This chapter contains an overview of iboga family alkaloids. Synthesis of iboga alkaloids and their analogues has been discussed in this chapter. Finally, motivation of our work has been discussed.
Introduction

Ibogaine is a naturally occurring indole alkaloid which is found in a variety of African shrubs of the Tabernanthe genus.\textsuperscript{1-4} It was first extracted from the \textit{Tabernanthe Iboga} root in 1901 by Dybowsky and Landrin.\textsuperscript{5} Structure of ibogaine (1) was established in 1957 through chemical studies\textsuperscript{6} and X-ray crystallographic investigations\textsuperscript{7} have fixed the configuration of ethyl group (Figure 1). Members of this family of alkaloids combine the structural features of indole and isoquinuclidinyl ring fused by a seven-membered indoloazepine ring. There are some eighty structurally closely related monoterpenic indole alkaloids which belong to the iboga-alkaloid family and few of the important members of this family have been shown in figure 1.

Catharanthine, (8) (Figure 2) is another variant of the iboga-alkaloids isolated from \textit{catharanthus roseus}.\textsuperscript{8-9} Catharanthine has a carbomethoxy group at the C16 with an isolated double bond. It is the chemical and presumably the biogenetic precursor of vinblastine and vincristine, two drugs used as chemotherapy in the treatment of a number of cancers.

Ibogaine has both psychoactive and stimulant properties. It has been claimed to be effective in treating addiction to opiate and stimulant drugs. In trials with humans, it ameliorated withdrawal symptoms and interrupted the addiction process. The corresponding program was patented in the USA under the trade name \textit{Lotsof Procedure}.\textsuperscript{10} However, this therapy has not been admitted as a clinical method because of side-effects, such as hallucinations at its high doses. Ibogaine produces neurodefeneration of Purkinje cells\textsuperscript{11} and whole-body tremors and ataxia in rats\textsuperscript{12} at high doses. (-)-18-Methoxycoronaridine (18 MC) (9) (Figure 2), a non-toxic iboga alkaloid congener was reported to be
acting as an antagonist at $\alpha_2\beta_4$ nicotinic receptor. It has ibogaine like affinity for kappa opioid receptors but significantly lower affinity for delta opioid receptors than ibogaine.\textsuperscript{13} Apart from their anti-addictive properties, iboga-alkaloids and their congeners show a wide variety of pharmacological effects, such as antifungal or antilipase,\textsuperscript{14} anti-HIV-1,\textsuperscript{15} anti-cholinesterasic\textsuperscript{16,17} and leishmanicide activities (against \textit{Leishmania amazonensi}).\textsuperscript{18}

**Literature Review**

In the year of 1965 Büchi was first to disclose a successful synthesis of racemic ibogaine and ibogamine\textsuperscript{19a,b}. Diels-Alder reaction of methyl vinyl ketone was carried out with dihydropyridine, which in turn was synthesized from pyridinium salt, (10). The Diels-Alder adduct (11) was then converted to 2-azabicyclo[2.2.2]octanone, in four steps. Cationic cyclization of (12) by PTSA and hot acetic acid gave the rearrangement product (13). The rearranged product (13) was then reduced by LiAlH$_4$ followed by oxidation at C-19; a subsequent elimination afforded the $\alpha$$\beta$-unsaturated ketone (14). Compound (14) underwent rearrangement in the presence of Zn/HOAc to yield the desired scaffold which was then converted to ibogamine and its epimer by Wolff-Kishner reduction (Scheme 1).

Analogous procedures were used to synthesize ibogaine and its epimer.

Huffman’s used the strategy of opening of cyclic epoxy ester (15) by tryptamine at high temperature to obtain a tryptamine-isoquinuclidine conjugate in one step. Further synthetic manipulations provided deethylibogamine\textsuperscript{20a,b} and ibogamine\textsuperscript{21} (Scheme 2). Using a similar approach and at the same time, Kuehne and Reider\textsuperscript{22} reported the synthesis of ibogamine via the formation of lactam (16) which was derived from the substituted epoxide (15).
Sallay developed a completely new route toward the synthesis of dl-ibogamine. Their method involved the formation of the seven-membered ring first, then completion of the isoquinuclidine and indole ring closures at the end of the synthesis. The cis-enedione (17) was converted to (18) using Beckmann rearrangement. Perbenzoic acid mediated epoxidation gave the regioselective epoxide, which on treatment with LAH gave the hydroxy compound (19). Further synthetic manipulations gave the tricyclic ketone (20) which was then transformed to racemic ibogamine by Fischer indolizations (Scheme 3).

Trost has reported the cyclization between C2 and C16 using Ag-Pd-catalyzed olefin arylation and the organo-palladium intermediate was reduced by NaBH₄ to give deethylibogamine in 40-50% yield (Scheme 4). His group also reported the enantioselective synthesis of ibogamine in 1978 where the Diels-Alder addition step was carried out enantioselectively using a chiral auxiliary. The chirality of the product was introduced in the initial step cycloaddition reaction. (E,E)-1 - (S-2'-Phenyl-2'-methoxyacetox)-1,3-hexadiene) (21b) and acrolein gave 80% (3R,4S,6R) of (22a) and 20% 3S,4R,6S (22b) isomer which was determined with the help of the O-methylmandeloyl group by NMR spectroscopy. Reductive amination with tryptamine and NaBH₄ gave compound (23). Pd(Ph₃)₄
mediated cyclization followed by palladium-silver catalyzed olefin arylation produced an 80 : 20 mixture of (+)-(2) and (-)-(2).

Grieco et al.\textsuperscript{26} reported the synthesis of racemic ibogamine and epiibogamine. Their approach involved the initial formation of 2-substituted tryptamine by the reaction with suitably substituted cyclic allyl acetate in the presence of Li[Co(B\textsubscript{9}H\textsubscript{9}C\textsubscript{2}H\textsubscript{n})\textsubscript{2}] as a catalyst. Hydroboration oxidation of (24) afforded the alcohol which was then converted to ketone (25) by oxidation in next step. CBz deprotection and reductive amination afforded (26). Heating at 220 °C followed by reduction with LiAlH\textsubscript{4} gave dl-epiibogamine as a major and dl-ibogamine as a minor isomer, respectively (Scheme 5).

Sundberg and coworkers used an intermolecular Diels-Alder reaction approach toward the synthesis of dihydrodeethylcatharanthine\textsuperscript{27} and also extended it to the synthesis of several other
analogues. Carbamate deprotection of Diels-Alder adduct (27) by p-TsOH in CH₃CN gave the amine which was then converted to 20-deethyl-6-norcatharanthine (28) in the presence of formaldehyde followed by treatment with sodium-amalgam (Scheme 6).

![Scheme 6]

Diels-Alder adduct (29) was also used as a precursor for the synthesis of 5,6-homologues of the iboga alkaloid skeleton. Deprotection of the Diels-Alder adduct followed by alkylation and silver ion promoted cyclization gave mixture of compound (30) and (31). Compound (31) was then converted to compound (32) under reductive condition (Scheme 7). In 1998, Sundberg reported the synthesis of two new types of racemic catharanthine-analogues. The [2,3] fusion present in catharanthine was replaced by [2,1] (33) and [3,2] fusions (34), respectively (Scheme 8).

![Scheme 7]

White et al. reported the synthesis of (-) ibogamine using asymmetric Diels-alder reaction as the key step (Scheme 9). The diene (35) was selected for this study. Diene was prepared from 1-butyne by hydroboration with catecholborane, followed by Suzuki cross-coupling with a bromo ether. The reaction of (35) with benzoquinone in the presence of the (S)-BINOL complex (36) (30 mol %) afforded the unstable
endo-adduct (37) in good yield. This diketone was reduced under Luche conditions to obtain hydroxy ketone (38). Saturation of both olefinic bonds was accomplished by hydrogenation over rhodium on alumina and resulted in endo-orientation of all four substituents on the cis-fused decalin framework. Oxidation of the diol then gave diketone (39). Selective protection of the less hindered ketone as its dimethyl ketal was accompanied along with the loss of the tert-butyldimethylsilyl ether. The trisopropylsilyl ether of the primary alcohol was converted to anti-oxime using hydroxylamine hydrochloride which underwent smooth Beckmann rearrangement in the presence of

Reagents and conditions: i) NaH, THF, 81%; ii) NaBH₄, BF₃OEt₂, 54%; iii) hv, 23%; iv) NaBH₄, BF₃OEt₂, 54%
chloride to afford lactam (40). Silyl deprotection followed by tosylation and cyclization using sodium hydride gave compound (41). After transketalization of (41) with acetone, the resultant keto lactam was subjected to Fischer indolization with phenylhydrazine. Reduction of this lactam with borane produced crystalline (-)-ibogamine (Scheme 9).

Hodgson's group has reported\textsuperscript{32} enantioselective synthesis of dehydroisoquinuclidine by desymmetrization of a tropenone in the presence of a chiral lithium amide. The optically pure dehydroisoquinuclidine was then used towards the synthesis of (+)-ibogamine and the final step cyclization was completed using Trost's mixed metal-mediated cyclization method (Scheme 10).

Borschberg's group reported the first enantioselective synthesis of (-)-(1R)-ibogamin-19-ol (Scheme 11).\textsuperscript{33} The key intermediate (52)\textsuperscript{34} was synthesized in optically active form starting from L-glutamic acid and (2S)-but-3-en-2-ol. When (49) was treated under Mitsunobu condition compound (50) was isolated. Silyl protection of compound (50) followed by LiAlH\textsubscript{4} reduction, Swern oxidation and two other steps provided compound (51). (+)-(51) Was found to be the major isomer in 96% yield and the diastereometric ratio was found to be 92%. When compound (51) treated with acid, (52) was isolated. Treatment with Zn-AcOH, followed by DCC coupling with tosylated indole-3-propionic acid followed by few more steps gave compound (54). Benzyl deprotection followed by Swern oxidation and ketal formation produced compound (55). Tosyl deprotection was carried out using Na/Hg, KH\textsubscript{2}PO\textsubscript{4} in 72% yield. The C2-C16 cyclization in the synthesis of ibogamine was achieved earlier by PTSA in boiling benzene; however, this procedure gave poor yield in the cyclization of (55). After some unsuccessful attempts, acetyl chloride in strictly anhydrous glacial acetic acid was found to be suitable for the cyclization to give (56) in 72% yield. Di-deacetylation was carried out in two steps using excess
of lithium aluminium hydride and BF₃.OEt₂. The final deoxygenation at C-16 was carried out using LiAlH₄-AlCl₃ complex in THF. (-)-Ibogamin-19-ol (58) was synthesized in 20% overall yield from (52).

Conclusion

Though there are reports on the isolation of eighty structurally related iboga-alkaloids, most of the synthetic efforts, except very few, are for simple representatives such as ibogamine, ibogaine, coronaridine and catharanthine and their analogues. Few methods have been reported for the
synthesis of optically active compounds. In the majority of cases, construction of the rigid isoquinuclidine ring involves Diels-Alder reaction as one of the steps followed by cyclization leads to the formation of the hydroazepine ring. The reported methods lack flexibility in order to achieve several other iboga-alkaloids that are closely related to each other.

References


Synthesis of New Series of Iboga Analogues

Synthesis of new iboga-analogues, replacing indole ring by benzofuran moiety has been described in this chapter. Starting materials are the suitably substituted benzofuran derivatives and have been synthesized by Pd-catalyzed reactions. The conversion of endo-6-methylcarboxylate substituted dehydroisoquinuclidine to exo-isomer, a key component of iboga-alkaloids has been discussed in this chapter.
**Introduction**

Anti-addictive properties of ibogaine\(^1,2\) have been known for decades. Apart from their anti-addictive properties, iboga-alkaloids and their congeners show a wide variety of pharmacological effects. However, the clinical application of ibogaine is limited because natural ibogaine (2) is tremorigenic,\(^3\) and neurotoxic, particularly due to the degeneration of brain cells (purkinje cells) if the dose is high.\(^4\) Chemical modifications of iboga-alkaloids (Figure 1) have been reported in order to have more potent analogues or congeners.\(^5\) Mostly, the analogues have been reported either on the modification of indoloazepine ring of the natural scaffold or in the mode of fusion of the indole ring to isoquinuclidine moiety (indole-[3,2]- fusion).

![Figure 1](image)

We have designed a synthetic route to new iboga-analogues replacing the indole ring with a benzofuran moiety. The benzofuran moiety was chosen because it is a bioisostere of indole, the pharmacological properties might be unchanged. The methylcarboxylate at the C-19 carbon could be easily manipulated for further derivatization, as substitution at this carbon has biological importance. Moreover these compounds are expected to be more stable than the natural ibogaine which is heat and light sensitive and spontaneously oxidize in solution.

**Results and Discussion**

We have designed our retrosynthetic strategy in such a way that the manipulation of phenyl-, heteroaryl (benzofuran/benzothiophene), indoloazepine and substitution at the C-19 carbon could be achieved easily (Scheme 1). Mixed metal mediated cyclization was used for the final step cyclization between C-2 and C-16. Benzofuran isoquinuclidine fused compounds (6)-(8) and (15) to (17) could be broken into two components, 3- or 2-substituted benzofuran alcohols (9)-(11) and (18)-(20), respectively. The common fragment, dehydroisoquinuclidines (21), was synthesized from pyridine using Diels-Alder reaction.

The requisite dehydroisoquinuclidine was synthesized according to the literature procedure\(^6\) (Scheme 2). Mixture of endo- (21a) and exo- (21b) isomers were separated by alumina column using
dichloromethane as a eluent and obtained a ratio of 3.2:1 in favour of the less polar endo-product (21a). Both isomers were characterized using chemical (formation of iodolactonized product (22)) and spectral (NMR) techniques. Cbz-deprotection of (21a) and (21b) were performed separately using 20% HBr-AcOH and HBr salt of (23a) and (23b) were then used in the next step for the synthesis of iboga-analogues.

Natural ibogaine (2) carries an exo-substituted ethyl side chain at C 20. During cycloaddition reaction we obtained the exo- (21b) product as the minor isomer, consequently we tried to improve the yield of our exo-Diels-Alder product. Our initial effort for the conversion of kinetically controlled endo-product to exo-isomer using LDA at 50 °C furnished a complex mixture. Reducing the quenching temperature gave moderate conversion at 25 °C. We tried the isomerization of (23a) following the literature procedure but failed to isolate any product and the mass spectra of the crude
product shown a peak corresponding to ester hydrolysed product. However, under similar conditions, the Cbz-protected endo-isomer (21a) underwent 90% conversion to the exo-isomer (21b) (Table 1).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base used</th>
<th>Quenching tempt (°C)</th>
<th>Quencher</th>
<th>Source</th>
<th>Ratio&lt;sup&gt;b&lt;/sup&gt; exo:endo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>LDA&lt;sup&gt;c&lt;/sup&gt;</td>
<td>50</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;O</td>
<td></td>
<td>&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>2.</td>
<td>LDA</td>
<td>50</td>
<td>t-BuOH</td>
<td></td>
<td>&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>3.</td>
<td>LDA</td>
<td>25</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>56:44</td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>LDA</td>
<td>25</td>
<td>t-BuOH</td>
<td>53:47</td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>LDA</td>
<td>25</td>
<td>HCl(0.5 N)</td>
<td></td>
<td>&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>6.</td>
<td>LDA</td>
<td>0</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>30:70</td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td>LDA</td>
<td>0</td>
<td>t-BuOH</td>
<td>28:72</td>
<td></td>
</tr>
<tr>
<td>8.</td>
<td>LDA</td>
<td>-78</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>22:78</td>
<td></td>
</tr>
<tr>
<td>9.</td>
<td>LDA</td>
<td>-78</td>
<td>t-BuOH</td>
<td>18:82</td>
<td></td>
</tr>
<tr>
<td>10.</td>
<td>NaOMe</td>
<td>65</td>
<td>MeOH</td>
<td>90:10</td>
<td></td>
</tr>
</tbody>
</table>

Reagents and conditions: <sup>a</sup> all the reactions were carried out using 0.15 mmol of endo isomer 21a; <sup>b</sup> isolated yield; <sup>c</sup> complex mixture isolated

The 3-benzofuranalcohols (9), (10) and (11) were synthesized using Larock’s heteroannulation reaction<sup>7</sup> between 2-iodophenol and internal alkynes (24), (25) and (26) followed by the treatment with tetrabutylammonium fluoride, respectively (Scheme 3). Internal alkynes were in

---

![Scheme 3](image-url)
turn synthesized from corresponding terminal alkynols in the presence of n-BuLi and tert-butyldimethylsilyl chloride in good yield. Attempted tosylation of 3-Benzofuran alcohols gave us the tosylated products (31) and (32) from compound (10) and (11), respectively. Interestingly, we isolated the chlorinated product (30) in case of compound (9) during tosylation. Compounds (30), (31) and (32) were then conjugated separately to isoquinuclidine (23a) or (23b) in the presence of K₂CO₃ / CH₃CN to obtain bezofuran-isoquinuclidine fused iboga analogues.

Pd(II)-Ag(I) mixed metal mediated cyclization was applied to key intermediates (7a) and (7b) to obtain (4a) and (4b) in 22% and 42% yields, respectively (Scheme 4). The final step cyclization method failed in case of compounds (6) and (8) in both exo- and endo- isomers.

For the synthesis of [3, 2] fused iboga analogues, the requisite 2-benzofuran alcohols were synthesized in one pot from 2-iodophenol via Sonogashira coupling with terminal alkynols at room temperature (Scheme 5). Subsequent tosylation provided us the similar observation as for 3-benzofuran alcohols. Chlorinated product (33) was isolated in case of compound (18), whereas
tosylated products (34) and (35) were isolated from (19) and (20), respectively. Conjugation with (23a) or (23b) afforded 2-substituted benzo furan isoquinuclidine derivatives (15)-(17) in good yield.

When compound (16a) was subjected to the mixed-metal-mediated cyclization method, gratifyingly the reaction proceeded smoothly to give the desired product (13a) in 27% yield. A similar cyclization of the compound (16b) also delivered the product (13b), though in better yield (46%) (Scheme 6). Internal cyclization method also failed in case of compounds (15) and (17) in both endo- and exo-isomers.

Mixed metal mediated internal alkylation reaction proceeded in case of (7) and (16). Cyclization reactions failed in case of both higher ([8] and [17]) and lower analogues ([6] and [15]). According to the proposed mechanism (scheme 7) mixed metal (Pd-Ag) bring aromatic and isoquinuclidine ring closer to form seven-membered ring. In case of higher homologues both rings are far away from each other, mixed-metal failed to bring them closer. We expected the formation of
products in case of lower homologues since both rings are close to each other. The final step cyclization may be failed due to steric reason.

Conclusion

In conclusion, the synthesis of new iboga analogues has been described. Our synthetic approach is non-biochemical, extremely short, flexible and also anticipated that minor modifications of the starting materials (phenol and alkynes) should provide access to several other analogues of this alkaloid family for biological screening. Also functional group transformation of C19 ester can provide us the true SAR to optimize the potency and efficacy of the analogues.

References

EXPERIMENTAL

Crystallographic data

Crystal structure determination was performed on Bruker, version 2.1-0; Bruker AXS, Inc.: Madison, WI, 2006 machine.

Infrared Spectra

Infrared spectra were recorded on Shimadzu FTIR-8300 spectrometer. Spectra were calibrated against the polystyrene absorption at 1601 cm\(^{-1}\). Solid samples were recorded as KBr discs and liquids as thin films in between NaCl plates.

Nuclear magnetic resonance spectra

\(^1\)H NMR spectra were recorded on Bruker-Avance DPX-300 and DPX-500 instruments in CDCl\(_3\) solutions, unless otherwise stated. Chemical shifts are reported with respect to tetramethylsilane (Me\(_4\)Si) as the internal standard (for \(^1\)H NMR) and the central line (77.16 ppm) of CDCl\(_3\) (for \(^13\)C NMR). The chemical shifts are expressed in parts per million (\(\delta\)) downfield from Me\(_4\)Si. The standard abbreviations s, d, t, q and m refer to singlet, doublet, triplet, quartet and multiplet respectively. Coupling constant (\(J\)), whenever discernible, have been reported in Hz.

Mass spectra

High Resolution Mass Spectra (HRMS) were measured in a QTOF I (quadrupole-hexapole-TOF) mass spectrometer with an orthogonal Z-spray-electrospray interface on Micro (YA-263) mass spectrometer (Manchester, UK).

Chromatography

Reactions were monitored by thin-layer chromatography (TLC). TLC was performed with silica gel 60 F\(_{254}\) aluminium sheets (Merck). Visualization of the spots on TLC plates was achieved either by using UV light or by charring with ethanolic vanillin solution, phosphomolybdic acid solution and ninhydrin solution as required. Column chromatography was usually carried out with silica gel (100-200 mesh) and flash chromatography with silica gel (230-400 mesh). The columns were usually eluted with petroleum ether-AcOEt solvent systems. For polar compounds DCM-AcOEt solvent systems were used. Petroleum ether refers to the fraction of boiling point 60-80 °C.

General

All moisture and air sensitive reactions were performed under argon atmosphere with dry, freshly distilled solvents under anhydrous conditions using standard syringe-septum technique. Tetrahydrofuran (THF), benzene, toluene, dimethoxymethane and diethyl ether were distilled from sodium benzophenone ketyl. DCM, HMPA, DMF and DMSO were distilled freshly from sodium hydride. MeOH was distilled from its alkoxide (formed by the reaction with activated magnesium) and stored over 4Å molecular sieves. \(\beta\)-Butanol was dried over sodium and freshly used. Amines were distilled over potassium hydroxide pellets and stored over the same.

A usual workup of the reaction mixture consists of extraction with common organic solvents (ether, AcOEt, DCM), washing with water, brine, drying over Na\(_2\)SO\(_4\), and then concentrated under reduced
pressure on a rotary evaporator unless specified. Yields (isolated) were reported after purification of the crude either by column chromatography or by vacuum distillation.

Atom numbering of (4a) and (13a):
Crystallographic Data

<table>
<thead>
<tr>
<th></th>
<th>(4a)</th>
<th>(13a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C_{19}H_{21}NO_{3}</td>
<td>C_{19}H_{21}NO_{3}</td>
</tr>
<tr>
<td>Formula weight</td>
<td>311.37</td>
<td>311.37</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Triclinic</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P-1</td>
<td>P2(1)/c</td>
</tr>
<tr>
<td>a, Å</td>
<td>6.776(5)</td>
<td>9.4436(6)</td>
</tr>
<tr>
<td>b, Å</td>
<td>10.083(8)</td>
<td>9.9179(6)</td>
</tr>
<tr>
<td>c, Å</td>
<td>13.432(11)</td>
<td>17.9711(12)</td>
</tr>
<tr>
<td>α, deg</td>
<td>103.71(2)</td>
<td>90.00</td>
</tr>
<tr>
<td>β, deg</td>
<td>103.08(2)</td>
<td>90.232(2)</td>
</tr>
<tr>
<td>γ, deg</td>
<td>98.64(2)</td>
<td>90.00</td>
</tr>
<tr>
<td>Volume, Å³</td>
<td>848.1(12)</td>
<td>1683.17(19)</td>
</tr>
<tr>
<td>Z</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>D_{calc}, Mg/m³</td>
<td>1.219</td>
<td>1.229</td>
</tr>
<tr>
<td>μ Mo-Kα, mm⁻¹</td>
<td>0.082</td>
<td>0.083</td>
</tr>
<tr>
<td>F(000)</td>
<td>332</td>
<td>664</td>
</tr>
<tr>
<td>θ range, deg</td>
<td>1.62-17.88</td>
<td>2.16-27.48</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>3546</td>
<td>18501</td>
</tr>
<tr>
<td>Refins unique</td>
<td>1144</td>
<td>4156</td>
</tr>
<tr>
<td>R(int)</td>
<td>0.0622</td>
<td>0.0428</td>
</tr>
<tr>
<td>Data (I&gt;2σ(I))</td>
<td>885</td>
<td>3217</td>
</tr>
<tr>
<td>Parameters refined</td>
<td>209</td>
<td>209</td>
</tr>
<tr>
<td>Goodness-of-fit on F²</td>
<td>2.315</td>
<td>3.361</td>
</tr>
<tr>
<td>R1 [I&gt;2σ(I)]</td>
<td>0.1755</td>
<td>0.4483</td>
</tr>
<tr>
<td>wR2</td>
<td>0.4667</td>
<td>0.4483</td>
</tr>
<tr>
<td>Residuals eÅ⁻³</td>
<td>-0.378, 2.675</td>
<td>-0.420, 6.891</td>
</tr>
</tbody>
</table>
Selected bond lengths (Å) and angles (°) for (4a)

<table>
<thead>
<tr>
<th>Bond/ Angle</th>
<th>Length/ Angle</th>
</tr>
</thead>
<tbody>
<tr>
<td>N(1)-C(16)</td>
<td>1.503(17)</td>
</tr>
<tr>
<td>N(1)-C(12)</td>
<td>1.507(17)</td>
</tr>
<tr>
<td>N(1)-C(10)</td>
<td>1.525(16)</td>
</tr>
<tr>
<td>C(11)-C(8)</td>
<td>1.51(2)</td>
</tr>
<tr>
<td>C(11)-C(15)</td>
<td>1.549(19)</td>
</tr>
<tr>
<td>C(11)-C(12)</td>
<td>1.58(2)</td>
</tr>
<tr>
<td>C(12)-C(17)</td>
<td>1.505(17)</td>
</tr>
<tr>
<td>C(16)-N(1)-C(12)</td>
<td>107.7(10)</td>
</tr>
<tr>
<td>C(16)-N(1)-C(10)</td>
<td>109.1(11)</td>
</tr>
<tr>
<td>C(12)-N(1)-C(10)</td>
<td>113.2(10)</td>
</tr>
<tr>
<td>C(8)-C(11)-C(15)</td>
<td>115.4(12)</td>
</tr>
<tr>
<td>C(8)-C(11)-C(12)</td>
<td>109.3(13)</td>
</tr>
<tr>
<td>C(15)-C(11)-C(12)</td>
<td>104.5(11)</td>
</tr>
<tr>
<td>C(17)-C(18)</td>
<td>1.511(6)</td>
</tr>
<tr>
<td>C(6)-C(5)</td>
<td>1.394(6)</td>
</tr>
<tr>
<td>O(3)-C(5)-C(4)</td>
<td>125.4(4)</td>
</tr>
<tr>
<td>C(7)-C(12)-C(11)</td>
<td>113.4(4)</td>
</tr>
<tr>
<td>C(7)-C(12)-C(13)</td>
<td>115.4(4)</td>
</tr>
<tr>
<td>C(13)-C(12)-C(11)</td>
<td>108.0(4)</td>
</tr>
<tr>
<td>C(8)-C(9)-C(10)</td>
<td>110.5(4)</td>
</tr>
<tr>
<td>N(1)-C(15)-C(14)</td>
<td>110.6(4)</td>
</tr>
</tbody>
</table>

Selected bond lengths (Å) and angles (°) for (13a)

<table>
<thead>
<tr>
<th>Bond/ Angle</th>
<th>Length/ Angle</th>
</tr>
</thead>
<tbody>
<tr>
<td>N(1)-C(10)</td>
<td>1.520(6)</td>
</tr>
<tr>
<td>N(1)-C(11)</td>
<td>1.522(6)</td>
</tr>
<tr>
<td>N(1)-C(15)</td>
<td>1.509(6)</td>
</tr>
<tr>
<td>C(7)-C(12)</td>
<td>1.505(6)</td>
</tr>
<tr>
<td>C(7)-C(8)</td>
<td>1.365(6)</td>
</tr>
<tr>
<td>C(17)-C(18)</td>
<td>1.511(6)</td>
</tr>
<tr>
<td>C(6)-C(5)</td>
<td>1.394(6)</td>
</tr>
<tr>
<td>O(3)-C(5)-C(4)</td>
<td>125.4(4)</td>
</tr>
<tr>
<td>C(7)-C(12)-C(11)</td>
<td>113.4(4)</td>
</tr>
<tr>
<td>C(7)-C(12)-C(13)</td>
<td>115.4(4)</td>
</tr>
<tr>
<td>C(13)-C(12)-C(11)</td>
<td>108.0(4)</td>
</tr>
<tr>
<td>C(8)-C(9)-C(10)</td>
<td>110.5(4)</td>
</tr>
<tr>
<td>N(1)-C(15)-C(14)</td>
<td>110.6(4)</td>
</tr>
</tbody>
</table>
To a stirred solution of dry pyridine (2.0 mL, 24.8 mmol) in dry methanol (30 mL) was added sodium borohydride (1.12 g, 29.76 mmol) portionwise at -70 °C. Benzyl chloroformate (3.2 mL, 22.6 mmol) was then added dropwise over a period of 15 minutes at such a rate that the inner temperature remained under -60 °C. After stirring for 1 h, the resulting reaction mixture was gradually warmed to 0 °C. Water (30 mL) was added and the reaction mixture was extracted with diethyl ether (3 x 30 mL). The combined organic extracts were washed with 1 N HCl (35 mL), 1 N NaOH (40 mL), water (30 mL) and brine (30 mL), dried over Na₂SO₄ and concentrated in vacuo to get the crude dihydropyridine (5.06 g, 90%) as a pale yellow oil, which was used in the next step without further purification.

In a sealed tube containing mixture of 1,2-dihydropyridine (5.0 g, 23.22 mmol) and methyl acrylate (25 g, 290.38 mmol) was heated at 160 °C for a period of 2 days. The reaction mixture was cooled, diluted with CH₂Cl₂ (75 mL) and washed with water (3 x 40 mL). The dichloromethane layer was dried over anhydrous Na₂SO₄ and concentrated in vacuo. The residual oil was purified by silica gel column chromatography (100-200 mesh) to get Cbz-protected dehydroisoquinuclidine (21) (5.05 g, 72%) as a colorless oil. The endo- and exo-isomers were then separated by alumina column chromatography using dichloromethane as eluent to obtain the endo product (21a) (3.84 g, 55%, less polar) and exo product (21b) (1.21 g, 17%, more polar).

A solution of LiOH.H₂O (50 mg, 1.2 mmol) in water (2 mL) was added dropwise to the endo Diels-Alder adduct (21a) (200 mg, 0.66 mmol) in THF (5 mL) and the resulting solution was stirred at room temperature for 5 h (monitored by TLC). The organic solvent was removed in vacuo. Saturated aqueous solution of NaHCO₃ was added (5 mL) and the reaction mixture was extracted with ethyl acetate (2 x 5 mL). The aqueous phase was acidified with dil HCl and further washed with ethyl acetate (10 mL). The combined organic phases were dried over anhydrous Na₂SO₄ and concentrated in vacuo to get the corresponding acid (180 mg, 95%).

An aqueous solution (3 mL) of NaHCO₃ (150 mg, 1.8 mmol), KI (560 mg, 3.4 mmol) and I₂ (250 mg, 0.98 mmol) were added to the solution of acid (180 mg, 0.63 mmol) in CH₂Cl₂ at 0 °C. The reaction mixture was stirred at room temperature for overnight, poured into aqueous Na₂S₂O₃ solution (10 mL) to decompose the excess I₂ and extracted with CH₂Cl₂ (2 x 10 mL). The organic layer was washed with H₂O (10 mL), brine (10 mL) and dried over Na₂SO₄ and concentrated in vacuo to afford the corresponding iodolactone (22) as white solid. Yield: 230 mg, 83%. Rf (2.3:1, petroleum ether/EtOAc) = 0.44. ¹H NMR (500 MHz, CDCl₃): δ 2.09 and 2.12 (1H, br s), 2.23-2.28 (1H, m), 2.36 and 2.41 (1H, br s), 2.8-2.84 and 2.85-2.89 (1H, m), 3.39-3.43 (1H, m), 3.99-4.06 (1H, m), 4.39 (1H, br s), 4.77 and 4.93 (1H, t, j = 5.0 Hz), 5.03 and 5.08 (1H, d, j = 5.5 Hz), 5.21 (2H, m), 7.34 (5H, m); ¹³C NMR (125 MHz, CDCl₃):* δ 25.2, 25.7, 27.0, 33.48 and 33.6, 36.5 and 36.6, 47.90 and 48.03, 48.7, 49.3, 67.9 and 68.0,
83.6 and 83.8, 128.0, 128.4, 128.6, 128.7, 128.8, 135.9 and 136.2, 155.6, 175.7; HRMS (ESI) (M + Na)+ calculated for C_{16}H_{14}N_2O_4Na+= 436.0022, found 436.0020.

An oil containing (21b) (2.20 g, 7.30 mmol) dissolved in 20% hydrogen bromide / acetic acid (15 mL) and stirred for 1 h at room temperature. The solution was evaporated in vacuo to dryness to get a sticky mass of hydrobromide salt. The hydrobromide salt was repeatedly washed with dry hexane (3 x 10 mL) to remove the benzyl bromide impurity. Removal of solvent afforded hydrobromide salt (23b). HBr as brown solid. HRMS (ESI) (M + H)+ calculated for C_9H_14NO_2H+= 168.1025, found 168.1011.

**Enolization and protonation of compound (21a)**

A flame dry flask was charged with disopropylamine (0.039 mL, 0.278 mmol) in freshly dry THF (2 mL). The reaction mixture was cooled to -78 °C followed by dropwise addition of n-BuLi (0.174 mL of a 1.6 M solution in dry THF, 0.278 mmol), warmed to 0 °C over a period of 30 min. The reaction mixture was again cooled to -78 °C. Isoquinuclidine (21a) (70 mg, 0.232 mmol) in dry THF (2 mL) was added over a period of 5 min. The resulting mixture was stirred for 2 h at the same temperature and it was quenched with appropriate proton source (according to Table 1).

**(a) Enolate quenching at 50 °C**

Enolate of compound (21a) (87 mg, 0.289 mmol) was added dropwise to the water (2.0 mL) at 50 °C.

**(b) Enolate quenching at room temperature**

Enolate derived from (21a) (57 mg, 0.189 mmol) was slowly warmed to room temperature followed by dropwise addition of dry t-BuOH (0.053 mL, 0.567 mmol). Reaction mixture was diluted with dichloromethane (10 mL). The combined organic extracts were washed with water (5 mL), brine (5 mL) and dried over Na_2SO_4. Removal of solvent in vacuo yielded 46 mg as the crude product, which was purified by alumina column using dichloromethane as eluent to obtain 23 mg, exo- and 21 mg, endo-isomer.

**(c) Enolate quenching at 0 °C**

Enolate of endo- Diels-Alder product (21a) (83 mg, 0.275 mmol) was warmed to 0 °C over a period of time followed by dropwise addition of water (0.049 mL, 0.825 mmol). Work up and purification procedure was same as discussed above.

**(d) Enolate quenching at -78 °C**

Dry t-BuOH (0.094 mL, 0.992 mmol) was added dropwise to the reaction mixture containing enolate of (21a) (101 mg, 0.332 mmol) at -78 °C and was stirred for 30 min. Compound was purified following the same protocol.
A solution of prop-3-yn-1-ol (1.04 mL, 14.3 mmol) in dry THF (25 mL) was cooled to -60 °C, n-BuLi (22.5 mL of 1.6 M in hexane, 34.3 mmol) was added over a period of 30 min. The temperature of the reaction vessel was raised to -20 °C and stirred for a period of 1 h, cooled to -50 °C, and treated with tert-butylidimethylsilyl chloride (4.7 g, 31.5 mmol) in THF (20 mL) over a period of 20 min. The reaction mixture was then allowed to warm to room temperature and stirred for overnight. The resulting solution was cooled to -5 °C and treated with 1% aqueous NH₄Cl (10 mL). The reaction mixture was extracted with petroleum ether (2 x 30 mL), the combined extracts were washed with water (30 mL) and saturated brine (30 mL). The petroleum ether was dried over Na₂SO₄ and evaporated to obtain a colorless liquid, yield: 2.84 g, 70.0%. ¹H NMR (300 MHz, CDCl₃): δ 0.097 (6H, s), 0.125 (6H, s), 0.907 (9H, s), 0.93 (9H, s), 4.32 (2H, s).

Compound (25) was prepared from but-3-yn-1-ol following same procedure as for (24) in 56% as colorless liquid. ¹H NMR (300 MHz, CDCl₃): δ 0.07 (12H, s), 0.896 (9H, s), 0.923 (9H, s), 2.40 (2H, t, J = 7.0 Hz), 3.72 (2H, t, J = 7.0 Hz).

Compound (26) was prepared from pent-4-yn-1-ol in 73% as colorless liquid. ¹H NMR (300 MHz, CDCl₃): δ 0.05 (6H, s), 0.07 (6H, s), 0.89 (9H, s), 0.92 (9H, s), 1.73 (2H, m), 2.28 (2H, m), 3.70 (2H, td, J= 6.0, 1.8 Hz).

2-Iodophenol (3.02 g, 13.7 mmol) and tert-butyl(3-(tert-butyldimethylsilyl)prop-2-ynyloxy)dimethylsilane (3.54 g, 12.5 mmol) (24) were dissolved in dry DMF (30.0 mL), followed by addition of lithium chloride (0.52 g, 12.5 mmol) and sodium carbonate (7.9 g, 74.8 mmol). The reaction vessel was evacuated and flushed with argon three times. Palladium acetate (0.224 g) was added; the reaction mixture was again flushed with argon and heated at 100 °C for 3 h. The reaction mixture was cooled to room temperature and diluted with petroleum ether (45 mL) and water (25 mL). The mixture was filtered through a pad of celite and washed with petroleum ether (30 mL). The organic layers were separated and the aqueous phase was extracted again with petroleum ether (50 mL). The petroleum ether was washed with water (100 mL), saturated brine (50 mL) and dried over Na₂SO₄. The crude product was subjected to column chromatography on silica gel (100-200 mesh) eluting with petroleum ether to obtain the pure compound (27) as yellow oil. Yield: 3.76 g, 80%. ¹H NMR (300 MHz, CDCl₃): δ 0.167 (6H, s), 0.407 (6H, s), 0.961 (9H, s), 0.982 (9H, s), 4.89 (2H, s), 7.25 (2H, m), 7.49 (2H, d), 7.71 (2H, d). ¹³C NMR (75 MHz, CDCl₃): δ 17.5, 18.6, 26.1, 26.6, 111.3, 120.7, 122.1, 124.5, 128.7, 130.8, 158.1, 158.3.
Compound (28) was synthesized as yellow oil from 2-iodophenol and (25) in 66% yield. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 0.49 (6H, s), 0.86 (6H, s), 1.36 (9H, s), 1.45 (9H, s), 3.47 (2H, $t, J = 7.5$ Hz), 4.34 (2H, $t, J = 7.5$ Hz), 7.51-7.60 (2H, m), 7.74-7.77 (1H, m), 7.96-7.98 (1H, m); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 16.6, 17.9, 26.2, 26.9, 28.4, 64.2, 110.9, 120.7, 122.4, 124.6, 127.9, 129.6, 157.9, 158.7.

Compound (29) was synthesized as yellow oil from 2-iodophenol and tert-buty1(5-(tert-butyldimethylsilyl)pent-4-ynyloxy)dimethylsilane (26) in 71% yield. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 0.076 (6H, s), 0.372 (6H, s), 0.932 (9H, s), 0.968 (9H, s), 1.88 (2H, m), 2.82 (2H, $t, J = 8.0, 2.5$ Hz), 3.72 (2H, $t, J = 6.0$ Hz), 7.22 (2H, m), 7.44 (1H, $d, J = 1.0$ Hz), 7.57 (1H, $d, J = 1.1$ Hz).

Compound (27) (3.84 g, 10.19 mmol) was dissolved in 40.0 mL of dry THF followed by addition of tetrabutylammonium fluoride (24.8 mL of 1.0 M in THF). The reaction mixture was stirred at room temperature for overnight. The reaction mixture was diluted with 30 mL of EtOAc, washed with water (2 x 15 mL). The combined organic extracts were washed with saturated brine (20 mL), dried over Na$_2$SO$_4$. The crude product obtained was purified by column chromatography on silica gel (100-200 mesh) to yield the compound (9) as brown oil. Yield: 0.996 g, 66.0%. $R_f$ (5:1, petroleum ether/EtOAc) = 0.42. IR (neat/CHCl$_3$): $\nu$ 3400, 3018, 2999, 1452, 1215 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.71 (1H, br s), 4.83 (2H, $s$), 7.29 (2H, $m$), 7.48 (1H, $d, J = 6.0$ Hz), 7.60 (1H, $s$), 7.68 (1H, $d, J = 9.0$ Hz); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 55.9, 111.4, 117.3, 119.7, 122.5, 124.4, 128.3, 142.1, 155.5.

The compound (10) was prepared from (28) as brown oil. Yield: 84%. $R_f$ (5:1, petroleum ether/EtOAc) = 0.46. IR (neat/CHCl$_3$): $\nu$ 3350, 2929, 1452, 1184, 744 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.92 (1H, br s), 2.95 (2H, $t, J = 6.2$ Hz), 3.92 (2H, $t, J = 6.2$ Hz), 7.24-7.35 (2H, m), 7.49-7.52 (1H, $d, J = 6.0$ Hz), 7.52 (1H, $s$), 7.58 (1H, $d, J = 9.0$ Hz); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 27.1, 61.8, 111.6, 116.9, 119.6, 122.5, 124.5, 128.1, 142.2, 155.5.

Compound (11) was prepared from (29) as pale brown oil following similar protocol. Yield: 72.0%. $R_f$ (5:1, petroleum ether/EtOAc) = 0.47. IR (neat/CHCl$_3$): $\nu$ 3356, 2950, 1457, 1207, 870 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 2.05 (3H, $m$), 2.80 (2H, $t, J = 6.0$ Hz), 3.75 (2H, $t, J = 6.0$ Hz), 7.25 (2H, $m$), 7.45 (1H, $s$), 7.49 (1H, $d, J = 6.0$ Hz), 7.58 (1H, $d, J = 6.0$ Hz); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 19.8, 31.8, 62.2, 111.5, 119.5, 119.9, 122.3, 124.2, 128.2, 141.2, 155.4.
To a stirred solution of p-toluenesulfonyl chloride (1.26 g, 6.6 mmol), triethylamine (1.52 mL, 10.9 mmol) and 4-dimethylaminopyridine (0.06 g, 0.5 mmol) in dry CH$_2$Cl$_2$ (10 mL) was added slowly a solution of benzofuran-ethanol (10) (0.89 g, 5.5 mmol) in dry CH$_2$Cl$_2$ (10.0 mL) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and left for overnight at room temperature. The reaction mixture was diluted with CH$_2$Cl$_2$ (20 mL). The dichloromethane layer was washed with water (2 x 10 mL), dried over Na$_2$SO$_4$. The crude product was purified by column chromatography on silica gel (100-200 mesh) to obtain the compound (31) as a colorless solid. Melting point: 71 °C, Yield: 1.21 g, 70%. Rf (4:1, petroleum ether/EtOAc) = 0.53. IR (neat/CHCl$_3$): v 1596, 1454, 1352, 1168, 976 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): δ 2.37 (3H, s), 3.02 (2H, t, $J$ = 6.6 Hz), 4.27 (2H, t, $J$ = 6.6 Hz), 7.15-7.29 (4H, m), 7.37-7.44 (3H, m), 7.63 (2H, d, $J$ = 8.2 Hz); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 21.7, 23.8, 68.9, 111.6, 115.1, 119.3, 122.6, 124.4, 127.4, 127.8, 129.8, 132.7, 142.4, 144.8, 155.3; HRMS (ESI) (M + Na)$^+$ calculated for C$_{17}$H$_{15}$O$_4$SNa$^+$= 339.0668, found 339.0667.

Compound (30) was synthesized from (9) following same procedure in 60% yield. IR (neat, CHCl$_3$): v 2934, 1459, 1245, 1111, 965 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): δ 4.76 (2H, s), 7.28-7.37 (2H, m), 7.49-7.51 (2H, d, $J$= 9.0 Hz), 7.67-7.71 (2H, m); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 34.4, 110.9, 115.7, 119.8, 123.3, 124.5, 129.7, 142.1, 155.1.

Compound (32) was obtained from (11) following same procedure in 55% yield. IR (neat/CHCl$_3$): v 1602, 1456, 1323, 1168, 982 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): δ 2.05 (2H, m), 2.44 (3H, s), 2.73 (2H, t, $J$= 7.3 Hz), 4.10 (2H, t, $J$= 6.1 Hz), 7.27 (5H, m), 7.44 (2H, m), 7.77 (2H, d, $J$=8.1 Hz); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 19.4, 21.6, 69.5, 111.5, 118.5, 119.4, 122.4, 124.3, 127.9, 140.8, 141.5, 144.8, 155.2. HRMS (ESI) (M + Na)$^+$ calculated for C$_{16}$H$_{15}$O$_4$SNa$^+$= 353.0823 found 353.0823.

A suspension of K$_2$CO$_3$ (0.05 g, 3.16 mmol) in anhydrous CH$_3$CN (5.0 mL) containing the isoquinuclidine salt (23a).HBr (0.23 g, 1.4 mmol) and tosyl compound (31) (0.4 g, 1.26 mmol) was refluxed for 14 h then cooled to rt and filtered through a pad of celite, washed with EtOAc (2 x 7 mL). The combined organic extracts were concentrated in vacuo and purified by column chromatography (100-200 mesh silica gel) ($R_f$ = 0.42, PE:EtOAc, 1.5:1) as a pale yellow oil; Yield: 0.31 g, 79%. IR (neat, CHCl$_3$): v 2949, 1737, 1457, 1197, 746 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): δ 1.75-1.81 (2H, m), 2.08 (1H, d, $J$ = 15.7 Hz), 2.57-2.62 (2H, m), 2.78-2.90 (3H, m), 3.03 (1H, dd, $J$ = 8.7, 1.2 Hz), 3.10-3.12 (1H, m), 3.65 (3H, s), 3.87 (1H, m), 6.20 (1H, dd, $J$ = 7.3, 6.0 Hz), 6.47 (1H, t, $J$ = 7.3 Hz), 7.20-7.31 (2H, m), 7.44-7.46 (2H, m), 7.55 (1H, d, $J$ = 7.2 Hz); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 22.9,
26.1, 30.9, 43.9, 51.9, 54.5, 54.7, 57.6, 111.6, 118.6, 119.7, 122.4, 124.2, 128.4, 129.6, 134.9, 141.5, 155.3, 174.5; HRMS (ESI) (M + H)+ calculated for C18H21NO3H+= 312.1600 found 312.1596.

Prepared following the same procedure as for (7a) (via conjugation of (23b)HBr and (31). Purified by column chromatography (100-200 mesh silica gel) using EtOAc in petroleum ether (PE) as eluent to obtain the compound (7b) in 73% yield, (Rf = 0.44, PE:EtOAc, 4:1) as a pale yellow oil.

IR (neat, CHCl3): v 2949, 1732, 1197, 746 cm⁻¹; ¹H NMR (300 MHz, CDCl3): δ 1.36-1.44 (1H, m), 1.92 (1H, dt, J = 9.2, 2.4 Hz), 2.19 (1H, dq, J = 12.8, 3.3 Hz), 2.41-2.50 (2H, m), 2.58 (1H, br s), 2.67-2.82 (3H, m), 3.21 (1H, dd, J = 9.0, 2.0 Hz), 3.60 (3H, s), 3.85 (1H, br s), 6.26 (1H, dd, J = 7.6, 5.7 Hz), 6.49 (1H, t, J = 7.25 Hz), 7.21-7.27 (2H, m), 7.43-7.50 (3H, m); ¹³C NMR (75 MHz, CDCl3): δ 22.5, 24.4, 31.1, 45.4, 51.8, 54.8, 55.3, 57.2, 111.4, 118.6, 119.5, 122.2, 124.0, 128.5, 129.9, 135.3, 141.9, 155.1, 174.9; HRMS (ESI) (M + H)+ calculated for C₁₉H₂₁NO₃H+= 312.1600 found 312.1596.

Prepared following similar procedure as for (7a). Yield: 68%. IR (neat, CHCl3): v 2947, 1737, 1452, 1201, 1091, 748 cm⁻¹; ¹H NMR (300 MHz, CDCl3): δ 1.70-1.81 (2H, m), 1.97-2.01 (1H dd, J = 19.3, 2.3 Hz), 2.59 (1H, br s), 2.96-3.00 (1H, dd, J = 19.3, 1.8 Hz), 3.11-3.14 (1H, m), 3.49-3.53 (1H, d, J = 13.6 Hz), 3.60 (3H, s), 3.74-3.78 (1H, d, J = 13.6 Hz), 3.84-3.86 (1H, dd, J = 8.0, 5.3), 6.47-6.51 (1H, t, J = 7.8, 7.0 Hz), 7.22-7.28 (2H, m), 7.45-7.47 (1H, m), 7.51 (1H, s), 7.69-7.72 (1H, d, J = 7.6 Hz); ¹³C NMR (75 MHz, CDCl3): δ 26.1, 30.9, 44.3, 51.1, 51.7, 53.6, 54.3, 111.3, 118.4, 120.5, 122.3, 124.2, 127.9, 129.2, 134.9, 142.5, 155.5, 174.4; HRMS (ESI) (M + H)+ calculated for C₁₈H₁₉NO₃H+= 298.1443 found 298.1436.

Compound (6b) was prepared following similar procedure as for (7b). Yield: 62%. IR (neat, CHCl3): v 2947, 1735, 1452, 1199, 748 cm⁻¹; ¹H NMR (500 MHz, CDCl3): δ 1.35-1.41 (1H, m), 1.92-1.95 (1H, dt, J = 9.5, 2.5 Hz), 2.16-2.20 (1H, m), 2.39-2.43 (1H, m), 2.57 (1H, br s), 3.15-3.18 (1H, dd, J = 19.0, 2.5 Hz), 3.40 (4H, m), 3.60-3.63 (1H, d, J = 13.5 Hz), 3.84-3.86 (1H, m), 6.26-6.29 (1H, m), 6.50-6.54 (1H, t, J = 7.5, 8.0 Hz), 7.20-7.28 (2H, m), 7.43-7.44 (2H, m), 7.61-7.62 (1H, d, J = 8.0 Hz); ¹³C NMR (125 MHz, CDCl3): δ 24.4, 31.2, 45.3, 51.3, 51.6, 54.1, 54.9, 111.2, 118.8, 121.0, 122.4, 124.3, 128.2, 129.7, 135.7, 142.5, 155.7, 174.8; HRMS (ESI) (M + H)+ calculated for C₁₈H₁₉NO₃H+= 298.1443 found 298.1436.
Compound (8a) was prepared following similar procedure as for (7a). Yield: 78%. IR (neat, CHCl₃): ν 2947, 1732, 1454, 1197, 746 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.73-1.76 (2H, m), 1.81-1.89 (2H, m), 1.94-1.98 (1H, d, J = 9.5 Hz), 2.27-2.35 (1H, m), 2.54-2.56 (2H, m), 2.62-2.71 (2H, m), 2.90-2.92 (1H, d, J = 9.4 Hz), 3.10 (1H, br s), 3.63 (3H, s), 3.76 (1H, br s), 6.13-6.17 (1H, t, J = 6.5 Hz), 6.40-6.45 (1H, t, J = 7.3 Hz), 7.19-7.30 (2H, m), 7.39 (1H, s), 7.44-7.47 (1H, d, J = 7.8 Hz), 7.54-7.56 (1H, d, J = 7.4); ¹³C NMR (75 MHz, CDCl₃): δ 21.2, 26.0, 27.6, 30.7, 43.8, 51.7, 54.3, 54.5, 57.3, 111.4, 119.6, 120.3, 122.2, 124.1, 128.3, 129.5, 134.7, 141.1, 155.4, 174.5. HRMS (ESI) (M + H)+ calculated for C₂₀H₂₃NO₃H⁺= 326.1756 found 326.1750.

Compound (8b) was prepared following general procedure as for (7b). Yield: 73%. IR (neat, CHCl₃): ν 2945, 1737, 1452, 1197, 746 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.34-1.42 (1H, t, J = 12.2 Hz), 1.65-1.83 (3H, m), 2.13-2.21 (2H, m), 2.43-2.49 (2H, m), 2.55 (1H, m), 2.59-2.71 (2H, m), 3.13-3.16 (1H, d, J = 9.2 Hz), 3.70 (1H, s), 3.81 (1H, br s), 6.20-6.24 (1H, t, J = 6.7 Hz), 6.42-6.47 (1H, t, J = 7.2 Hz), 7.19-7.29 (2H, m), 7.38 (1H, s), 7.44-7.46 (1H, d, J = 7.7 Hz), 7.53-7.56 (1H, d, J = 7.3 Hz); ¹³C NMR (75 MHz, CDCl₃): δ 20.6, 24.4, 27.3, 30.9, 45.3, 51.8, 54.9, 56.9, 111.4, 119.6, 120.4, 122.1, 123.9, 135.1, 141.2, 175.0; HRMS (ESI) (M + H)+ calculated for C₂₀H₂₃NO₃H⁺= 326.1756 found 326.1750.

To a slurry of bis(acetonitrile)palladium dichloride (0.194 g, 0.75 mmol) in CH₃CN (1.5 mL) was added Et₃N (52 µL, 0.37 mmol) under an argon atmosphere. Silver tetrafluoroborate (0.29 g, 1.48 mmol) was added and the orange heterogeneous mixture immediately became yellow. After 15 minutes, a solution of (7a) (0.12 g, 0.37 mmol) in CH₃CN (2.0 mL) was added. The deep red solution was then stirred for 1 h at room temperature then heated at 70 °C for 12 h under argon atmosphere. The reaction mixture was cooled to 0 °C, MeOH (1.0 mL) was added, followed by addition of NaBH₄ (0.016 g, 0.43 mmol) portionwise. The solution was stirred for 1 h at 0 °C. The reaction mixture was filtered through a pad of celite, washed with methanol (5 mL). The organic extract was concentrated in vacuo and purified by column chromatography (100-200 mesh silica gel) using EtOAc in PE as eluent and obtained the compound (4a) (0.029 g, 22%) as a colorless oil (Rf = 0.47, PE:EtOAc, 2:3:1). IR (neat, CHCl₃): ν 2946, 1735, 1445, 1197, 746 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 1.77-1.82 (1H, m), 1.98-2.09 (2H, m), 2.13 (1H, br s), 2.34-2.40 (1H, m), 2.86 (1H, dd, J = 17.8, 7.0 Hz), 3.0 (1H, dt, J = 12.8, 3.0 Hz), 3.26-3.33 (3H, m), 3.40 (1H, t, J = 10.0 Hz), 3.71 (3H, s), 3.73 (1H, br s), 3.98 (1H, dd, J = 12.5, 6.3 Hz), 4.20 (1H, t, J = 9.5 Hz), 7.21-7.27 (2H, m), 7.38 (1H, dd, J = 7.0, 1.5 Hz), 7.42 (1H, dd, J = 7.5, 1.5 Hz); ¹³C NMR (125 MHz, CDCl₃): δ 20.0, 26.1, 26.9, 31.4, 31.8, 40.2,
The procedure was same as reported for the synthesis of (4a). The crude product obtained from (7b) (0.132 g, 0.42 mmol) was purified by column chromatography (100-200 mesh silica gel) using EtOAc in petroleum ether (PE) as eluent to get the compound (4b) (0.048 g, 42%) as a colorless oil ($R_f = 0.39$, PE:EtOAc, 2.3:1). IR (neat, CHCl$_3$): $\nu$ 2933, 2864, 1735, 1456, 1203, 748 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 1.71 (1H, dq, $J = 15.0, 3.5$ Hz), 1.77-1.83 (1H, m), 1.98 (1H, br s), 2.04-2.09 (1H, m), 2.27-2.31 (1H, m), 2.52-2.54 (1H, m), 2.69 (1H, ddd, $J = 11.0, 6.5, 1.6$ Hz), 2.98 (1H, d, $J = 9.0$ Hz), 3.04 (1H, dt, $J = 9.0, 3.0$ Hz), 3.18-3.24 (2H, m), 3.29-3.36 (2H, m), 3.56 (1H, br s), 3.73 (3H, m), 7.19-7.23 (2H, m), 7.36 (1H, dd, $J = 6.8, 1.75$ Hz), 7.40 (1H, dd, $J = 6.5, 2.0$ Hz); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 10.2, 25.9, 26.4, 33.2, 39.6, 45.4, 49.1, 52.1, 52.9, 56.1, 110.7, 116.3, 118.8, 122.3, 123.5, 130.7, 153.7, 159.2, 175.2; HRMS (ESI) (M + H)$^+$ calculated for C$_{10}$H$_{11}$NO$_3$H$^+$ = 312.1600, found 312.1593.

To a well stirred mixture of 2-iodophenol (0.50 g, 2.27 mmol), palladium acetate (0.026 g, 0.11 mmol) and triphenylphosphine (0.003 g, 0.003 g, 0.11 mmol) in dry triethylamine (5.0 mL) was added propargyl alcohol (0.14 g, 2.5 mmol) under argon atmosphere. The reaction mixture was then stirred for overnight at room temperature. Reaction mixture was concentrated, diluted with EtOAc (20 mL), the EtOAc layer was washed with H$_2$O (2 x 10 mL) and brine (10 mL). The organic layer was dried over Na$_2$SO$_4$, concentrated in vacuo. After column purification on silica gel (100-200 mesh), the compound (18) was obtained as yellow oil. Yield: 0.31 g, 92.0%. $R_f$ (4:1, petroleum ether/EtOAc) = 0.45. IR (neat/CHCl$_3$): $\nu$ 3323, 1722, 1450, 1253, 1012, 748 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 2.23 (1H, br s), 4.79 (2H, s), 6.67 (1H, s), 7.22-7.33 (2H, m), 7.48-7.50 (1H, d, $J = 8.0$ Hz), 7.56-7.59 (1H, d, $J = 7.8$ Hz); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 58.2, 104.2, 111.4, 121.3, 122.9, 124.5, 128.3, 155.2, 165.5.

Compound (19) was prepared following similar procedure as for (18). Yield: 87.0%. $R_f$ (4:1, petroleum ether/EtOAc) = 0.43. IR (neat/CHCl$_3$): $\nu$ 3365, 1602, 1454, 1251, 1047, 750 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 1.98-2.06 (1H, m), 2.89 (2H, t, $J = 7.5$ Hz), 3.73 (2H, br s), 6.42 (1H, s), 7.18-7.24 (2H, m), 7.39-7.49 (2H, m); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 24.9, 61.9, 102.3, 110.8, 120.3, 122.6, 123.3, 128.9, 154.8, 158.8.

Compound (20) was prepared following similar procedure as for (18). Yield: 85.0%. $R_f$ (4:1, petroleum ether/EtOAc) = 0.43. IR (neat/CHCl$_3$): $\nu$ 3350, 2945,
To a stirred solution of p-toluenesulfonyl chloride (0.45 g, 2.7 mmol), triethylamine (0.68 mL, 4.9 mmol) and 4-dimethylaminopyridine (0.04 g, 0.33 mmol) in dry CH$_2$Cl$_2$ (5 mL) was added slowly a solution of benzofuran-2-ylethanol (19) (0.32 g, 1.97 mmol) in dry CH$_2$Cl$_2$ (5.0 mL) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and left for overnight at room temperature. The reaction mixture was diluted with CH$_2$Cl$_2$ (15 mL). The organic layer was washed with water (2 x 10 mL), brine (10 mL), dried over Na$_2$SO$_4$. The crude product was purified by column chromatography on silica gel (100-200 mesh) and obtained the pure compound (34) as a colorless solid. Melting point: 69 °C. Yield: 0.46 g, 74%. R$_f$ (4:1, petroleum ether/EtOAc) = 0.49. IR (neat/CHCl$_3$): v 1599, 1456, 1352, 1172, 979 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): δ 2.27 (3H, s), 3.02 (2H, t, $J = 6.0$ Hz), 4.27 (2H, t, $J = 6.5$ Hz), 6.33 (1H, s), 7.06-7.13 (4H, m), 7.14 (1H, d, $J = 1.5$ Hz), 7.22 (1H, d, $J = 8.0$ Hz), 7.36 (2H, d, $J = 1.0$ Hz); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 21.6, 28.6, 67.4, 104.3, 110.8, 120.6, 122.7, 123.7, 127.8, 128.5, 129.7, 132.7, 144.8, 153.2, 154.7; HRMS (ESI) (M + Na)$^+$ calculated for C$_{17}$H$_{16}$O$_4$SNa$^+$ = 339.0667, found 339.0665.

Compound (33) was prepared following similar procedure as for (34). Colorless liquid, yield: 62%, R$_f$ (4:1, petroleum ether/EtOAc) = 0.68. IR (neat, CHCl$_3$): ν 2939, 2854, 1452, 1255, 1109, 956 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): δ 4.64 (2H, s), 6.67 (1H, s), 7.15-7.18 (1H, dd, $J = 7.0, 3.0$ Hz), 7.23-7.26 (1H, t, $J = 8.0$ Hz), 7.41-7.42 (1H, d, $J = 8.0$ Hz), 7.47-7.49 (1H, d, $J = 8.0$ Hz); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 37.8, 106.2, 111.5, 121.4, 123.1, 125.1, 127.9, 152.6, 155.4.

Compound (35) was prepared following similar procedure as for (34). Colorless solid. Melting point: 74 °C. Yield: 70%. R$_f$ (4:1, petroleum ether/EtOAc) = 0.49. IR (neat, CHCl$_3$): ν 1928, 1593, 1450, 1348, 1172, 923, 742, 549 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): δ 1.96-2.05 (2H, m), 2.34 (3H, s), 2.72-2.77 (2H, t, $J = 7.2$ Hz), 3.99-4.03 (2H, t, $J = 6.1$ Hz), 6.20 (1H, s), 7.08-7.13 (3H, m), 7.21-7.24 (2H, m), 7.35 (1H, m), 7.68-7.71 (2H, d, $J = 7.5$ Hz); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 21.6, 24.3, 26.9, 69.2, 102.8, 110.7, 120.3, 122.5, 123.4, 127.9, 128.6, 129.8, 132.9, 144.8, 154.6, 156.9.
Using the similar procedure as for (7a), (16a) was prepared from (34) (0.86 g, 2.7 mmol) and (23a).HBr (0.5 g, 3.0 mmol) in presence of K$_2$CO$_3$ (0.94 g, 6.8 mmol). The crude product was subjected to column chromatography (100-200 mesh silica gel) for purification and elution with EtOAc in PE gave the compound (16a) (0.71 g, 83%), \( \delta_{R} = 0.52 \), PE:EtOAc, 15:1 as a pale yellow oil. IR (neat, CHCl$_3$): \( \nu = 3407, 2949, 1732, 1454, 1251 \text{ cm}^{-1} \); $^1$H NMR (500 MHz, CDCl$_3$): \( \delta = 1.68-1.80 \text{ (2H, m)}, 2.01-2.05 \text{ (1H, dt, } J = 9.5, 2.5 \text{ Hz)}, 2.59 \text{ (1H, br s)}, 2.63-2.66 \text{ (1H, m)}, 2.86-2.95 \text{ (3H, m)}, 2.97 \text{ (1H, dd, } J = 9.7, 2.0 \text{ Hz)}, 3.08-3.11 \text{ (1H, m)}, 3.62 \text{ (3H, s)}, 3.82-3.83 \text{ (1H, m)}, 6.18 \text{ (1H, dt, } J = 6.5 \text{ Hz)}, 6.40 \text{ (1H, s)}, 6.44 \text{ (1H, t, } J = 7.25 \text{ Hz)}, 7.15-7.21 \text{ (2H, m)}, 7.39 \text{ (1H, d, } J = 9.0 \text{ Hz)}, 7.45-7.47 \text{ (1H, dd, } J = 7.0, 1.5 \text{ Hz}); $^{13}$C NMR (125 MHz, CDCl$_3$): \( \delta = 26.0, 28.1, 30.8, 44.0, 51.8, 54.26, 54.66, 55.97, 56.03, 60.4, 102.5, 110.77, 110.89, 120.3, 122.49, 122.69, 123.25, 123.66, 128.9, 129.6, 134.8, 154.7, 157.6, 174.4; HRMS (ESI) (M + H)$^+$ calculated for C$_{19}$H$_{21}$N$_2$O$_3$H$^+$ = 312.1600, found 312.1592.

Compound (16b) was prepared from (34) (0.72 g, 2.27 mmol) in the presence of (23b).HBr and K$_2$CO$_3$ following similar procedure. The crude product was subjected to column chromatography (100-200 mesh silica gel) for purification and elution with EtOAc in PE gave the compound (16b) (0.53 g, 75%), \( \delta_{R} = 0.49 \), PE:EtOAc, 4:1 as a pale yellow oil. IR (neat, CHCl$_3$): \( \nu = 2947, 1735, 1454, 1253, 1197, 742 \text{ cm}^{-1} \); $^1$H NMR (500 MHz, CDCl$_3$): \( \delta = 1.36-1.42 \text{ (1H, m)}, 1.91 \text{ (1H, dt, } J = 9.0, 2.5 \text{ Hz)}, 2.17 \text{ (1H, ddd, } J = 12.5, 4.3, 2.6 \text{ Hz)}, 2.41-2.45 \text{ (1H, m)}, 2.48-2.52 \text{ (1H, m)}, 2.58 \text{ (1H, br s)}, 2.75-2.99 \text{ (3H, m)}, 3.20 \text{ (1H, dd, } J = 9.0, 2.0 \text{ Hz)}, 3.55 \text{ (3H, s)}, 3.83-3.85 \text{ (1H, m)}, 6.26 \text{ (1H, dd, } J = 7.5, 6.5 \text{ Hz)}, 6.40 \text{ (1H, s)}, 6.48 \text{ (1H, t, } J = 7.5 \text{ Hz)}, 7.14-7.21 \text{ (2H, m)}, 7.36-7.40 \text{ (1H, m)}, 7.45-7.48 \text{ (1H, m)}; $^{13}$C NMR (125 MHz, CDCl$_3$): \( \delta = 24.4, 27.8, 31.1, 45.4, 51.8, 54.9, 55.2, 56.06, 102.51, 102.55, 110.8, 120.31, 120.51, 122.5, 123.14, 123.57, 129.18, 129.94, 135.4, 154.6, 158.1, 174.9; HRMS (ESI) (M + H)$^+$ calculated for C$_{19}$H$_{21}$N$_2$O$_3$H$^+$ = 312.1600, found 312.1595.

Following general procedure as for (7a) compound (15a) was prepared in 71% yield. IR (neat, CHCl$_3$): \( \nu = 2949, 1736, 1454, 1194, 1167, 749 \text{ cm}^{-1} \); $^1$H NMR (500 MHz, CDCl$_3$): \( \delta = 1.69-1.72 \text{ (1H, m)}, 1.81-1.86 \text{ (1H, t, } J = 11.0 \text{ Hz)}, 2.07-2.09 \text{ (1H, d, } J = 9.5 \text{ Hz)}, 2.61 \text{ (1H, br s)}, 3.05-3.07 \text{ (1H, d, } J = 10.0 \text{ Hz)}, 3.17-3.19 \text{ (1H, br s)}, 3.56-3.59 \text{ (1H, d, } J = 14.0 \text{ Hz)}, 3.62 \text{ (3H, s)}, 3.76-3.79 \text{ (1H, d, } J = 14.5 \text{ Hz)}, 3.89 \text{ (1H, br s)}, 6.20-6.22 \text{ (1H, t, } J = 5.5 \text{ Hz)}, 6.47-6.50 \text{ (1H, t, } J = 7.0 \text{ Hz)}, 6.57 \text{ (1H, s)}, 7.18-7.26 \text{ (2H, m)}, 7.47-7.48 \text{ (1H, d, } J = 7.5 \text{ Hz)}, 7.51-7.53 \text{ (1H, d, } J = 7.0 \text{ Hz)}; $^{13}$C NMR (125 MHz, CDCl$_3$): \( \delta = 26.2, 30.9, 44.2, 51.9, 53.7, 54.13, 54.34, 105.1, 111.4, 120.8, 122.7, 123.9, 128.5, 129.4, 135.1, 155.2, 155.8, 174.4; HRMS (ESI) (M + H)$^+$ calculated for C$_{16}$H$_{18}$NO$_3$H$^+$ = 298.1443 found 298.1436.
Compound (15b) was prepared in 64% yield from compound (33) and (23b). HBr. IR (neat, CHCl₃): ν = 2943, 1742, 1450, 1193, 1167, 746 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ = 1.30-1.35 (1H, t, J = 11.5 Hz), 1.92-1.94 (1H, d, J = 9.0 Hz), 2.10-2.15 (1H, d, J = 12.5 Hz), 2.34-2.36 (1H, d, J = 11.0 Hz), 2.52 (1H, br s), 3.20-3.21 (1H, d, J = 9.0 Hz), 3.40-3.45 (1H, d, J = 14.5 Hz), 3.55-3.57 (4H, m), 3.79 (1H, br s), 6.16-6.19 (1H, t, J = 6.5 Hz), 6.40-6.45 (2H, m), 7.09-7.17 (2H, m), 7.29 (1H, d, J = 8.0 Hz), 7.33-7.36 (1H, d, J = 7.5 Hz); ¹³C NMR (125 MHz, CDCl₃): δ = 24.2, 31.1, 45.2, 51.8, 54.02, 54.26, 54.83, 104.4, 110.97, 120.6, 122.5, 123.6, 128.6, 129.7, 135.6, 154.9, 156.4, 174.8; HRMS (ESI) (M + H)⁺ calculated for C₁₈H₁₉N₂O₃H⁺ = 298.1443 found 298.1436.

Following general procedure as for (7a) compound (17a) was prepared in 79% yield. IR (neat, CHCl₃): ν = 2949, 1735, 1454, 1253, 1197, 750 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ = 1.67-1.78 (2H, m), 1.84-1.95 (3H, m), 2.29-2.34 (1H, m), 2.55-2.61 (2H, m), 2.73-2.83 (2H, m), 2.92 (1H, dd, J = 9.5, 2.0 Hz), 3.07-3.11 (1H, m), 3.63 (3H, s), 3.77 (1H, br s), 6.13-6.16 (1H, m), 6.33 (1H, s), 6.42 (1H, t, J = 7.5 Hz), 7.14-7.22 (2H, m), 7.38 (1H, t, J = 7.45-7.47 (1H, m); ¹³C NMR (125 MHz, CDCl₃): δ = 26.16, 26.33, 26.39, 30.9, 51.8, 54.4, 54.6, 57.2, 102.1, 110.8, 120.3, 122.5, 123.2, 129.11, 129.62, 134.8, 154.8, 159.4, 174.6; HRMS (ESI) (M + H)⁺ calculated for C₂₀H₂₃N₂O₃H⁺ = 326.1756, found 326.1751.

Following general procedure as for (7b) compound (17b) was prepared in 74% yield from (35) and (23b). IR (neat, CHCl₃): ν = 2947, 1737, 1600, 1454, 1251, 1197, 750 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ = 1.38-1.42 (1H, m), 1.73-1.79 (2H, m), 1.82 (1H, dt, J = 9.0, 2.5 Hz), 2.16-2.21 (2H, m), 2.43-2.56 (3H, m), 2.73-2.79 (2H, m), 3.15 (1H, dd, J = 9.0, 2.0 Hz), 3.73 (3H, s), 3.80 (1H, br s), 6.21 (1H, m), 6.36 (1H, s), 6.44-6.47 (1H, t, J = 7.2 Hz), 7.15-7.21 (2H, m), 7.39-7.41 (1H, d, J = 8.0 Hz), 7.46-7.48 (1H, m); ¹³C NMR (125 MHz, CDCl₃): δ = 24.5, 25.8, 26.3, 31.1, 45.5, 51.9, 55.01, 55.14, 56.9, 101.9, 110.8, 120.2, 122.4, 123.1, 129.2, 129.9, 135.3, 154.8, 159.9, 175.1; HRMS (ESI) (M + H)⁺ calculated for C₂₀H₂₃N₂O₃H⁺ = 326.1756, found 326.1749.

The crude product obtained after cyclization of (16a) (0.47 g, 1.52 mmol) was subjected to column purification. Elution with EtOAc in PE gave the compound (13a) (0.13 g, 27%) as a colorless oil (Rf = 0.45, PE:EtOAc, 4:1). IR (neat): ν = 2947, 1735, 1454, 1253, 1197, 742 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 1.67-1.71 (1H, m), 2.04-2.08 (2H, m), 2.14 (1H, br s), 2.38-2.39 (1H, m), 2.94-3.01 (2H, m), 3.19 (1H, t, J = 10.0 Hz), 3.25 (1H, d, J = 13.0 Hz), 3.47 (1H, t, J = 12.0 Hz), 3.55-3.61 (1H,
The crude product obtained from compound (16b) (0.12 g, 0.37 mmol) was purified by column chromatography on silica gel using EtOAc in PE as eluent to yield the compound (13b) (0.053 g, 46%) as a colorless oil ($R_f = 0.38$, PE:EtOAc, 4:1). IR (neat, CHCl$_3$): $\nu$ 2953, 1732, 1607, 1450, 1251, 745 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 1.51 (1H, dq, $J = 13.0, 3.3$ Hz), 1.77-1.83 (1H, m), 1.97 (1H, br s), 2.05-2.11 (1H, m), 2.27-2.32 (1H, m), 2.71-2.75 (2H, m), 2.95 (1H, $dt, J = 9.0$ Hz), 3.04 (1H, $dt, J = 9.0, 3.0$ Hz), 3.13-3.26 (3H, m), 3.48 (1H, br s), 3.53-3.60 (1H, m), 3.73 (3H, s), 7.17-7.22 (2H, m), 7.35-7.38 (2H, m); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 25.7, 26.11, 26.36, 33.2, 34.1, 45.9, 49.1, 50.8, 51.9, 58.1, 110.6, 118.3, 121.6, 122.2, 123.5, 129.7, 151.9, 153.8, 175.3; HRMS (ESI) (M + H)$^+$ calculated for C$_{19}$H$_{21}$NO$_3$H$^+$ = 312.1600, found 312.1594.
Spectral data
\[ \text{CBz} \]
\[ ^{13}\text{C} \text{NMR 125 MHz} \]

\[ \text{21a} \]
$^1$H NMR 300 MHz

$^{13}$C NMR 75 MHz
**1H NMR 500 MHz**

![1H NMR 500 MHz](image)

**13C NMR 125 MHz**

![13C NMR 125 MHz](image)
**1H NMR 500 MHz**

**13C NMR 125 MHz**
1H NMR 500 MHz

13C NMR 125 MHz
In this chapter we have synthesized an important intermediate of ibogaine in optically pure form. We selected an optically pure compound as starting material and the chirality was maintained during the course of reaction.
Introduction

Ibogamine (1) is the simplest representative of iboga-family alkaloids; accordingly several methods have been developed towards the synthesis of this alkaloid. Most of the reports described the synthesis of ibogamine (1) in racemic form (Figure 1). Few methods have been reported for the synthesis of optically active ibogamine and discussed in chapter 1a (Scheme 4, 9 and 10). The asymmetric routes were involved either using chiral auxiliary or chiral catalyst towards the synthesis of isoquinuclidine ring which was then used in ibogamine synthesis. Borschberg’s group reported the first enantioselective synthesis of (-)-(19R)-ibogamin-19-ol (Chapter 1a, Scheme 11) starting from L-glutamic acid and (2S)-but-3-en-2-ol, however, their method involved a large number of steps. In this context, it is necessary to have an easy and flexible synthetic route towards the synthesis of ibogaine, ibogamine and their analogues in optically pure form.

Results and Discussion

Our retrosynthesis is based on Huffman’s6 and Kuehene’s7 approach where they used the racemic epoxide (5) as an intermediate (Scheme 1). This six-membered epoxide (5) can be synthesized in optically active form using commercially available quinic acid as the starting material. This epoxide can be opened up either by tryptamine or 5-methoxy tryptamine to get ibogamine or ibogaine, respectively. Moreover, the presence of olefinic double bond in compound (6) can give various types of
other iboga-alkaloids or their analogues, depending on the use of selective reducing or oxidizing agents.

Synthesis of (6) has been described in the following section. Treatment of D-(-) quinic acid with p-toluenesulphonic acid in 2,2-dimethoxypropane gave the acetonide which lactonized immediately to afford (7) in high yield (Scheme 2). Next step was the deoxygenation of the tertiary alcohol (7). A one-step deoxygenation of 2-hydroxylactones or their acetates was reported in literature using samarium diiodide as an electron-transfer reagent in conjunction with a proton source in high yield. We converted the alcohol (7) to the corresponding acetate (8) using acetic anhydride. Deoxygenation reaction proceeded well in small scale (0.2 mmol) following their procedure, however, in large scale (3.9 mmol) reaction; we failed to isolate the desired product (Scheme 2). Large number of spots was found in the TLC plate after the reaction. The amount of SmI₂ required (3.0 equivalent) was quiet high to carry out the reaction.

![Scheme 2](image)

We then planned to use Barton’s deoxygenation reaction via the formation of xanthate intermediate. Accordingly, the tertiary alcohol (7) was converted to the corresponding xanthate (9).

![Scheme 3](image)
Deoxygenation of (9) was carried out by treatment with tributyltinhydride in presence of catalytic amount of AIBN in good yield (Scheme 3). Ring open up of lactone (10) was carried out by dropwise addition of sodium methoxide in methanol at 0 °C in 78% yield. Conversion of alcohol (11) to the corresponding mesylate (12) was performed using mesylchloride, triethylamine in dichloromethane solvent. Acetonide deprotection of (12) was carried out using 80% acetic acid to afford diol (13) in almost quantitative yield. Epoxide (14) was in turn synthesized from diol (13) using DBU as base and THF as solvent under refluxing condition.

Oxidation of epoxy alcohol (14) was carried out using several oxidizing agents but PDC in dichloromethane gave the best result (77%) to the epoxy ketone (15) (Scheme 4). Olefination of compound (15) was carried out using ethyltriphenylphosphonium bromide as Wittig reagent to obtain alkene (6) in 75% yield. The epoxide (6) could be used for ibogaine or ibogamine synthesis according to Huffman's or Kuehene's method (Chapter 1a, Scheme 2).

\[
\begin{array}{c}
\text{Scheme 4} \\
\begin{array}{c}
\text{14} \xrightarrow{i} \text{CO}_2\text{Me} \\
\text{CO}_2\text{Me} \xrightarrow{ii} \text{CO}_2\text{Me}
\end{array}
\end{array}
\]

*Reagents and conditions: i) PDC, 4 A\textsuperscript{0} MS, Ac\textsubscript{2}O, CH\textsubscript{2}Cl\textsubscript{2}, 77%, ii) ethyltriphenylphosphonium bromide, n-BuLi, THF, -78 °C to -30 °C*

Conclusion

In conclusion we have synthesized a key intermediate (6) of iboga alkaloids in optically pure form. Synthetic route has been designed in such a way that the desired chiral centers have been introduced through the functional group manipulation of D-quinic acid. This intermediate can be used for the synthesis of iboga family alkaloids. Work towards the synthesis of ibogamine, ibogaine and ibogamin-19-ol in optically pure form is going on.

References

EXPERIMENTAL:

Optical rotations

Specific optical rotations \([\alpha]D\) were measured using Jasco P-1020 digital polarimeter at stated temperature, solvent and concentration was in gm/100 mL.

General write up of Experimental Section: As described in Chapter 1b.

To a suspension of (-)-quinic acid (3.0 g, 15.6 mmol) was added p-toluenesulfonic acid monohydrate (0.31 g, 1.62 mmol) in 2,2-dimethoxypropane (20.0 mL) was stirred for 24 h at rt. The reaction mixture was quenched with cold saturated aqueous NaHCO₃ (10.0 mL). The aqueous layer was extracted with EtOAc (3×10 mL), the organic layers were combined and washed with brine (10 mL), dried over Na₂SO₄ and concentrated in vacuo. The residue was washed with 5% ether/hexanes (100 mL). The white crystals were dried in a vacuum oven for 24 h yielding 3,4-O-isopropylidenequinic acid-1,5-lactone (7). Yield: 2.76 g, 82%. TLC (1:19 EtOAc/petroleum ether) \(R_f = 0.61\). \([\alpha]D^{26} = -27.5 (c 0.85, CHC13); \) IR (neat/CHCl₃): \(v 3427, 1778, 1161, 1076, 758 \text{ cm}^{-1}; \) H NMR (500 MHz, CDCl₃): \(\delta 1.32 (3H, s), 1.51 (3H, s), 2.15-2.18 (1H, dd, J= 14.8, 3.0 Hz), 2.29-2.39 (2H, m), 2.61-2.64 (1H, d, J= 11.5 Hz), 3.17 (1H, s), 4.29-4.30 (1H, d, J= 6.0 Hz), 4.47-4.50 (1H, m), 4.70-4.72 (1H, dd, J= 6.5, 2.5 Hz); \) C NMR (125 MHz, CDCl₃): \(\delta 24.4, 27.1, 34.4, 38.3, 71.7, 72.3, 75.9, 109.9, 179.0\); HRMS (ESI) (M + Na)⁺ calculated for C₁₀H₁₄O₅Na⁺ = 237.0739 found 237.0739.

To a solution of compound (7) (1.38 gm, 6.44 mmol) in dry dichloromethane (10.0 mL) was added acetic anhydride (0.92 mL, 9.66 mmol), DMAP (0.079 gm, 0.65 mmol) and pyridine (1.29 mL, 16.1 mmol) at 0 °C. The reaction mixture was allowed to warm at room temperature and stirred for a period of 1 h. The reaction mixture was diluted with CH₂Cl₂ (20 mL), washed with water (2×10 mL) and brine (10 mL). Organic layer was dried over Na₂SO₄, dried in vacuo. The residue was purified by column chromatography on silica gel (100-200 mesh) to yield the compound (8) as white solid. Yield: 1.42 g, 86%. TLC (2% EtOAc/petroleum ether) \(R_f = 0.60.\) H NMR (500 MHz, CDCl₃): \(\delta 1.33 (3H, s), 1.51 (3H, s), 2.11 (3H, s), 2.29-2.32 (1H, dd, J= 14.2, 3.0 Hz), 2.41-2.46 (1H, m), 2.52-2.54 (1H, d, J= 11.5 Hz), 3.02-3.05 (1H, m), 4.31-4.32 (1H, d, J= 6.0 Hz), 4.53-4.56 (1H, m), 4.76-4.77 (1H, dd, J= 5.5, 2.0 Hz); \) C NMR (125 MHz, CDCl₃): \(\delta 20.9, 24.3, 26.9, 30.3, 35.3, 71.1, 72.4, 75.3, 76.1, 109.8, 124.0, 149.1, 169.1, 173.4; \) HRMS (ESI) (M + Na)⁺ calculated for C₁₂H₁₆O₆Na⁺ = 279.0845 found 279.0845.
To a suspension of potassium hydride (35% dispersion, 1.11 g, 9.7 mmol) in dry THF (15 mL) was added a solution of (7) (1.38 g, 6.44 mmol) in THF (15 mL) dropwise at 0 °C. Evolution of hydrogen was ceased within 0.5 h. Carbondisulfide (0.77 mL, 12.88 mmol) was added in one portion at 0°C and the mixture was stirred for another 0.5 h. After adding methyl iodide (0.79 mL, 12.88 mmol), the reaction was complete within 1 h. Saturated NH₄Cl (5.0 mL) was added and the reaction mixture was extracted with ether (3x20 mL). The ethereal layer was washed with water (2x20 mL), brine (20 mL) and dried over Na₂SO₄, concentrated in vacuo. The crude product obtained was purified by column chromatography on silica gel (100-200 mesh) to yield the pure xanthate as white solid. Yield: 1.63 g, 83%.

[α] = -6.4 (c 1.29, CHCl₃); 1R (neat/CHCl₃): ν 2987, 1799, 1211, 1068, 756 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 1.29-1.30 (3H, d, J = 6.5 Hz), 1.48-1.49 (3H, d, J = 6.5 Hz), 2.50-2.51 (3H, d, J = 7.0 Hz), 2.54-2.55 (1H, d, J = 4.5 Hz), 2.63-2.67 (1H, t, J = 7.0 Hz), 3.62-3.66 (1H, dd, J = 11.5, 7.0 Hz), 4.29-4.30 (1H, d, J = 6.5 Hz), 4.52-4.56 (1H, dd, J = 11.2, 6.0 Hz), 4.80-4.81 (1H, t, J = 4.0, 2.0 Hz); ¹³C NMR (125 MHz, CDCl₃): δ 19.5, 24.4, 26.9, 30.0, 36.4, 71.3, 72.6, 75.6, 82.5, 110.1, 172.0, 212.1; HRMS (ESI) (M + Na)⁺ calculated for C₁₀H₁₇O₅S₂Na⁺ = 327.0377 found 327.0377.

Argon was passed through a toluene (20 mL) solution containing (9) (1.63 g, 5.36 mmol) and AIBN (0.043 gm, 0.268 mmol) for 20 min. Tributyltinhydride (1.65 mL, 6.10 mmol) was added dropwise. The reaction mixture was heated at 105 °C for period of 1 h. The reaction mixture was evaporated to dryness and purified by column chromatography on silica gel (100-200 mesh) to obtain compound (10) as colorless crystalline solid. Yield: 0.73 g, 69%. [α] = -23.6 (c 2.41, CHCl₃); IR (neat/CHCl₃): ν 2985, 1790, 1157, 949, 669 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 1.23 (3H, s), 1.42 (3H, s), 1.97-2.02 (1H, m), 2.10-2.15 (1H, m), 2.19-2.24 (1H, m), 2.30-2.33 (1H, d, J = 12.0 Hz), 2.50-2.52 (1H, t, J = 5.0 Hz), 4.23-4.24 (1H, dd, J = 4.5, 1.5 Hz), 4.36-4.40 (1H, m), 4.59-4.61 (1H, dd, J = 5.8, 2.0 Hz); ¹³C NMR (125 MHz, CDCl₃): δ 24.5, 27.2, 28.1, 29.9, 35.5, 70.6, 72.9, 109.5, 179.0; HRMS (ESI) (M + H)⁺ calculated for C₁₀H₁₇O₅H⁺ = 199.0970 found 199.0938.

Sodium methoxide (1.3 gm, 24.0 mmol) in methanol (20 mL) was added to solution containing (10) (3.75 g, 18.92 mmol) in dry MeOH (25 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h then at room temperature for a period of 4 h. The reaction mixture was neutralized by adding acetic acid at 0 °C. Methanol was evaporated to dryness. The reaction mixture was diluted with EtOAc (40 mL), washed with water (10 mL) and brine (10 mL). Ethylacetate layer was concentrated in vacuo and purified by column chromatography on silica gel (100-200 mesh) to obtain compound (11) as colorless solid. Yield: 3.39 g, 78%. TLC (1:1 EtOAc/petroleum ether) Rf = 0.49. [α]²⁰ = -56.59 (c 5.65, CHCl₃); IR (neat/CHCl₃): ν 3454, 1735, 1240, 1057, 889 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 1.35 (3H, s), 1.47 (3H, s), 1.83-1.89 (1H, m), 2.10-2.14 (1H, m), 2.29-2.34 (1H, m), 2.69-2.75 (1H, t, J = 12.0, 2.0 Hz); ¹³C NMR (125 MHz, CDCl₃): δ 24.5, 27.2, 28.1, 29.9, 35.5, 70.6, 72.9, 109.5, 179.0; HRMS (ESI) (M + Na)⁺ calculated for C₁₀H₁₇O₅Na⁺ = 327.0377 found 327.0377.
4.0 Hz), 3.68 (3H, s), 3.71-3.76 (1H, m), 3.81-3.84 (1H, dd, \( j = 5.0, 1.0 \) Hz), 4.34-4.37 (1H, m); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \( \delta = 26.2, 28.4, 28.9, 32.7, 36.2, 52.1, 71.7, 73.6, 80.5, 109.0, 175.4 \); HRMS (ESI) (M + Na\(^+\)) calculated for C\(_{11}\)H\(_{14}\)O\(_5\)Na\(^+\) = 253.1052 found 253.1052.

To a solution of (11) (3.14 g, 13.6 mmol) was added triethylamine (4.89 mL, 34.1 mmol) in dry dichloromethane (20 mL). Mesylchloride (1.41 mL, 17.7 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for a period of 1.5 h. After completion of the reaction it was diluted with CH\(_2\)Cl\(_2\) (30 mL), washed with water (2x10 mL), brine (10 mL). Organic layer was dried over Na\(_2\)SO\(_4\), concentrated in vacuo and purified by column chromatography on silica gel (100-200 mesh) to obtain compound (12) as colorless solid. Yield: 3.70 g, 88%. TLC (1:1 EtOAc/petroleum ether) \( R_f = 0.64 \). [\( \alpha \)\]\(^D\) \( = -97.03 \) (c 2.40, CHCl\(_3\)); IR (neat/CHCl\(_3\)): \( \nu = 2987, 1734, 1356, 1174, 931, 819 \) cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta = 1.36 \) (3H, s), 1.53 (3H, s), 1.62-1.69 (1H, \( q, J = 12.5 \) Hz), 1.81-1.87 (1H, m), 2.35-2.40 (2H, m), 2.75-2.81 (1H, \( tt, J = 12.5, 3.5 \) Hz), 3.11 (3H, s), 3.69 (3H, s), 3.99-4.01 (1H, dd, \( J = 7.2, 5.5 \) Hz), 4.39-4.42 (1H, m), 4.60-4.65 (1H, m); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \( \delta = 26.2, 28.2, 28.9, 32.6, 36.1, 38.8, 52.2, 74.1, 82.9, 109.7, 173.9 \); HRMS (ESI) (M + Na\(^+\)) calculated for C\(_{12}\)H\(_{20}\)O\(_7\)Na\(^+\) = 331.0827 found 331.0828.

A suspension of (12) (3.5 g, 11.5 mmol) in 80% aqueous acetic acid (30 mL) was stirred for 3 h at 60 °C. After cooling to rt, the solvents were removed by co-evaporation with toluene (3x50 mL). The residue was dried in high vacuum to give (13) as colorless solid. Yield: 2.98 g, 98%. [\( \alpha \)\]\(^D\) \( = -51.44 \) (c 4.30, CHCl\(_3\)); IR (neat/CHCl\(_3\)): \( \nu = 3454, 1730, 1342, 1170, 962 \) cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta = 1.56-1.61 \) (1H, td, \( J = 12.5, 2.0 \) Hz), 1.65-1.72 (1H, \( q, J = 12.5 \) Hz), 2.11-2.16 (1H, dq, \( J = 14.0, 3.5, 2.5 \) Hz), 2.37-2.42 (1H, m), 2.86-2.92 (1H, tt, \( J = 12.5, 8.0, 3.5 \) Hz), 3.08 (3H, s), 3.35 (1H, br s), 3.55-3.57 (1H, \( t, J = 4.5 \) Hz), 3.64-3.66 (3H, \( d, J = 7.0 \) Hz), 3.69-3.71 (1H, \( d, J = 5.5 \) Hz), 4.16 (1H, br s), 4.72-4.77 (1H, m); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \( \delta = 32.9, 33.3, 35.6, 38.5, 52.1, 53.5, 69.4, 73.3, 81.3, 174.5 \); HRMS (ESI) (M + Na\(^+\)) calculated for C\(_{9}\)H\(_{16}\)O\(_7\)Na\(^+\) = 291.0514 found 291.0516.

To a solution of compound (13) (2.5 g, 9.32 mmol) in dry THF (20 mL) was added DBU (4.2 mL, 27.9 mmol). The reaction mixture was refluxed overnight at 70 °C. The reaction mixture was concentrated, diluted with ethylacetate (30 mL). Organic layer was washed with brine (10 mL), dried over Na\(_2\)SO\(_4\), concentrated in vacuo and purified by column chromatography on silica gel (100-200 mesh) to obtain compound (14) as colorless oil. Yield: 1.21 gm, 74%. [\( \alpha \)\]\(^D\) \( = -69.12 \) (c 5.40, CHCl\(_3\)); IR (neat/CHCl\(_3\)): \( \nu = 3566, 1732, 1437, 1215, 756 \) cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta = 1.63-1.68 \) (1H, \( m, J = 14.0 \) Hz), 1.82-1.85 (1H, \( d, J = 14.0 \) Hz), 1.94-1.99 (1H, \( qd, J = 8.8, 2.5 \) Hz), 2.22-2.26 (1H, \( dd, J = 15.5, 4.5 \) Hz), 2.36 (1H, m), 2.62-2.67 (1H, m), 3.34-3.36 (1H, \( t, J = 4.0 \) Hz), 3.43 (1H, br s), 3.66 (3H, s), 4.13 (1H,
To a dichloromethane solution (15 mL) of (14) (1.0 g, 5.81 mmol) was added 4Å molecular sieves (1.5 g), anhydrous sodium acetate (0.386 g, 4.71 mmol) and pyridinium dichromate (6.55 g, 17.4 mmol). After stirring the mixture at room temperature for 1 h, the reaction mixture was filtered through a pad of celite. The celite layer was washed with CH$_2$Cl$_2$, concentrated in vacuo and purified by column chromatography on silica gel (100-200 mesh) to obtain compound (15) as colorless oil. Yield: 0.76 gm, 77%. TLC (1:2.3 EtOAc/petroleum ether) $R_f = 0.53$. [α]$^D_{25} = -134.42$ (c 1.30, CHCl$_3$); IR (neat/CHCl$_3$): $v$ 1732, 1718, 1431, 1217, 750 cm$^{-1}$; $^1$H NMR (500 MHz, CDC$_3$): $\delta$ 2.03-2.09 (1H, dd, $\delta_1 = 11.0, 3.5$ Hz), 2.27-2.33 (1H, $q$, $\delta = 11.5, 7.0$ Hz), 2.60-2.64 (1H, td, $\delta = 15.0, 3.5$ Hz), 2.68-2.73 (1H, dd, $\delta = 18.8, 5.0$ Hz), 3.05-3.08 (1H, m), 3.26-3.27 (1H, $d$, $\delta = 4.0$ Hz), 3.62-3.64 (1H, $t$, $\delta = 3.5$ Hz), 3.69 (3H, s); $^{13}$C NMR (125 MHz, CDC$_3$): $\delta$ 26.2, 33.5, 38.4, 52.4, 54.2, 54.6, 174.0, 202.9; HRMS (ESI) (M + Na)$^+$ calculated for C$_8$H$_{12}$O$_4$Na$^+$= 193.0477 found 193.0476.

To a suspension of ethyltriphenylphosphonium bromide (0.614 g, 1.65 mmol) in anhydrous THF (10 mL) -78 °C was added (1.03 mL, 1.72 mmol) of n-BuLi (as a 1.6 M solution in hexane) under argon. The solution was allowed to warm to room temperature and stirred for 20 min, after which it was recooled to -78 °C, and the ketone (15) (0.114 g, 0.66 mmol) in 10 mL of anhydrous THF was added slowly at that temperature. The reaction mixture was allowed to warm to room temperature over a 1 h period and was quenched with water and extracted with ether. The organic layer was washed with brine, dried over sodium sulfate and the solvent was removed under vacuum. Purification of the crude product by silica gel flash column chromatography (100-200 mesh) afforded compound (6). Yield: 0.092 gm, 75%. TLC (1:9 EtOAc/petroleum ether) $R_f = 0.64$. [α]$^D_{25} = -74.27$ (c 0.30, CHCl$_3$); IR (neat/CHCl$_3$): $v$ 1732, 1434, 1208, 745 cm$^{-1}$; $^1$H NMR (500 MHz, CDC$_3$): $\delta$ 1.80-1.82 (3H, $dd$, $\delta = 7.8, 2.0$ Hz), 1.93-1.99 (1H, m), 2.07-2.12 (1H, $td$, $\delta = 13.2, 2.5$ Hz), 2.37-2.44 (2H, $td$, $\delta = 15.5, 3.0$ Hz), 2.56-2.59 (1H, m), 3.45-3.47 (1H, m), 3.67-3.72 (4H, m), 5.73-5.75 (1H, $dd$, $\delta = 7.2, 1.5$ Hz); $^{13}$C NMR (125 MHz, CDC$_3$): $\delta$ 12.9, 19.2, 27.8, 33.2, 36.3, 49.7, 51.56, 51.93, 53.48, 129.9, 130.04, 175.6; HRMS (ESI) (M + Na)$^+$ calculated for C$_{10}$H$_{14}$O$_3$Na$^+$= 205.0841 found 205.0842.
Spectral data
**Chapter-1c | 74**

**Figure 1c:**

- **1H NMR 500 MHz**
- **13C NMR 125 MHz**

**Chemical Structures:**
- CO$_2$Me
- 15

**NMR Data:**
- **NAME:** SP6,68-13C
- **EXPHD:** 1
- **PROCNO:** 1
- **Date:** 20110317
- **Time:** 11.58
- **MS:** 415
- **DS:** 4
- **SH:** 29761.904 Hz
- **FIDRES:** 0.908261 Hz
- **RG:** 32
- **DW:** 16.800 µsec
- **OS:** 6.9000 sec
- **TS:** 300.3 K
- **D1:** 2.00000000 sec
- **Dil:** 0.03000000 sec
- **SL:** 16384
- **SI:** 125.7577733 MHz
- **LB:** 1.00 Hz
- **GB:** 0
- **PC:** 1.015

**Additional Details:**
- **CPDPAIR:** 13C
- **PI:** 9.86 µsec
- **PL1:** 0.50 dB
- **PL2:** 1.06 dB
- **PL12:** 16.50 dB
- **PL13:** 23.00 dB
- **PL2K:** 15.58318813 µsec
- **PL12X:** 0.43693921 µsec
- **SF02:** 500.1320005 Hz

**Other Data Points:**
- **Signal Assignments:** 13C NMR 125 MHz
- **Chemical Shifts:** 1H NMR 500 MHz
In this chapter we checked the biological properties of our newly synthesized iboga analogues (described in chapter 1b). Those iboga analogues were screened to check their opioidergic properties against mu- and kappa-opioid receptors. Anti-choline esterase activities were also studied using those iboga analogues.
Introduction

Ibogaine (1), a naturally occurring plant alkaloid with a history of use as a medicinal and ceremonial agent in West Central Africa, has been suspected to be effective in the cure of drug abuse (Figure 1).\(^1\) The National Institute on Drug Abuse (NIDA) has given considerable support to animal research, and the U.S. Food and Drug Administration (FDA) has approved Phase I studies in humans. Evidence for ibogaine’s effectiveness includes a substantial preclinical literature on reduced drug self-administration and withdrawal in animals, and case reports in humans. Relatively less financial inducement is available for its development by the pharmaceutical industry because ibogaine occurs naturally, and its chemical structure cannot be patented. This has left the academic society with a crucial role in research on ibogaine. Several groups have reported on the results of pharmacological screens of the receptor binding profile of ibogaine.\(^2\)\(^-\)\(^4\) Ibogaine has low micromolar affinities for multiple binding sites within the central nervous system, including N-methyl-D-aspartate (NMDA), \(\kappa\)- and \(\mu\)-opioid receptors, sodium channels, and the serotonin transporter. Ibogaine binds to opioid receptors with binding affinities in the range of 0.13 to 26 \(\mu\)M. It has also been reported that \(\kappa\)-opioid agonists reportedly can mimic certain effects of ibogaine, such as reduced cocaine and morphine self-administration.\(^5\)\(-\)\(^7\) Evidence for ibogaine’s effectiveness in animal models of addiction includes observations of reductions in self-administration of morphine or heroin,\(^8\)\(^-\)\(^10\) cocaine,\(^11\)\(^-\)\(^12\) and alcohol.\(^13\) Other iboga alkaloids e.g. ibogamine (2), noribogaine (3) have also been reported to reduce morphine and cocaine self-administration in rats for a period of a day or longer following a single \(i.p\) dose.\(^11\)

Apart from anti-addictive properties, scientists have extracted different iboga analogues and shown their cholinesterase properties. Cholinesterases (ChE’s) are key enzymes in a range of important areas such as neurobiology, toxicology and pharmacology. AChE, also known as true ChE, is present mainly in the central nervous system. In 2005, a group from Brazil extracted four iboga analogues viz., coronaridine (5), voacangine (6), ibogamine (2), ibogaine (1), and reported their anti-cholinesterase activity (Figure 2).\(^15\) Another group from China reported AChE activity of eight iboga analogues extracted from *Ervatamia hainanensis*, in 2010.\(^16\) They evaluated acetylcholinesterase (AChE) inhibition activities for all the extracted compounds, in which compound (5) exhibited the
same level of activities as galantamine, a marketed cholinesterase inhibitor for the treatment of Alzheimer’s disease.

Though ibogaine (1) has a wide range of pharmacological properties, however, it produces various dose dependent physical effects: tremor, nausea and vomiting, ataxia, dystonia, light sensibility and other also. In this connection, (-)-18-methoxycoronaridine (18 MC) (4) (Figure 1), a non-toxic iboga alkaloid congener was reported in 1996 by a team led by Glick and Kuehne. 18-Methoxycoronaridine is a selective inhibitor of the αβ4 nicotinic receptor whereas ibogaine affects many different neurotransmitter systems simultaneously.

Based on these reports, we were interested to study the following biological activities using our benzofuran-substituted iboga-analogues.

1) To study the binding activities against opioid receptors (Collaboration with Dr. Sumnatra Das, IICB).

2) Evaluation of anti-cholinesterasic activities.

Results and discussion

We synthesized several new iboga analogues (discussed in chapter 1b) using a general synthesis route and the structure of the compounds are shown in figure 3. The binding activities against opioid receptors were completely done at Indian Institute of Chemical Biology (IICB) and part of the results has been discussed here briefly.
a) Opioidergic Properties

The opioidergic properties of these compounds were determined by a competitive binding assay using $^{125}$I-Dynorphine and $^{125}$I-DAMGO for $\kappa$- and $\mu$- receptors, respectively. Strong activity against $\mu$- opioid receptor was noticed in case of compound (11a) with negligible interactions with $\kappa$- receptor. IC$_{50}$ of compound (11a) was found to be 1.2 $\mu$M. In order to carry out the structure activity relationship (SAR) analysis, we synthesized several other compounds based on the structure of compound (11a) (Figure 4). First, we replaced the benzofuran nucleus by a benzyli ring (14), and activity was not noticed in case of compound (14). Similarly, we replaced the N-C bond by a carbamate linkage (15) and tested its opioidergic property. Binding affinity was also absent in case of compound (15). We reduced the double bond present in compound (11a) and the compound (16) again has shown the binding affinity against $\mu$- opioid receptor. From this study, we came to know the minimum structural requirement of the pharmacophore for opioidergic activities which will be explored further to get more potent compound.

b) Anti-cholinesterasic Activities

The most widely used AChE assay is the Ellman method.\textsuperscript{14} This assay uses the thiol esters ATCh as well as a synthetic substrate instead of the oxy ester acetylcholine or butyrylcholine. AChE hydrolyzes the ATCh to produce thiocholine, which in turn reacts with dithiobisnitrobenzoate (DTNB)
to produce a yellow 5-thio-2-nitrobenzoic acid (TNB) (Scheme 1). The color intensity of the product is measured at 412 nm, and it is proportional to the enzyme activity.

Since, our analogues (synthesized in chapter 1b) have the structural similarities with those showing activity against acetylcholine esterase, we planned screen our sixteen new analogues (Figure 3) against AChE. They failed to exhibit any inhibitory activity even at 500 µM concentration.

Conclusion

Since some of the compounds were found to have high affinity for the µ-opioid receptors, these would be further screened for analgesic activity by tail-flick assay. Compounds having potential analgesic activity would be evaluated for cross tolerance with morphine. Though our synthesized compounds have good structural similarity with iboga family alkaloids, however, the benzofuran analogues did not show any activity against acetylcholine esterase. We are trying to synthesize more iboga analogues to obtain a novel acetylcholine esterase inhibitor.

References:


EXPERIMENTAL:

General write up of Experimental Section: As described in Chapter 1b.

Opioidergic properties

Animals

The experimental protocols using animals have been approved by the Institutional Animal Ethics Committee and meet the guidelines of the Government of India. For binding experiments adult albino Balb/c mice, 20–30 g were used. Animals were housed seven per cage at room temperature and allowed to adapt to laboratory conditions for at least 2 days before the initiation of any experiment. The animals were housed under a standard light dark cycle with free access to food and water, except during testing.

Cell culture and stable transfection

C6 cells were transfected with human κ-opioid receptor in pcDNA using Lipofectamine. Stably transfected G418-resistant cells were grown in F12 medium containing 10% fetal calf serum, 50 μg/mL gentamicin, pen strep and 50 μg/mL G418 in 5% CO2 at 37 °C.

Membrane preparation

For opioid receptor binding studies, membranes were prepared from both the stably transfected cell line (for κ-opioid receptor binding) and from mouse brain (μ-opioid receptor binding). Stably transfected C6 gliomas, as described above, were harvested in ice cold phosphate-buffered saline and homogenized in 50 mM Tris–HCl, pH 7.4. The total membrane (TM) fraction was collected upon centrifugation at 30,000g for 20 min.

In case of membrane from mouse brain, mice was sacrificed by decapitation, brain dissected out and homogenized in ice-cold 50 mM Tris–HCl buffer (pH 7.4) followed by centrifugation at 20,000 rpm for 30 min. The pellet was resuspended in the same buffer and incubated for 20 min at 37 °C followed by centrifugation as above. The pellet was resuspended in ice-cold buffer and used for binding assay. Protein concentration was determined by the method described by25 with bovine serum albumin used as standard.

Iodination of Dynorphin

For κ-opioid receptor binding experiments, dynorphin (DPDYN) was labeled with 125I-sodium iodide by chloramines T method. The reaction was initiated when 10 μL of chloramines T (0.002 g/mL) dissolved in a 0.2 M phosphate buffer (pH 7.4) was added to a vial containing 10 μL of the compound (0.001 g/mL) dissolved in 0.2 M phosphate buffer, 10 μL 0.2 M phosphate buffer and 1 mCi of NaI. After 40 sec of reaction, 40 μL of sodium bisulfate (0.002 g/mL) was added. The reaction
mixture was diluted to 8 mL with 0.1% aqueous trifluoroacetic acid (TFA) and absorbed in Sep-Pak. After rinsing with 20 mL of 0.1% aqueous TFA, the mixture of labeled and unlabeled compound were eluted out in a 1 mL solution containing 99.9% acetonitrile with 0.1% TFA. Finally, the labeled compound was separated from the unlabeled compound by reverse phase high performance liquid chromatography on a C18 column with elution with a mobile phase acetonitrile/TFA/water. Fractions corresponding to monoiodinated compound were pooled and used for subsequent studies.

Radioligand binding

For µ-opioid receptor binding, membrane homogenates (300 µg protein) were incubated for 2 h at 25 °C in 1 ml of 50 mM Tris-HCl (pH 7.4) containing 2 nM [3H] DAMGO ([3H] DAMGO, NaI were from PerkinElmer (Boston, MA)). in presence and absence of cold naloxone to determine specific binding. Following incubation, bound radioligand was collected by filtering under vacuum in a Millipore filtration manifold using glass-fiber filters (GF/B; Whatman, Clifton, NJ), pretreated with 0.5% PEI. The filters were washed thrice with ice-cold buffer and the radioactivities retained on filters were counted in a liquid scintillation counter (Wallac, model 1409-411, Perkin Elmer, USA).

Acetylcholinesterase activity

Brain homogenate (BH) solution

10% (by weight) Brain homogenate (BH) obtained from Dr. Sumantra Das, IICB Kolkata in 100 mM phosphate buffer (pH 8.0 + 0.5% Triton X-100). 1:10 dilutions with phosphate (PBS) buffer contain 10 mM MgCl₂ pH 7.0. 20 µL of BH solution was used for the following reaction.

Blank test

20 µL of above BH solution was taken in an eppendorf, followed by addition of 6 µL of DTNB solution of 1 mM stock. 170 µL of 100 mM phosphate buffer (pH 8.0) and 2.5 µL of AcTCl (1 mM stock) was added respectively. The mixture was incubated for 0.5 h. After vortex yellow color was developed in the solution within few minutes.

Positive test in the presence of 5 µM Eserine

20 µL of above BH solution was taken in an eppendorf, followed by addition of 6 µL of DTNB solution of 1 mM stock. Diluted with 170 µL of 100 mM phosphate buffer (pH 8.0) followed by addition of 1.0 µL Eserine (a known inhibitor) of 1 mM stock. 2.5 µL of AcTCl (1 mM stock) was added to the mixture and incubated for 0.5 h. After vortex yellow color was not developed even after few hours.

Test in the presence of iboga-analogues

Following above condition experiment was carried out using our new iboga analogues. Iboga analogues were dissolved in DMSO to prepare 1 mM and 100 mM stock solution. Acetylcholine esterase activity was studied at 10 µM and 500 µM concentration of iboga analogues. None of them is showing activity against acetylcholinesterase.