine (1d) (Scheme 3).  

![Chemical diagram showing the synthesis of (-)-eseroline (1b) and (-)-physostigmine (1d).]

**Scheme 3.** Total synthesis of eseroline (1b) reported independently by Pikl et al. and Harley-Mason et al.

In 1954, Harley-Mason et al.  have reported racemic synthesis of (±)-eseroline (1b) from 2,5-dimethoxyacetophenone (6a) (Scheme 3). Initially, 2,5-dimethoxyacetophenone (6a) was condensed with ethyl cyanoacetate to produce ethyl 1-cyano-2-(2,5-dimethoxyphenyl)crotonate (6b) with 80% yield. Next, 6b was converted to 2-(2,5-dimethoxyphenyl)-2-methylbutane-1,4-diamine (6e) via the intermediacy of 6c and 6d by reacting with KCN followed by hydrogenation over PtO₂ in presence of HCl and next N,N'-dimethylation using benzylaldehyde and Mel under heating condition. Then demethylation by hydrobromic acid followed by potassium ferricyanide oxidation yielded the product (±)-eseroline (1b) via the intermediate p-benzoquinone with 67% yield over 2 steps (Scheme 3).

In 1977, Ikeda group  disclosed the synthesis of (±)-esermethole (1c) via a photochemical route from ethyl 2-cyano-6-methoxy-4-methylquinoline-1(2H)-carboxylate (7a) (Scheme 4). Photolysis of compound 7a in ethanol in pyrex tube yielded 10% *endo*-cyanocycloprop[6]indole 7b. Later, alkaline hydrolysis of 7b furnished the furo[2,3-b]indole 8a in 69% yield following in situ sequential hydrolysis, ring opening, hydrolysis of cyano group and recyclisation step. Finally, N-Methylation by methyl iodide followed by reduction using lithium...
aluminum hydride completed the synthesis of (±)-esermethole (1c) in 25% overall yield over 3 steps (Scheme 4).

Scheme 4. Total synthesis of (±)-esermethole (1c) by Ikeda et al. and (±)-flustramine B (1g) Hino et al.

In 1983, Hino and co workers\textsuperscript{75} reported that the precursor of 6-bromotryptamine derivative 9a can be utilized for the total synthesis of (±)-flustramine B (1g) as shown in Scheme 4. A successive double prenylation of 9a with an excess of prenyl bromide furnished 10a, which on subsequent hydrolysis followed by a reaction with MeI completed the total synthesis of (±)-flustramine B (1g) (Scheme 4).\textsuperscript{75-76}

Scheme 5. Synthesis of (±)-physostigmine (1d) by Fukumoto et al.
Later in 1986, Fukumoto and co-workers\textsuperscript{77} have described formal total synthesis of (±)-physostigmine (1d) (Scheme 5). Ozonolysis of 2-oxindole 5b followed by reductive amination and ester-aminolysis afforded expected lactam carbamate (11a) in 63% yield, which was further treated with K$_2$CO$_3$ in MeOH then dimethyl sulfide and aluminum trichloride in dichloromethane at room temperature furnished lactam (11b) with 63% yield. As the total synthesis of (±)-physostigmine (1d) is reported from compound 11b by Takano group\textsuperscript{78} (1982), this effort culminated in a formal total synthesis of 1d (Scheme 5).

\begin{center}
\begin{tikzpicture}
\node [text width=0.5\textwidth, align=left, above=0.5cm] at (0,0) {	extbf{Scheme 6.} Synthesis of (±)-debromoflustramine B (1f) by Christoffersen et al.};
\end{tikzpicture}
\end{center}

In 1995, the methylamide of 3-indolylacetic acid (9b) was utilized by Christoffersen,\textsuperscript{79} for a total synthesis of (±)-debromoflustramine B (1f) (Scheme 6). A reaction of 9b with 3,3-dimethylallyl bromide afforded monoprenylated pyrroloindolone 12a and 12b (Scheme 6). Reduction of 12b with LiAlH$_4$ completed the total synthesis of (±)-debromoflustramine B (1f) in 76% yield (Scheme 6).

\begin{center}
\begin{tikzpicture}
\node [text width=0.5\textwidth, align=left, above=0.5cm] at (0,0) {	extbf{Scheme 7.} Synthesis of (±)-debromoflustramine B (1f) from nitrovinylindole by Somei et al.};
\end{tikzpicture}
\end{center}

Later in 1997, Somei and co-workers,\textsuperscript{80} successfully synthesize 3-prenyl-3-(2-nitrovinyl)-2-oxindole 5c via a Claisen type rearrangement of nitrovinylindole 9cb which was prepared from 9c with 2-methyl-2-buten-2-ol (Scheme 7). Selective reduction of the nitrovinyl group to amine was carried out using Zn-Hg in HCl, followed...
by a sequence that involves $N_b$-carbomethoxylation afforded 5d in synthetically useful yield. Finally, a reductive cyclization followed by $N$-8-prenylation afforded (+)-debromoflustramine B (1f) (Scheme 7).

Scheme 8. Total synthesis of (+)-debromoflustramine A (1k) and B (1f) by Joseph-Nathan et al.

Later in 1999, Joseph-Nathan and co workers\(^9\) reported a potential straightforward route to a variety of marine Flustra foliacea alkaloids (Scheme 8). Initially Grignard addition onto 2-hydroxyindolenines (13a) yielded a prenylated and reverse prenylated 2-oxofuro[2,3-b]indoles with 77% yield (8b:8c = 40:60 ratio). Later Hydrolytic decyanation of the $\alpha$-cyano $\gamma$-lactones in presence of alumina afforded the corresponding $\gamma$-lactone 8d and 8e in 86% and 95% yield, respectively. Later, Moc (methyloxy carbonyl) group deprotection of compounds 8d and 8e using sodium methoxide and followed by $N$-alkylation by using $K_2CO_3$ and prenyl bromide yielded 70% and 60% of lactone 8f and 8g, respectively. Finally, total syntheses of debromoflustramines A (1k) and B (1f) were completed from 8f-g by aminolysis using methylamine followed by LiAlH$_4$ reduction (Scheme 8).

Scheme 9. Synthesis of (+)-debromoflustramine (1f) by Ganesan et al.
In 2003, an efficient biomimetic approach to (+)-debromoflustramine B (1f) was reported by Ganesan and co-workers (Scheme 9). The total synthesis of (+)-debromoflustramine B (1f) was accessed in two steps from tryptamin derivative 9d (Scheme 9). A zinc triflate mediated alkylation of 9d with prenyl bromide in the presence of DIPEA and tetrabutylammonium iodide gave 10b in 70% yield. Reduction of the carbamate group was performed with Red-Al to give (+)-debromoflustramine B (1f) in 96% yield. Modifications of Ganesan’s approach to the synthesis of 1f were also explored recently by the groups of Menéndez and Mitchell.

Scheme 10. Total synthesis of (+)-debromoflustramine B (1f) and E (1h) by Kobayashi et al.

Kobayashi and co workers have reported the complete total synthesis of (+)-debromoflustramines B (1f) and E (1h) from amide intermediate (5e) in 2007 (Scheme 10). Reduction of 5e using AlH$_3$.EtNMe$_2$ furnished cyclotryptamine skeleton 10c. Later to complete target molecule, compound 10c was treated under the Birch condition followed by prenylation to form (+)-debromoflustramine B (1f). Also, Birch reduction of 10c completed the total synthesis of (+)-debromoflustramine E (1h).

Scheme 11. Synthesis of (+)-debromoflustramine (1f) by Yang et al.

In 2013, Yang et. al. disclosed the total synthesis of (+)-debromoflustramine B (1f) (Scheme 11). The reaction of N-Boc-tryptamine (9e) and prenyl bromide in presence of triethyl borane and t-BuOK led to the
formation of 10d, which was subjected to further prenylation and reduction with LiAlH₄ completed the total synthesis of (±)-debromoflustramine B (1f) in 76% yield over 3 steps (Scheme 11).

Scheme 12. Synthesis of (±)-esermethole (1c) using copper-catalyzed vinylation by Li et al.

In 2014, Li and co-workers have developed an exo-selective copper-catalyzed vinylation of electron-deficient alkenes which tolerates a wide range of vinyl(aryl)iodonium triflates of types 14c (Scheme 12). Treatment of 4-methoxy-N-methylaniline 14a with methacryloyl chloride afforded conjugated enamide 14b with 95% yield, which was subsequently subjected to the key Cu(I)-catalyzed vinylation–cyclization to provide desired 2-oxindole 5f in 80% yield (Scheme 12). Ozonolysis of compound 5f followed by reductive amination in the presence of methylamine and LiAlH₄ furnished (±)-esermethole (1c) in 86% yield over two steps (Scheme 12).

Scheme 13. Synthesis of (±)-esermethole (1c) following intramolecular cascade by You et al.
In 2015, You et al. have developed a powerful method to establish pyrroloindoline (1) skeletons by an intermolecular cascade dearomatization of indole derivative (9f) with benzodithiolylium tetrafluoroborate (Scheme 13). Treatment of compound 15a under the Raney Ni/H₂ followed by reduction of the methylcarbamate group with LiAlH₄ afforded (±)-esermethole (1c) in 98% yield.

Later, the same group have developed another strategy for the synthesis of C3-methyl-substituted hexahydropyrrolo[2,3-b]indole alkaloid (±)-esermethole (1c) (Scheme 13). Compound 15b was synthesized from compound 9f in 81% yield, which was treated with LiAlH₄ to complete (±)-esermethole (1c) in 98% yield (Scheme 13).

Scheme 14. Synthesis of (±)-esermethole (1c) via a key deacylative pathway by Bisai et al.

In 2018, Bisai and co-workers have developed an efficient Pd(0)-catalyzed chemoselective deacylative allylation of N-acyl 2-oxindole with unprotected allyl alcohol (Scheme 14). This methodology was applied for a total synthesis of (±)-deoxyeseroline (1a) following a key oxidative cleavage followed by reductive cyclization. Further, the total synthesis of (±)-esermethole (1c) was achieved from (±)-deoxyeseroline (1a) in two steps.

Scheme 15. Synthesis of (±)-esermethole (1c) via a key electrophilic alkynylation pathway by Bisai et al.
In 2020, Bisai et al. have reported a direct alkynylation at C3 position of 3-methyl 2-oxindoles using a 5-(alkynyl)dibenzothiophenium triflate afforded compound 5h (Scheme 15). Later Nickel catalyzed controlled hydrogenation of compound 5h followed by hydroboration oxidation and further oxidation lead to form aldehyde intermediate 16b. Next, a reductive amination of 16b with methylenamine followed by a reductive cyclization by LiAlH4 to furnish (±)-deoxyeseroline (1a) (Scheme 15).  

5.2 Stereocontrolled synthesis of hexahydropyrrolo[2,3-b]indole alkaloids

The first enantioselective synthesis of (−)-physostigmine (1d) was reported by Takano group,78 from a readily available chiral synthon (S)-(−)-benzyl-2,3-epoxypropyl ether (−)-17a (Scheme 16). Compound (−)-17a was reacted with in-situ generated carbanion of 3-methoxy benzyl cyanide 17b using LDA (lithium amide of diisopropylamine) to produce cyano-alcohol (−)-17c as a mixture of diastereomer (Scheme 16). Later hydrolysis of (−)-17c yielded γ-lactone (−)-17d in 63% over 3 steps. The stereoselective insertion of methyl group from the less hindered face followed by hydrogenolysis in presence of H2 gas and catalytic Pd-C afforded hydroxyl lactone (−)-17e.

Scheme 16. First enantioselective synthesis of (−)-esermethol (1c) by Takano et al.

After hydrolysis oxidative cleavage with NaIO4 and reduction with NaBH4 followed by acid work up to furnished the compound (−)-17f (Scheme 16). Further, condensation of the lactone (−)-17f with 40% MeNH2 in water at 180 °C afforded lactam, which was reacted with the cupric nitrate tetrahydrate in Ac2O to furnish (−)-17g. Platinum catalyzed hydrogenation of (−)-17g furnished amine derivative (−)-11b which under reductive cyclization and followed by N-methylation lead to form (−)-esermethole 1c (Scheme 16).

In 1991, Wong et al. have92 described an enantioselective synthesis of (−)-esermethole (1c) (Scheme 17). Asymmetric alkylation of oxindole 5j with chloro acetonitrile in the presence phase transfer catalyst L yielded 83% of nitrile 5k with 73% ee (Scheme 17). Later, crude nitrile 5k was reduced by platinum catalyzed hydrogenation to the corresponding primary amine as an optically enriched mixture. Treatment of the amine
with dibenzoyl-D-tartaric acid in acetonitrile followed by a single recrystallization of the diastereomeric salt gave 48% yield of optically pure tartrate salt. Further NaOH treatment afforded optically pure amine (S)-5l, which was further treated ClCOOMe to form carbamate followed by reductive cyclization to furnish (−) esermethole (1c) (Scheme 17).

Scheme 17. Chiral PTC mediated synthesis of (−)-esermethole (1c) and (−)-physostigmine (1d) by Wong et al.

Scheme 18. Total synthesis of (−)-ardeemin (1l) and (−)-N-acetylardeemin (1m) by Danishefsky et al.
In 1994, Danishefsky and co-workers\(^9\) have reported the total syntheses of ardeemin (1l) and 5-N-acetylardeemin (1m). Bis-(Boc)tryptophan methyl ester 9g was converted to 3-selenenylation pyrroloindole 18a (Scheme 18). Treatment of 18a with methyl triflate and prenyl tributyl stannane furnished the desired reverse prenylated product 18b with 60% yield and 9:1 dr. After saponification of 18b, coupling with D-alanine methyl ester afforded 18d (Scheme 18). The diketopiperazine 18e was obtained in 76% yield upon deprotection of Boc group and ammonia-DMAP-induced cyclization. Following o-azidobenzoyl chloride acylation reaction, the resultant compound was reacted with tributylphosphate in benzene to afford ardeemin (1l) in 56% yield from 18e. Finally, acylation of 1l provided 5-N-acetylardeemin (1m) in 82% yield (Scheme 18).

\[\text{Scheme 19. Asymmetric Heck cyclization assisted total synthesis of } (-)-\text{physostigmine (1d)} \text{ by Overman et al.}\]

In 1998, Overman et al.\(^9\) have disclosed asymmetric approach to hexahydropyrrolo[2,3-b]indole alkaloid, (-)-physostigmine (1d) (Scheme 19). Asymmetric Heck cyclization of 19c with 20% Pd-(S)-BINAP [formed in situ from 10% Pd\(_2\)(dba)_3.CHCl\(_3\) and 23% (S)-BINAP] afforded predominantly (diastereoselectivity = 98:2) the oxindole (E)-enoxysilane (S)-5m which upon treatment with dilute HCl to provide oxindole aldehyde (S)-16c in 84% yield and 95% ee (Scheme 19). Later, condensation with methylamine followed by reduction of crude imine with excess LiAlH\(_4\) in refluxing THF afforded (-)-esermethole (1c), Finally, BBr\(_3\) mediated demethylation and followed by the treatment with NaH and methyl isocyanate afforded (-)-physostigmine (1d) (Scheme 19).

In 2004, MacMillan and co-workers\(^9\) have reported total synthesis of (-)-flustramine B (1g) following a key Michael addition/cyclization to construct the pyrroloindoline core via iminium catalysis pathway (Scheme 20). 6-Bromo tryptamine derivative 9g was reacted with acrolein in the presence of imidazolidinone catalyst, followed by reduction of formyl group by NaBH\(_4\) yielded 10e in 78% yield with 90% ee. Later, compound 10e was converted to terminal olefin (-)-10f in two steps over 89% yield. Cross-metathesis of 10f with 2-methyl-2-butene in the presence of catalytic Grubbs 2nd genration catalyst afforded (-)-10g in 94% yield. Finally, Boc
group deprotection followed by \(N\)-methylation under reductive amination afforded \((-\)-flustramine B \((1g)\) (Scheme 20).

\[
\begin{align*}
\text{(9g') + MeNHBoc} & \xrightarrow{(20 \text{ mol%}) \text{DCM, } -40 \degree \text{C}} \text{NaBH}_4, \text{MeOH} \\
& \xrightarrow{78\% \text{ yield}} \text{Br} \quad \text{Me} \quad \text{Me} \\
(10e) & \xrightarrow{i) \text{MsCl} \quad \text{ii) NO}_2\text{PhSeCN} \quad \text{H}_2\text{O}_2} \xrightarrow{89\% \text{ yield}} \text{Br} \quad \text{Me} \quad \text{Me} \\
(10f) & \xrightarrow{i) \text{TMSI} \quad \text{ii) HCHO} \quad \text{NaBH}_4} \xrightarrow{89\% \text{ yield}} \text{Me} \quad \text{Me} \\
& \quad \text{Grubbs 2nd Den. Cat.} \\
& \quad \text{(-)-flustramine B (1g)}
\end{align*}
\]

**Scheme 20.** MacMillan’s organocatalyzed synthesis of \((-\)-flustramine B \((1g)\).

In 2006, Trost and co-workers\(^9\) have developed a Pd-catalyzed C-3 allylation of 3-substituted indole \((9h)\) to give the corresponding 3,3-disubstituted indolines \((-\)-20a\) in 84\% ee (Scheme 21). Enantioenriched compound \((-\)-20a\) was treated tetrabutylammonium hydrogen monopersulfate (oxone) and acetic acid give oxindole \((-\)-16d\) in 79\% yield. Later, \(N\)-Methylation followed by oxidative cleavage lead to form aldehyde \((-\)-16b\), which was further react with methyl amine followed reductive cyclization furnished \((-\)-esermethole \((1c)\) (Scheme 21).

\[
\begin{align*}
\text{(9h) + MeNHBoc} & \xrightarrow{(3 \text{ equiv.}) \text{THF, 97\%}} \xrightarrow{1 \text{ equiv. } 9\text{-BBN-(C}_8\text{H}_{13}) \quad 2.5 \text{ mol\% Pd}_2(\text{dba})_3 \quad 7.5 \text{ mol\% } (S,S)-L \quad 4 \degree \text{C, } 20 \text{ h}} \xrightarrow{91\% \text{ yield}} \text{Me} \quad \text{Me} \\
(10e) & \xrightarrow{\text{NBu}_2\text{HSO}_3 \quad \text{AcOH, CH}_3\text{CN}} \xrightarrow{79\%} \text{Me} \quad \text{Me} \\
(10f) & \xrightarrow{i) \text{NaH, Mel} \quad \text{THF, 97\%} \quad \text{ii) OsO}_4, \text{NMO} \quad \text{CH}_3\text{Cl}_2 \quad \text{then NaO}_2 \quad \text{acetone/ H}_2\text{O}} \xrightarrow{87\%} \text{MeNH}_2\text{HCl} \quad \text{Et}_3\text{N, MgSO}_4 \quad \text{THF} \quad \text{then LiAlH}_4, 86\% \\
& \xrightarrow{(-)-16b} \quad \text{(-)-esermethole (1c)}
\end{align*}
\]

**Scheme 21.** Enantioselective C-3 allylation directed total synthesis of \((-\)-esermethole \((1c)\) by Trost et al.
Scheme 22. Nickel catalyzed total synthesis of \((-\)-esermethole (1c) by Nakao et al.

In 2008, Nakao and co-workers\(^97\) have demonstrated a Nickel/AlMe\(_2\)Cl-catalyzed intramolecular arylcyanation of alkenes to get 21b in 96% ee (Scheme 22). Oxidation of the C-2 position of indoline 21b afforded 2-oxindole \((-\)-5k with 40% yield. Later, cyanide reduction followed by cyclization in presence of LiAlH\(_4\), and then N-methylation completed the total synthesis of \((-\)-esermethole (1c) (Scheme 22).

Scheme 23. Synthesis of \((+\)-esermethole \(\text{ent-}(1c)\) and \((+\)-physostigmine \(\text{ent-}(1d)\) by Barbas III et al.

In 2009, Barbas III and co-workers\(^98\) have demonstrated organocatalytic approach to the hexahydropyrrrolo[2,3-\(b\)]indole alkaloid via a 1,4-addition of oxindole 5j’ on to nitroethylene (Scheme 23). This reaction afforded compound \((+\)-5m in 65% yield with 96% ee (after one recrystallization). Raney nickel reduction of the nitro group followed by a reaction of resultant amine with methyl carbamate provided the key intermediate \((+\)-5n in 80% over 2 steps, which underwent reductive cyclization with LiAlH\(_4\) to afford \((+\)-esermethole \(\text{ent-}(1c)\) in 90% yield (Scheme 23).
Scheme 24. Total synthesis of (−)-5-N-acetylardeemin (1m) by Kawasaki et al.

In 2010, Kawasaki et al. have demonstrated the first total synthesis of (−)-fructigenine (1n) and a novel approach to (−)-5-N-acetylardeemin (1m) through a common imine intermediate (+)-20b. They have synthesized pyrroloindoline imine (+)-20b intermediate starting from 1-acetylindolin-3-one via a key domino olefination/isomerization/Claisen rearrangement (OIC) followed by reductive cyclization and regioselective oxidation process. With this key intermediate in hand, they have completed the total synthesis of fructigenine A (1n). N-Boc-L-phenylalanine and p-methoxyphenyl (PMP) isonitrile were reacted with (+)-20b to afford dipeptide (+)-22a in 78% yield via Ugi three-component reaction. Removal of Boc group of (+)-22a with TFA leads to smooth cyclization in refluxing toluene afforded diketopiperazine (+)-22b. Later, NaOH mediated epimerization of (+)-22b completed the total synthesis of (−)-fructigenine (1n). Along similar line, (−)-5-N-acetylardeemin (1m) was synthesized from the intermediate (+)-20b (Scheme 24). Compound (+)-20b was reacted with N-Boc-D-alanine and isonitrile to provide (+)-22c. Further, (+)-22c was reacted with trifluoroacetic acid followed by a reaction with phosphorus oxychloride to furnished the desired product (−)-5-N-acetylardeemin (1m) (Scheme 24).

Scheme 25. Mo-catalyzed asymmetric synthesis of (−)-esermethole (1c) by Zhang et al.
In 2011, Trost and Zhang have developed enantioselective Mo-catalyzed asymmetric allylic alkylation (AAA) reactions for the generation of quaternary stereocenters at the 3-position of 3-alkyl oxindole 5j (Scheme 25). Asymmetric allylation of 5j under the optimized conditions proceeded to afford (−)-16e with 95% yield and 99% ee (after recrystallization). Oxidation of the allylated product (−)-16e, (OsO₄, NMO, and then NaIO₄) provided the aldehyde (−)-16c in 92% yield. Later imine formation with methyl amine and followed by reductive cyclization afforded (−)-esermethole (1c), which had been transformed to (−)-physostigmine (1d) and (−)-phenserine (1e), in two steps (Scheme 25).

![Scheme 26](image)

Scheme 26. Synthesis of (+)-flustramine B (ent-1g) by Trost et al.

In 2011, Trost and co-workers have demonstrated a palladium-catalyzed asymmetric prenylation of 2-oxindoles via a π-prenyl organometallic species (Scheme 26). Compound 5o was treated with Boc protected reverse prenyl moiety in presence of Pd₂dba₃.CHCl₃ and ligand L under optimized condition to afford linear prenylated product 5p in 99% ee. Later, hydrolysis of cyano group followed by amide formation furnished 5q in 74% yield, which was further treated with alane-N,N-dimethyl ethylamine complex to complete the total synthesis of (−)-flustramines B (ent-1g) (Scheme 26).

In 2012, Garg and co-workers have developed a concise and practical synthesis of (+)-phenserine (ent-1e), following an interrupted Fischer indolization (Scheme 27). Hemiaminal (23b) was reacted with p-methoxy phenyl hydrazine (23a) in AcOH medium to afford pyrrolidinoindoline (10h) in 78% yield. Reduction of carbamate 10h by Red-Al afforded (±)-esermethole (1c). Later, the treatment of (±)-esermethole (1c) with (−)-di tolyl-L-tartaric acid in THF led to crystallization to furnish (−)-esermethole (ent-1c). Next, Krapcho demethylation of (±)-esermethole (ent-1c) and carbomylation yielded (+)-phenserine (ent-1e) in 74% over 2 steps (Scheme 27).
Scheme 27. Synthesis of (+)-esermethole (ent-1c), (+)-phenserine (ent-1e) following interrupted Fischer indolization by Garg et al.

Scheme 28. Chiral brønsted acids mediated synthesis of (−)-debromoflustramine (1f) by Antilla et al.

In 2012, Antilla and co-workers\textsuperscript{103} have disclosed chiral Brønsted acid, such as (R)-TRIP (2,4,6-triisopropylphenyl binaphthyl phosphoric acid) catalyzed enantioselective formation of pyrroloindolines (Scheme 28). N-Moc tryptamine 9i was treated with methyl venyl ketone (MVK) in presence chiral Brønsted acid under standard condition to furnish enantioenriched 24a in 91% yield with 93% ee. Later Wittig
olefination of the chiral double Michael product, 24a produced high yield of 24b. A Ru-catalyzed isomerization of terminal olefin followed by reductive N-methylation completed the total synthesis of (−)-de bromoflustramine B (1f) (Scheme 28).

Scheme 29. Copper catalyzed enantioselective synthesis of (−)-pseudophrynaminol (1o) and (−)-de bromoflustramine E (1h) by Zhang et al.

In 2012, Zhang et. al. have developed a stereocontrolled copper catalyzed Intramolecular alkylation of o-bromoanilides bearing a chiral sulfinyl amide unit to synthesize the precursors for the total synthesis of flustramine as well as pseudophrynamine alkaloids (Scheme 29). Next, in presence of different alkyl bromide copper mediated strategy completed the synthesis of targeted molecules 25c and 25d. Treatment of these key intermediates 25c and 25d with HCl and MeOH afforded amine compounds 25e and 25f with 88% and 85%
yield, respectively (Scheme 29). Further, DIBAL-H reduction followed by benzyl group deprotection under Birch reduction provided pseudophrynaminol (1o) and debromoflustramine E (1h) with 85% and 98% yield, respectively (Scheme 29).

**Scheme 30.** Ir Catalyzed reverse Prenylated pyrroloindoline synthesis by Carreira et al.

In 2014, Carreira and co-workers\(^\text{105}\) have developed a direct C3 selective reverse prenylation of tryptamine derivative (9j). The methodology employs a readily accessible Ir-catalyst and a simple dimethyl allyl carbonate as precursor for the prenyl group with a variety of 3-substituted-1H-indoles as substrates, involving the formation of vicinal quaternary centers (Scheme 30). The diastereoselective reaction with tryptophan methyl ester enables access to a adaptable hexahydropyrrolo[2,3-b]indole intermediate, which they used as precursor for the stereoselective synthesis of (+)-aszonalenin (9k) and (−)-brevicompanine B (9l) (Scheme 30).

**Scheme 31.** Enantioselective pyrroloindoline synthesis by Reisman et al.

---

**Arkivoc 2020, i, 437-471**

©AUTHOR(S)
In the same year, Reisman et al. have reported enantioselective approach to pyrroloindolines from C3-allylated indole and 2-amidoacrylates using SnCl4-(R)-3,3-dichloro-BINOL catalyst (Scheme 31). This strategy depends on a formal (3+2) cycloaddition reaction. Following this methodology, they had successfully completed the total syntheses of (−)-lansai B (9n) and (+)-nocardioazines A (9o) and B (9p) (Scheme 31).

Scheme 31. Enantioselective organocatalytic syntheses of various pyrroloindoline alkaloids by Bisai et al.

In the year 2015, Bisai et al. have developed enantioselective organocatalytic hydroxymethylation of 2-oxindole using paraformaldehyde as a C1 unit with 81% yield and 90% ee (Scheme 32). Starting from the enantioenriched compound, they carried out the total synthesis of (−)-deoxyeseroline (1a), (−)-eseroline (1b) and (−)-pseudophrynamine (1d). Compound was treated with NaBH4 followed by palladium catalyzed hydrogenolysis afforded hexahydropyrroloindoline core, which upon xanthate mediated reduction (with n-tributyl tin hydride in the presence of AIBN) afforded (−)-deoxyeseroline (1a).

Scheme 32. Total syntheses of C-prenylated pyrroloindoline alkaloids by Bisai et al.
Further treatment with HBr and DMSO to afford C-5 brominated compound (24h) which was further reacted with NaOMe and Cul furnished the total synthesis of (−)-eseremethole (1c) with 78% yield. A further Dess-Martin periodinane (DMP) oxidation of compound (24g) followed by Witting homologation afforded aldehyde (26c). Next, a reaction with a stabilized Witting followed by LiAlH₄ reduction furnished (−)-pseudophrynamine 272A (1p). The latter on subsequent oxidation with DMP completed the first total synthesis of (−)-pseudophrynamine 270 (1q) (Schemes 32 and 33).

Recently, in 2018, You group have developed a palladium-catalyzed asymmetric dearomative prenylation of tryptamine derivatives 9i to afford 24h in 95% ee (Scheme 34). With 24h in hand, concise total syntheses of (−)-flustramine B (1g), (−)-debromoflustramine B (1g), (−)-pseudophrynaminol (1o) were completed in few steps (Schemes 34).

Scheme 34. Palladium-catalyzed asymmetric dearomative prenylation by You et al.

In 2019, Xu et. al. have reported the total synthesis of (−)-fructigenine A (1n) in a highly convergent and biomimetic fashion from the commercially available (S)-tryptophan. Starting from L-tryptaphone derivative, AlCl₃ mediated one-pot diastereoselective Meerwein–Eschenmoser–Claisen (MEC) rearrangement was developed to construct C3 reverse prenylated oxindole (27c).

Scheme 35. Synthesis of (−)-fructigenine A (1n) by Xu et al.
Compound 27c was converted to 27d in 20% yield over 4 steps. Later, compound 27d was coupled with L-Fmoc-phenylalanine and cyclized upon Fmoc removal to synthesize diketopiparizine 27e. Finally, acetylation of compound 27e completed the total synthesis of (--)-fructigenine A (1n) (Schemes 35).

6. Conclusions

This review is intended to provide an overview of the complex hexahydropyrrolo[2,3-b]indole alkaloids where biosynthetic relationship and synthetic approaches to this family of alkaloids have been discussed elaborately. The fascinating molecular architecture of the members of this natural product family has stimulated the interest of numerous synthetic chemists which has led to a number of creative synthetic approaches and beautiful total syntheses. Although, the biological activities of only a few numbers of hexahydropyrrolo[2,3-b]indole alkaloids are reported, the exhaustive biological potential of the majority of hexahydropyrrolo[2,3-b]indole alkaloids has yet to be evaluated. The knowledge from biological studies would be useful in screening these products for therapeutic applications.

7. Acknowledgements

AB sincerely thanks the SERB, DST, Govt. of INDIA [CRG/2019/000113], the Council of Scientific and Industrial Research (CSIR), Govt. of India [02(0295)/17/EMR-II], and Ministry of Earth Science (MoES), Govt. of India [MoES-2/DS/J/2007 PC-IV] for generous support. Facilities from IISER Bhopal and IISER Kolkata is gratefully acknowledged.

8. References and Notes

   https://doi.org/10.1002/chem.201001451

   PMID: 6675420

   https://doi.org/10.1016/S0099-9598(08)60084-X

   https://doi.org/10.1021/jm00171a001


   https://doi.org/10.1039/CT9252700247

   https://doi.org/10.1016/0014-2999(82)90256-4
   [https://doi.org/10.1021/np0105984](https://doi.org/10.1021/np0105984)

   [https://doi.org/10.1021/np900282j](https://doi.org/10.1021/np900282j)

   [https://doi.org/10.7164/antibiotics.46.374](https://doi.org/10.7164/antibiotics.46.374)

   [https://doi.org/10.7164/antibiotics.46.380](https://doi.org/10.7164/antibiotics.46.380)

   [https://doi.org/10.1248/cpb.37.2937](https://doi.org/10.1248/cpb.37.2937)

   [https://doi.org/10.1021/jo00241a019](https://doi.org/10.1021/jo00241a019)

   [https://doi.org/10.1021/np50068a020](https://doi.org/10.1021/np50068a020)

   [https://doi.org/10.1039/NP9910800251](https://doi.org/10.1039/NP9910800251)

   [https://doi.org/10.1021/np010506a](https://doi.org/10.1021/np010506a)


   [https://doi.org/10.1023/B:JOEC.0000030270.65594.f4](https://doi.org/10.1023/B:JOEC.0000030270.65594.f4)

   [https://doi.org/10.1021/ja01307a051](https://doi.org/10.1021/ja01307a051)

   [https://doi.org/10.1021/cr00021a014](https://doi.org/10.1021/cr00021a014)

   [https://doi.org/10.1039/A900201D](https://doi.org/10.1039/A900201D)

   [https://doi.org/10.1021/ja00508a073](https://doi.org/10.1021/ja00508a073)

   [https://doi.org/10.1021/jo00330a011](https://doi.org/10.1021/jo00330a011)

   [https://doi.org/10.1021/np50109a020](https://doi.org/10.1021/np50109a020)

   [https://doi.org/10.1021/np010506a](https://doi.org/10.1021/np010506a)

   [https://doi.org/10.1177/1934578X0800300421](https://doi.org/10.1177/1934578X0800300421)

   [https://doi.org/10.1139/v86-218](https://doi.org/10.1139/v86-218)

https://doi.org/10.1073/pnas.0307113101

https://doi.org/10.1021/jo00098a011

https://doi.org/10.1073/pnas.0308177101


PMCID: PMC3802583

PMCID: PMC5277160

PMID: 4911115

https://doi.org/10.1111/j.1365-2044.1988.tb05755.x

http://doi.org/10.1126/science.7046051

http://doi.org/10.1126/science.6338589

PMID: 2676871

http://jpet.aspetjournals.org/content/88/1/39

PMID: 2676871

http://doi.org/10.1126/science.174.4011.788


http://doi.org/10.1126/science.7046051

http://doi.org/10.1126/science.6338589

https://link.springer.com/content/pdf/10.1007/BF01839269.pdf
https://doi.org/10.1039/P70000001770
   https://doi.org/10.1021/ja00103a034
   https://doi.org/10.1021/ja980788+
   https://doi.org/10.1073/pnas.0308177101
   https://doi.org/10.1021/ja0608139
   https://doi.org/10.1021/ja980788+
   https://doi.org/10.1021/ja903520c
   https://doi.org/10.1021/jo9023107
    https://doi.org/10.1002/chem.201002569
    https://doi.org/10.1021/ja2020873
    https://doi.org/10.1021/jo202078z
    https://doi.org/10.1002/anie.201203553
    https://doi.org/10.1021/o1012056
    https://doi.org/10.1021/ja509893s
    https://doi.org/10.1002/anie.201402571
    https://doi.org/10.1021/acs.orglett.5b03082
    https://doi.org/10.1038/s41929-018-0111-8
    http://doi.org/10.1039/C9SC05252F
Author’s Biographies

Alakesh Bisai received his M.Sc. degree in Organic Chemistry from Banaras Hindu University and obtained Ph.D. in synthetic Organic Chemistry under the supervision of Professor Vinod K. Singh from the Department of Chemistry, Indian Institute of Technology Kanpur in Sept. 2006. Immediately afterward, he moved to the College of Chemistry, University of California at Berkeley, where he held postdoctoral position in the research group of Professor Richmond Sarpong. During his stay at Berkeley, he completed concise total synthesis of ‘lycopodium alkaloids’ lyconadin A which received considerable attention from the synthetic community. During his Postdoctoral research, he received the GRC (Gordon Research Conference) award to Post-docs by Chair, 17th GRC on Stereochemistry (2008), RI. In Dec. 2009, he left Berkeley and joined the Department of Chemistry, IISER Bhopal as an Assistant Professor. In Nov. 2013, he was appointed as an Associate Professor in the Department Chemistry. The research focus of the AB research group includes the total synthesis of architecturally interesting biologically active natural products that provide an ideal platform for the invention of new strategies and highly selective organic transformations. A number of naturally occurring architecturally intriguing biological relevant secondary metabolites sharing all-carbon quaternary stereocenters have been synthesized by his research group at IISER Bhopal. He is the recipient of Young Scientist Award by the CRSI (2018), Research Grant for Young Scientist by the DST (2011) and the BRNS, DAE (2011). Since January, 2018, he has been working as a Professor of Chemistry at IISER Bhopal. In May, 2019, he moved to IISER Kolkata and setting up his new reasearch laboratory on Natural Product Synthesis. He has been awarded the prestigious ‘CRSI Bonze Medal’ for the year 2021 in recognition of his contributions in Chemical Sciences.

Avishek Roy was born in Midnapore, India on July 20, 1992. He completed his Bachelors in Chemistry (Hons.) from Garhbeta College, Vidyasagar University in 2012 and Masters in Chemistry from Vidyasagar University in 2014. He has received prestigious GATE and direct CSIR-SRF fellowships from the Govt. of India. Very recently he completed his Ph.D. in Organic Chemistry entitled as "Asymmetric Approaches to Hetero Dimeric
Pyrrolinoindoline Alkaloids, Chimonanthidine and Calycanthidine” under the supervision of Prof. Alakesh Bisai from IISER Bhopal, India in 2020.

**Arindam Maity** was born in 1994 at Purba Medinipur, West Bengal, India. He graduated from Midnapore College in 2014 and completed his Master of Science (M.Sc.) in Chemistry from Vidyasagar University, India in 2016. He is presently pursuing his Ph.D degree in the field of Organic Total Synthesis at Indian Institute of Science Education and Research, Bhopal under the supervision of Prof. Alakesh Bisai. He is currently working on “Asymmetric Total Synthesis of Hexahydropyrrolo[2,3-b]indole Alkaloids”.

**Saina Shaheeda M K** completed her Bachelors in Science and Masters of Science in Chemistry (BS-MS dual degree) in 2017 from the Indian Institute of Science Education and Research Bhopal (IISER Bhopal). She is the recipient of the prestigious Inspire fellowship from the Govt. of India. During her BSMS dual degree program, Saina had completed her MS thesis in ‘AB Research Group’ at IISER Bhopal. Currently, she is continuing her Ph.D. in same group in total synthesis of naturally occurring alkaloids and working on “Asymmetric Total Synthesis of Hexahydropyrrolo[2,3-b]indole Alkaloids”.

©AUTHOR(S)
Rahul Giri was born on January 04, 1996 in Hazaribag, Jharkhand, India. After completing his elementary schooling from Kendriya Vidyalaya BSF Meru Hazaribag in 2013, he decided to move to Acharya Narendra Dev College (ANDC), University of Delhi where he received his Bachelor of Science (Honours) in Chemistry in 2016. Subsequently, he moved to the IISER BHOPAL in 2017 for his Integrated-PhD studies in AB Research Group with Prof. Alakesh Bisai. His current research focus is on “Total synthesis of hexahydropyrrolo[2,3-b]indole alkaloids of biological relevance”.

This paper is an open access article distributed under the terms of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/)