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Total synthesis of ibogaine, epiibogaine and their analogues

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ABSTRACT

Efficient total synthesis of ibogaine, epiibogaine and their analogues has been described. An intramolecular reductive-Heck type cyclization was used for the construction of seven-membered indoloazepine ring to access iboga-skeleton. Larock's heteroannulation reaction was employed for the creation of suitably substituted indole and Diels–Alder reaction was employed for the construction of the isoquinuclidine ring present in iboga alkaloids.

1. Introduction

Ibogaine (**2**) is a naturally occurring plant indole alkaloid of iboga family. To date about 80 structurally closely related monoterpenoid indole alkaloids belong to this family. Most of the iboga alkaloids were isolated from *Tabernanthe* or *Tabernaemontana* species of plants belonging to the Apocynaceae family.[1] Members of this class of alkaloids consist of a characteristic bridgehead nitrogen containing tricyclic framework by the fusion of seven-membered indoloazepine ring with a rigid isoquinuclidine ring (Fig. 1). Catharanthine (**4**) is another variant of the iboga alkaloids having a CO_2Me at the C16, which was isolated from *Catharanthus roseus*.[2] Ibogaine appears to be the most abundant and is a potent psychoactive substance among iboga alkaloids.

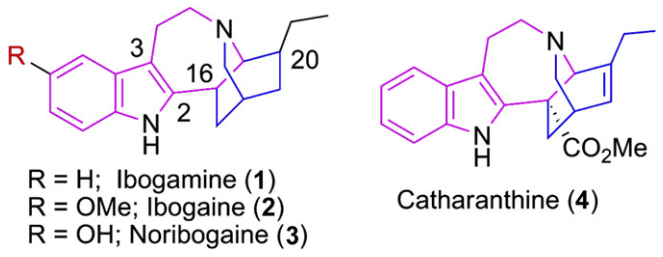

Fig. 1. Iboga alkaloids.

Ibogaine exhibits a wide range of pharmacological properties and it has been under active investigation as an anti-addictive agent.[3] Pharmacology of ibogaine is quite complex, affecting many different neurotransmitter systems simultaneously.[4] In metabolic pathway ibogaine undergoes demethylation to give noribogaine (**3**). The better pharmacological profile of ibogaine over ibogamine is due to the presence of methoxy group in 5-position of indole. However, in many cases high doses of ibogaine is required, which causes side effects[5] such as hallucinations, degeneration of cerebeller purkinje cells, whole body tremors and ataxia in rats. Apart from psychoactive properties, ibogaine and its congeners show a wide variety of pharmacological effects,[6] such as antifungal or antilipase, anti-HIV-1, anti-cholinesterasic and leishmanicide activities (against *Leishmania amazonensi*).

Until now only the total synthesis of ibogaine was reported by Buchi et al. in 1966.[7] Total synthesis of ibogamine and its analogues has been reported several times.[1] However, most of the synthesis suffers from several limitations such as less flexible to give other members and their analogues, low yielding, harsh reaction conditions and involves noncatalytic pathway. In the Büchi's synthesis of ibogaine, synthesis of cyclization precursor is a multistep process[7] and cyclization in hot acetic acid results in rearranged product formation. Trost's ibogamine synthesis via mixed Pd(II)–Ag(I) metal mediated cyclization[8] was low yielding and not economical as it required 1–2 equiv of palladium catalyst and 2–4 equiv of $AgBF_4$.

The unique structure of iboga alkaloids and their potential involvement in many biological activities has driven us to develop a unified strategy towards the total synthesis of iboga alkaloids and their analogues that might be useful for the evaluation of

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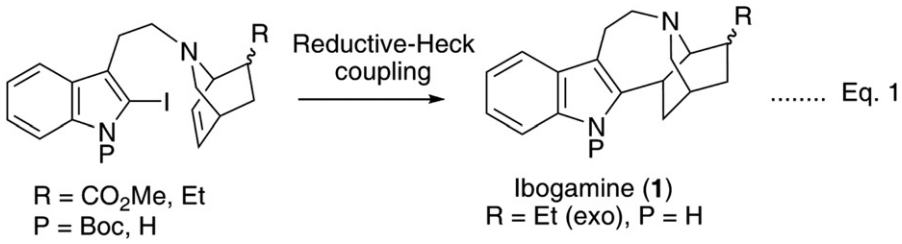
pharmacological profile. Recently, we have reported an efficient approach to the synthesis of ibogamine and its analogues (Eq. 1), employing reductive-Heck coupling as a key step.[9] In continuation of our interest in the synthesis of iboga alkaloids and their analogues employing Pd-catalysed reactions, herein, we report the extension of this strategy for the total synthesis of ibogaine, epiibogaine and their several analogues.



..... Eq. 1

2. Results and discussion

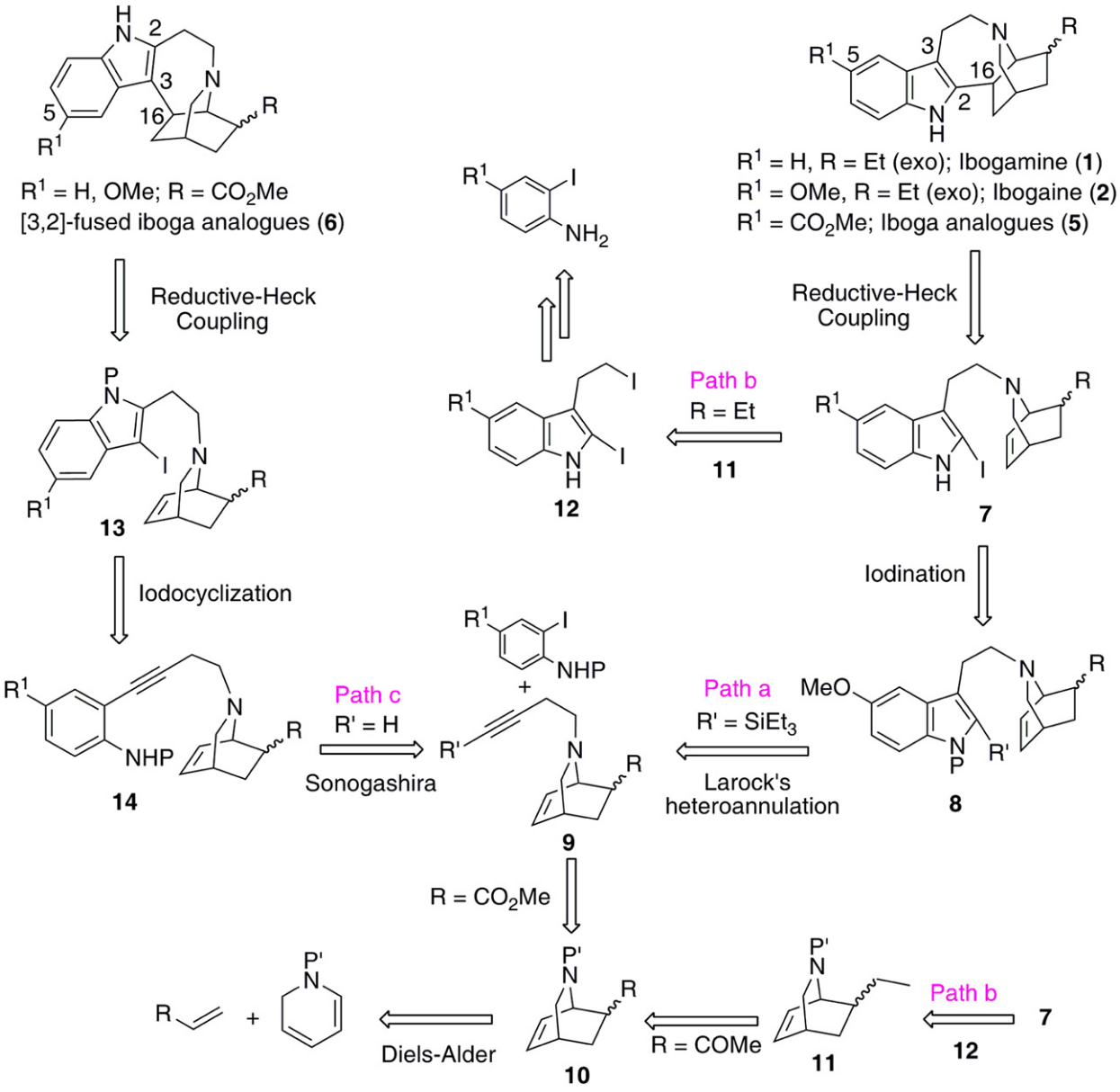
The structural feature present within iboga alkaloids that demanded immediate consideration of the bridged nitrogen containing tricyclic framework. This impressive fusion of six-, six- and seven-membered nitrogen containing rings was seen as the major hurdle towards the total synthesis. It was realized that the polycyclic framework could be drastically simplified via disconnection of the C2–C16 bond through the realization of reductive-Heck type cyclization to give 3-substituted indole **7**, since Heck coupling or oxidative-Heck coupling would lead to a highly strained bridgehead olefinic system (Scheme 1).[9] The cyclization precursor, a suitably 3-substituted indole **7** could be obtained either via convergent Larock's heteroannulation reaction[10] between isoquinuclidine substituted internal alkyne **9** and 2-iodoaniline followed by iodination (path a) or initial construction of the required substituted indole part **12** prior to the connection with isoquinuclidine ring **11** (path b). The required isoquinuclidine ring **10** could be readily obtained via Diels–Alder reaction between dihydropyridine and methyl acrylate or methyl vinyl ketone. On the other hand [3,2]-fused iboga analogues **6** could be realized through similar reductive-Heck coupling of suitably 2-substituted cyclization precursors **13**. The cyclization precursors, 3-iodo 2-substituted indoles **13** for the synthesis of [3,2]-fused iboga analogues **6**, could be efficiently obtained by iodocyclization of **14**. 2-Alkynyl anilines **14** can be easily synthesized by Sonogashira reaction of terminal alkynes **9** (when R′=H; path c) with 2-iodoaniline (Scheme 1).

For the synthesis of ibogaine and its analogues, the required Boc-protected 4-methoxy-2-iodoaniline **16** was synthesized according to Scheme 2. Reaction of *m*-iodophenol with diazonium salt of sulphanilic acid followed by reduction by sodium dithionite provided 4-hydroxy-2-iodoaniline in good yield,[11] which on methylation provided 4-methoxy-2-iodoaniline **15** in 54% yield from *m*-iodophenol. Boc protection of **15** gave **16** in 89% yield.

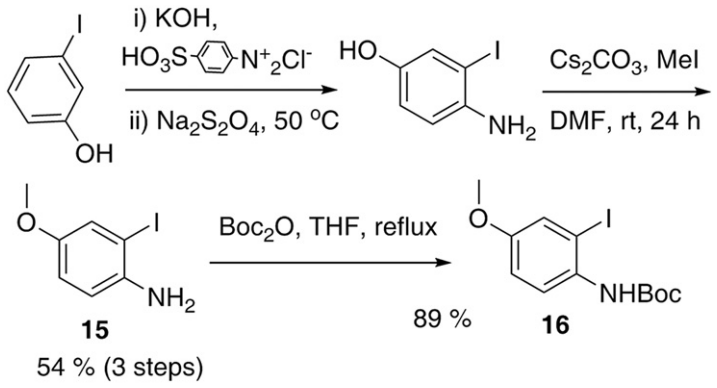
The heteroannulation reaction of **16** with isoquinuclidine containing internal alkyne **9a** at 90 °C provided 2,3-disubstituted indole **8a** in 72% yield.[10b] The internal alkynes **9a** and **9b** were prepared from Cbz-protected dihydropyridine following the reported procedure.[10b] Iodination of **8a** using 1.2 equiv of ICl resulted in an inseparable mixture of mono and diiodinated products **7a** and **7b** without full consumption of starting material (Scheme 3). Formation of such diiodo product was not observed previously, when 5-position of indole was unsubstituted.[9] Methoxy group in the 5-position of indole of **8a** makes 6-position more electron rich leading to diiodinated product formation. We used excess ICl (2.5 equiv) for full consumption of the starting material **8a**, keeping in mind that inseparable mixture of mono and diiodinated products will be used in the next reductive-Heck cyclization step, which may not hamper the cyclization process. The inseparable mixture of monoiodinated product **7a** and diiodinated product **7b**, which mostly contain the diiodinated product **7b** was then subjected for the reductive-Heck coupling reaction. Reductive-Heck coupling of this mixture provided the desired product **5a** in very good yield. Another expected cyclized product **5c** was inseparable from some other unidentified products. Although we could not take a clean ^{1}H NMR of **5c** but mass spectra of column collected fraction indicated the presence of product **5c** in the product mixture. It is worth to mention here that **7a** was the major component in the mixture of **7a** and **7b**, after cyclization, the desired product **5a** became the major component in the mixture of products, which implies that under reductive-Heck coupling condition, the diiodo compound **7b** underwent cyclization at the 2-position of indole and at the same time it underwent deiodination at the 6-position of indole (Scheme 3). Addition of catalyst (10 mol%), PPh_3 (20 mol%) and reducing agent (2 equiv) in two batches gave 58% yield of iboga analogue **5a**. Using the same reaction sequence C19-*endo*-carbomethoxy substituted iboga analogue **5b** was obtained in 26% overall yield from Boc-protected 4-methoxy-2-iodoaniline **16**. In case of iodination of **8b** with 2.2 equiv of ICl, we isolated mostly the diiodinated compound **7c**. Reductive-Heck coupling of **7c** gave desired *endo*-carbomethoxy substituted iboga analogue **5b** in 53% yield. Another expected cyclized product **5d** was detected only by mass spectra as it was inseparable from some other unidentified products (Scheme 3).

Based on our experience while synthesizing ibogamine,[9] we realized that the replacement of carbomethoxy side chain (R=CO_2Me) in isoquinuclidine substituted internal alkyne **9** by ethyl side chain (R=Et) failed to give the heteroannulation product **8c** according to 'path a' (Scheme 4). Thus we followed 'path b' (Scheme 1) for the synthesis of ibogaine (**2**) and epiibogaine (**2a**) where initial construction of the required substituted indole part **12** prior to the connection with isoquinuclidine ring **11** is considered (Scheme 5).

Heteroannulation reaction of 4-methoxy-2-iodoaniline **15** with disilylated alkyne **18** afforded 5-methoxy-2,3-disubstituted indole **19a** and mono desilylated indole **19b** in very good yields. Iodination of **19a** by NIS[12] followed by silyl deprotection using TBAF afforded 5-methoxy-2-iodotryptol **20**, which was immediately iodinated and purified to obtain 5-methoxy-2-iodotryptoyl iodide **12b** in 58% yield from **19a**. Compound **19b** was converted to **19a** as iodination

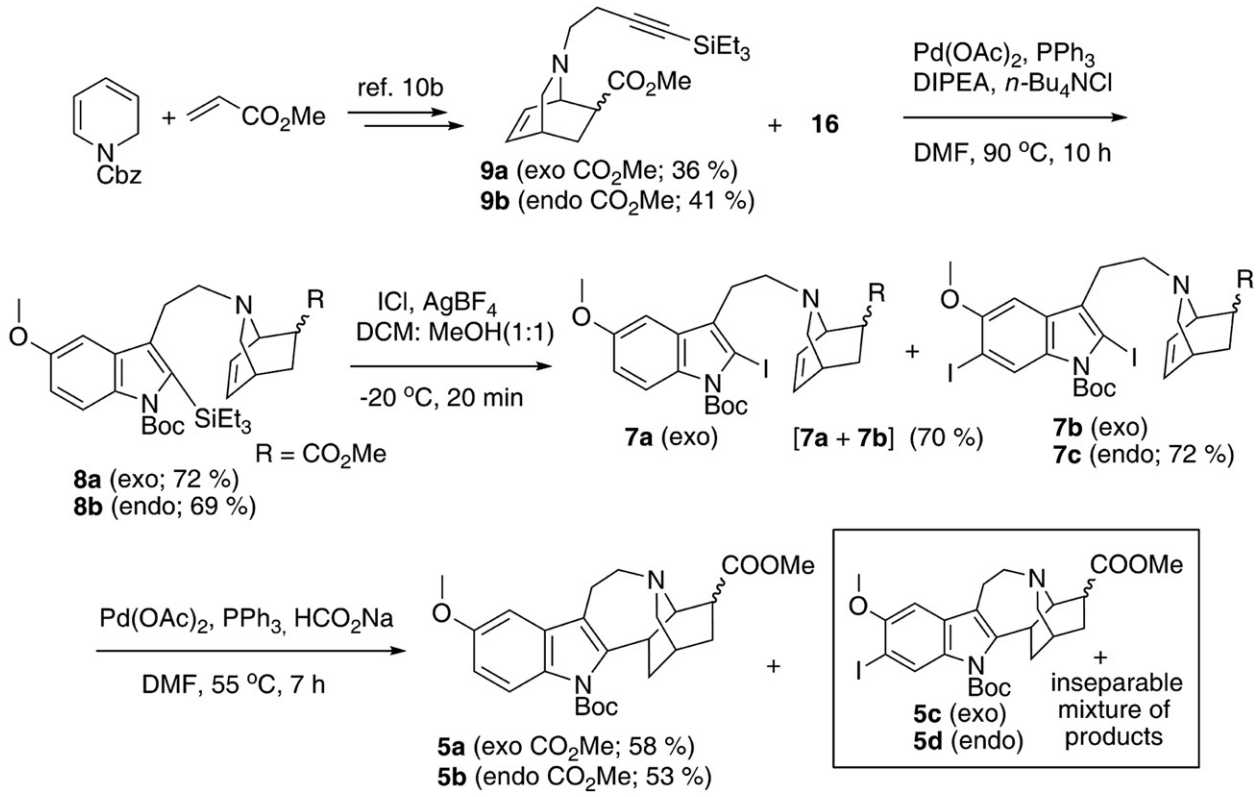


Scheme 1. Retrosynthetic analysis.

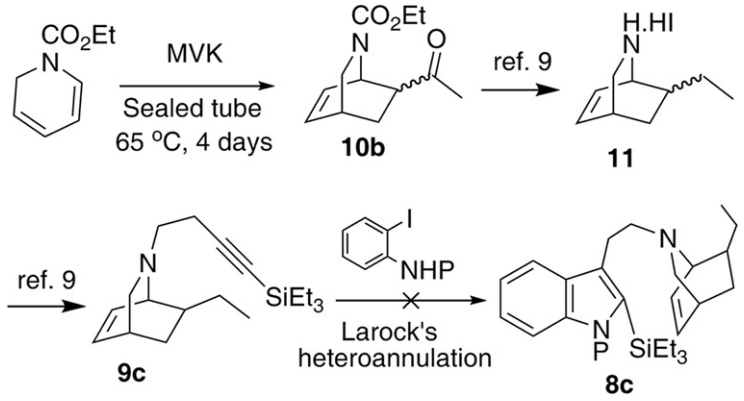


Scheme 2. Synthesis of Boc-protected 4-methoxy-2-iodoaniline.

of **19b** by NIS was not clean. The reaction between isoquinuclidine amine **11** and 5-methoxy-2-iodotryptoyl iodide **12b** in acetonitrile using K_2CO_3 as a base was not clean.[9] We isolated the undesired product **21** in 28% yield, where yield of the cyclization precursors **7d** and **7e** was low (Scheme 5). To avoid the cyclopropane ring formation at 3-position of indole, we tried several other conditions by changing the reaction parameters such as temperature, solvents and bases but in all the cases the reaction was not satisfactory.



Scheme 3. Synthesis of methoxy substituted [2,3]-fused iboga analogues.

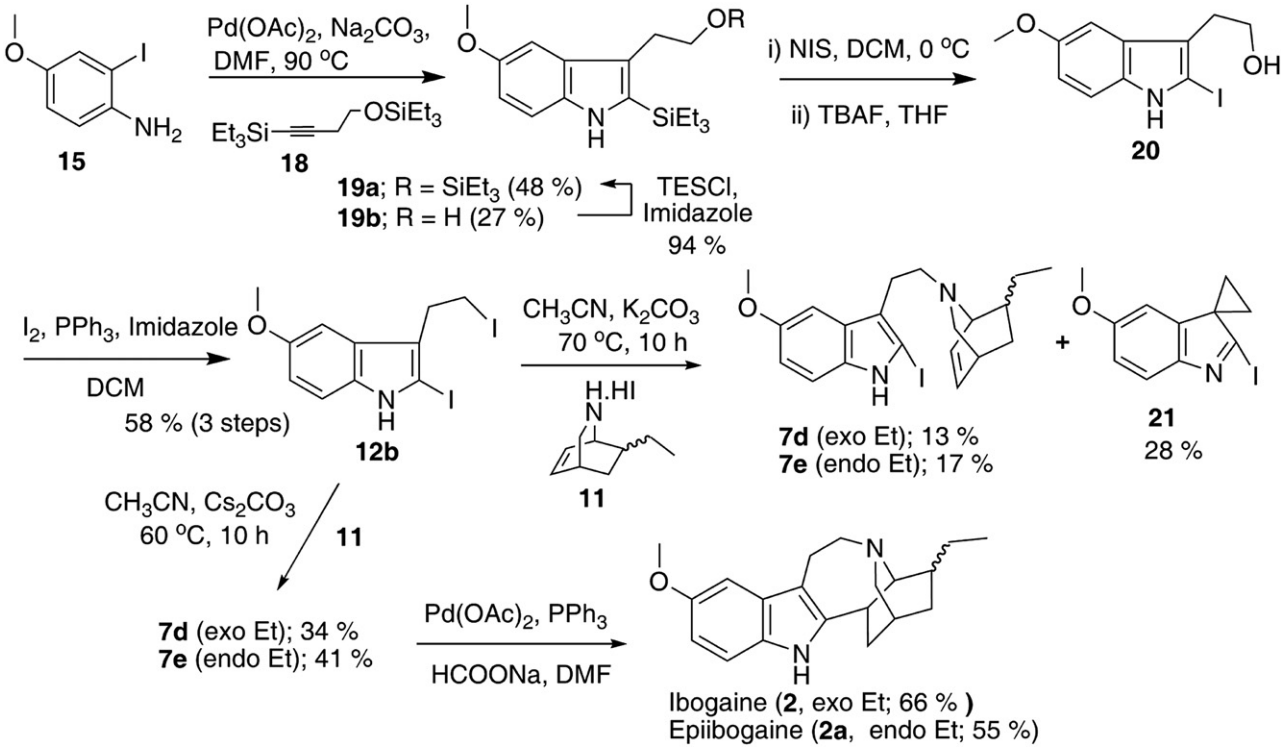


Scheme 4. Initial attempt to the synthesis of ibogamine precursor.

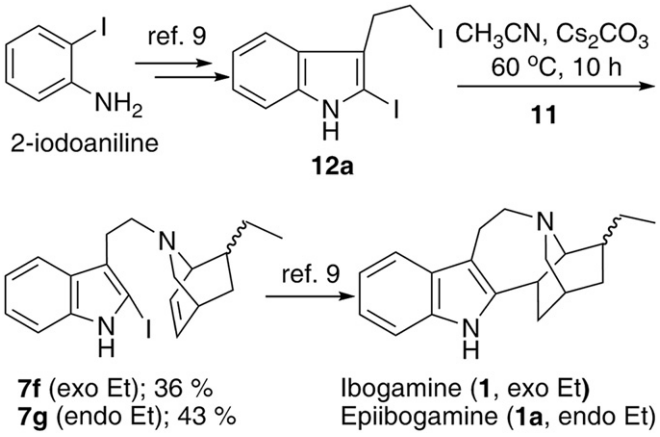
Finally, using Cs_2CO_3 as a base, we were able to suppress the formation of undesired product **21**. The cyclization precursors **7d** and **7e** were obtained in 34% and 41% yields, respectively. Reductive-Heck coupling of **7d** and **7e** was carried out separately in DMF and obtained ibogaine (**2**) and epiibogaine (**2a**) in 66% and 55% yields, respectively (Scheme 5). Such a clean and good conversion in the synthesis of cyclization precursors **7d** and **7e** from **12b** using Cs_2CO_3 as a base prompted us to revise the similar step in the synthesis of cyclization precursors for the synthesis of ibogamine and epiibogamine.[9] A better yield of cyclization precursors **7f** (36%) and **7g** (43%) was obtained from compound **12a** than earlier (**7f**: 27% and **7g**: 35%) when K_2CO_3 was used as a base[9] (Scheme 6).

After the synthesis of ibogaine and epiibogaine, we were interested in the synthesis of [3,2]-fused iboga analogues by applying the reductive-Heck coupling reaction according to 'path c' (Scheme 1). Sonogashira coupling between Boc-protected 2-iodoaniline and isoquinuclidine containing terminal alkyne **9d** afforded 2-alkynyl aniline **14a** in excellent yield. Attempted Larock's iodocyclization of compound **14a** failed to give the desired product 2-substituted 3-iodo indole[13] **13a** (Scheme 7). By changing solvent (such as CH_3CN, DCM, $CHCl_3$), base (K_2CO_3, $NaHCO_3$, TBAF) and the iodinating agent (I_2, ICl, NIS) we were not able to get the desired product **13a** in satisfactory yield.

To obtain the 3-iodo cyclization precursor, we followed a slightly different synthetic route discussed in Scheme 8. One-pot Sonogashira reaction between Boc-protected 2-iodoaniline and terminal alkyne **9d** followed by TBAF mediated indolization in DMF afforded 2-substituted indole **22a** in 66% yield.[14] TFA-mediated Boc-deprotection of **22a** followed by iodination using NIS in DCM provided the desired 3-iodo cyclization precursor **13b**



Scheme 5. Synthesis of ibogaine and epiibogaine.



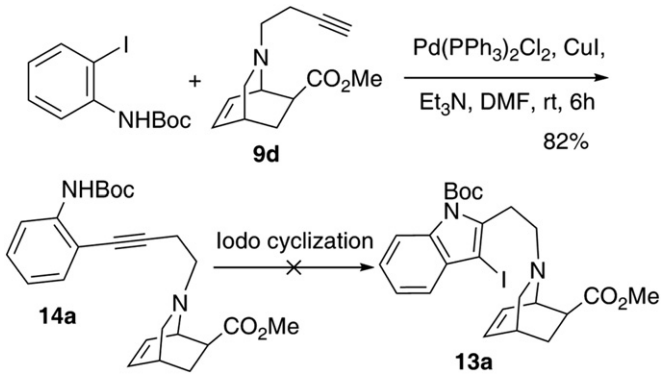
Scheme 6. Revised synthesis of ibogamine and epiibogamine precursors.

in excellent yield. The cyclization precursor **13b** was then subjected to reductive-Heck coupling condition[9] and obtained [3,2]-fused iboga analogue **6a** in 78% yield. With this success in the synthesis of **6a** using reductive-Heck coupling, we were interested to the synthesis of several other [3,2]-fused iboga analogues using the similar reaction sequence. Accordingly, C19-*endo*-carbomethoxy substituted [3,2]-fused iboga analogue **6b** was synthesized in 36% overall yield from isoquinuclidine alkyne **9e** (Scheme 8).

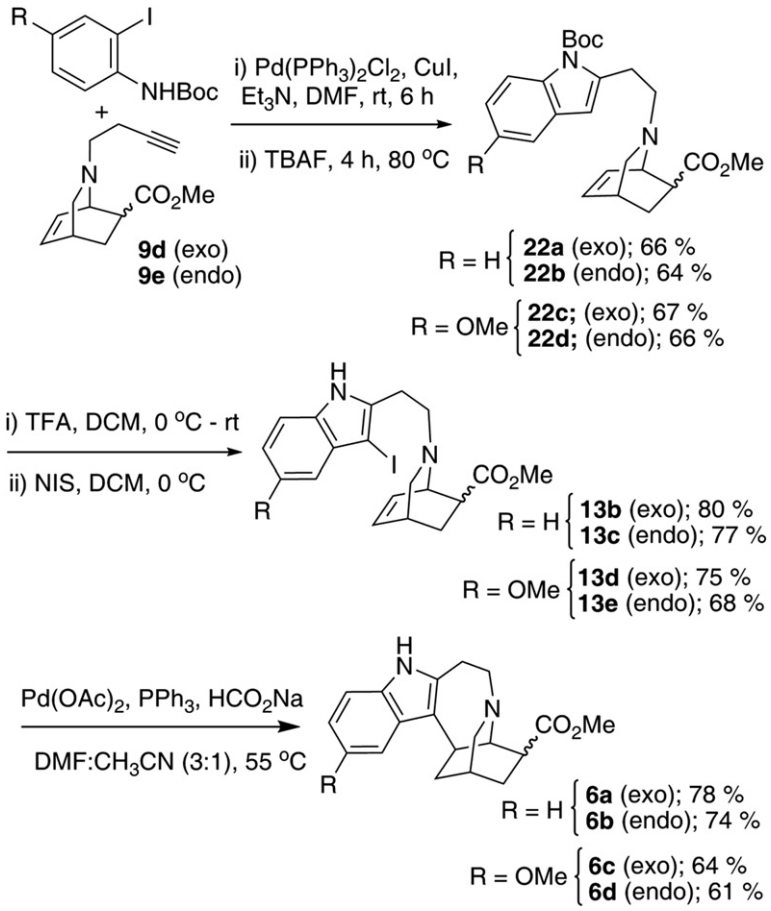
Following the same strategy, methoxy substituted [3,2]-fused iboga analogues **6c** and **6d** were synthesized from Boc-protected 4-methoxy-2-iodoaniline in good yields (Scheme 8). One-pot Sonogashira and indolization reaction between Boc-protected 4-methoxy-2-iodoaniline and isoquinuclidine containing terminal alkynes **9d** and **9e** separately afforded 2-substituted indoles **22c** and **22d** in 67% and 66% yields, respectively. Boc-deprotection followed by iodination using NIS in DCM of **22c** and **22d** provided the 3-iodo cyclization precursors **13d** and **13e** in very good yields. Finally, reductive-Heck cyclization of **13d** and **13e** furnished methoxy substituted [3,2]-fused iboga analogues **6c** and **6d** in 64% and 61% yields, respectively.

3. Conclusions

An efficient synthetic strategy towards the total synthesis of ibogaine, epiibogaine and their analogues has been described. Larock's heteroannulation reaction was employed for the construction of suitably substituted indole. An intramolecular reductive-Heck type cyclization was used for the construction of seven-membered indoloazepine ring to access iboga-skeleton. Diels–Alder reaction was employed for the construction of the isoquinuclidine ring, a unique skeleton of iboga alkaloids. Most of the steps involve Pd-catalysed reaction and are very mild and efficient. Starting from 4-methoxy-2-iodoaniline, ibogaine **2** (9.8%)



Scheme 7. An attempt to the synthesis of cyclization precursor for [3,2]-fused analogue.



Scheme 8. Synthesis of [3,2]-fused iboga analogues.

and epiibogaine **2a** (9.7%) were obtained in overall 19.5% yield. The overall yield of [3,2]-fused iboga analogues was 27–41%.

4. Experimental section

4.1. General

All reagents were purchased from commercial sources and used without further purification, unless otherwise stated. All reactions were carried out in oven-dried glassware under an argon atmosphere using anhydrous solvents, standard syringe and septum techniques unless otherwise indicated. Petroleum ether (PE) refers to the fraction of petroleum boiling between 60 and 80 °C. Organic extracts were dried over anhydrous Na_2SO_4 and then filtered prior to removal of all volatiles under reduced pressure on rotary evaporation. Chromatographic purification of products was accomplished using column chromatography on silica gels (mesh 100∼200). Thin-layer chromatography (TLC) was carried out on aluminium sheets, Silica Gel 60 F254 (Merck; layer thickness 0.25 mm). Visualization of the developed chromatogram was performed by UV light and/or vanillin stains. All melting points were uncorrected. Peak positions in ^1H and ^{13}C NMR spectra are indicated in parts per million (ppm) downfield from internal TMS in δ units. Unless otherwise indicated NMR spectra were taken in

$CDCl_3$ solution at 300 and 500 MHz for ^1H and 75 and 125 MHz for ^{13}C NMR. IR spectra were reported in absorption frequency (cm^{-1}). Mass spectra were recorded by Electron Spray Ionization (ESI) or Electronic Impact (EI). The parent ions $[M+H]^{+\bullet}$, $[M+Na]^{+\bullet}$ are quoted.

*4.1.1. tert-Butyl 2-iodo-4-methoxyphenylcarbamate (**16**).* *m*-Iodophenol (5.5 g, 25 mmol) was dissolved in water containing KOH (1.4 g, 25 mmol). A cold solution of diazotized sulfanilic acid (5.1 g, 27.5 mmol) was added to the mixture with stirring at rt for 30 min followed by the addition of sodium hydrosulfite (12 g, 69 mmol). The colour of the solution was changed immediately upon the addition of sodium hydrosulfite and the solution was stirred at 45 °C for 20 min. Diethyl ether was added to the mixture, the mixture was filtered and the filtrate was concentrated. The solid was recrystallized from hot water to yield needles. Methyl iodide was added (0.98 mL, 15.7 mmol) to 4-amino-3-iodophenol (3.71 g, 15.8 mmol) in DMF (70 mL) in the presence of Cs_2CO_3 (13.45 g, 41.3 mmol). The reaction was left at rt for 48 h. The mixture was then diluted with water, extracted with diethyl ether, the combined organic extracts were washed with water, dried over Na_2SO_4, filtered and concentrated. The product was purified by silica gel column chromatography (PE/EtOAc 9:1) and obtained 4-methoxy-2-iodoaniline (**15**) as a light brown oil (3.36 g, 54%) from *m*-iodophenol.

To a solution of 4-methoxy-2-iodoaniline (3.0 g, 12.0 mmol) in THF (20 mL) was added di-*tert*-butyl dicarbonate (3.15 g, 14.5 mmol). The reaction mixture was refluxed for 2 days then quenched with water (15 mL). The solution was extracted with Et_2O (3×20 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated. The crude mixture was purified by silica gel column chromatography (2% EtOAc in PE) to yield *N*-Boc-2-iodo-4-methoxy aniline as a light brown solid (3.72 g, 89%). ^1H NMR (500 MHz, $CDCl_3$, δ): 7.82 (s, 1H), 7.29 (d, J=3.0 Hz, 1H), 6.88 (dd, J=9.0, 3.0 Hz, 1H), 6.53 (s, 1H), 3.75 (s, 3H), 1.52 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 156.21, 153.21, 132.54, 123.89, 122.24, 115.05, 80.87, 55.85, 28.48; IR (KBr, cm^{-1}): 3322, 2983, 1718; HRMS (ESI): $(M+Na)^+$ calcd for $C_{12}H_{16}INNaO_3^+$ 372.0067, found 372.0071.

*4.1.2. Methyl 2-(2-(1-(tert-butoxycarbonyl)-5-methoxy-2-(triethylsilyl)-1H-indol-3-yl)ethyl)-2-azabicyclo[2.2.2]oct-5-ene-7-carboxylate (**8a**).* Following the reported procedure,[10b] except slightly elevated temperature (90 °C), the 2,3-disubstituted indole **8a** was obtained as a light brown sticky material (304 mg, 72%). R_f=0.38 (PE/EtOAc 9:1); ^1H NMR (500 MHz, $CDCl_3$, δ): 7.80 (d, J=9.5 Hz, 1H), 6.93 (d, J=2.5 Hz, 1H), 6.88 (dd, J=9.5, 2.0 Hz, 1H), 6.47 (t, J=7.5 Hz, 1H), 6.23 (t, J=7.0 Hz, 1H), 3.93 (m, 1H), 3.87 (s, 3H), 3.76 (s, 3H), 3.27 (dd, J=9.5, 2.0 Hz, 1H), 2.90 (dt, J=12.5, 5.0 Hz, 1H), 2.76 (dt, J=12.5, 5.0 Hz, 1H), 2.56 (m, 2H), 2.48 (td, J=10.5, 3.0 Hz, 1H), 2.36 (dt, J=12.5, 5.0 Hz, 1H), 2.22 (m, 2H), 1.95 (m, 1H), 1.67 (s, 9H), 1.42 (m, 1H), 0.95 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 175.08, 155.59, 151.51, 135.37, 135.18, 132.86, 132.58, 131.72, 129.82, 116.03, 113.06, 101.71, 83.32, 59.47, 56.01, 55.20, 55.06, 51.86, 45.66, 31.23, 28.38, 25.20, 24.41, 8.27, 5.59; IR (neat, cm^{-1}): 2929, 1726, 1105, 729; HRMS (ESI): $(M+H)^+$ calcd for $C_{31}H_{47}N_2O_5Si^+$ 555.3249, found 555.3248.

*4.1.3. Methyl 2-(2-(1-(tert-butoxycarbonyl)-2-iodo-5-methoxy-1H-indol-3-yl)ethyl)-2-azabicyclo [2.2.2]oct-5-ene-7-carboxylate (**7a**) and methyl 2-(2-(1-(tert-butoxycarbonyl)-2,6-diiodo-5-methoxy-1H-indol-3-yl)ethyl)-2-azabicyclo[2.2.2]oct-5-ene-7-carboxylate (**7b**).* To a cooled solution (−20 °C) of compound **8a** (277 mg, 0.5 mmol) in DCM and MeOH (1:1) (4 mL) was added silver tetrafluoroborate (152 mg, 0.55 mmol) followed by dropwise addition of ICl (1.2 mL 1 M in DCM) under argon atmosphere. After 20 min of stirring the ice-salt bath was removed and DCM (10 mL) was added. The organic layer was washed with aq $Na_2S_2O_3$ solution and brine. The organic part was dried over anhydrous Na_2SO_4 and concentrated in vacuo, purified by silica gel column chromatography (PE/EtOAc 9:1) to obtain inseparable mixture (≈3:2) (214 mg,) of compounds **7a** and **7b** as light brown foam. [Mono+di]iodo (≈3:2): R_f ≈0.31 (PE/EtOAc 5:1); ^1H NMR (500 MHz, $CDCl_3$, δ): 8.45 (s, 1H-di), 7.87 (d, J=9.5 Hz, 1H-mono), 6.81 (d, J=2.5 Hz, 1H-di), 6.75 (s, 1H-mono), 7.73 (dd, J=9.5, 2.5 Hz, 1H-di), 6.38 (t, J=7.0 Hz, 1H), 6.18 (t, J=7.0 Hz, 1H), 3.85 (s, 3H-mono), 3.78 (s, 3H-di), 3.60 (s, 3H-mono), 3.57 (s, 3H-di), 3.18 (m, 1H), 2.72 (m, 1H), 2.62 (m, 1H), 2.50 (m, 2H), 2.37 (m, 1H), 2.24 (m, 1H), 2.12 (m, 1H), 1.88 (m, 1H), 1.62 [m, (18H+1H)], 1.35 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 175.05, 174.95, 155.86, 154.07, 149.53, 149.17, 135.35, 135.31, 133.72, 133.05, 130.87, 130.68, 130.11, 130.07, 127.92, 127.80, 126.56, 116.57, 112.81, 111.24, 99.17, 85.48, 84.90, 82.82, 79.69, 79.12, 57.08, 57.01, 56.92, 55.93, 55.45, 55.32, 54.99, 51.88, 45.48, 45.41, 31.25, 28.51, 28.45, 27.30, 27.20, 24.52.

*4.1.4. C19-exo-Carbomethoxy-substituted iboga analogue (**5a**).* To a mixture of compounds **7a** and **7b** (122 mg, ≈0.20 mmol) in dry DMF (2 mL) was added HCOONa (27 mg, 0.4 mmol) under argon atmosphere. The mixture was degassed and back-filled with argon then $Pd(OAc)_2$ (4.5 mg, 10 mol %) and PPh_3 (10.5 mg, 20 mol %) were added with stirring at 55 °C. After 3 h another batch of $Pd(OAc)_2$ (4.5 mg, 10 mol %), PPh_3 (10.5 mg, 20 mol %) and HCOONa (27 mg, 0.4 mmol) were added to the reaction mixture, stirred for another 4 h at that temperature. Solvent was removed in vacuo then H_2O (2 mL) and ethyl acetate (4 mL) were added to the residue. The aqueous phase was extracted with ethyl acetate (2×4 mL), the combined organic extracts were washed with brine (4 mL), dried (Na_2SO_4). The solvent was removed in vacuo and the crude material was purified by column chromatography (PE/EtOAc 5:1) to afford the desired iboga analogue **5a** (51 mg, 58%) as light yellow foam. The other expected cyclized product **5c** was inseparable from impurities. R_f=0.34 (PE/EtOAc 3:1); ^1H NMR (500 MHz, $CDCl_3$, δ): 7.86 (d, J=9.0 Hz, 1H), 6.84 (s, 1H), 6.82 (dd, J=9.0, 2.5 Hz, 1H), 3.96 (q, J=5.5 Hz, 1H), 3.85 (s, 3H), 3.71 (s, 3H), 3.50 (s, 1H), 3.25–3.10 (m, 4H), 2.99 (m, 1H), 2.76 (m, 1H), 2.62 (m, 1H), 2.34 (m, 1H), 2.25 (m, 1H), 2.0 (m, 1H), 1.71 (m, 2H), 1.67 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 175.38, 155.93, 150.60, 143.98, 131.40, 129.90, 117.16, 116.32, 111.80, 101.01, 83.63, 56.77, 55.87, 53.61, 51.98, 50.76, 46.70, 37.80, 34.23, 28.47, 26.19, 25.61, 20.77; IR (neat, cm^{-1}): 2973, 1734, 1718, 1132; HRMS (ESI): $(M+H)^+$ calcd for $C_{25}H_{33}N_2O_5^+$ 441.2384, found 441.2384.

*4.1.5. Methyl 2-(2-(1-(tert-butoxycarbonyl)-5-methoxy-2-(triethylsilyl)-1H-indol-3-yl)ethyl)-2-azabicyclo[2.2.2]oct-5-ene-7-carboxylate (**8b**).* Compound **8b** (214 mg, 69%) was synthesized following the procedure described for the synthesis of 2,3-disubstituted indole **8a**. R_f=0.31 (PE/EtOAc 4:1); ^1H NMR (500 MHz, $CDCl_3$, δ): 7.81 (d, J=9.0 Hz, 1H), 6.99 (s, 1H), 6.89 (dd, J=9.0, 2.5 Hz, 1H), 6.43 (t, J=7.0 Hz, 1H), 6.18 (m, 1H), 3.89 (m, 1H), 3.86 (s, 3H), 3.65 (s, 3H), 3.15 (m, 1H), 3.04–2.91 (m, 3H), 2.70 (dt, J=12.5, 5.0 Hz, 1H), 2.63 (m, 1H), 2.48 (dt, J=12.0, 5.0 Hz, 1H), 2.16 (dd, J=7.5, 2.0 Hz, 1H), 1.81 (m, 1H), 1.74 (m, 1H), 1.67 (s, 9H), 0.95 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 174.62, 155.65, 151.52, 135.39, 134.76, 132.80, 132.61, 131.44, 129.90, 116.10, 113.24, 101.63, 83.42, 59.35, 56.06, 54.57, 51.88, 43.72, 30.96, 29.84, 28.52, 26.29, 25.12, 8.29, 5.68; IR (neat, cm^{-1}): 2951, 1726, 1105, 729; HRMS (ESI): $(M+H)^+$ calcd for $C_{31}H_{47}N_2O_5Si^+$ 555.3249, found 555.3249.

4.1.6. Methyl 2-(2-(1-(tert-butoxycarbonyl)-2,6-diiodo-5-methoxy-1H-indol-3-yl)ethyl)-2-azabicyclo[2.2.2]oct-5-ene-7-carboxylate

(***7c***). Only the diiodinated compound **7c** (122 mg, 72%) was obtained exclusively as light brown foam according to the procedure described for the iodination of compound **8a**. R_f=0.28 (PE/EtOAc 3:1); ^{1}H NMR (500 MHz, $CDCl_3$, δ): 8.46 (s, 1H), 6.93 (s, 1H), 6.45 (t, *J*=7.0 Hz, 1H), 6.15 (m, 1H), 4.02 (br s, 1H), 3.87 (s, 3H), 3.58 (s, 3H), 3.21 (m, 1H), 3.14 (d, *J*=10.0 Hz, 1H), 2.90 (dt, *J*=11.5, 5.5 Hz, 1H), 2.84 (dt, *J*=11.0, 5.0 Hz, 1H), 2.71 (dt, *J*=11.5, 5.0 Hz, 1H), 2.66 (br s, 1H), 2.45 (dt, *J*=11.5, 5.0 Hz, 1H), 2.15 (td, *J*=10.0, 2.5 Hz, 1H), 1.81 (m, 1H), 1.70 (m, 1H), 1.63 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 173.80, 154.18, 149.01, 135.77, 133.57, 130.59, 128.83, 126.55, 99.11, 85.55, 82.97, 79.66, 56.93, 55.99, 53.94, 53.58, 53.48, 52.00, 42.37, 30.42, 28.34, 25.87; IR (neat, cm^{-1}): 2953, 1725, 1105, 728; HRMS (ESI): $(M+H)^+$ calcd for $C_{25}H_{31}I_2N_2O_5^+$ 693.0317, found 693.0319.

*4.1.7. C19-endo-Carbomethoxy substituted iboga analogue (**5b**).* Fol lowing the procedure described for the cyclization of a mixture of **7a** and **7b**, compound **7c** (1.5 g, 2.94 mmol) afforded iboga analogue **5b** (26 mg, 53%) as light brown foam. R_f=0.26 (PE/EtOAc 3:1); ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.95 (dd, *J*=8.0, 2.5 Hz, 1H), 6.85 (s, 1H), 6.83 (dd, *J*=8.0, 2.5 Hz, 1H), 3.85 (s, 3H), 3.78 (m, 1H), 3.67 (s, 3H), 3.41 (s, 1H), 3.36 (m, 1H), 3.24–3.17 (m, 3H), 3.05 (m, 2H), 2.68 (d, *J*=11.0 Hz, 1H), 2.30 (m, 1H), 2.12 (m, 1H), 2.02 (m, 1H), 1.92 (m, 1H), 1.67 (m, 1H), 1.64 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 173.34, 156.17, 150.29, 141.55, 130.30, 130.03, 117.68, 116.60, 112.68, 100.72, 84.28, 55.91, 55.81, 54.80, 52.33, 52.22, 42.80, 33.19, 32.14, 28.37, 25.55, 21.75, 20.19; IR (neat, cm^{-1}): 2971, 1732, 1716, 1134; HRMS (ESI): $(M+H)^+$ calcd for $C_{25}H_{33}N_2O_5^+$ 441.2384, found 441.2382.

*4.1.8. 5-Methoxy-2-(triethylsilyl)-3-(2-(triethylsilyloxy)ethyl)-1H-indole (**19a**).* A dry flask was charged with 4-methoxy-2-iodoaniline (1.13 g, 4.56 mmol), disilylated alkyne **18** (1.63 g, 5.48 mmol), palladium(II)acetate (101 mg, 0.456 mmol), Na_2CO_3 (1.43 g, 13.68 mmol) and DMF (12 mL) under argon atmosphere and heated at 90 °C for 8 h. DMF and volatiles were removed in vacuo. Ethyl acetate (15 mL) and water (15 mL) were added to the residue. The aqueous phase was extracted with ethyl acetate (3×15 mL). The combined organic extract was washed with 5% $NaHCO_3$ (20 mL) and brine (30 mL), and solvent was removed by rotary evaporation. The crude product was purified by silica gel column chromatography (PE/EtOAc) to give indole **19a** (918 mg, 48%) as a light brown oil and **19b** (376 mg, 27%) as a light brown sticky material.

To a stirred solution of **19b** (305 mg, 1 mmol) and imidazole (340 mg, 5 mmol) in DCM (4 mL) was added TESCl (251.7 mL, 1.5 mmol) under argon atmosphere at 0 °C. Stirring was continued for another 2 h at 0 °C then the reaction was quenched with ice-water, organic part was separated, dried over Na_2SO_4, the solvent was removed by rotary evaporation. The crude product was purified by silica gel column chromatography to give indole **19a** (394 mg, 94%) as a light brown oil. R_f=0.52 (PE/EtOAc 25:1). ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.73 (s, 1H), 7.16 (dd, *J*=8.5, 2.5 Hz, 1H), 6.97 (d, *J*=2.0 Hz, 1H), 6.76 (dd, *J*=8.5, 2.5 Hz, 1H), 3.78 (s, 3H), 3.72 (t, *J*=7.5 Hz, 3H), 3.00 (t, *J*=7.5 Hz, 3H), 0.92 (m, 18H), 0.80 (q, *J*=8.0 Hz, 6H), 0.56 (q, *J*=8.0 Hz, 6H); IR (neat cm^{-1}): 3398, 2955, 1620, 736; HRMS (ESI): $(M+H)^+$ calcd for $C_{23}H_{42}NO_2Si_2^+$ 420.2749, found 420.2748.

*4.1.9. 2-Iodo-3-(2-iodoethyl)-5-methoxy-1H-indole (**12b**).* To a cooled (0 °C) solution of compound **19a** (868 mg, 2.06 mmol) in dry DCM (15 mL) was added NIS (558 mg, 2.48 mmol) under argon atmosphere. Stirring was continued for 40 min at 0 °C. DCM (10 mL) was added to the reaction mixture and washed with aq $Na_2S_2O_3$ solution and brine. The organic part was dried over anhydrous Na_2SO_4 and concentrated in vacuo to give 1.1 g of crude product, which was used in the next step without purification.

To the above crude product (1 g) in dry THF (10 mL) was added TBAF (4 mL, 1 M in THF) under argon atmosphere at 0 °C and stirring was continued for 2 h at 0 °C. Then the reaction was quenched with saturated aq NH_4Cl solution, extracted with Et_2O (2×20 mL). The combined organic extracts were dried over Na_2SO_4, the solvent was removed in vacuo to give the crude product **20** (541 mg), which was used in the next step without purification.

To a stirred solution of above crude product **20** (500 mg) in DCM (5 mL) were added imidazole (245 mg, 3.6 mmol), PPh_3 (471 mg, 1.8 mmol) and I_2 (457 mg, 1.8 mmol) at 0 °C. Stirring was continued for 4 h at 0 °C. The reaction mixture was diluted with DCM followed by washing with aq $Na_2S_2O_3$ solution and brine. The organic part was dried over anhydrous Na_2SO_4, concentrated in vacuo and the crude material was purified by silica gel column chromatography (PE/EtOAc 19:1) to give compound **12b** (514 mg) as light yellow crystalline solid in 58% overall yield from **19a**. R_f=0.46 (PE/EtOAc 9:1); mp: 127–129 °C; ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.97 (s, 1H), 7.20 (d, *J*=9.0 Hz, 1H), 6.95 (d, *J*=2.0 Hz, 1H), 6.81 (dd, *J*=9.5 Hz, 1H), 3.86 (s, 3H), 3.35–3.24 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 154.52, 134.20, 127.41, 121.30, 112.67, 111.39, 99.98, 78.64, 56.12, 31.86, 4.23; IR (KBr, cm^{-1}): 3374.6, 2955.4, 1168.9, 746.3; HRMS (ESI): $(M+Na)^+$ calcd for $C_{11}H_{11}I_2NNaO^+$ 449.8828, found 449.8824.

*4.1.10. 7-Ethyl-2-(2-(2-iodo-5-methoxy-1H-indol-3-yl)ethyl)-2-azabicyclo[2.2.2]oct-5-ene (**7d**) and 7-ethyl-2-(2-(2-iodo-5-methoxy-1H-indol-3-yl)ethyl)-2-azabicyclo[2.2.2]oct-5-ene (**7e**).* A suspension of Cs_2CO_3 (568 mg, 1.75 mmol) in anhydrous CH_3CN (6 mL) containing deprotected isoquinuclidine **11** (205 mg, 0.77 mmol) and diiodo compound **12b** (300 mg, 0.70 mmol) was heated at 60 °C for 10 h then the reaction mixture was cooled to rt and filtered through a pad of Celite and washed with EtOAc (10 mL). The filtrate was concentrated in vacuo and purified by column chromatography on silica gel (DCM/MeOH as eluent with gradual increase in concn of MeOH from 0.5% to 1.5%) to give **7d** (103 mg, 34%) and **7e** (125 mg, 41%) as light yellow foam.

Compound **7d**: ^{1}H NMR (500 MHz, $CDCl_3$, δ): 8.0 (br s, 1H), 7.17 (m, 1H), 7.01 (s, 1H), 6.77 (dd, *J*=8.5, 2.5 Hz, 1H), 6.31 (m, 2H), 3.85 (s, 3H), 3.32 (br s, 1H), 3.20 (br s, 1H), 2.79 (m, 2H), 2.68 (m, 1H), 2.46 (br s, 2H), 2.01 (d, *J*=9.5 Hz, 1H), 1.64–1.57 (m, 2H), 1.49 (t, *J*=11.0 Hz, 1H), 1.31 (br m, 1H), 0.95 (dd, *J*=13.0, 6.5 Hz, 1H), 0.88 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 154.16, 134.32, 133.06, 132.74, 128.05, 112.14, 11.12, 104.14, 100.54, 78.39, 58.54, 56.52, 56.15, 55.90, 41.09, 31.69, 29.80, 27.24, 19.18, 12.61; IR (neat, cm^{-1}): 3243, 2951, 1647, 1446, 747; HRMS (ESI): $(M+H)^+$ calcd for $C_{20}H_{26}IN_2O^+$ 437.1084, found 437.1084.

Compound **7e**: ^{1}H NMR (500 MHz, $CDCl_3$, δ): 8.54 (br s, 1H), 7.17 (d, *J*=8.5 Hz, 1H), 7.07 (s, 1H), 6.76 (dd, *J*=8.5, 2.5 Hz, 1H), 6.48 (t, *J*=7.5 Hz, 1H), 6.16 (t, *J*=7.5 Hz, 1H), 3.85 (s, 3H), 3.71 (br s, 1H), 3.28 (d, *J*=10.0 Hz, 1H), 3.00 (td, *J*=12.5, 4.5 Hz, 1H), 2.88 (m, 2H), 2.64 (s, 1H), 2.60 (td, *J*=11.0, 3.5 Hz, 1H), 2.28 (br d, *J*=10.5 Hz, 2H), 1.87 (td, *J*=11.0, 2.0 Hz, 1H), 1.22 (m, 2H), 1.03 (m, 1H), 0.86 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 154.37, 135.27, 135.20, 134.26, 127.83, 123.43, 112.49, 111.32, 100.14, 78.37, 57.24, 57.07, 56.21, 53.54, 38.59, 30.95, 30.03, 28.58, 24.87, 11.53; IR (neat, cm^{-1}): 3305, 2937, 1642, 745; HRMS (ESI): $(M+H)^+$ calcd for $C_{20}H_{26}IN_2O^+$ 437.1084, found 437.1084.

*4.1.11. 2′-Iodo-5′-methoxyspiro[cyclopropane-1,3′-indole] (**21**).* ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.57 (d, *J*=9.0 Hz, 1H), 6.84 (dd, *J*=8.5, 2.5 Hz, 1H), 6.57 (d, *J*=2.5 Hz, 1H); 3.81 (s, 3H), 1.83 (dd, *J*=8.5, 4.5 Hz, 2H), 1.62 (dd, *J*=8.0, 4.5 Hz, 2H); ^{13}C NMR (125 MHz,

$CDCl_3$, δ): 158.27, 150.68, 143.15, 121.10, 112.17, 104.13, 55.91, 43.25, 19.17.

*4.1.12. Ibogaine (**2**) and epiibogaine (**2a**).* To a solution of compound **7d** (70 mg, 0.16 mmol) in dry DMF (2 mL) was added HCOONa (27 mg, 0.4 mmol) under argon atmosphere. The mixture was degassed and back-filled with argon then $Pd(OAc)_2$ (3.5 mg, 10 mol %) and PPh_3 (8 mg, 20 mol %) were added with stirring at 55 °C. The reaction mixture was heated for 6 h at that temperature. Solvent was removed in vacuo then H_2O (2 mL) and DCM (4 mL) were added to the residue. The aqueous phase was extracted with DCM (2×4 mL), the combined organic extracts were washed with brine (4 mL) and dried (Na_2SO_4). The solvent was removed in vacuo and the crude material was purified by column chromatography (DCM/MeOH gradual increase in concn of MeOH from 1% to 2%) to afford ibogaine (**2**) (33 mg, 66%) as light yellow dense oil. R_f=0.37 (DCM/MeOH 14:1); ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.69 (br s, 1H), 7.16 (d, J=9.0 Hz, 1H), 6.91 (s, 1H), 6.78 (d, J=8.5 Hz, 1H), 3.85 (s, 3H), 3.51 (m, 1H), 3.31–3.19 (m, 3H), 3.08 (d, J=10.0 Hz, 1H), 2.97 (m, 2H), 2.86 (d, J=13.5 Hz, 1H), 2.11 (m, 1H), 1.92 (m, 3H), 1.67–1.61 (m, 4H), 1.29 (m, 1H), 0.91 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 154.30, 129.98, 129.92, 111.32, 111.11, 108.87, 58.32, 56.19, 55.91, 54.84, 50.18, 41.73, 33.88, 29.84, 27.54, 26.03, 20.40, 12.07; IR (neat, cm^{-1}): 3383, 2922, 1612, 1461; HRMS (ESI): $(M+H)^+$ calcd for $C_{20}H_{27}N_2O^+$ 311.2118, found 311.2118.

Similarly, epiibogaine (**2a**) was obtained as light yellow dense oil (27 mg, 55%), which was crystallized on standing. R_f=0.31 (DCM/MeOH 9:1); mp: 176–179 °C; ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.80 (br s, 1H), 7.16 (d, J=9.0 Hz, 1H), 6.91 (s, 1H), 6.78 (dd, J=8.5, 1.5 Hz, 1H), 3.85 (s, 3H), 3.38 (m, 2H), 3.29 (m, 2H), 3.10 (d, J=10.5 Hz, 2H), 3.02 (s, 1H), 2.76 (d, J=16.0 Hz, 1H), 2.15 (br s, 1H), 2.07 (m, 2H), 1.94 (br s, 1H), 1.65 (dd, J=11.0, 2.5 Hz, 1H), 1.39 (m, 2H), 1.10 (dd, J=13.0, 5.5 Hz, 1H), 0.93 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 154.34, 129.71, 129.60, 111.33, 111.24, 109.62, 100.29, 57.74, 56.15, 55.14, 49.68, 34.64, 32.93, 31.21, 28.10, 25.82, 19.95, 12.07; IR (KBr, cm^{-1}): 3401, 2926, 1613, 1463; HRMS (ESI): $(M+H)^+$ calcd for $C_{20}H_{27}N_2O^+$ 311.2118, found 311.2117.

*4.1.13. Methyl 2-(2-(1-(tert-butoxycarbonyl)-1H-indol-2-yl)ethyl)-2-azabicyclo[2.2.2]oct-5-ene-7-carboxylate (**22a**).* General procedure: to a mixture of *N*-Boc-2-iodoaniline (450 mg, 1.41 mmol), terminal alkyne **9d** (370 mg, 1.69 mmol) and Et_3N (3 mL) in DMF (6 mL) were added $Pd(PPh_3)_2Cl_2$ (49 mg, 0.071 mmol) and CuI (27 mg, 0.141 mmol) under argon. The reaction mixture was stirred at rt for 6 h and then *tetra*-butylammonium fluoride (TBAF) (1.0 M in THF, 4.23 mmol) was added dropwise to the reaction mixture. The reaction mixture was heated at 80 °C for 4 h and concentrated in vacuo. The resulting residue was partitioned between water and dichloromethane. The aqueous layer was further extracted with dichloromethane (2×10 mL). The combined organic extracts were dried over Na_2SO_4, evaporated in vacuo to give the crude product, which was purified by column chromatography on silica gel (PE/EtOAc 6:1) to afford the isoquinuclidine containing indole **22a** (384 mg, 66%) as a light yellow oil. R_f=0.46 (PE/EtOAc, 4:1); ^{1}H NMR (500 MHz, $CDCl_3$, δ): 8.06 (d, J=7.8 Hz, 1H), 7.44 (m, 1H), 7.24–7.14 (m, 2H), 6.47 (t, J=6.6 Hz, 1H), 6.37 (s, 1H), 6.27 (m, 1H), 3.90 (ddd, J=5.7, 2.7, 1.2 Hz, 1H), 3.60 (s, 3H), 3.20 (dd, J=9.0, 2.1 Hz, 1H), 3.12–3.10 (m, 2H), 2.18 (ddd, J=12.6, 4.2, 2.4 Hz, 1H), 1.93 (dt, J=9.3, 2.4 Hz, 1H), 1.69 (s, 9H), 1.44–1.34 (ddt, J=12.9, 11.1, 2.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 174.8, 150.5, 140.5, 136.4, 135.1, 130.0, 129.5, 123.1, 122.5, 119.7, 115.5, 107.5, 83.6, 57.1, 55.0, 54.9, 51.7, 45.3, 31.6, 28.9, 28.3, 24.4; IR (neat, cm^{-1}): 2947, 1732, 1454, 1329; HRMS (ESI): $(M+H)^+$ calcd for $C_{24}H_{30}N_2O_4H^+$ 411.2278, found 411.2274.

*4.1.14. Methyl 2-(2-(3-iodo-1H-indol-2-yl)ethyl)-2-azabicyclo[2.2.2]oct-5-ene-7-carboxylate (**13b**).* General procedure: 30% TFA in DCM (3 mL) was added to a flask containing compound **22a** (200 mg, 0.48 mmol) at 0 °C under argon atmosphere with stirring. The solution was warmed to rt and stirring was continued for another 3 h at rt. DCM and volatiles were removed in vacuo. Saturated aq $NaHCO_3$ solution (3 mL) and ethyl acetate (5 mL) were added to the residue. The aqueous phase was extracted with ethyl acetate (3×5 mL). The combined organic extracts were washed with brine (10 mL) and dried (Na_2SO_4). Solvent was removed in vacuo to give the crude product (142 mg, 95%) as light yellow foam, which was used in the next step without purification.

To a cold (0 °C), stirred solution of the above crude material (120 mg, 0.38 mmol) in dry DCM (4 mL) was added NIS (90 mg, 0.40 mmol) under argon atmosphere. Stirring was continued for 30 min at 0 °C. To the reaction mixture about 10 mL of DCM was added, washed with aq $Na_2S_2O_3$ solution and brine. The organic part was dried over anhydrous Na_2SO_4, concentrated in vacuo, the crude product was purified by column chromatography on silica gel (PE/EtOAc, 5:1) to give cyclization precursor **13b** (139 mg, 84%) as light yellow foam. R_f=0.44 (PE/EtOAc 3:1); ^{1}H NMR (500 MHz, $CDCl_3$, δ): 10.59 (br s, 1H), 7.61 (d, J=8.0 Hz, 1H), 7.37 (d, J=7.5 Hz, 1H), 7.18 (t, J=7.5 Hz, 1H), 7.13 (t, J=7.5 Hz, 1H), 6.54 (m, 1H), 6.30 (m, 1H), 3.77 (m, 1H), 3.65 (s, 3H), 3.33 (dd, J=10.0, 2.0 Hz, 1H), 2.89–2.76 (m, 3H), 2.70 (m, 1H), 2.55 (m, 2H), 2.15 (td, J=13.0, 2.5 Hz, 1H), 2.00 (dd, J=7.0, 2.5 Hz, 1H), 1.56 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 176.42, 140.50, 136.47, 135.32, 130.10, 129.90, 121.96, 120.05, 120.00, 111.95, 56.71, 56.60, 55.99, 54.12, 52.45, 44.99, 30.79, 25.11, 24.53; IR (neat, cm^{-1}): 3219, 2947, 1724, 743; HRMS (ESI): $(M+H)^+$ calcd for $C_{19}H_{22}IN_2O_2^+$ 437.0720, found 437.0721.

*4.1.15. Iboga analogue (**6a**).* General procedure: following the reductive-Heck coupling procedure described for the synthesis of ibogaine (**2**), iboga analogue **6a** was obtained in 78% (43 mg) yield. Only exception is that mixed solvent system DMF and CH_3CN (3:1) were used. R_f=0.52 (CH_2Cl_2/MeOH 20:1); mp: 99–100 °C; ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.58 (br s, 1H), 7.37 (d, J=7.5 Hz, 1H), 7.18 (d, J=8.0 Hz, 1H), 7.02 (m, 2H), 3.63 (s, 3H), 3.56 (m, 1H), 3.39 (m, 1H), 3.24 (ddd, J=11.0, 4.5, 1.5 Hz, 1H), 3.14 (m, 2H), 3.00 (m, 1H), 2.94 (m, 1H), 2.73 (m, 1H), 2.40 (td, J=16.5, 3.0 Hz, 1H), 2.28 (m, 1H), 2.10 (m, 1H), 1.90 (m, 1H), 1.71 (m, 1H), 1.48 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 175.7, 134.7, 133.2, 128.6, 121.1, 119.1, 117.5, 110.2, 58.3, 52.4, 51.9, 49.6, 46.4, 35.1, 34.7, 26.1, 26.0, 25.32; IR (KBr, cm^{-1}): 3397, 2928, 2858, 1727, 1460 cm^{-1}; HRMS (ESI): $(M+H)^+$ calcd for $C_{19}H_{22}N_2O_2H^+$ 311.1754, found 311.1754.

*4.1.16. Methyl 2-(2-(1-(tert-butoxycarbonyl)-1H-indol-2-yl)ethyl)-2-azabicyclo[2.2.2]oct-5-ene-7-carboxylate (**22b**).* Following the general procedure described for the synthesis of compound **22a** (above), compound **22b** was obtained as light yellow oil in 64% (116 mg) yield. R_f=0.37 (PE/EtOAc, 3:1); ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.06 (d, J=8.4 Hz, 1H), 7.43 (dm, J=6.6 Hz, 1H), 7.21 (td, J=8.1, 1.5 Hz, 1H), 7.16 (td, J=7.2, 1.5 Hz, 1H), 6.42 (t, J=6.9 Hz, 1H), 6.36 (s, 1H); 6.20 (ddd, J=8, 5.4,1.2 Hz, 1H), 3.87 (ddd, J=5.4, 3.3, 1.2 Hz, 1H), 3.64 (s, 3H), 3.23–3.10 (m, 3H), 3.03–2.99 (dd, J=9.3, 1.8 Hz, 1H), 2.93–2.86 (m, 1H), 2.64–2.55 (m, 2H), 2.11–2.03 (dt, J=9.3, 2.4 Hz, 1H), 1.80–1.71 (m, 2H), 1.68 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 174.5, 150.5, 140.2, 136.5, 134.8, 129.6, 129.4, 123.3, 122.6, 119.8, 115.6, 107.5, 83.8, 57.2, 54.6, 54.2, 51.8, 43.9, 30.8, 29, 28.44, 28.35, 28.24, 26.1; IR (neat, cm^{-1}): 2926, 2949, 1732, 1454; HRMS (ESI): $(M+H)^+$ calcd for $C_{24}H_{30}N_2O_4H^+$ 411.2278, found 411.2275.

*4.1.17. Methyl 2-(2-(3-iodo-1H-indol-2-yl)ethyl)-2-azabicyclo[2.2.2]oct-5-ene-7-carboxylate (**13c**).* Following the general procedure as described for the synthesis of compound **13b** (above), compound **13c** was obtained as light yellow foam in 77% yield from compound

22b. R_f=0.32 (PE/EtOAc, 3:1); ^{1}H NMR (500 MHz, $CDCl_3$, δ): 10.40 (br s, 1H), 7.39 (d, J=7.5 Hz, 1H), 7.30 (d, J=8.0 Hz, 1H), 7.16 (m, 2H), 6.52 (t, J=7.5 Hz, 1H), 6.23 (t, J=7.0 Hz, 1H), 3.90 (s, 1H), 3.66 (s, 3H), 3.15 (m, 1H), 3.07 (dd, J=9.5, 1.5 Hz, 1H), 2.95–2.84 (m, 3H), 2.67 (m, 2H), 2.15 (dd, J=10.0, 2.5 Hz, 1H), 1.89 (m, 1H), 1.80 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 174.05, 140.67, 135.88, 135.32, 130.40, 129.35, 122.24, 120.39, 120.36, 111.18, 57.65, 56.37, 54.41, 53.72, 52.01, 43.97, 30.71, 26.30, 25.46; IR (neat, cm^{-1}): 3332, 2942, 1726, 745; HRMS (ESI): $(M+H)^+$ calcd for $C_{19}H_{22}IN_2O_2^+$ 437.0720, found 437.0719.

*4.1.18. Iboga analogue (**6b**).* Following the reductive-Heck coupling procedure as for the synthesis of iboga analogue **6a**, compound **13c** was converted to the iboga analogue **6b** in 74% (38 mg) yield as a light brown solid. R_f=0.42 (CH_2Cl_2/MeOH, 20:1); mp:149–151 °C; ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.74 (br s, 1H), 7.40 (d, J=7.5 Hz, 1H), 7.25 (d, J=8.0 Hz, 1H), 7.09 (m, 2H), 3.70 (s, 3H), 3.64–3.59 (m, 1H), 3.35 (m, 3H), 3.22 (m, 1H), 3.15 (m, 2H), 3.05 (m, 1H), 2.56 (td, J=16.5, 3.0 Hz, 1H), 2.21 (m, 2H), 2.00 (m, 1H), 1.92 (m, 1H), 1.48 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 175.0, 134.6, 133.3, 128.5, 121.3, 119.3, 119.0, 117.6, 110.2, 57.2, 52.7, 52.0, 49.54, 46.2, 35.2, 30.7, 26.0, 25.8, 25.0; IR (KBr, cm^{-1}): 3339, 2931, 1732, 1458; HRMS(ESI): $(M+H)^+$ calcd for $C_{19}H_{22}N_2O_2H^+$ 311.1754, found 311.1759.

*4.1.19. Methyl 2-(2-(1-(tert-butoxycarbonyl)-5-methoxy-1H-indol-2-yl)ethyl)-2-azabicyclo[2.2.2] oct-5-ene-7-carboxylate (**22c**) and methyl 2-(2-(1-(tert-butoxycarbonyl)-5-methoxy-1H-indol-2-yl)ethyl)-2-azabicyclo[2.2.2]oct-5-ene-7-carboxylate (**22d**).* Following the general procedure described for the synthesis of compound **22a**, compounds **22c** (176 mg) and **22d** (173 mg) were synthesized from *N*-Boc-4-methoxy-2-iodoaniline in 67% and 66% yields, respectively, as light yellow oil.

Compound **22c**: ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.93 (d, J=9.0 Hz, 1H), 6.91 (d, J=2.5 Hz, 1H), 6.81 (dd, J=9.0, 2.5 Hz, 1H), 6.45 (t, J=7.5 Hz, 1H), 6.28 (s, 1H), 6.26 (m, 1H), 3.88 (m, 1H), 3.82 (s, 3H), 3.58 (s, 3H), 3.19 (dd, J=9.0, 2.0 Hz, 1H), 3.10–2.97 (m, 2H), 2.78 (m, 1H), 2.55 (m, 1H), 2.44 (m, 2H), 2.16 (td, J=10.0, 2.5 Hz, 1H), 1.92 (td, J=10.5, 2.5 Hz, 1H), 1.66 (s, 9H), 1.37 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 174.81, 155.73, 150.42, 141.26, 135.09, 131.14, 130.27, 129.95, 116.20, 111.47, 107.48, 102.56, 83.44, 57.05, 55.65, 54.89, 51.70, 45.31, 31.03, 28.91, 28.27, 24.37; IR (neat, cm^{-1}): 2947, 1730, 1223, 847; HRMS (ESI): $(M+H)^+$ calcd for $C_{25}H_{33}N_2O_5^+$ 441.2384, found 441.2383.

Compound **22d**: ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.96 (d, J=9.0 Hz, 1H), 6.93 (d, J=2.5 Hz, 1H), 6.85 (dd, J=9.0, 2.5 Hz, 1H), 6.46 (t, J=7.5 Hz, 1H), 6.31 (s, 1H), 6.22 (m, 1H), 3.88 (m, 1H), 3.84 (s, 3H), 3.65 (s, 3H), 3.19–3.12 (m, 3H), 3.03 (dd, J=9.0, 2.0 Hz, 1H), 2.90 (m, 1H), 2.61 (m, 2H), 2.10 (td, J=9.0, 2.5 Hz, 1H), 1.80 (m, 1H), 1.75 (m, 1H), 1.69 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 174.52, 155.85, 150.42, 141.04, 134.70, 131.20, 130.23, 129.68, 116.33, 111.74, 107.45, 102.62, 83.63, 57.25, 55.70, 54.63, 54.28, 51.75, 43.98, 30.88, 29.26, 28.33, 26.12; IR (neat, cm^{-1}): 2949, 1726, 1122, 846; HRMS (ESI): $(M+H)^+$ calcd for $C_{25}H_{33}N_2O_5^+$ 441.2384, found 441.2384.

*4.1.20. Methyl 2-(2-(3-iodo-5-methoxy-1H-indol-2-yl)ethyl)-2-azabicyclo[2.2.2]oct-5-ene-7-carboxylate (**13d**) and methyl 2-(2-(3-iodo-5-methoxy-1H-indol-2-yl)ethyl)-2-azabicyclo[2.2.2] oct-5-ene-7-carboxylate (**13e**).* Following the general procedure described earlier for the synthesis of cyclization precursor **13b**, compounds **13d** (94 mg) and **13e** (85 mg) were synthesized from **22c** and **22d** in 75% and 68% yields, respectively, as light yellow foam.

Compound **13d**: R_f=0.33 (PE/EtOAc 3:1). ^{1}H NMR (500 MHz, $CDCl_3$, δ): 10.49 (br s, 1H), 7.48 (d, J=9.0 Hz, 1H), 6.81 (d, J=7.5 Hz, 1H), 6.80 (s, 1H), 6.50 (t, J=7.5 Hz, 1H), 6.28 (m, 1H), 3.87 (s, 3H), 3.72 (m, 1H), 3.62 (s, 3H), 3.29 (d, J=9.0 Hz, 1H), 2.81 (m, 2H), 2.75–2.67 (m, 2H), 2.53 (m, 2H), 2.12 (m, 1H), 1.96 (d, J=9.5 Hz, 1H), 1.50 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 176.38, 154.73, 141.05, 135.27, 131.41, 130.47, 129.84, 129.76, 112.69, 112.19, 101.82, 56.65, 56.60, 56.00, 54.03, 52.40, 44.96, 30.96, 25.10, 24.47; IR (neat, cm^{-1}): 3246, 2947, 1724, 719; HRMS (ESI): $(M+H)^+$ calcd for $C_{20}H_{24}IN_2O_3^+$ 467.0826, found 467.0826.

Compound **13e**: R_f=0.31 (PE/EtOAc, 2:1); ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.47 (br s, 1H), 7.18 (d, J=8.5 Hz, 1H), 6.82 (m, 2H), 6.51 (t, J=7.0 Hz, 1H), 6.22 (m, 1H), 3.91 (m, 1H), 3.88 (s, 3H), 3.64 (s, 3H), 3.14 (m, 1H), 3.04 (dd, J=9.5, 2.0 Hz, 1H), 2.93–2.84 (m, 3H), 2.69 (m, 2H), 2.13 (td, J=9.5, 2.5 Hz, 1H), 1.88 (m, 1H), 1.80 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 173.99, 154.97, 141.14, 135.40, 130.92, 130.85, 129.29, 112.48, 112.05, 102.25, 563,56.05, 54.42, 53.71, 52.01, 43.88, 30.70, 26.27, 25.56; IR (neat, cm^{-1}): 3284, 2946, 1723, HRMS (ESI): $(M+H)^+$ calcd for $C_{20}H_{24}IN_2O_3^+$ 467.0826, found 467.0822.

*4.1.21. C19-Carbomethoxy substituted [3,2]-fused iboga analogues (**6c**) and (**6d**).* Following the reductive-Heck coupling procedure described for the synthesis of ibogaine (**2**), compounds **13d** and **13e** were converted separately to the iboga analogues **6c** (32 mg) and **6d** (30 mg) in 64% and 61% yields, respectively, as a light brown solid.

Compound **6c**: R_f=0.44 (CH_2Cl_2/MeOH, 15:1); mp: 84–86 °C; ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.55 (br s, 1H), 7.15 (d, J=9.0 Hz, 1H), 6.88 (d, J=2.5 Hz, 1H), 6.78 (dd, J=8.5, 2.5 Hz, 1H), 3.85 (s, 3H), 3.72 (s, 3H), 3.60 (m, 1H), 3.49 (s, 1H), 3.25 (m, 3H), 3.15 (d, J=8.5 Hz, 1H), 3.01 (d, J=9.5 Hz, 1H), 2.82 (ddd, J=11.5, 5.5, 2.0 Hz, 1H), 2.50 (d, J=16.5 Hz, 1H), 2.35 (m, 1H), 2.17 (m, 1H), 2.00 (m, 1H), 1.80 (m, 1H), 1.55 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 175.69, 154.12, 134.38, 133.06, 129.92, 129.13, 119.27, 110.91, 100.13, 58.41, 56.15, 52.55, 51.92, 49.69, 46.52, 35.22, 34.88, 26.26, 26.02, 25.48; IR (KBr, cm^{-1}): 3335, 2942, 1726, 747; HRMS (ESI): $(M+H)^+$ calcd for $C_{20}H_{25}N_2O_3^+$ 341.1860, found 341.1860.

Compound **6d**: R_f=0.42 (CH_2Cl_2/MeOH, 9:1); mp: 115–118 °C; ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.59 (br s, 1H), 7.15 (d, J=8.5 Hz, 1H), 6.82 (d, J=2.5 Hz, 1H), 6.78 (dd, J=8.5, 2.0 Hz, 1H), 3.83 (s, 3H), 3.71 (s, 3H), 3.58 (m, 1H), 3.39–3.31 (m, 3H), 3.19–3.13 (m, 3H), 3.06 (d, J=10.0 Hz, 1H), 2.58 (d, J=16.5 Hz, 1H), 2.23 (m, 2H), 2.02 (m, 1H), 1.95 (m, 1H), 1.50 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 174.74, 154.33, 134.10, 129.82, 128.91, 118.81, 111.25, 111.03, 100.28, 57.28, 56.27, 53.06, 52.11, 49.86, 45.71, 35.10, 30.44, 25.94, 25.80, 25.04; IR (KBr, cm^{-1}): 3365, 2945, 1724, HRMS (ESI): $(M+H)^+$ calcd for $C_{20}H_{25}N_2O_3^+$ 341.1860, found 341.1862.

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Supplementary data

^{1}H and ^{13}C NMR spectra for all the new compounds described herein are available free of charge via the Internet. Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.tet.2012.06.027.

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