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A concise route to iboga-analogues via the formation of suitably substituted-2-indoles

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ABSTRACT

A concise route to iboga-analogues has been developed. Important steps include a Pd-catalyzed Sonogashira coupling of Boc-2-idodaniline with terminal alkynes and the formation of 2-substituted indoles in the presence of tetrabutylammonium fluoride to give the key intermediate, dehydroisoquinuclidine-containing indole. The final step cyclization between indole-3-position and dehydroisoquinuclidine ring was achieved using Pd(II)–Ag(I) mixed metal-mediated cyclization method. Both exo- and endo-substitution with $-CO_2Me$ at C19 have been reported.

Iboga alkaloids are derived from the root bark of the African shrub *Tabernanthe Iboga*. Members of this family of alkaloids have characteristic indole-[2,3] fusion with isoquinuclidine ring by a seven-membered indoloazepine ring[1] (Fig. 1). These natural products have been claimed to be effective in treating human addiction to multiple drugs of abuse, including alcohol, heroin, and cocaine.[2] However, ibogaine **2** is tumorigenic,[3] and its neurotoxicity, particularly a degeneration of brain cells (purkinje cells) has been demonstrated[4] if the dose is high. Apart from anti addictive properties, iboga-alkaloid congeners show potent leishmanicide effects against *Leishmania amazonensis*[5a] and show anti-cholinesterase activity.[5b] Since chemical modifications of the natural product have been the major means for the exploration of the more potent analogues, a limited number of its analogues and congeners have so far been accessible.[6] Thus an efficient synthetic route is necessary for the synthesis of iboga analogues and derivatives which might be useful for the evaluation of pharmacological profiles and their biological (receptorial) target.[7]

Mostly, the analogues have been reported[6a,b] on the modification of indoloazepine ring of the natural scaffold (5,6-homologues or 6-nor of the iboga alkaloid skeleton). There is only one report[6c] on the synthesis of type **3** analogue (indole-[3,2] fusion) (Fig. 1). All the reported syntheses began with 1-benzenesulfonylindole-2-acrylates or 2-indoleacetic acid as starting material. Unlike the 3-isomer, 2-indoleacetic acid is not very easily available commercially and both the starting materials were synthesized in a number of steps.

Moreover, these methods require a prefunctionalized heterocyclic indole for the modification of indole sub-system in order to have heterocyclic analogues. But a limited number of prefunctionalized heterocyclic indoles are commercially available and are very

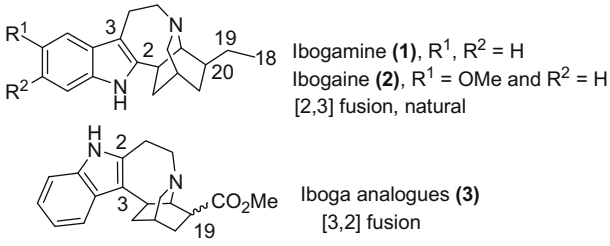

Figure 1. Iboga alkaloid family.

expensive. In addition, the reported syntheses lack the flexibility required to provide access to the more elaborate representatives on both indole and isoquinuclidine rings especially substitution at the C20 carbon (**1,2**) which has an important role in biological activities.[5a,8]

Herein we describe a convenient approach to the synthesis of iboga-analogues **3a** and **3b**, respectively, with CO_2Me substitution at C19 which could be used as a handle for derivatization (Scheme 1). As can be seen from our retrosynthetic analysis of **3** if the C3–C16 bond is disconnected, the new target molecule will be 2-substituted indole, **4** which could be obtained from 2-alkynylated aniline, **5**.

Further strategic disconnection of compound **5** shows the presence of 2-iodoaniline and alkyne-substituted isoquinuclidine **6** (route 1). Initially we thought that there might be a problem in Sonogashira coupling of compound **6** with Boc-2-iodoaniline and we therefore worked in a parallel route 2 to the synthesis of the key intermediate **4** via the formation of **5**. Synthesis of the requisite isoquinuclidine-substituted terminal alkyne **6** for the palladium-catalyzed 2-substituted indole formation is outlined in Scheme 2. The isoquinuclidine ring **8** was synthesized according to the literature procedure[9] with a slight modification (Supplementary

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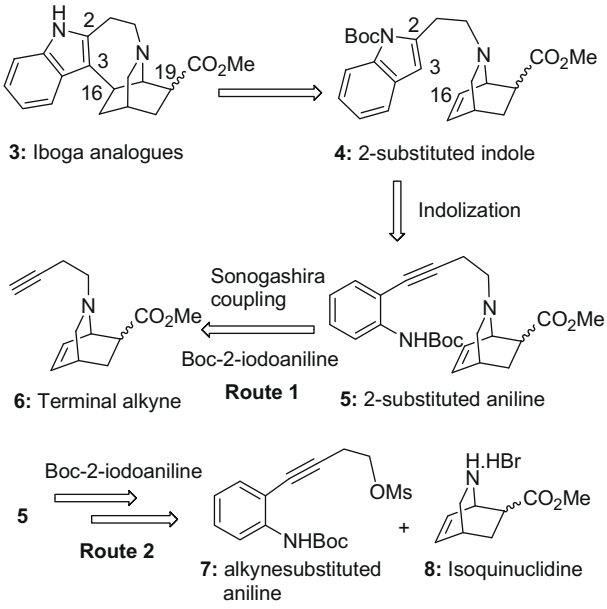
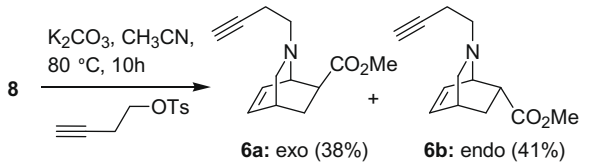


Scheme 1. Retrosynthetic strategy.



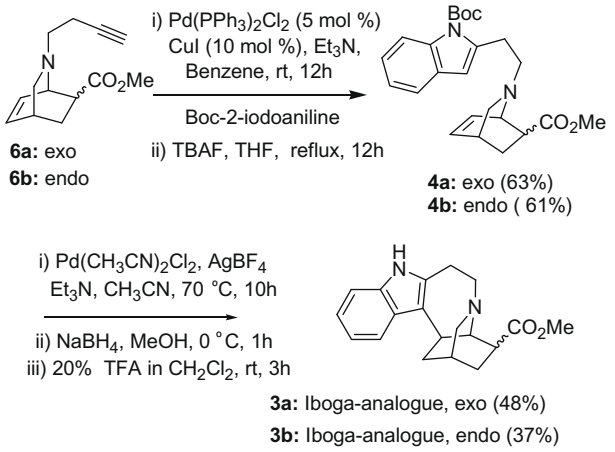
Scheme 2. Synthesis of isoquinuclidine-substituted alkynes.

data). The separation of the exo- and endo-isomers was difficult at this stage though its separation was reported[10] earlier via the formation of iodolactone in a multistep process. Here we used the material **8** directly in the next step.

The compound **8** was converted to the alkynylated isoquinuclidine **6** and its mixture of exo- and endo-isomers was then separated by column chromatography on silica gel to give **6a** and **6b**, respectively, in 1:1.1 ratio (Scheme 2). These were characterized by ^{1}H NMR. The tosylated alkyne was in turn synthesized from 3-butyn-1-ol in 95% yield. The Sonogashira coupling of terminal alkynes **6a** and **6b** with *N*-Boc-protected 2-iodoaniline was achieved under standard conditions and indolization of such aniline derivatives by the reported procedures[11] was attempted, but this gave a mixture of products. Mostly these procedures worked well for either free $-NH_2$, benzyl, tosyl, mesyl or acetyl-protected aniline. Finally we found that the Sonogashira coupling product efficiently cyclized to 2-substituted indoles **4a** and **4b**, respectively, for both exo- and endo-isomers on treatment with tetrabutylammonium fluoride (TBAF) under refluxing conditions[12] in one pot.

Pd(II)–Ag(I) mixed metal-mediated cyclization (at the 2-position of indole derivative)[13] was originally developed for the synthesis of ibogamine and we applied this methodology to its analogues **4a** and **4b** separately which afforded analogue compounds **3a** and **3b** in 48% and 37% yield, respectively (Scheme 3). Comparatively better yields were obtained in this case which may be due to the better susceptibility for electrophilicity of the indole 3-position than the 2-position. Interestingly, complex molecules such as iboga-analogues were synthesized just using a two-pot reaction.

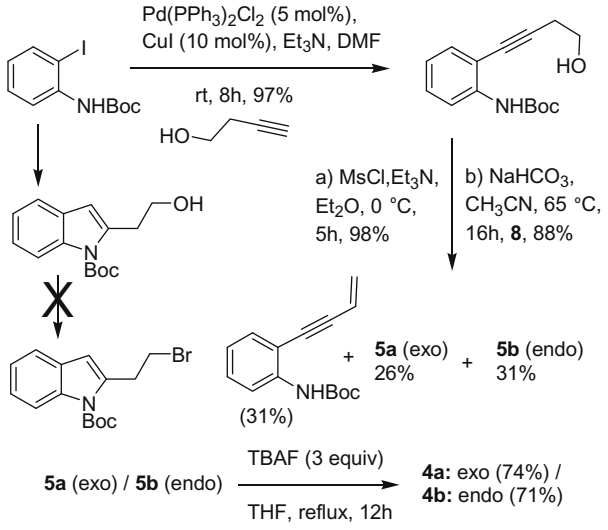
According to route 2, the compound **7** was synthesized from Boc-protected 2-iodoaniline via Sonogashira coupling with 3-butyn-1-ol at room temperature followed by mesylation. It is worthy



Scheme 3. Synthesis of iboga-analogues **3**.

to mention here that the Sonogashira-coupled product underwent cyclization to give a Boc-protected-indole-2-ethanol at high temperature (80 °C) and we tried to convert it to the bromo derivative according to the literature procedure[14] but we failed to isolate the desired product. It is reported[14] that such a bromo indole compound is obtained in poor yield when indole-2-ethanol was treated with carbon tetrabromide and triphenylphosphine. The mesylated compound **7** was then treated with **8** in the presence of $NaHCO_3$ and three products were isolated in which the desired **5a** and **5b** were obtained in 26% and 31% yield, respectively. These compounds were converted to **4a** and **4b** on treatment with TBAF in reflux condition as described earlier (Scheme 4).

In summary, we have developed a convenient approach toward the synthesis of iboga analogues using palladium-mediated Sonogashira coupling and indolization reactions as the key steps. Our synthetic approach is extremely short and flexible and we obtained (exo + endo) products **3**[15] in very high yield (overall yield 53% from Boc-2-iodoindole) in route 1. We have reported divergent approach (route 2) and the overall yield of **3** (exo + endo) was 17%. It is anticipated that minor modifications of the starting materials (indole and alkyne) should provide access to several other analogues of this alkaloid family for biological screening. Work in this direction is now underway and the results will be reported in due course.



Scheme 4. Synthesis of 2-substituted indoles **4a** and **4b**.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.028.

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15. Experimental section and spectral data for some key compounds (PE stands for petroleum ether): *Compounds* **6a** and **6b**. A suspension of K_2CO_3 (1.84 g, 13.28 mmol) in anhydrous CH_3CN (10 mL) containing the compound **8** (1.64 g, 6.64 mmol) and alkyne **6** (1.48 g, 6.64 mmol) was refluxed for 10 h, then cooled to room temperature, filtered through a Celite pad, and washed with EtOAc (10 mL). The combined organic extracts were concentrated in vacuo and purified by column chromatography on silica using EtOAc in petroleum ether (initially with 4% EtOAc and then with 10% EtOAc in PE) as eluent to give isoquinuclidine-containing alkynes **6a** (549 mg, 37.5%) as a pale yellow oil (R_f = 0.38, PE:EtOAc, 9:1) and **6b** (595 mg, 41%) as a pale yellow oil (R_f = 0.32, PE:EtOAc, 4:1).
Exo **6a**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.40 (dd, J = 7.7, 6.85 Hz, 1H), 6.20–6.16 (ddd, J = 7, 5.4, 1.35 Hz, 1H), 3.75 (ddd, J = 5.3, 2.65, 1.4 Hz, 1H), 3.67 (s, 3H), 3.10–3.06 (dd, J = 9, 2.2 Hz, 1H), 2.61–2.53 (m, 1H), 2.50 (br m, 1H), 2.38–2.34 (m, 1H), 2.28–2.22 (m, 1H), 2.18–2.12 (m, 2H), 2.07 (m, 1H), 1.87 (dd, J = 2.5, 2.45 Hz, 1H), 1.82–1.77 (dt, J = 9, 2.5 Hz, 1H), 1.36–1.28 (ddt, J = 12.0, 9.8, 2.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.7, 135.2, 129.7, 83.0, 68.5, 56.5, 54.7, 54.6, 51.8, 45.2, 30.9, 24.2, 18.3; IR (neat): ν 3296, 2939, 2118, 1736, 1435 cm^{-1}; HRMS (ESI) (M+H)$^+$ calcd for $C_{13}H_{17}NO_2H^+$ 220.1332, found 220.1337.
Endo **6b**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.39 (td, J = 7.4, 1.1 Hz, 1H), 6.13 (ddd, J = 8, 5.3, 1.3 Hz, 1H), 3.75 (ddd, J = 6, 3.3, 1.4 Hz, 1H), 3.59 (s, 3H), 3.06–3.0 (m, 1H), 2.92–2.88 (dd, J = 9.4, 2.0 Hz, 1H), 2.70–2.65 (m, 1H), 2.55 (br m, 1H), 2.44–2.37 (m, 1H), 2.29–2.25 (m, 2H), 1.96 (t, J = 2.5 Hz, 1H), 1.93 (m, 1H), 1.73–1.67 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.3, 134.7, 129.5, 82.8, 68.9, 56.6, 54.4, 54.1, 51.8, 43.9, 30.7, 25.9, 18.4; IR (neat): ν 3300, 3053, 2949, 2116, 1736, 1435 cm^{-1}; HRMS (ESI) (M+H)$^+$ calcd for $C_{13}H_{17}NO_2H^+$ 220.1332, found 220.1336.
Compound **4a**. To a mixture of *N*-Boc-2-iodoaniline (450 mg, 1.41 mmol), **6a** (370 mg, 1.69 mmol), $Pd(PPh_3)_2Cl_2$ (49 mg, 0.071 mmol), and CuI (27 mg, 0.141 mmol) were added Et_3N (3 mL) and anhydrous benzene (6 mL) under an argon atmosphere. The reaction mixture was stirred at room temperature for 12 h. Tetrabutylammonium fluoride (TBAF) (1.0 M in THF, 4.23 mmol) was added dropwise to the reaction mixture. The reaction mixture was refluxed for 12 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 and evaporated in vacuo to give the crude product which was purified by flash column chromatography on silica gel (PE:EtOAc, 5:1) to afford the isoquinuclidine-containing indole **4a** (367 mg, 63.4%) as a light yellow oil. R_f = 0.52 (PE:EtOAc, 2:1); ^{1}H NMR (300 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), 2.82–2.78 (m, 1H), 2.57 (br s, 1H), 2.47–2.41 (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 (75 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, 31.1, 28.9, 28.3, 24.4; IR (neat): ν 2947, 1732, 1454, 1329 cm^{-1}; HRMS (ESI) (M+H)$^+$ calcd for $C_{24}H_{30}N_2O_4H^+$ 411.2278, found 411.2274.
Compound **4b**. The procedure was same as reported for the synthesis of **4a** (above). The crude product was purified by flash column chromatography on silica gel (PE:EtOAc, 3:1) to afford the isoquinuclidine-containing indole **4b** (354 mg, 61%) as a light yellow oil. R_f = 0.52 (PE:EtOAc, 1:1); ^{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, 29.17, 28.44, 28.35, 28.24, 26.1; IR (neat): ν 2926, 2949, 1732, 1454 cm^{-1}; HRMS (ESI) (M+H)$^+$ calcd for $C_{24}H_{30}N_2O_4H^+$ 411.2278, found 411.2275.
Compound **3a**. To a slurry of bis(acetonitrile)palladium dichloride (179 mg, 0.70 mmol) in CH_3CN (1.5 mL) was added Et_3N (46 μL, 0.35 mmol) under an argon atmosphere. Silver tetrafluoroborate (275 mg, 1.40 mmol) was added and the orange heterogeneous mixture immediately became yellow. After 10 min, a solution of dehydroisoquinuclidine **4a** (144 mg, 0.35 mmol) in CH_3CN (2.0 mL) was added. The deep red solution was then stirred for 1 h at room temperature and then heated at 70 °C for 10 h. The reaction mixture was cooled to 0 °C and MeOH (1.5 mL) was added followed by $NaBH_4$ (13 mg, 0.35 mmol) in portions. The solution was stirred for 1 h at 0 °C, water (1 mL) was added, and the solution was acidified with cold 2 N aq HCl. The mixture was filtered through a pad of Celite to remove palladium black, extracted with ether (20 mL), and then basified with cold concentrated aq NH_4OH. The basic aq solution was extracted with ethyl acetate (3 × 15 mL). The organic extracts were combined, dried, and concentrated in vacuo to give *N*-Boc-protected and deprotected crude mixture which was used in the next step without purification.
The crude mixture was treated with 20% TFA in CH_2Cl_2 (2 mL) at 0 °C and then the reaction mixture was stirred for 3 h at room temperature. CH_2Cl_2 and volatiles were removed in vacuo and then 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 × 10 mL); the combined organic extracts were washed with brine (10 mL) and the solvent was removed by rotary evaporation. The crude product was subjected for purification by column chromatography on silica gel. Elution with 0.5–0.7% MeOH in CH_2Cl_2 gave the exo-analogue **3a** (52 mg, 48%) as a light brown solid. R_f = 0.54 (CH_2Cl_2:MeOH, 20:1); mp 99–100 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75 (br s, 1H), 7.45 (dd, J = 6.6, 1.8 Hz, 1H), 7.25 (dd, J = 6.6, 1.8 Hz, 1H), 7.16–7.07 (m, 2H), 3.73 (s, 3H), 3.62–3.57 (m, 1H), 3.48 (t, J = 1.8 Hz, 1H), 3.34–3.28 (ddd, J = 11.1, 4.5, 1.5 Hz, 1H), 3.24–3.20 (m, 2H), 3.10–3.08 (dt, J = 9.3, 2.7 Hz, 1H), 3.02 (dt, J = 9.0, 1.8 Hz, 1H), 2.83–2.79 (ddd, J = 11.1, 5.4, 2.4 Hz, 1H), 2.48–2.42 (dt, J = 16.5, 2.7 Hz, 1H), 2.40–2.32 (m, J = 13.5 Hz, 1H), 2.21–2.11 (ddt, J = 12.9, 12.3, 2.7 Hz, 1H), 2.00–1.96 (m, 1H), 1.80 (ddt, J = 13.0, 10.2, 3.0 Hz, 1H), 1.57–1.51 (ddd, J = 13.2, 7.5, 3.0 Hz, 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): ν 3396, 2928, 2858, 1728, 1460.1 cm^{-1}; HRMS (ESI) (M+H)$^+$ calcd for $C_{19}H_{22}N_2O_2H^+$ 311.1754, found 311.1754; Anal. Calcd for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.14; N, 9.03. Found: C, 73.28; H, 7.02; N, 8.59.
Compound **3b**. The procedure was same as reported for the synthesis of **3a** (above).The crude product was subjected for purification by column chromatography on silica gel. Elution with 0.5–0.7% MeOH in CH_2Cl_2 gave the endo-analogue **3b** (40 mg, 37%) as a light brown solid, R_f = 0.42 (CH_2Cl_2:MeOH, 20:1); mp 149–151 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.83 (br s, 1H), 7.40 (d, J = 7.5 Hz, 1H), 7.25 (d, J = 7.2 Hz, 1H), 7.09 (m, 2H), 3.71 (s, 3H), 3.66–3.58 (m, 1H), 3.35 (m, 3H), 3.24–3.12 (m, 3H), 3.24–3.04 (m, 4H), 2.55–2.49 (dt, J = 16.5, 2.7 Hz, 1H), 2.27–2.19 (m, 2H), 2.00 (m, 1H), 1.91 (ddt, J = 13.8, 11.1, 3.0 Hz, 1H), 1.52–1.46 (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): ν 3339, 2931, 1732, 1458 cm^{-1}; HRMS (ESI) (M+H)$^+$ calcd for $C_{19}H_{22}N_2O_2H^+$ 311.1754, found 311.1759.