Tetrahedron Letters 53 (2012) 1671–1674

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Reductive Heck coupling: an efficient approach toward the iboga alkaloids. Synthesis of ibogamine, epiibogamine and iboga analogs

Goutam Kumar Jana, Surajit Sinha *

Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Kolkata 700032, India

ARTICLE INFO

Article history:
Received 15 December 2011
Revised 18 January 2012
Accepted 22 January 2012
Available online 28 January 2012

Keywords:
Reductive-Heck coupling
Iboga alkaloids
Indoloazepine
Heteroannulation
Palladium catalyst

ABSTRACT

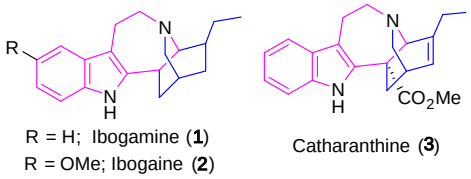
A mild and efficient synthetic route to the iboga scaffold by employing reductive-Heck type annulation is described. The utility of this process is demonstrated by the direct access to the ibogamine, epiibogamine and iboga-analogs. The cyclization precursors were readily obtained from 2-iodoaniline by heteroannulation reaction with suitable alkynes followed by iodination.

Iboga alkaloids are pharmacologically important indole alkaloids, consist of seven membered indoloazepine ring fused with a rigid isoquinuclidine ring (Fig. 1).[1] Such indoloazepine ring system is also present in several other bioactive natural products[2] and medicinally important molecules.[3] Pharmacological properties of iboga-alkaloids have been reviewed many times.[4] Iboga modified structures exhibit many interesting pharmacological properties[5] such as anti-addictive, antifungal or antilipase, anti-HIV-1, anticholinesterasic, anti-leishmanicide activities. Iboga-alkaloids, particularly catharanthine (**3**) is known to involve in the biochemical pathways for the generation of structurally more complex vinca alkaloids vinblastine and vincristine, two drugs used in the treatment of a number of human cancers.[6]

Construction of seven membered indoloazepine ring is the crucial step in the synthesis of iboga alkaloids.[1] Several methods are available in the literature such as electrocyclic ring closure,[7] mixed-metal-mediated cyclization,[8] Fischer indolization[9] and reductive amination[10] for the creation of this ring system to access the total synthesis of ibogaine or ibogamine. Other syntheses[1] have followed these approaches for the construction of indoloazepine ring leading to the synthesis of iboga alkaloids. However, most of these strategies suffer from several limitations concerning flexibility, yields and reaction conditions. In the Büchi's method, synthesis of cyclization precursor is a multistep process and cyclization in hot acetic acid results in rearranged product formation.[7] Our earlier strategy[11a] involved Trost's cyclization method[8] for the synthesis of iboga analogs. Though, the method involved direct C–H bond activation, the yield was low and not economical as it required 1–2 equiv of palladium catalyst and 2–4 equiv of $AgBF_4$.

It is therefore highly desirable to develop new efficient and economical methods for the construction of the indoloazepine core structure of the iboga-scaffold. Herein, we describe a catalytic, mild and efficient method to achieve this transformation for the synthesis of ibogamine and iboga analogs.

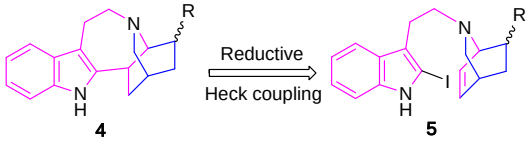
Conceptually β-H elimination is prohibited in the Pd-catalyzed Heck type C–C bond forming reaction, where rigid double bond is involved.[12] Accordingly, we envisioned that reductive-Heck type



R = H; Ibogamine (**1**)
R = OMe; Ibogaine (**2**)

Catharanthine (**3**)

Figure 1. Iboga-family alkaloids.



Scheme 1. Synthetic strategy for reductive-Heck coupling.

* Corresponding author.
E-mail address: ocss5@iacs.res.in (S. Sinha).

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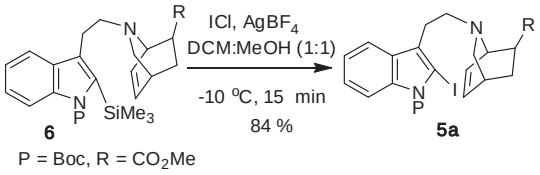
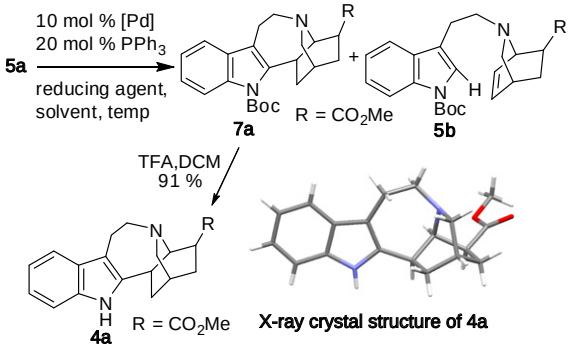
doi:10.1016/j.tetlet.2012.01.097



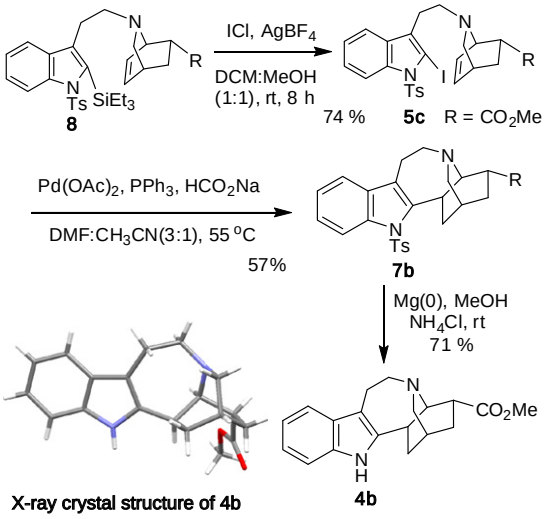
Scheme 2. Synthesis of cyclization precursor **5a**.

Table 1
Optimization of reductive-Heck coupling condition[a]

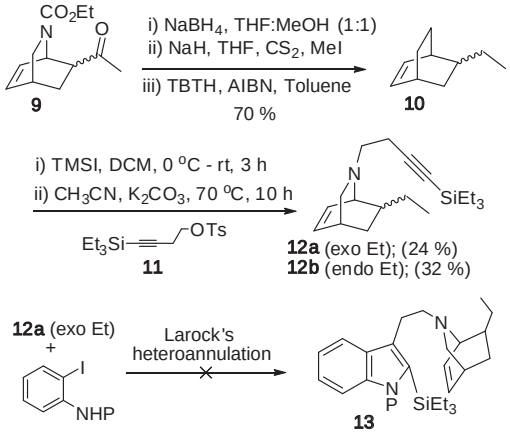


Entry	Conditions (reducing agent, solvent, temp, time)	Yield[d] (%)	
		7a	**5b**
1[b]	HCO_2H, piperidine, DMF, 80 °C, 2 h	20	66
2[c]	HCO_2H, piperidine, DMF, 80 °C, 2 h	15	60
3	HCO_2H, piperidine, DMF, 80 °C, 2 h	25	60
4	HCO_2H, piperidine, DMF, rt, 10 h	15	12
5	HCO_2H, piperidine, DMF, 50 °C, 4 h	40	45
6	HCO_2Na, DMF, 50 °C, 5 h	50	36
7	**HCO_2Na, DMF/CH_3CN (3:1), 55 °C, 6 h**	**68**	**15**
8	HCO_2H, DMF/CH_3CN (3:1), 55 °C, 8 h	51	11

[a] All reactions were carried out using 10 mol % of $Pd(OAc)_2$ and 20 mol % of ligand(PPh_3).
[b] $Pd(PPh_3)_4$(10 mol %).
[c] Without ligand.
[d] Isolated yields.



Scheme 3. Synthesis of C-19 *endo*-substituted Iboga-scaffold **4b**.



Scheme 4. Synthesis of cyclization precursor for Ibogamine.

annulation could be a useful method to the indoloazepine ring system containing a fused isoquinuclidine ring, since Heck coupling or oxidative-Heck coupling would lead to a highly strained bridgehead olefinic system (Scheme 1).

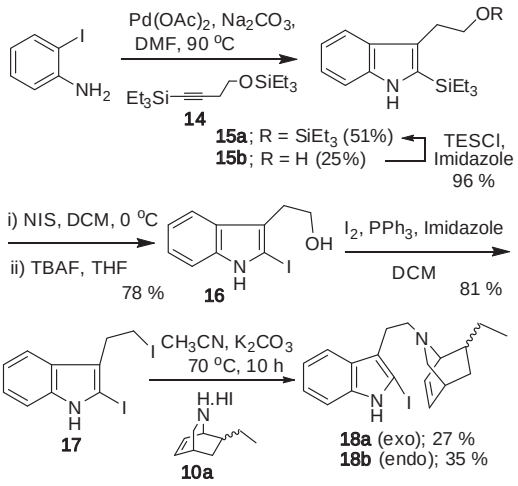
To check the feasibility of the reductive-Heck type annulation reaction, initially we took **5a**, a cyclization precursor which directly would lead to the C-19 *exo*-substituted iboga-scaffold. The cyclization precursor **5a** was prepared from Boc-protected 2-iodoaniline by heteroannulation reaction[11] followed by iodination using ICl in the presence of $AgBF_4$ (Scheme 2). Initially, we had used NIS for iodionation but the yield was not satisfactory. After several experimentations, we found that mixed solvent system in the presence of $AgBF_4$ was suitable to afford the cyclization precursor **5a** in very good yield.

Initial attempt of the reductive-Heck type annulation using $Pd(PPh_3)_4$ as catalyst and formic acid–piperidine as reducing system in DMF at 80 °C resulted mostly in the deiodinated compound **5b** (Table 1, entries 1–3).[13]

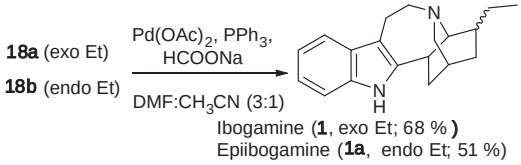
Performing the reaction at 50 °C by using $Pd(OAc)_2$ in the presence of PPh_3 afforded the desire product **7a** in a 40% yield[14] (Table 1, entry 5). When formic acid and piperidine were replaced with sodium formate,[15] a less effective reducing agent, the yield of desired product was increased by upto 50%. We were pleased to find that a mix solvent system, DMF and acetonitrile in 3:1 ratio afforded the expected product **7a** in a 68% yield (Table 1, entry 7). We failed to achieve this conversion when 5 mol % of the catalyst and 10 mol % of the ligand were used. Under this condition, about 60% of the starting material was consumed and the reaction did not proceed further even after prolonged stirring. The X-ray crystal structure of **4a** which was obtained after Boc deprotection of **7a** showed the desired connectivity.

Then we turned our attention to the synthesis of C-19 epimer of **4a** using the optimized reductive-Heck coupling condition. The synthesis of **8** from Ts-protected 2-iodoaniline gave better yield when TES connected alkyne was used.[11a] Iodination of 2-triethylsilyl substituted indole **8** required room temperature and longer reaction time in comparison to 2-trimethylsilyl substituted indole **6** (Scheme 3). Under the optimized coupling condition, the cyclized product was obtained in a 57% yield which after Ts-deprotection by Mg(0) in methanol furnished C-19 epimeric iboga scaffold **4b**.

With this success, our next aim was the synthesis of ibogamine (**1**)[1] to demonstrate a suitable application of this transformation. For the synthesis of ibogamine and epiibogamine, we initially followed convergent protocol to access the cyclization precursors (Scheme 4). Compound **9** was obtained by the Diels–Alder reaction between dihydropyridine and methyl vinyl ketone as an inseparable epimeric mixture (3:4).[16] After reduction with $NaBH_4$, the resulting mixture of diastereoisomeric alcohols was converted into



Scheme 5. Alternative synthesis of cyclization precursors.



Scheme 6. Final step for the synthesis of ibogamine and epiibogamine.

the corresponding xanthates. Without separation, the mixture of xanthates on radical deoxygenation[17] afforded inseparable *exo* and *endo* mixture of dehydroisoquinuclidine **10** with some TBTH byproducts in a 70% overall yield from **9**. Deprotection of dehydroisoquinuclidine **10** and N-alkylation with tosylated alkyne **11** afforded isoquinuclidine containing alkynes **12a** and **12b** (3:4) in moderate yields. Attempted heteroannulation reaction of alkyne **12a** with 2-iodoaniline was disappointing though it worked well previously[11a] when CO_2Me substituted (instead of ethyl) dehydroisoquinuclidine containing alkyne was used. We tried several conditions, but in all the cases complex mixture was obtained with very low amount of expected product which was inseparable from the alkyne **12a**.

So we turned our attention toward an alternative route for the efficient synthesis of cyclization precursors **18a** and **18b** (Scheme 5). To avoid these problems, we considered initial construction of indole part from 2-iodoaniline by use of a simple disilylated alkyne **14** prior to the connection with isoquinuclidine ring **10a**. The heteroannulation reaction of 2-iodoaniline with alkyne **14** gave the expected product **15a** and mono-desilylated compound **15b** in good yields. Iodination of **15a** by NIS followed by silyl deprotection using TBAF afforded 2-iodotryptol **16** which was not quite stable. The compound **16** was immediately iodinated and purified to obtain tryptoyl iodide **17** in a 63% yield from **15a**. Compound **15b** was converted to **15a** as iodination of **15b** using NIS was not clean. Reaction of **10a** with 2-iodo tryptoyl iodide **17** in acetonitrile afforded separable cyclization precursors **18a** and **18b** in good yields.

With the cyclization precursors **18a** and **18b** in hand, we then applied optimized reductive-Heck cyclization condition separately to obtain ibogamine (**1**) and epiibogamine (**1a**) in 68% and 51% yields, respectively (Scheme 6).

In summary, we have described a novel entry to direct construction of iboga skeleton[18] based on reductive-Heck type cyclization. The cyclization step is catalytic, mild, and efficient. With this cyclization as the key step, total synthesis of ibogamine[18] and epiibogamine[18] has been achieved. Syntheses of cyclization precursors also involve Pd-catalyzed heteroannulation reaction. The application of this protocol for the synthesis of other iboga alkaloids and their analogs will be reported shortly.

Acknowledgments

We thank Dr. N.N. Adarsh for crystal structure and DST, India, for financial support. G.K.J. is thankful to CSIR, India for fellowship.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.01.097.

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18. Experimental procedure and spectral data of some key compounds:
*Cyclization precursor **5a**:*
To a cooled solution (−15 °C) of compound **6** (500 mg, 1.16 mmol) in DCM and MeOH (1:1, 4 mL) was added silver tetrafluoroborate (230 mg, 0.83 mmol) followed by the dropwise addition of ICl (1.4 mL, 1 M) under argon atmosphere. After 15 min of stirring the ice-salt bath was removed and 10 mL of DCM was added to the reaction mixture. The organic layer was washed with aq $Na_2S_2O_3$ solution, brine and dried over anhydrous Na_2SO_4. The organic part was concentrated in vacuo, purified by silica gel column chromatography using EtOAc in petroleum ether (PE/EtOAc 9:1) as eluent to get the compound **5a** (520 mg, 84%) as a light brown foam. R_f = 0.23 (PE/EtOAc 9:1). ^{1}H NMR (500 MHz, $CDCl_3$, δ): 8.05 (dd, *J* = 6.5, 2.5 Hz, 1H), 7.45 (dd, *J* = 6.0, 2.5 Hz, 1H), 7.21 (m, 2H), 6.46 (t, *J* = 7.5 Hz, 1H), 6.25 (t, *J* = 6.5 Hz, 1H), 3.93 (dd, *J* = 4.0, 1.5 Hz, 1H), 3.69 (s, 3H), 3.27 (dd, *J* = 9.5, 2.0 Hz, 1H), 2.86–2.81 (ddd, *J* = 13.5, 11.0, 6.0 Hz, 1H), 2.77–2.71 (ddd, *J* = 13.0, 11.0, 5.0 Hz, 1H), 2.60 (m, 2H), 2.45 (dt, *J* = 10.5, 5.0 Hz, 1H), 2.30 (td, *J* = 11.5, 5.0 Hz, 1H), 2.20 (dt, *J* = 14.0, 3.5 Hz, 1H), 1.98 (dt, *J* = 9.0, 2.5 Hz, 1H), 1.70 (s, 9H), 1.42 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 174.97, 149.51, 138.22, 135.23, 130.03, 129.85, 128.22, 124.32, 122.66,118.37, 115.60, 85.00, 78.64, 57.07, 55.15, 55.12, 51.82, 45.45, 31.19, 28.44, 27.27, 24.44; IR (neat): 2947, 1732, 1444 cm^{-1}. HRMS (ESI) $(M+H)^+$ calcd for $C_{24}H_{30}IN_2O_4^+$ 537.1245, found 537.1246.

*Iboga scaffold **7a**:*

Optimized reductive-Heck coupling condition: Dry DMF (1.50 mL) and CH_3CN (0.50 mL) were added to a flask containing compound **5a** (150 mg, 0.28 mmol) under argon atmosphere followed by the addition of HCOONa (38 mg, 0.56 mmol). The mixture was degassed and finally back-filled with argon then $Pd(OAc)_2$ (6 mg, 10 mol %) and PPh_3 (14.5 mg, 20 mol %) were added with stirring. The mixture was heated for 6 h at 55 °C. Solvents were 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 layers 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 (silica gel, gradient of PE/EtOAc from 7:1 to 5:1) to give deiodinated compound **5b** (17 mg, 15%) and the title compound **7a** (78 mg, 68%) as light yellow solid. Compound **7a**: R_f = 0.21 (PE/EtOAc 5:1). mp 159–161 °C. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.98 (dd, *J* = 7.0, 2.0 Hz, 1H), 7.40 (dd, *J* = 7.0, 2.5 Hz, 1H), 7.23 (m, 2H), 3.95 (dd, *J* = 11.0, 6.0 Hz, 1H), 3.71 (s, 3H), 3.52 (s, 1H), 3.28–3.20 (m, 1H), 3.14 (m, 2H), 3.12 (dt, *J* = 9.5, 2.5 Hz, 1H), 3.00 (d, *J* = 9.5 Hz, 1H), 2.77 (ddd, *J* = 11.0, 5.0, 2.5 Hz, 1H), 2.68 (dt, *J* = 16.0, 2.5 Hz, 1H), 2.35 (m, 1H), 2.26 (m, 1H), 2.00 (m, 1H), 1.74 (m, 1H), 1.68 (s, 9H), 1.66 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 175.41, 150.71, 143.19, 135.24, 130.58, 123.56, 122.46, 117.92, 117.27, 115.45, 83.82, 56.81, 53.63, 51.99, 50.78, 46.76, 37.86, 34.36, 28.50, 26.25, 25.68, 20.70; IR (KBr, cm^{-1}): 2976, 1729, 1724, 1458, 1155, 754; HRMS (ESI) $(M+H)^+$ calcd for $C_{24}H_{31}N_2O_4^+$ 411.2278, found 411.2276.

*Compound **17***: To a stirred solution of **16** (400 mg, 1.39 mmol) in DCM (5 mL) were added imidazole (189 mg, 2.78 mmol), PPh_3 (366 mg, 1.4 mmol) and I_2 (355 mg, 1.4 mmol) at 0 °C. Stirring was continued for 4 h at 0 °C. DCM (5 mL) was added to the reaction mixture. The organic layer was washed 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 (EtOAc/PE 19:1) to give compound **17** (447 mg, 81%) as light yellow crystalline solid. R_f = 0.51 (PE/EtOAc 9:1), mp 107–109 °C. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 8.05 (s, 1H), 7.54 (d, *J* = 7.5 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.15 (m, 2H), 3.33 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 138.97, 127.05, 122.73, 121.73, 120.29, 117.85, 110.63, 31.85, 4.21; IR (KBr, cm^{-1}): 3364, 2957, 1445, 1169, 741; (ESI) $(M+Na)^+$ calcd for $C_{10}H_9I_2NNa^+$ 419.8717, found 419.8713.

*Cyclization precursors **18a** and **18b**:*

A suspension of K_2CO_3 (333 mg, 2.4 mmol) in anhydrous CH_3CN (6 mL) containing deprotected isoquinuclidine **10a** (319 mg, 1.2 mmol) and 2-iodo compound **17** (400 mg, 1.0 mmol) was heated at 70 °C for 10 h then the reaction mixture was cooled to room temperature and filtered through a pad of Celite and washed with EtOAc (10 mL). The combined organic extracts were concentrated in vacuo and purified by column chromatography on silica gel (DCM/MeOH as eluent with gradual increase in conc. of MeOH from 0.5–1.5%) to give **18a** (109 mg, 27%) and **18b** (142 mg, 35%) as light yellow foam.

Compound **18a**: ^{1}H NMR (500 MHz, $CDCl_3$, δ): 8.04 (br s, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.11 (t, *J* = 7.5 Hz, 1H), 7.07 (t, *J* = 8.0 Hz, 1H), 6.31 (m, 2H), 3.28 (br s, 1H), 3.20 (d, *J* = 9.0 Hz, 1H), 2.84–2.69 (m, 2H and 1H), 2.45 (m, 2H), 2.02 (d, *J* = 8.5 Hz, 1H), 1.55 (m, 2H), 1.46 (m, 1H), 1.32 (m, 1H), 0.96 (m, 1H), 0.88 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 139.04, 132.97, 132.86, 127.70, 123.38, 122.23, 120.90, 119.73, 118.27, 110.04, 58.74, 56.45, 56.33, 41.24, 31.77, 29.85, 27.20, 26.40, 12.62; IR (Neat, cm^{-1}): 3206, 2957, 1653, 1448, 746; HRMS (ESI) $(M+H)^+$ calcd for $C_{19}H_{24}IN_2^+$ 407.0979, found 407.0977.

Compound **18b**: ^{1}H NMR (500 MHz, $CDCl_3$, δ): 8.60 (br s, 1H), 7.92 (d, *J* = 6.5 Hz, 1H), 7.33 (d, *J* = 7.0 Hz, 1H), 7.08 (m, 1H), 6.66 (t, *J* = 7.5 Hz, 1H), 6.40 (t, *J* = 7.0 Hz, 1H), 4.23 (br s, 1H), 4.07 (br d, *J* = 9.0 Hz, 1H), 3.54 (br t, *J* = 10.0 Hz, 1H), 3.21 (br t, *J* = 8.0 Hz, 1H), 3.12 (dt, *J* = 12.0, 5.0 Hz, 1H), 2.85 (br s, 1H), 2.77 (br t, *J* = 7.0 Hz, 1H), 2.22 (br d, *J* = 10.5 Hz, 1H), 2.11 (br m, 1H), 2.03 (m, 1H), 1.72–1.68 (m, 2H), 1.28 (d, *J* = 11.5 Hz, 1H), 1.00 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 138.91, 137.96, 127.99, 127.04, 124.35, 122.77, 120.58, 119.20, 115.99, 110.67, 56.64, 55.91, 55.61, 38.44, 29.11, 27.21, 27.08, 17.78, 12.58; IR (Neat, cm^{-1}): 3206, 2957, 1653, 746; HRMS (ESI) $(M+H)^+$ calcd for $C_{19}H_{24}IN_2^+$ 407.0979, found 407.0975.

*Ibogamine (**1**):*

The procedure was same as described for the cyclization of compound **5a** (above), ibogamine (**1**) was obtained as a pale brown oil (68%), which was crystallized upon standing; R_f = 0.34 (DCM/MeOH 20:1), mp 137–139 °C. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.82 (br s,1H), 7.47 (d, *J* = 7.5 Hz, 1H), 7.27 (d, *J* = 9.0 Hz, 1H), 7.13 (t, *J* = 7.5 Hz, 1H), 7.09 (t, *J* = 7.0 Hz, 1H), 3.51 (br d, *J* = 15.5 Hz, 1H), 3.34–3.19 (m, 3H), 3.09 (d, *J* = 10,0 Hz, 1H), 3.03 (d, *J* = 6.0 Hz, 2H), 2.82 (d, *J* = 14.5 Hz, 1H), 2.10 (t, *J* = 12.5 Hz, 1H), 1.93 (s, 1H), 1.86 (td, *J* = 10.0, 2.5 Hz, 1H), 1.69–1.52 (m, 4H), 1.31 (m, 1H), 0.91 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 141.97, 134.84, 129.91, 121.12, 119.27, 118.05, 110.22, 109.41, 57.73, 54.34, 50.12, 42.15, 41.67, 34.37, 32.30, 27.96, 26.70, 20.83, 12.06; IR (KBr, cm^{-1}): 3394, 2924, 1612, 1461; HRMS (ESI) $(M+H)^+$ calcd for $C_{19}H_{25}N_2^+$ 281.2012, found 281.2011.

*Epiibogamine (**1a**):*

R_f = 0.33 (DCM/MeOH 12:1), mp 185–188 °C. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 8.08 (br s, 1H), 7.47 (d, *J* = 7.5 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.14 (m, 2H), 3.52 (br m, 2H), 3.30 (br s, 1H), 3.24 (m, 2H), 3.11–3.01 (m, 2H), 2.40 (br s, 1H), 2.21 (m, 1H), 2.07 (m, 3H), 1.67 (m, 1H), 1.43 (m, 2H), 1.10 (m, 1H), 0.94 (t, *J* = 6.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 134.46, 129.68, 127.96, 121.13, 119.40, 117.92, 110.35, 110.09, 60.79, 57.37, 54.76, 49.73, 35.13, 31.77, 29.84, 28.47, 26.40, 20.31, 12.25; IR (KBr, cm^{-1}): 3401, 2923, 1611, 1463; HRMS (ESI) $(M+H)^+$ calcd for $C_{19}H_{25}N_2^+$: 281.2012, found 281.2012.