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Enantiospecific total synthesis of indole alkaloids (+)-eburnamonine, (−)-aspidospermidine and (−)-quebrachamine

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ABSTRACT

An enantiospecific total synthesis of indole alkaloids eburnamonine, aspidospermidine and quebrachamine is described from lactic acid. Synthesis of all three alkaloids is accomplished from a single chiral building block. Johnson–Claisen rearrangement of a chiral allyl alcohol is the main feature for the installation of the required quaternary centre.

1. Introduction

Indole alkaloids occupy an important position in natural product chemistry, mainly because of their biological activity.[1] These alkaloids continue to spur interest in synthetic organic chemists for more than half a century and have served as bench mark targets for the development and application of innovative strategies. It was interesting to note that in spite of a number of advances in the synthesis of these alkaloids, asymmetric approaches are rather limited. One of the effective strategies for the total synthesis of natural products in an enantiopure form was the use of abundant chiral pool compounds. In this context, our group has extensively used tartaric acid, and in recent years lactic acid for the syntheses of natural products of therapeutic significance.[2] Here in, we describe in detail our efforts[3] aimed at the synthesis of alkaloids eburnamonine **1**[4,5] aspidospermidine **2**[5h,6,7] and quebrachamine **3**[8,9] (Fig. 1) from lactic acid.

Our approach for the syntheses of indole alkaloids from a single chiral component is shown below (Scheme 1). We anticipated that a multifunctional chiral building block, such as **4**, provides the necessary functionalities, which can easily be manipulated to access these structurally diverse indole alkaloids. As depicted in Scheme 1, alkene in **4** can be used as a surrogate for an aldehyde to construct the indoline skeleton of eburnamonine **1** via the Pictet–Spengler reaction, while the same alkene can instead be used as a ring closing metathesis (RCM) partner in the assembly of eburnamonine **1**. Similarly, elaboration of the primary alcohol and manipulation of the ester functionality can lead to the assembly of other alkaloids aspidospermidine **2** and quebrachamine **3**. Construction of the intermediate **4** possessing a chiral quaternary centre was envisaged by Johnson–Claisen *ortho* ester rearrangement of the allylic alcohol **5** derived from (*S*)-ethyl lactate **6**.

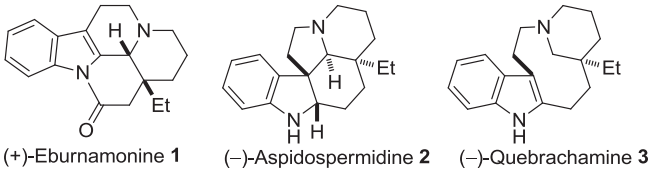

Fig. 1. Indole alkaloids **1**–**3**.

2. Results and discussion

Accordingly, the synthesis commenced with the homologation of the aldehyde, obtained from the reduction of the ester **7**, by Wittig–Horner olefination with the ylide **8**[10] to furnish the α,β-unsaturated ester **9** in 73% yield. DIBAL-H reduction of the ester **9** yielded the corresponding alcohol (93% yield), which was protected as the MOM ether **10** in 97% yield. Treatment of **10** with TBAF furnished the allylic alcohol **5** in 88% yield. Johnson–Claisen *ortho* ester rearrangement of **5** with triethylorthoacetate in presence of

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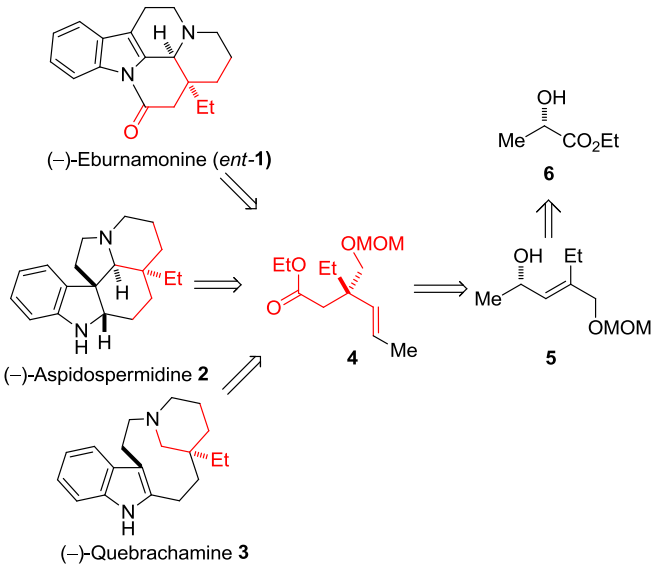
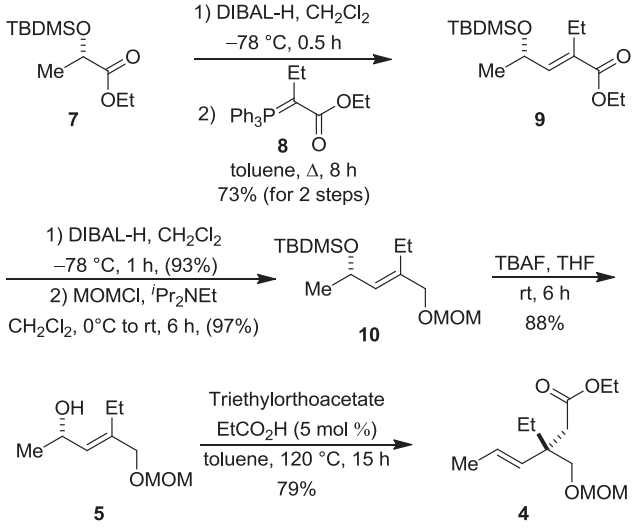


Scheme 1. Retrosynthesis for alkaloids **1**–**3**.

catalytic amount of propionic acid resulted in the ester **4** containing the quaternary centre in 79% yield (Scheme 2).

2.1. Total synthesis of (+)-eburnamonine 1

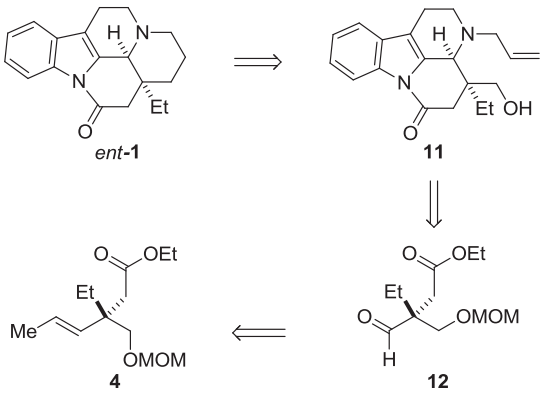
After the successful construction of the chiral building block, we envisioned the application of **4** in the synthesis of eburnamonine **1**.



Scheme 2. Synthesis of the chiral building block **4**.

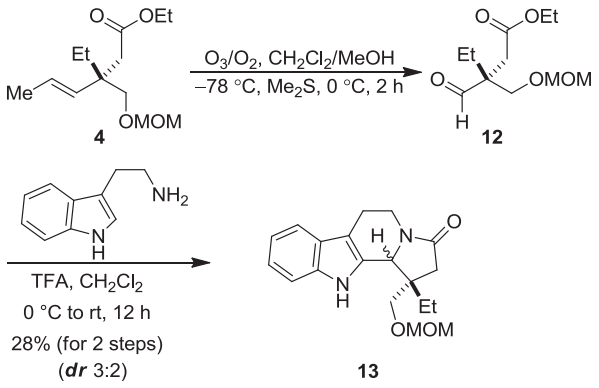
As depicted in Scheme 3, synthesis of (−)-eburnamonine *ent*-**1** was anticipated by elaboration of the alcohol in **11**, the synthesis of which was planned by Pictet–Spengler reaction of the aldehyde **12** with tryptamine or *N*-allyl tryptamine. The aldehyde in turn was envisaged by the ozonolysis of the alkene **4**.

Thus, ozonolysis of the olefin in **4** furnished the aldehyde **12**, which without further purification was treated with tryptamine in presence of TFA. Contrary to the expected product, we isolated a tetracyclic compound **13**, which consisted of a β-carboline fused to a five-membered lactam, resulting from the lactamization of the secondary amine of the intermediate carboline with the ester. This finding corroborates the fact that the greater nucleophilicity of the



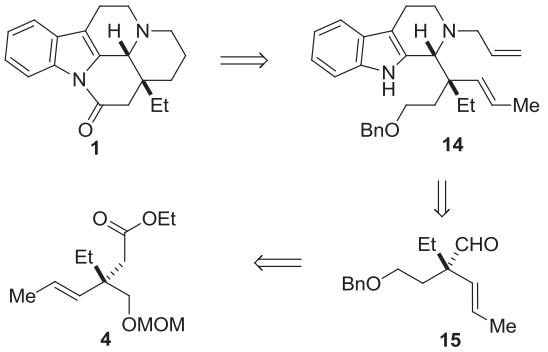
Scheme 3. Retrosynthesis for (−)-eburnamonine (*ent*-**1**).

secondary amine makes the formation of five-membered lactam more facile, than that of a six-membered lactam with the weakly nucleophilic indole –NH (Scheme 4). The product **13** was formed in 28% yield in a 3:2 diastereomeric ratio and the diastereomers were separable by column chromatography.



Scheme 4. Formation of the tetracycle **13**.

Interestingly, the Pictet–Spengler reaction of **12** with *N*-allyl tryptamine did not proceed at all. At this stage, we redrew our retrosynthesis and as depicted in Scheme 5, synthesis of eburnamonine **1** was envisaged by RCM reaction of **14** followed by the known oxidative lactamization with the indole –NH. Pictet–-Spengler reaction of the aldehyde **15** derived from **4** was chosen as an appropriate precursor for the synthesis of **14**.

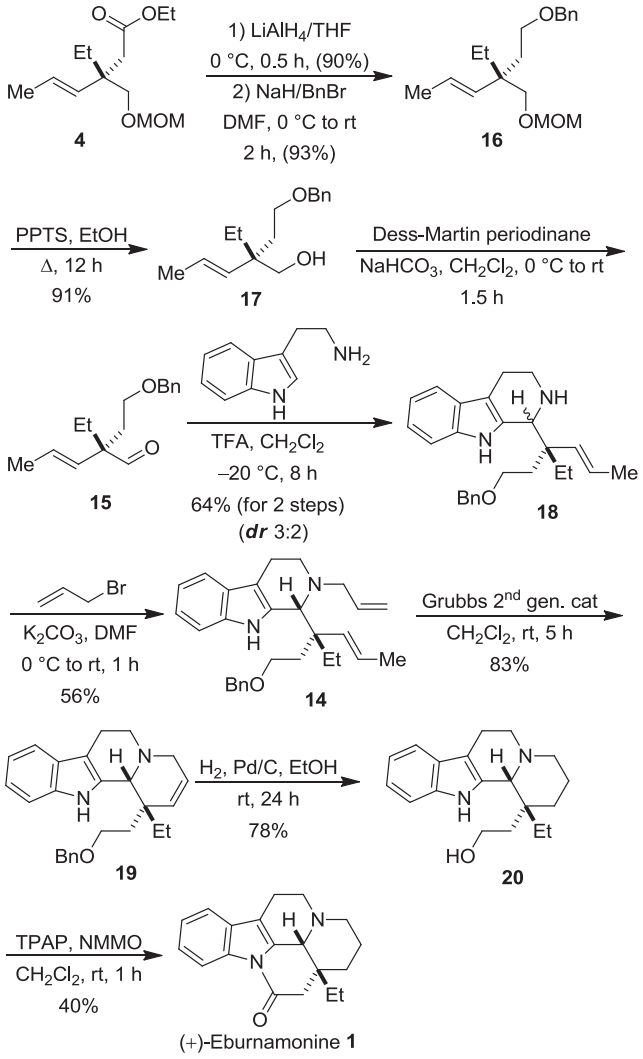


Scheme 5. Modified retrosynthesis for (+)-eburnamonine **1**.

Consequently, reduction of the ester in **4** with $LiAlH_4$ produced the alcohol (90% yield), which on further reaction with NaH/BnBr afforded the benzyl ether **16** in 93% yield. Deprotection of the MOM group in **16** with PPTS in refluxing EtOH afforded the primary

alcohol **17** in 91% yield. Oxidation of the alcohol resulted in the aldehyde **15**, which without further purification was used in the next reaction. Thus Pictet–Spengler reaction of the aldehyde **15** with tryptamine at −20 °C furnished the β-carboline **18** as an inseparable 3:2 diastereomeric mixture in 64% yield. Interestingly, performing the reaction at 0 °C or at room temperature furnished **18** in 66% yield but with reversed diastereomeric ratio (2:3).

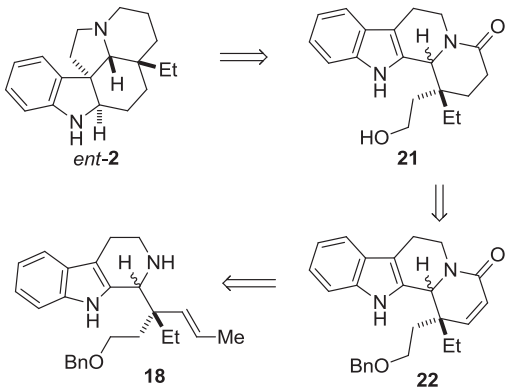
Allylation of **18** furnished a separable mixture of *N*-allylcarbolines and the required major diastereomer **14** was isolated in 56% yield.[11] RCM reaction of the diene with Grubbs second generation catalyst led to the product **19** in 83% yield. Hydrogenation of the alkene in **19** with concomitant deprotection of the benzyl ether afforded the primary alcohol **20** in 78% yield. Following a protocol described by Schultz and Pettus,[5e] oxidation of **20** with TPAP/NMMO furnished (+)-eburnamonine **1** in 40% yield (Scheme 6). The spectral and physical data were in complete agreement with that reported in literature.[5c]



Scheme 6. Total synthesis of (+)-eburnamonine **1**.

2.2. Total synthesis of (−)-aspidospermidine 2

After successfully accomplishing the synthesis of (+)-eburnamonine **1**, application of the carboline **18** in the synthesis of (+)-aspidospermidine *ent*-**2** was undertaken. As portrayed in Scheme 7, synthesis of *ent*-**2** was anticipated via the known



Scheme 7. Retrosynthesis for (+)-aspidospermidine (*ent*-**2**).

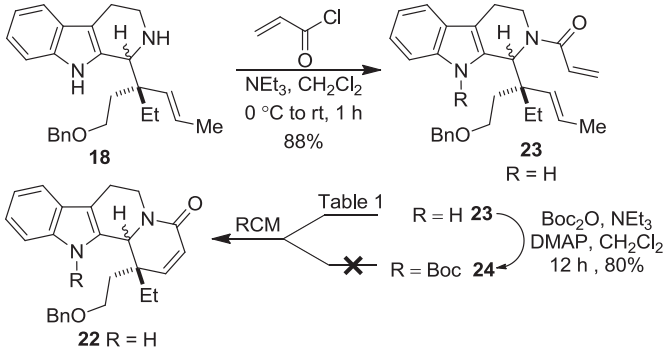
conversion of the alcohol **21** to aspidospermidine.[6c] Formation of the alcohol **21** was envisaged from the benzyl ether **22**, the synthesis of which is planned by the RCM of the acryl amide derived from the carboline **18**.

Accordingly, acryl amide **23** was prepared by reaction of the carboline **18** with acryloyl chloride in presence of triethyl amine in 88% yield. Surprisingly, RCM reaction of the acryl amide **23** was found to be sluggish. A series of conditions were explored and the best yield of the product **22** was found to be 39% by employing 20 mol % of Hoveyda–Grubbs second generation[12] catalyst (Table 1). Protection of the indole –NH in **23** as the Boc carbamate **24**, did not facilitate the RCM reaction (Scheme 8).

Table 1
RCM reaction of **23** under various conditions

S. No.	Catalyst loading	Solvent	Temp (°C)	Time (h)	Yield
1	Grubbs first gen (5 mol %)	CH_2Cl_2	50	12	—[a]
2	Grubbs second gen (10 mol %)	CH_2Cl_2	50	12	12%
3	Grubbs second gen (5 mol %)+$Ti(O^iPr)_4$(1 equiv)	Toluene	120	12	—[a]
4	Grubbs second gen (10 mol %)+$Ti(O^iPr)_4$(20 mol %)	Toluene	120	36	17%
5	Hoveyda–Grubbs second (5 mol %)	Toluene	120	12	—[a]
6	Hoveyda–Grubbs second (20 mol %)	Toluene	120	18	39%

[a] Starting material was recovered with no appreciable reaction.

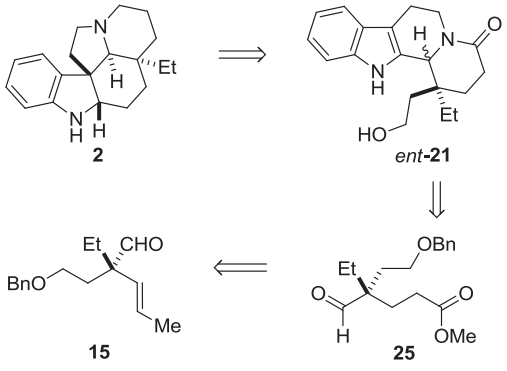


Scheme 8. Synthesis of **22**.

With the RCM of **23** providing moderate yields of the required product **22**, an alternate strategy for the synthesis of aspidospermidine was undertaken. Thus, synthesis of the lactam *ent*-**21** was planned by Pictet–Spengler reaction of the aldehyde **25** with concomitant lactamization. Synthesis of the aldehyde **25** was

planned from **15** via a two carbon homologation of the aldehyde in **15** followed by ozonolysis (Scheme 9).

Accordingly, aldehyde **15** was elaborated to the unsaturated ester **26** by Wittig–Horner olefination. Regioselective reduction of



Scheme 9. Modified retrosynthesis for (−)-aspidospermidine **2**.

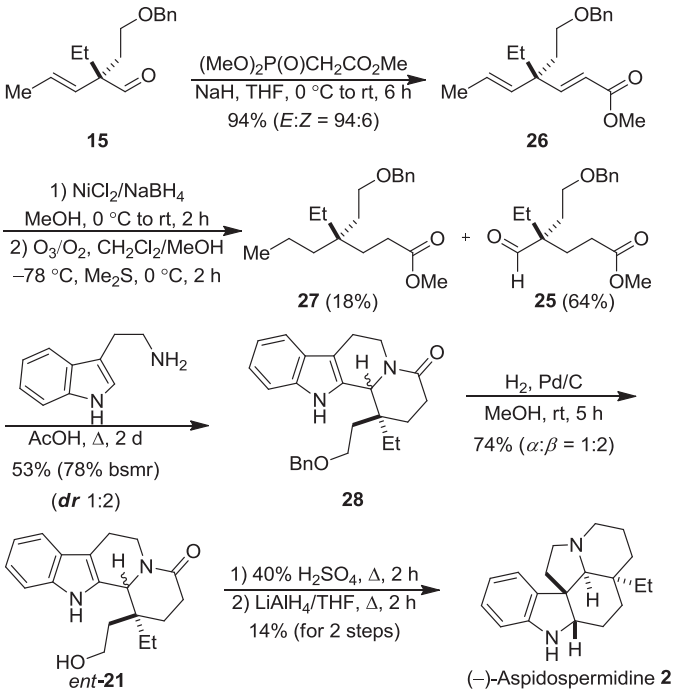
the unsaturated double bond in **26** was accomplished with $NaBH_4$ in presence of $NiCl_2$,[13] to afford the required compound as an inseparable mixture with **27** resulting from the saturation of both double bonds. To circumvent the problem with isolation of the required compound, ozonolysis was carried out on the mixture, which furnished the aldehyde **25** in 64% yield along with **27** in 18% yield.

Pictet–Spengler reaction of the aldehyde **25** with tryptamine generated the carboline, which underwent in situ lactamization with the ester to furnish the lactam **28** in 53% yield as an inseparable mixture of diastereomers. Debenzylation of **28** furnished the primary alcohol *ent*-**21** in 74% yield and the diastereomers were separable by chromatography.[14] Although the diastereomers were separable, we proceeded with the mixture as the newly formed stereogenic centre is of no consequence in the known final step. Thus, treatment of *ent*-**21** with 40% H_2SO_4 followed by reduction with $LiAlH_4$ afforded aspidospermidine **2** in 14% yield for two steps (Scheme 10).[5e,6c] The spectral and physical data of the synthetic sample were in agreement with that reported in literature.[15]

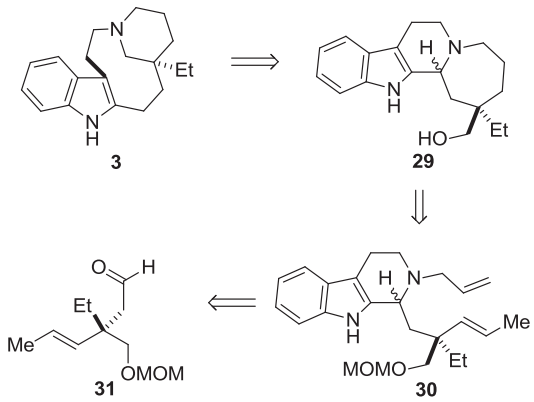
2.3. Total synthesis of (−)-quebrachamine 3

After the successful synthesis of aspidospermidine **2**, application of the chiral building block **4** in the synthesis of another structurally diverse indole alkaloid, (−)-quebrachamine **3** was undertaken. Synthesis of **3** was envisaged from the known intermediate **29** via Hoffmann degradation of the corresponding mesylate.[8f] Synthesis of **29** was anticipated by RCM of the diene **30**, which can be derived from the aldehyde **31** via Pictet–Spengler reaction with tryptamine (Scheme 11).

Thus, reduction of the ester **4** with DIBAL-H afforded the corresponding aldehyde **31**, which on Pictet–Spengler reaction with tryptamine furnished the β-carbolines **32** in 66% yield as a 1:1 inseparable mixture of diastereomers. Allylation of the carboline **32** afforded a separable mixture of the dienes **30**α (32% yield) and **30**β (31% yield).[16] RCM of the dienes **30**α and **30**β with Grubbs second generation catalyst produced the azepines **33**α and **33**β in 71% and 67% yields, respectively, which were hydrogenated to the corresponding azepanes **34**α (75% yield) and **34**β (79% yield). Deprotection of the MOM group in **34**α and **34**β with 6 N HCl gave the known primary alcohols **29**α and **29**β[8j] in 60% and 57% yields, respectively. Treatment of **29**α and **29**β with MsCl/pyridine followed by refluxing the pre-formed mesylate in $CHCl_3$ afforded



Scheme 10. Total synthesis of (−)-aspidospermidine **2**.

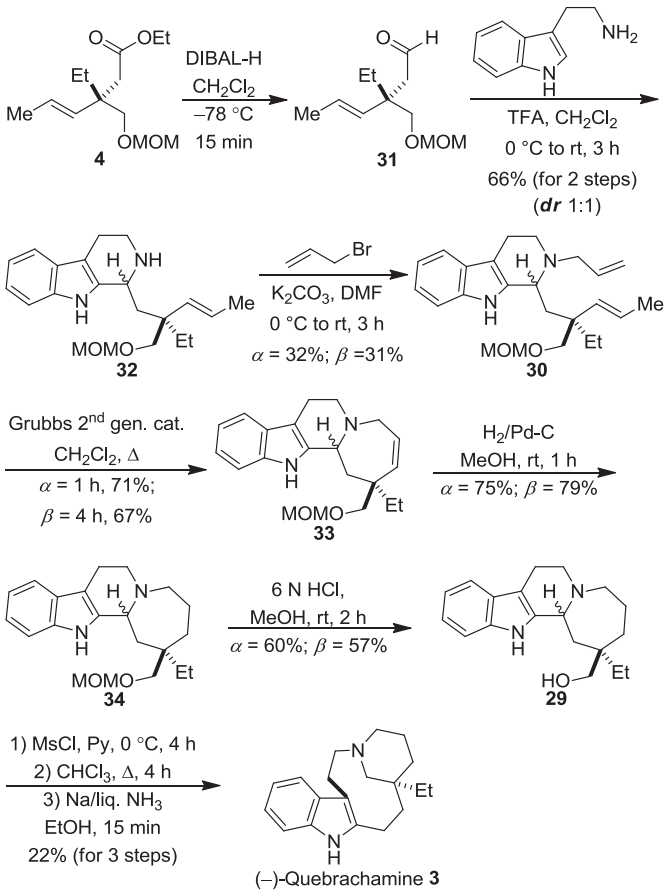


Scheme 11. Retrosynthesis for (−)-quebrachamine **3**.

the quaternary salt. Reductive ring opening of the quaternary salt with Na/liquid NH_3 furnished (−)-**3** in 22% yield for three steps (Scheme 12).[8f] The spectral and physical data of synthetic quebrachamine were in agreement with that reported in literature.[9d]

3. Conclusion

In conclusion, a linear strategy for the synthesis of structurally diverse indole alkaloids (+)-eburnamonine, (−)-aspidospermidine and (−)-quebrachamine was presented from a single chiral building block. The key chiral building block was prepared from (*S*)-ethyl lactate using Johnson–Claisen rearrangement as the pivotal reaction. The total synthesis of eburnamonine was accomplished in a 15 step linear sequence with 3.2% overall yield, aspidospermidine in 17 steps with 1.2% overall yield and quebrachamine in 15 steps with 1.3% overall yield. The strategy depicted is useful for synthesis of numerous analogues of these natural products and natural product like compounds.



Scheme 12. Total synthesis of (−)-quebrachamine **3**.

4. Experimental section

4.1. General

Column chromatography was performed on silica gel, Acme grade 100–200 mesh and/or on neutral alumina, SD-Fine grade. TLC plates were visualized either with UV, in an iodine chamber, or with phosphomolybdic acid spray. All reagents were purchased from commercial sources and were used without additional purification. THF was freshly distilled over Na–benzophenone ketyl. Melting points were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 400 MHz machine in $CDCl_3$ or DMSO-d_6 as solvent with TMS as reference unless otherwise indicated. Unless stated otherwise, all reactions were performed under inert atmosphere. All specific rotations were determined at 24 °C. HRMS was obtained using a micromass-QTOF spectrometer using electrospray ionization (ESI).

*4.1.1. (S,E)-Ethyl 4-((tert-butyldimethylsilyl)oxy)-2-ethylpent-2-enoate (**9**).* To a stirred solution of the ester **7** (0.42 g, 1.81 mmol) in dry CH_2Cl_2 (5 mL) was added DIBAL-H (2.0 mL of 1.0 M solution in toluene, 2.00 mmol) dropwise at −78 °C for a period of 5 min under argon atmosphere. The reaction mixture was stirred at the same temperature for 30 min. After completion of the reaction (TLC), it was quenched by the addition of a saturated aqueous solution of potassium sodium tartrate (10 mL), diluted with Et_2O (10 mL) and stirred for 1 h at room temperature. The aqueous layer was extracted with Et_2O (2×10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated to yield the crude aldehyde, which was used in the next step without further purification.

To a stirred solution of the crude aldehyde (obtained above) in dry toluene (10 mL) was added phosphorane **8** (1.36 g, 3.62 mmol) under nitrogen atmosphere and the reaction mixture was refluxed for 8 h. After completion of the reaction (TLC), it was cooled to room temperature and most of the solvent was evaporated off. The crude residue thus obtained was purified by silica gel column chromatography using petroleum ether/CH_2Cl_2 (7:3) as eluent to afford **9** (0.38 g, 73%) as a colourless oil. R_f 0.65 (50% CH_2Cl_2/petroleum ether); $[\alpha]_D^{24}$ −2.6 (*c* 1.1, $CHCl_3$); IR (neat): ν_{max} 2960, 2935, 1717, 1239, 1087 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 6.63 (d, *J*=8.3 Hz, 1H), 4.70–4.54 (m, 1H), 4.19 (q, *J*=7.1 Hz, 2H), 2.39–2.15 (m, 2H), 1.30 (t, *J*=7.1 Hz, 3H), 1.24 (d, *J*=6.3 Hz, 3H), 1.03 (t, *J*=7.5 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 167.7, 145.1, 131.6, 65.6, 60.5, 25.8 (3C), 24.2, 20.4, 18.1, 14.2, 14.0, −4.5, −4.7; HRMS: [M+Na] found 309.1862. $C_{15}H_{30}O_3Si$+Na requires 309.1862.

*4.1.2. (S,E)-6-Ethyl-8,10,10,11,11-pentamethyl-2,4,9-trioxa-10-silado dec-6-ene (**10**).* To a stirred solution of the ester **9** (0.75 g, 2.62 mmol) in dry CH_2Cl_2 (10 mL) was added DIBAL-H (5.8 mL of 1.0 M solution in toluene, 5.80 mmol) dropwise at −78 °C for a period of 10 min under argon atmosphere. The reaction mixture was then stirred at the same temperature for 1 h. After completion of the reaction (TLC), it was quenched by the addition of a saturated aqueous solution of potassium sodium tartrate (30 mL), diluted with EtOAc (20 mL) and stirred for 1 h at room temperature. The aqueous layer was extracted with EtOAc (2×15 mL). The combined organic layers were washed with brine (15 mL) and dried over anhydrous Na_2SO_4. The crude residue obtained after evaporation of the solvent was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1) as eluent to afford the allylic alcohol (0.60 g, 93%) as a colourless oil. R_f 0.35 (20% EtOAc/petroleum ether); $[\alpha]_D^{24}$ +4.8 (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 3351, 2960, 2932, 1255, 1084 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 5.40 (d, *J*=8.3 Hz, 1H), 4.67–4.50 (m, 1H), 4.02 (s, 2H), 2.23–1.94 (m, 2H), 1.72 (br s, 1H), 1.19 (d, *J*=6.2 Hz, 3H), 1.00 (t, *J*=7.6 Hz, 3H), 0.86 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 138.9, 130.9, 66.0, 65.2, 25.8 (3C), 25.0, 21.2, 18.1, 13.3, −4.5, −4.7; HRMS: [M+Na] found 267.1753. $C_{13}H_{28}O_2Si$+Na requires 267.1756.

To a stirred solution of the allylic alcohol (0.13 g, 0.53 mmol) in dry CH_2Cl_2 (2 mL) were added diisopropylethylamine (0.55 mL, 3.18 mmol) and MOMCl (0.16 mL, 2.12 mmol) at 0 °C under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 6 h. After completion of the reaction (TLC), it was poured into cold water (5 mL). It was then extracted with EtOAc (2×10 mL). The combined organic layers were washed with brine (5 mL) and dried over anhydrous Na_2SO_4. The crude residue obtained after evaporation of the solvent was purified by column chromatography using petroleum ether/EtOAc (9:1) as eluent to afford **10** (0.15 g, 97%) as a colourless oil. R_f 0.65 (10% EtOAc/petroleum ether); $[\alpha]_D^{24}$ −0.8 (*c* 1.1, $CHCl_3$); IR (neat): ν_{max} 2960, 2934, 1152, 1087, 1047 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 5.43 (d, *J*=8.3 Hz, 1H), 4.59 (s, 2H), 4.67–4.50 (m, 1H), 3.96 (s, 2H), 3.36 (s, 3H), 2.21–1.97 (m, 2H), 1.19 (d, *J*=6.1 Hz, 3H), 1.00 (t, *J*=7.5 Hz, 3H), 0.86 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 135.5, 133.2, 95.3, 70.2, 65.2, 55.2, 25.8 (3C), 25.0, 21.4, 18.1, 13.0, −4.4, −4.6; HRMS: [M+Na] found 311.2016. $C_{15}H_{32}O_3Si$+Na requires 311.2018.

*4.1.3. (S,E)-4-((Methoxymethoxy)methyl)hex-3-en-2-ol (**5**).* To a stirred solution of the TBS ether **10** (0.15 g, 0.52 mmol) in dry THF (3 mL) was added TBAF (0.78 mL of 1.0 M solution in THF, 0.78 mmol) at room temperature under nitrogen atmosphere. The reaction mixture was stirred at the same temperature for 6 h. After completion of the reaction (TLC), it was poured into water (5 mL)

and extracted with EtOAc (2×10 mL). The combined organic layers were washed with brine (5 mL) and dried over anhydrous Na_2SO_4. The residue obtained after evaporation of the solvent was purified by column chromatography using petroleum ether/EtOAc (6:4) as eluent to afford alcohol **5** (0.08 g, 88%) as a colourless oil. R_f 0.25 (40% EtOAc/petroleum ether); $[\alpha]_D^{24}$ −6.7 (*c* 1.3, $CHCl_3$); IR (neat): ν_{max} 3423, 2969, 2936, 1150, 1046 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 5.42 (d, *J*=8.7 Hz, 1H), 4.58 (s, 2H), 4.66–4.49 (m, 1H), 3.93 (s, 2H), 3.33 (s, 3H), 2.19 (br s, 1H), 2.24–1.19 (m, 2H), 1.21 (d, *J*=6.3 Hz, 3H), 0.98 (t, *J*=7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 138.8, 131.4, 95.4, 70.2, 63.8, 55.2, 23.6, 21.4, 13.4; HRMS: [M+Na] found 197.1155. $C_9H_{18}O_3$+Na requires 197.1154.

*4.1.4. (S,E)-Ethyl 3-ethyl-3-((methoxymethoxy)methyl)hex-4-enoate (**4**).* To a stirred solution of the alcohol **5** (0.26 g, 1.5 mmol) in dry toluene (9 mL) were added triethylorthoacetate (1.36 mL, 7.50 mmol) and propionic acid (3 mg, 0.05 mmol) under nitrogen atmosphere. The resulting solution was heated at 120 °C for 8 h. Later propionic acid (3 mg, 0.05 mmol) was added and the heating continued for further 7 h. After completion of the reaction (TLC), the reaction mixture was cooled to room temperature and most of the solvent was evaporated off and the crude residue thus obtained was purified by silica gel column chromatography using petroleum ether/Et_2O (9:1) as eluent to afford **4** (0.29 g, 79%) as a colourless oil. R_f 0.40 (20% Et_2O/petroleum ether); $[\alpha]_D^{24}$ −4.7 (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 2968, 2936, 1735, 1113, 1051 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 5.40–5.32 (m, 2H), 4.62 (s, 2H), 4.09 (q, *J*=7.1 Hz, 2H), 3.52 (s, 2H), 3.35 (s, 3H), 2.44 and 2.38 (ABq, J_1=J_2=13.9 Hz, 2H), 1.68 (d, *J*=5.0 Hz, 3H), 1.52 (q, *J*=7.3 Hz, 2H), 1.23 (t, *J*=7.2 Hz, 3H), 0.83 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 171.9, 134.6, 124.1, 96.8, 71.5, 59.9, 55.2, 42.3, 39.7, 28.4, 18.4, 14.2, 7.9; HRMS: [M+Na] found 267.1571. $C_{13}H_{24}O_4$+Na requires 267.1572.

*4.1.5. Preparation of γ-lactams (**13a**) and (**13b**).* Ozone was bubbled through a pre cooled (−78 °C) solution of the ester **4** (0.13 g, 0.53 mmol) in a mixture of CH_2Cl_2:MeOH (4:1, 8 mL), containing solid $NaHCO_3$ (0.02 g) till the pale blue colour persisted. Excess ozone was flushed off with oxygen and Me_2S (0.2 mL) was added. The reaction mixture was warmed up to 0 °C and stirred at the same temperature for 2 h. The reaction mixture was filtered through a short pad of Celite and the Celite pad was washed with EtOAc (20 mL) to yield the crude aldehyde **12**, which was used in the next step without further purification.

To a stirred solution of the aldehyde **12** (obtained above) in dry CH_2Cl_2 (3 mL) was added tryptamine (0.09 g, 0.56 mmol) at room temperature under nitrogen atmosphere. The reaction mixture was cooled to 0 °C and CF_3CO_2H (0.06 mL, 0.80 mmol) was added slowly. It was then slowly allowed to warm up to room temperature and stirred for 12 h. After completion of the reaction (TLC), it was cautiously quenched with saturated aqueous solution of $NaHCO_3$ (5 mL). The reaction mixture was poured into water (5 mL) and was extracted with EtOAc (2×15 mL). The combined organic layers were washed with brine (5 mL) and dried over anhydrous Na_2SO_4. The crude residue obtained after evaporation of solvent was purified by silica gel column chromatography using petroleum ether/EtOAc (1:1) as eluent to afford **13a** (0.03 g, 17%) and **13b** (0.02 g, 11%) as pale yellow oils.

Compound **13a**: R_f 0.45 (EtOAc); $[\alpha]_D^{24}$ +38.8 (*c* 0.5, $CHCl_3$); IR (neat): ν_{max} 3296, 2928, 1673, 1441, 1049 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.45 (br s, 1H), 7.49 (d, *J*=7.7 Hz, 1H), 7.33 (d, *J*=8.0 Hz, 1H), 7.24–7.06 (m, 2H), 4.75 (s, 1H), 4.59–4.45 (m, 1H), 4.41 and 4.38 (ABq, J_1=J_2=6.4 Hz, 2H), 3.42 and 3.33 (ABq, J_1=J_2=10.1 Hz, 2H), 3.18 (s, 3H), 3.00–2.76 (m, 3H), 2.48 and 2.28 (ABq, J_1=J_2=16.8 Hz, 2H), 2.08–1.95 (m, 1H), 1.90–1.74 (m, 1H), 1.08 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 172.6, 136.4, 129.9, 126.8, 122.2, 119.6, 118.2, 110.9, 110.8, 97.0, 70.1, 62.7, 55.5, 45.0, 39.5, 38.2, 29.3, 20.8, 9.0; HRMS: [M+Na] found 351.1684. $C_{19}H_{24}N_2O_3$+Na requires 351.1685.

Compound **13b**: R_f 0.45 (EtOAc); $[\alpha]_D^{24}$ −38.0 (*c* 0.2, $CHCl_3$); IR (neat): ν_{max} 3318, 2927, 1680, 1443, 1048 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.81 (br s, 1H), 7.51 (d, *J*=7.8 Hz, 1H), 7.35 (d, *J*=8.1 Hz, 1H), 7.26–7.05 (m, 2H), 4.92 (s, 1H), 4.89 and 4.86 (ABq, J_1=J_2=6.5 Hz, 2H), 4.54 (dd, J_1=12.8, J_2=5.5 Hz, 1H), 3.84 and 3.62 (ABq, J_1=J_2=9.4 Hz, 2H), 3.50 (s, 3H), 3.05–2.74 (m, 3H), 2.43 and 2.27 (ABq, J_1=J_2=16.5 Hz, 2H), 1.45–1.18 (m, 2H), 0.77 (t, *J*=7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 171.3, 135.8, 129.6, 126.8, 122.0, 119.4, 118.3, 111.0, 109.6, 96.9, 72.5, 63.7, 56.0, 44.9, 39.0, 37.7, 22.8, 20.8, 7.5; HRMS: [M+Na] found 351.1680. $C_{19}H_{24}N_2O_3$+Na requires 351.1685.

*4.1.6. (S,E)-(((3-Ethyl-3-((methoxymethoxy)methyl)hex-4-en-1-yl) oxy)methyl)benzene (**16**).* $LiAlH_4$ (0.09 g, 2.37 mmol) was suspended in dry THF (2 mL) and a solution of the ester (0.28 g, 1.15 mmol) **4** in dry THF (4 mL) was added dropwise over 10 min at 0 °C and was stirred at the same temperature for 30 min. After completion of the reaction (TLC), the reaction mixture was cautiously quenched by addition of EtOAc (5 mL). The reaction mixture was then filtered to remove the inorganic precipitate formed. The precipitate was washed with EtOAc (30 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the residue obtained after evaporation of the solvent was purified by column chromatography using petroleum ether/EtOAc (7:3) as eluent to afford the alcohol (0.21 g, 90%) as a colourless oil. R_f 0.50 (30% EtOAc/petroleum ether); $[\alpha]_D^{24}$ −8.2 (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 3421, 2934, 2883, 1111, 1048 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 5.35 (dq, J_1=16.0, J_2=6.1 Hz, 1H), 5.25 (d, *J*=16.0 Hz, 1H), 4.58 (s, 2H), 3.61 (t, *J*=6.8 Hz, 2H), 3.38 (s, 2H), 3.33 (s, 3H), 2.48 (br s, 1H), 1.66 (d, *J*=6.2 Hz, 3H), 1.75–1.56 (m, 2H), 1.39 (qd, J_1=7.5, J_2=2.5 Hz, 2H), 0.76 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 135.8, 123.9, 96.7, 72.2, 59.1, 55.3, 41.7, 38.6, 28.4, 18.4, 7.8; HRMS: [M+Na] found 225.1467. $C_{11}H_{22}O_3$+Na requires 225.1467.

To a stirred solution of the alcohol (0.20 g, 0.99 mmol) (obtained above) in dry DMF (2 mL) was added NaH (0.08 g of 60% suspension in mineral oil, 2.0 mmol) at 0 °C under nitrogen atmosphere. The reaction mixture was stirred at the same temperature for 30 min. Benzyl bromide (0.18 mL, 1.52 mmol) was then added slowly and the reaction mixture was stirred for 2 h at room temperature. After completion of the reaction (TLC), it was cautiously quenched by addition of ice cold water. The reaction mixture was then poured into water (20 mL) and was extracted with EtOAc (2×15 mL). The combined organic layers were washed with brine (15 mL) and dried over anhydrous Na_2SO_4. The crude residue obtained after evaporation of the solvent was purified by column chromatography using petroleum ether/EtOAc (9:1) as eluent to afford **16** (0.27 g, 93%) as a colourless oil. R_f 0.70 (15% EtOAc/petroleum ether); $[\alpha]_D^{24}$ −3.0 (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 2930, 2880, 1148, 1108, 1048 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.38–7.20 (m,5H), 5.35 (dq, J_1=16.0, J_2=5.9 Hz, 1H), 5.27 (d, *J*=16.0 Hz, 1H), 4.57 (s, 2H), 4.47 (s, 2H), 3.49 (t, *J*=7.6 Hz, 2H), 3.35 (dd, J_1=12.5, J_2=9.5 Hz, 2H), 3.30 (s, 3H), 1.83–1.61 (m, 2H), 1.67 (d, *J*=5.7 Hz, 3H), 1.40 (qd, J_1=7.5, J_2=3.8 Hz, 2H), 0.79 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 138.6, 135.8, 128.3 (2C), 127.6 (2C), 127.4, 123.6, 96.7, 72.9, 72.0, 67.0, 55.2, 41.5, 34.6, 28.2, 18.5, 7.8; HRMS: [M+Na] found 315.1933. $C_{18}H_{28}O_3$+Na requires 315.1936.

*4.1.7. (S,E)-2-(2-(Benzyloxy)ethyl)-2-ethylpent-3-en-1-ol (**17**).* To a stirred solution of the MOM ether (0.43 g, 1.47 mmol) **16** in EtOH (10 mL) was added pyridinium *p*-toluenesulfonate (1.86 g, 7.41 mmol) and the resulting solution was refluxed for 12 h. After completion of the reaction (TLC), it was cooled to room temperature and most of the solvent was evaporated off. The crude residue thus obtained was dissolved in CH_2Cl_2 (15 mL) and was neutralized

by addition of solid $NaHCO_3$ (1.68 g, 20 mmol). The reaction mixture was filtered through a short pad of Celite and the Celite pad was washed with CH_2Cl_2 (30 mL). The solvent was evaporated off and the residue thus obtained was purified by silica gel column chromatography using petroleum ether/EtOAc (8:2) as eluent to afford **17** (0.33 g, 91%) as a colourless oil. R_f 0.30 (15% EtOAc/petroleum ether); $[\alpha]_D^{24}$ −14.5 (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 3442, 2930, 2877, 1098, 1042 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.42–7.23 (m, 5H), 5.37 (dq, J_1=16.0, J_2=6.3 Hz, 1H), 5.21 (dd, J_1=16.0, J_2=1.0 Hz, 1H), 4.50 (s, 2H), 3.54 (t, *J*=5.8 Hz, 2H), 3.48 (dd, J_1=11.4, J_2=6.2 Hz, 1H), 3.36–3.31 (m, 1H), 2.82 (t, *J*=7.0 Hz, 1H), 1.69 (d, *J*=6.2 Hz, 3H), 1.70–1.66 (m, 2H), 1.39 (q, *J*=7.4 Hz, 2H), 0.79 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 137.8, 135.9, 128.4 (2C), 127.7 (3C), 124.5, 73.2, 67.0, 66.9, 43.4, 34.5, 28.2, 18.5, 7.9; HRMS: [M+Na] found 271.1684. $C_{16}H_{24}O_2$+Na requires 271.1674.

*4.1.8. (R)-2-Allyl-1-((S,E)-1-(benzyloxy)-3-ethylhex-4-en-3-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (**14**).* To a stirred solution of the alcohol (0.045 g, 0.18 mmol) **17** in dry CH_2Cl_2 (2 mL) were added $NaHCO_3$ (0.076 g, 0.90 mmol) and Dess–Martin periodinane (0.12 g, 0.27 mmol) at 0 °C under nitrogen atmosphere. The reaction mixture was warmed to room temperature and stirred for 1.5 h at room temperature. After completion of the reaction (TLC), it was quenched by addition of saturated aqueous solutions of $NaHCO_3$ (3 mL) and $Na_2S_2O_3$ (3 mL). The reaction mixture was diluted with Et_2O (5 mL) and the aqueous phase was extracted with Et_2O (2×5 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4 and concentrated. The crude aldehyde **15** thus obtained as a colourless oil was used as such in the next step without further purification.

To a stirred solution of the aldehyde **15** in dry CH_2Cl_2 (1 mL) was added tryptamine (0.025 g, 0.16 mmol) at room temperature under nitrogen atmosphere. The reaction mixture was cooled to −78 °C and CF_3CO_2H (0.02 mL, 0.24 mmol) was slowly added. It was then slowly allowed to warm up to −20 °C and stirred at the same temperature for 8 h. After completion of the reaction (TLC), it was cautiously quenched with a saturated aqueous solution of $NaHCO_3$ (3 mL). The resulting solution was poured into water (5 mL) and extracted with EtOAc (2×10 mL). The combined organic layers were washed with brine (5 mL) and dried over anhydrous Na_2SO_4. The crude residue obtained after evaporation of solvent was purified by a rapid silica gel column chromatography using petroleum ether/EtOAc (3:7) as eluent to afford **18** (0.039 g, 64%) as a pale yellow oil.

To a stirred solution of the carboline **18** (0.039 g, 0.10 mmol) in dry DMF (1 mL) were added K_2CO_3 (0.028 g, 0.20 mmol) and allyl bromide (0.02 mL, 0.20 mmol) at 0 °C under nitrogen atmosphere. The reaction mixture was stirred at 10 °C for 1 h. After completion of the reaction (TLC), it was poured into water (5 mL) and extracted with EtOAc (2×10 mL). The combined organic layers were washed with brine (5 mL) and dried over anhydrous Na_2SO_4. The crude diastereomeric mixture obtained after evaporation of the solvent was separated and purified by silica gel column chromatography using petroleum ether/EtOAc (9:1) as eluent to afford **14** (0.024 g, 56%) as a pale yellow foam and the minor diastereomer in (0.016 g) 38% yield.

Compound **14**: R_f 0.50 (10% EtOAc/petroleum ether); $[\alpha]_D^{24}$ −27.1 (*c* 0.8, $CHCl_3$); IR (neat): ν_{max} 3366, 2929, 2879, 1458, 1094 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.07 (br s, 1H), 7.50 (d, *J*=7.5 Hz, 1H), 7.41–7.27 (m, 5H), 7.17 (d, *J*=7.8 Hz, 1H), 7.07–7.00 (m, 2H), 5.94 (dq, J_1=16.0, J_2=6.8 Hz, 1H), 5.27 (d, *J*=15.9 Hz, 1H), 5.13 (ddt, J_1=17.0, J_2=12.4, J_3=6.2 Hz, 1H), 5.07 (d, *J*=12.7 Hz, 1H), 5.01 (d, *J*=17.0 Hz, 1H), 4.56 (s, 2H), 3.75 (s, 1H), 3.69 (dd, J_1=6.0, J_2=5.2 Hz, 2H), 3.53 (td, J_1=7.5, J_2=5.0 Hz, 1H), 3.18 (dd, J_1=7.5, J_2=5.7 Hz, 1H), 3.02 (dd, J_1=7.5, J_2=5.8 Hz, 1H), 2.92 (dd, J_1=13.8, J_2=6.2 Hz, 1H), 2.85–2.75 (m, 1H), 2.42 (dd, J_1=15.7, J_2=5.3 Hz, 1H), 2.19–2.09 (m, 1H), 2.09–1.99 (m, 1H), 1.80–1.70 (m, 1H), 1.68–1.58 (m, 1H), 1.55 (d, *J*=6.1 Hz, 3H), 0.84 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 137.8, 137.7, 137.3, 135.5, 132.6, 128.6 (2C), 127.9 (3C), 127.1, 123.5, 120.9, 118.4, 117.7, 116.7, 110.6, 109.0, 73.7, 67.2, 62.6, 58.5, 46.3, 45.0, 34.0, 26.4, 18.4, 16.6, 8.9; HRMS: [M+H] found 429.2906. $C_{29}H_{36}N_2O$+H requires 429.2906.

Minor diastereomer: R_f 0.40 (10% EtOAc/petroleum ether); $[\alpha]_D^{24}$ +4.4 (*c* 0.7, $CHCl_3$); IR (neat): ν_{max} 3350, 2935, 2880, 1456, 1097 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.22 (br s, 1H), 7.51 (d, *J*=7.5 Hz, 1H), 7.39–7.19 (m, 6H), 7.20–7.05 (m, 2H), 5.99–5.79 (m, 1H), 5.40 (d, *J*=16.1 Hz, 1H), 5.32 (ddt, J_1=15.9, J_2=11.8, J_3=5.9 Hz, 1H), 5.05 (d, *J*=15.9 Hz, 1H), 5.04 (d, *J*=11.3 Hz, 1H), 4.50 (s, 2H), 3.67–3.49 (m, 3H), 3.46–3.36 (m, 1H), 3.20 (dd, J_1=13.3, J_2=6.2 Hz, 1H), 3.10–2.90 (m, 2H), 2.86–2.76 (m, 1H), 2.43 (dd, J_1=15.7, J_2=4.8 Hz, 1H), 2.22–2.12 (m, 1H), 2.00–1.90 (m, 1H), 1.67 (d, *J*=5.7 Hz, 3H), 1.57 (q, *J*=7.3 Hz, 2H), 0.79 (t, *J*=7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 138.3, 136.9, 135.6, 132.5, 128.4 (2C), 127.8 (3C), 127.6, 127.1, 123.6, 121.3, 118.9, 117.9, 116.7, 110.5, 109.8, 73.2, 67.1, 62.8, 58.7, 47.1, 44.7, 31.6, 29.4, 18.4, 16.6, 8.1; HRMS: [M+H] found 429.2906. $C_{29}H_{36}N_2O$+H requires 429.2906.

*4.1.9. (1S,12bR)-1-(2-(Benzyloxy)ethyl)-1-ethyl-1,4,6,7,12,12b-hexahydroindolo[2,3-a]quinolizine (**19**).* To a stirred solution of the diene **14** (0.024 g, 0.06 mmol) in dry CH_2Cl_2 (6 mL) was added Grubbs second generation catalyst (0.002 g, 0.003 mmol) under argon atmosphere and the reaction mixture was stirred at room temperature for 5 h. After completion of the reaction (TLC), most of the solvent was evaporated off and the crude residue thus obtained was purified by silica gel column chromatography using petroleum ether/EtOAc (7:3) as eluent to afford **19** (0.018 g, 83%) as a yellow foam. R_f 0.30 (40% EtOAc/petroleum ether); $[\alpha]_D^{24}$ +179.2 (*c* 0.6, $CHCl_3$); IR (neat): ν_{max} 3371, 2960, 2930, 1458, 1048 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.78 (br s, 1H), 7.49 (d, *J*=7.5 Hz, 1H), 7.33 (d, *J*=8.0 Hz, 1H), 7.34–7.06 (m, 7H), 5.87 (dd, J_1=10.1, J_2=4.6 Hz, 1H), 5.44 (d, *J*=10.1 Hz, 1H), 4.36 (s, 2H), 3.64 (s, 1H), 3.58 (qd, J_1=6.0, J_2=2.9 Hz, 1H), 3.52 (qd, J_1=6.0, J_2=3.0 Hz, 1H), 3.33 (dd, J_1=16.4, J_2=4.7 Hz, 1H), 3.09 (dd, J_1=10.9, J_2=4.8 Hz, 1H), 3.01 (d, *J*=16.4 Hz, 1H), 2.98–2.80 (m, 1H), 2.78 (d, *J*=16.4 Hz, 1H), 2.58 (td, J_1=8.4, J_2=3.0 Hz, 1H), 2.02–1.92 (m, 1H), 1.87 (q, *J*=7.7 Hz, 2H), 1.46–1.36 (m, 1H), 1.10 (t, *J*=7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 138.7, 136.2, 133.6, 132.9, 128.2 (2C), 127.5 (2C), 127.2, 126.8, 126.1, 121.5, 119.3, 117.9, 111.9, 110.7, 72.7, 68.0, 61.2, 55.1, 52.4, 43.0, 37.4, 32.5, 21.6, 8.9; HRMS: [M+H] found 387.2436. $C_{26}H_{30}N_2O$+H requires 387.2436.

*4.1.10. 2-((1R,12bR)-1-Ethyl-1,2,3,4,6,7,12,12b octahydroindolo[2,3-a]quinolizin-1-yl)ethanol (**20**).* To a stirred solution of the alkene **19** (0.018 g, 0.05 mmol) in dry EtOH (2 mL) was added pre-activated palladium on charcoal (10% w/w, 0.02 g) under nitrogen atmosphere. The reaction mixture was then allowed to stir under hydrogenation atmosphere (under hydrogen balloon) at room temperature for 24 h. After completion of the reaction (TLC), it was filtered through a short pad of Celite and the Celite pad was washed with $CHCl_3$ (20 mL). The solvent was evaporated off and the crude residue thus obtained was purified by silica gel column chromatography using EtOAc/MeOH (19:1) as eluent to afford **20** (0.01 g, 78%) as a white solid. R_f 0.25 (5% MeOH/EtOAc); $[\alpha]_D^{24}$ +85.8 (*c* 0.4, $CHCl_3$), [lit:[5e] $[\alpha]_D^{24}$ −98.0 (*c* 1.0, $CHCl_3$) for the enantiomer]; mp (165–168 °C; lit:[5e] mp 165–168 °C); IR (KBr): ν_{max} 3649, 3252, 2922, 1462, 1096 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.84 (br s, 1H), 7.47 (d, *J*=7.7 Hz, 1H), 7.31 (d, *J*=8.0 Hz, 1H), 7.15 (t, *J*=7.3 Hz, 1H), 7.09 (t, *J*=7.5 Hz, 1H), 3.75 (td, J_1=11.6, J_2=2.4 Hz, 1H), 3.44 (dt, J_1=11.8, J_2=4.4 Hz, 1H), 3.36 (s, 1H), 3.09 (d, *J*=4.7 Hz, 1H), 3.08 (s, 1H), 3.07–2.97 (m, 1H), 2.72–2.62 (m, 1H), 2.67 (s, 1H), 2.45 (td, J_1=11.7, J_2=3.0 Hz, 1H), 2.23–2.00 (m, 1H), 1.89–1.54 (m, 6H), 1.37 (d, *J*=15.0 Hz, 1H), 1.26 (s, 1H), 1.12 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 136.0, 132.2, 126.7, 121.7, 119.4, 118.2, 111.9,

110.6, 67.1, 58.7, 56.3, 54.0, 40.9, 38.8, 35.7, 323., 23.0, 21.3, 8.5; HRMS: [M+H] found 299.2120. $C_{19}H_{26}N_2O$+H requires 299.2123.

*4.1.11. (+)Eburnamonine (**1**).* To a solution of the alcohol **20** (0.01 g, 0.03 mmol) in CH_2Cl_2 (1 mL) were added a small amount of 4 Å molecular sieves and *N*-methylmorpholine *N*-oxide (0.007 g, 0.06 mmol) under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 10 min and tetrapropylammonium perruthenate (0.001 g, 0.003 mmol) was introduced into the reaction mixture. The reaction mixture was stirred for 1 h at room temperature, and after completion of the reaction, it was filtered through a short pad of Celite, which was washed with CH_2Cl_2 (20 mL). The organic layer was washed with saturated Na_2SO_3 (8 mL), brine (5 mL), saturated $CuSO_4$ (5 mL) and dried over anhydrous Na_2SO_4. The crude residue obtained after evaporation of the solvent was purified by rapid column chromatography using EtOAc as eluent to afford **1** (0.004 g, 40%) as a white solid. R_f 0.45 (5% MeOH/EtOAc); $[\alpha]_D^{24}$ +87.5 (*c* 0.2, $CHCl_3$), [lit:[5c] $[\alpha]_D^{24}$ −88.0 (*c* 0.09, $CHCl_3$) for the enantiomer]; mp (171–172 °C) [lit:[5e] mp 173–176 °C]; IR (KBr): ν_{max} 2926, 2854, 1696, 1452, 1370 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.37 (d, *J*=7.8 Hz, 1H), 7.43 (d, *J*=7.2 Hz, 1H), 7.39–7.23 (m, 2H), 3.99 (s, 1H), 3.34 (dd, J_1=14.0, J_2=6.7 Hz, 1H), 3.31–3.21 (m, 1H), 2.98–2.84 (m, 1H), 2.68 and 2.59 (ABq, J_1=J_2=16.7 Hz, 2H), 2.57–2.45 (m, 1H), 2.53–2.40 (m, 1H), 2.40 (dd, J_1=11.2, J_2=3.0 Hz, 1H), 2.13–1.97 (m, 1H), 1.83–1.58 (m, 4H), 1.44 (q, *J*=13.7 Hz, 2H), 1.03 (td, J_1=13.7, J_2=3.8 Hz, 1H), 0.93 (t, *J*=7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 167.6, 134.2, 132.0, 130.1, 124.3, 123.8, 118.1, 116.3, 112.6, 57.7, 50.7, 44.4, 44.3, 38.5, 28.4, 27.0, 20.7, 16.6, 7.6; HRMS: [M+H] found 298.1811. $C_{19}H_{24}N_2O$+H requires 298.1810.

*4.1.12. Preparation of the acryl amide (**23**).* To a stirred solution of the carboline **18** (0.06 g, 0.15 mmol) in dry CH_2Cl_2 (2 mL) was added Et_3N (0.08 mL, 0.60 mmol) followed by acryloyl chloride (0.02 mL, 0.30 mmol) at 0 °C under nitrogen atmosphere. The reaction mixture was stirred at 10 °C for 1 h. After completion of the reaction (TLC), it was poured into water (5 mL) and was extracted with EtOAc (2×10 mL). The combined organic layers were washed with brine (5 mL) and dried over anhydrous Na_2SO_4. The crude mixture obtained after evaporation of the solvent was purified by silica gel column chromatography using petroleum ether/EtOAc (8:2) as eluent to afford **23** (0.06 g, 88%) as an inseparable diastereomeric mixture as a pale yellow foam. R_f 0.30 (30% EtOAc/petroleum ether); $[\alpha]_D^{24}$ +9.5 (*c* 1.5, $CHCl_3$); IR (neat): ν_{max} 3330, 2933, 1638, 1618, 1452 cm^{-1}; For major diastereomer: ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.74 (br s, 1H), 7.45–7.10 (m, 9H), 6.71 (dd, J_1=16.8, J_2=10.6 Hz, 1H), 6.24 (dd, J_1=16.8, J_2=1.4 Hz, 1H), 6.02 (s, 1H), 5.70 (dd, J_1=10.7, J_2=1.5 Hz, 1H), 5.44–5.17 (m, 2H), 4.66–4.44 (m, 2H), 4.21–4.06 (m, 2H), 3.99–3.81 (m, 2H), 3.78 (t, *J*=7.9 Hz, 2H), 2.83–2.71 (m, 2H), 2.09–1.94 (m, 1H), 1.67 (d, *J*=4.1 Hz, 3H), 1.68–1.56 (m, 1H), 0.84 (t, *J*=5.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 167.3, 138.1, 135.9, 135.2, 132.0, 128.5 (2C), 128.4, 127.9 (2C), 127.6, 127.4, 126.5, 124.4, 121.6, 119.1, 117.7, 110.9, 108.9, 73.2, 66.8, 54.3, 47.3, 41.8, 32.7, 29.0, 22.0, 18.4, 8.1; HRMS: [M+Na] found 465.2519. $C_{29}H_{34}N_2O_2$+Na requires 465.2518.

*4.1.13. Preparation of **22**.* A solution of the diene **23** (0.02 g, 0.05 mmol) dissolved in dry toluene (3 mL) and was refluxed. A solution of the Hoveyda–Grubbs second generation catalyst (0.006 g) dissolved in 2 mL toluene was added to the reaction mixture under reflux for a period of 6 h with the aid of syringe pump under argon atmosphere. The reaction mixture was stirred under reflux for further 18 h. Most of the solvent was evaporated off and the crude residue thus obtained was purified by silica gel column chromatography using petroleum ether/EtOAc (6:4) as eluent to afford **24** (0.007 g, 39%) as a brown oil. R_f 0.35 (60% EtOAc/petroleum ether); $[\alpha]_D^{24}$ −112.1 (*c* 0.7, $CHCl_3$); IR (neat): ν_{max} 3353, 2927, 1666, 1608, 1434 cm^{-1}; For major diastereomer: ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.52 (br s, 1H), 7.50 (d, *J*=7.6 Hz, 1H), 7.39–7.03 (m, 8H), 6.34 (d, *J*=9.9 Hz, 1H), 6.11 (d, *J*=9.9 Hz, 1H), 5.06–4.86 (m, 1H), 4.63 and 4.58 (ABq, J_1=J_2=11.4 Hz, 2H), 3.96–3.83 (m, 1H), 3.78 (t, *J*=7.9 Hz, 2H), 2.96–2.73 (m, 4H), 2.20–2.08 (m, 1H), 2.06–1.95 (m, 1H), 1.33–1.19 (m, 1H), 0.98–0.83 (m, 1H), 0.68 (t, *J*=7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 164.4, 149.0, 136.7, 135.8, 130.5, 128.7 (2C), 128.4, 128.3, 128.0 (2C), 127.5, 121.6, 119.2, 117.9, 112.1, 111.0, 74.0, 67.3, 58.4, 44.0, 39.4, 35.4, 25.8, 20.8, 8.0; HRMS: [M+Na] found 423.2043. $C_{26}H_{28}N_2O_2$+Na requires 423.2048.

*4.1.14. (S,2E,5E)-Methyl 4-(2-(benzyloxy)ethyl)-4-ethylhepta-2,5-dienoate (**26**).* To a stirred solution of the alcohol (0.33 g, 1.33 mmol) **17** in dry CH_2Cl_2 (8 mL) were added $NaHCO_3$ (0.56 g, 6.65 mmol) and Dess–Martin periodinane (0.846 g, 2.00 mmol) at 0 °C under nitrogen atmosphere. The reaction mixture was warmed up to room temperature and stirred at room temperature for 1.5 h. After completion of the reaction (TLC), it was quenched by addition of saturated aqueous solutions of $NaHCO_3$ (10 mL) and $Na_2S_2O_3$ (10 mL) and diluted with Et_2O (10 mL). The aqueous phase was extracted with Et_2O (2×10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated. The crude aldehyde **15** thus obtained as colourless oil was used as such in the next step without further purification.

Sodium hydride (0.106 g of 60% dispersion in mineral oil, 2.66 mmol) was suspended in dry THF (8 mL) and trimethylphosphonoacetate (0.48 mL, 3.33 mmol) was added dropwise at 0 °C under nitrogen atmosphere. The reaction mixture was stirred at 0 °C for 30 min and then a solution of the aldehyde **15** (obtained above) in THF (5 mL) was slowly added. The reaction mixture was warmed up to room temperature and was stirred at room temperature for 6 h. After completion of the reaction (TLC), it was quenched by addition of saturated aqueous NH_4Cl solution (5 mL) and diluted with ice cold water (10 mL). The aqueous phase was extracted with EtOAc (2×15 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated. The crude residue thus obtained was purified by silica gel column chromatography using petroleum ether/diethyl ether (9:1) as eluent to afford the *E*-ester (*E*=0.36 g, 90%) **26** as a colourless oil. R_f 0.40 (10% EtOAc/petroleum ether); $[\alpha]_D^{24}$ −1.9 (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 2938, 2860, 1725, 1650, 1275 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.41–7.21 (m, 5H), 6.92 (d, *J*=16.1 Hz, 1H), 5.77 (d, *J*=16.1 Hz, 1H), 5.42 (dq, J_1=16.0, J_2=6.1 Hz, 1H), 5.31 (d, *J*=16.0 Hz, 1H), 4.46 (s, 2H), 3.73 (s, 3H), 3.45 (t, *J*=7.4 Hz, 2H), 1.87 (td, J_1=6.9 Hz, J_2=2.0 Hz, 2H), 1.70 (d, *J*=6.0 Hz, 3H), 1.52 (q, *J*=7.3 Hz, 2H), 0.81 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 167.3, 155.2, 138.3, 134.8, 128.3 (2C), 127.5 (2C), 127.4, 125.2, 119.1, 72.9, 66.9, 51.4, 44.4, 36.3, 30.6, 18.2, 8.4; HRMS: [M+Na] found 325.1781. $C_{19}H_{26}O_3$+Na requires 325.1780.

*4.1.15. (S)-Methyl 6-(benzyloxy)-4-ethyl-4-formylhexanoate (25) and (S)-methyl 4-(2-(benzyloxy)ethyl)-4-ethylheptanoate (**27**).* To a stirred solution of the ester **26** (0.225 g, 0.75 mmol) in MeOH (8 mL) was added $NiCl_2 \cdot 6H_2O$ (0.045 g, 25 mol %) followed by $NaBH_4$ (0.114 g, 3.0 mmol) portionwise at 0 °C. The reaction mixture was warmed to room temperature and stirred at room temperature for 2 h. Methanol was then evaporated off and the crude residue thus obtained was dissolved in EtOAc (25 mL) and was filtered through a short pad of Celite. The organic layer was washed with water (10 mL), brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated. The crude residue thus obtained was purified by silica gel column chromatography

using petroleum ether/Et_2O (9:1) to afford a colourless oil (0.212 g).

Ozone was bubbled through a pre cooled (−78 °C) solution of the above compound (0.21 g) in a mixture of CH_2Cl_2:MeOH (4:1, 8 mL), containing solid $NaHCO_3$ (0.02 g) till the pale blue colour persisted. Excess ozone was flushed off with oxygen and Me_2S (0.4 mL) was added. The reaction mixture was then warmed up to 0 °C and was stirred at the same temperature for 4 h. The reaction mixture was then filtered through a short pad of Celite and the Celite pad was washed with EtOAc (20 mL). The solvent was evaporated off and the crude residue thus obtained was purified by silica gel column chromatography using petroleum ether/EtOAc (8:2) as eluent to afford **25** (0.14 g, 64%) and **27** (0.036 g, 16%) as colourless oils.

Compound **25**: R_f 0.40 (20% EtOAc/petroleum ether); $[\alpha]_D^{24}$ +0.4 (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 2951, 2880, 2716, 1737, 1454 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.43 (s, 1H), 7.39–7.21 (m, 5H), 4.42 (s, 2H), 3.65 (s, 3H), 3.44 (t, *J*=6.2 Hz, 2H), 2.21 (t, *J*=8.8 Hz, 2H), 2.06–1.72 (m, 4H), 1.68–1.40 (m, 2H), 0.80 (t, *J*=7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 205.1, 173.6, 137.9, 128.3 (2C), 127.5 (3C), 73.1, 65.6, 51.6, 50.3, 32.7, 28.3, 25.7, 23.9, 7.5; HRMS: [M+Na] found 315.1575. $C_{17}H_{24}O_4$+Na requires 315.1572.

Compound **27**: R_f 0.40 (10% EtOAc/petroleum ether); $[\alpha]_D^{24}$ −0.3 (*c* 1.3, $CHCl_3$); IR (neat): ν_{max} 2935, 2874, 1740, 1454, 1103 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.41–7.20 (m, 5H), 4.49 (s, 2H), 3.65 (s, 3H), 3.47 (t, *J*=7.5 Hz, 2H), 2.29–2.15 (m, 2H), 1.63–1.49 (m, 4H), 1.31–1.24 (m, 6H), 0.87 (t, *J*=6.7 Hz, 3H), 0.78 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 174.7, 138.5, 128.3 (2C), 127.5 (2C), 127.4, 73.0, 66.5, 51.5, 38.6, 36.6, 35.2, 31.2, 28.7, 28.5, 16.1, 14.8, 7.4; HRMS: [M+Na] found 329.1936. $C_{19}H_{30}O_3$+Na requires 329.1936.

*4.1.16. (1S,12bS)-1-Ethyl-1-(2-hydroxyethyl)-1,2,3,6,7,12b-hexahydroindolo[2,3-a]quinolizin-4(12H)-one (ent-**21**α) and (1S,12bR)-1-ethyl-1-(2-hydroxyethyl)-1,2,3,6,7,12b-hexahydroindolo[2,3-a]quinolizin-4(12H)-one (ent-**21**β).* To a stirred solution of the aldehyde (0.049 g, 0.17 mmol) **25** in dry AcOH (3 mL) was added tryptamine (0.03 g, 0.19 mmol) at room temperature under nitrogen atmosphere. The reaction mixture was heated to reflux and stirred at the same temperature for 48 h. It was later cautiously quenched by addition of saturated aqueous solution of $NaHCO_3$ (20 mL). The resulting solution was poured into water (10 mL) and extracted with EtOAc (2×10 mL). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. The crude residue obtained after evaporation of solvent was purified by a rapid silica gel column chromatography using petroleum ether/EtOAc (3:7) as eluent to afford **28** a 1:2 inseparable mixture of diastereomers (0.036 g, 53%) as a pale yellow oil.

To a stirred solution of the benzyl ether **28** (0.106 g, 0.26 mmol) in dry MeOH (3 mL) was added pre-activated palladium on charcoal (10% w/w, 0.055 g) under nitrogen atmosphere. The reaction mixture was stirred under hydrogen atmosphere (under hydrogen balloon) at room temperature for 5 h. After completion of the reaction (TLC), it was filtered through a short pad of Celite and the Celite pad was washed with EtOAc (10 mL). The solvent was evaporated off and the crude residue thus obtained was purified separated by silica gel column chromatography using petroleum ether/EtOAc (2:8) as eluent to afford *ent*-**21**β (0.04 g, 49%) and *ent*-**21**α (0.02 g, 25%) as pale yellow solids.

Compound ent-**21**β: R_f 0.40 (EtOAc); $[\alpha]_D^{24}$ −142.6 (*c* 0.5, MeOH). [lit:[14] $[\alpha]_D^{24}$ +141.2 (*c* 0.24, MeOH) for the enantiomer] mp (111–112 °C), [lit:[12] mp 123–127 °C]; IR (KBr): ν_{max} 3379, 2938, 1594, 1470 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.68 (br s, 1H), 7.49 (d, *J*=7.7 Hz, 1H), 7.35 (d, *J*=8.0 Hz, 1H), 7.24–7.02 (m, 2H), 5.18 (s, 1H), 5.12 (d, *J*=10.6 Hz, 1H), 4.20–3.98 (m, 2H), 2.89–2.63 (m, 3H), 2.54 (dd, J_1=6.8, J_2=3.2 Hz, 1H), 2.50 (dd, J_1=11.2, J_2=6.8 Hz, 1H), 2.30–2.13 (m, 1H), 2.14–1.89 (m, 2H), 1.80 (dd, J_1=15.8, J_2=4.4 Hz, 1H), 1.65–1.41 (m, 2H), 0.99–0.81 (m, 1H), 0.70 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 170.5, 136.1, 131.8, 126.5, 121.5, 119.2, 117.9, 112.3, 111.2, 61.0, 58.0, 41.1, 39.3, 37.8, 29.2, 26.8, 24.0, 21.2, 7.0; HRMS: [M+Na] found 335.1735. $C_{19}H_{24}N_2O_2$+Na requires 335.1735.

Compound ent-**21**α: R_f 0.30 (EtOAc); $[\alpha]_D^{24}$ −187.0 (*c* 0.2, MeOH). [lit:[12] $[\alpha]_D^{24}$ +188.1 (*c* 0.15, MeOH) for the enantiomer]; mp 253–254 °C, [lit:[12] mp 264–268 °C for the enantiomer]; IR (KBr): ν_{max} 3296, 2923, 1608, 1436 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ_H 10.25 (br s, 1H), 7.44 (d, *J*=8.0 Hz, 1H), 7.41 (d, *J*=7.8 Hz, 1H), 7.06 (t, *J*=7.4 Hz, 1H), 6.97 (t, *J*=7.4 Hz, 1H), 4.90 (dd, J_1=10.6, J_2=3.4 Hz, 1H), 4.83 (s, 1H), 4.17 (t, *J*=5.2 Hz, 1H), 3.38–3.16 (m, 4H), 2.78–2.54 (m, 2H), 2.42–2.28 (m, 2H), 2.03–1.69 (m, 3H), 1.60–1.46 (m, 1H), 1.44–1.32 (m, 1H), 1.05 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 169.3, 136.8, 131.8, 126.1, 121.2, 118.8, 117.6, 111.9, 111.2, 60.3, 56.6, 40.3, 38.5, 35.3, 29.7, 29.1, 27.5, 21.1, 8.6; HRMS: [M+Na] found 335.1738. $C_{19}H_{24}N_2O_2$+Na requires 335.1735.

*4.1.17. (−)Aspidospermidine (**2**).* A stirred solution of a mixture of *ent*-**21**α and *ent*-**21**β (0.03 g, 0.1 mmol) in 40% H_2SO_4 was heated to 100–110 °C for 2 h. After completion of the reaction (TLC), it was cooled to 0 °C and diluted with CH_2Cl_2 (10 mL). The reaction mixture was made basic by addition of 25% (w/v) aq NaOH. The aqueous phase was extracted with CH_2Cl_2 (2×15 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated. The crude residue thus obtained was used immediately in the next reaction.

To a stirred solution of above residue in dry THF (2 mL) was added $LiAlH_4$ (0.038 g, 1 mmol) at 0 °C. The reaction mixture was then refluxed for 1.5 h. After completion of the reaction (TLC), it was cooled to 0 °C and was treated with 25% (w/v) aq KOH (2 mL) and was stirred at room temperature for 20 min. It was then filtered through a short pad of Celite using CH_2Cl_2 (40 mL) and was washed with brine (10 mL), dried over anhydrous Na_2SO_4. The crude mixture obtained after evaporation of the solvent was purified by silica gel column chromatography using petroleum ether/EtOAc (6:4) as eluent to afford **2** (0.004 g, 14%) as an amorphous powder. R_f 0.40 (10% MeOH/EtOAc); $[\alpha]_D^{24}$ −12.0 (*c* 0.2, EtOH), [lit:[15] $[\alpha]_D^{24}$ +17.0 (EtOH) for the enantiomer]; mp 104–106 °C, [lit:[15] mp 116–118 °C]; IR (KBr): ν_{max} 3432, 2926, 2855, 1650 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.08 (d, *J*=7.3 Hz, 1H), 7.02 (t, *J*=7.4 Hz, 1H), 6.73 (t, *J*=7.4 Hz, 1H), 6.64 (d, *J*=7.7 Hz, 1H), 3.51 (dd, J_1=10.7, J_2=5.8 Hz, 1H), 3.20–3.00 (m, 2H), 2.36–2.20 (m, 2H), 2.23 (s, 1H), 2.15–1.86 (m, 2H), 1.81–1.29 (m, 8H), 1.09 (qd, J_1=13.2, J_2=4.3 Hz, 2H), 0.95–0.78 (m, 1H), 0.64 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 149.4, 135.7, 127.1, 122.8, 119.0, 110.3, 71.3, 65.7, 53.9, 53.4, 53.0, 38.8, 35.7, 34.5, 30.0, 28.1, 23.0, 21.8, 6.8; HRMS: [M+H] found 283.2163. $C_{19}H_{26}N_2$+H requires 283.2174.

*4.1.18. (S)-2-Allyl-1-((S,E)-2-ethyl-2-((methoxymethoxy)methyl)pent-3-en-1-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (**30**α) and (R)-2-allyl-1-((S,E)-2-ethyl-2-((methoxymethoxy)methyl)pent-3-en-1-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (**30**β).* To a stirred solution of the ester **4** (0.1 g, 0.41 mmol) in dry CH_2Cl_2 (1.5 mL) was added DIBAL-H (0.50 mL of 1.0 M in toluene, 0.50 mmol) dropwise at −78 °C for a period of 2 min under argon atmosphere. The reaction mixture was stirred at the same temperature for 15 min. After completion of the reaction (TLC), it was quenched by the addition of saturated aqueous solution of potassium sodium tartrate (4 mL). The reaction mixture was diluted with Et_2O (5 mL) and was stirred at room temperature for 1 h. The aqueous layer was extracted with Et_2O (2×5 mL) and the combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4 and

concentrated to yield the crude aldehyde **31**, which was used in the next step without further purification.

To a stirred solution of the aldehyde **31** in dry CH_2Cl_2 (2 mL) was added tryptamine (0.066 g, 0.41 mmol) at room temperature under nitrogen atmosphere. The reaction mixture was cooled to 0 °C and CF_3CO_2H (0.05 mL, 0.62 mmol) was slowly added. It was then slowly warmed to room temperature and stirred for 3 h. After completion of the reaction (TLC), it was cautiously quenched by addition of saturated aqueous solution of $NaHCO_3$ (5 mL). The resulting solution was poured into water (5 mL) and was extracted with EtOAc (2×10 mL). The combined organic layers were washed with brine (5 mL) and dried over anhydrous Na_2SO_4. The crude residue obtained after evaporation of solvent was purified by a rapid silica gel column chromatography using EtOAc as eluent to afford **32** (0.093 g, 66%) as a pale yellow oil.

To a stirred solution of the carboline **32** (obtained above) (0.092 g, 0.27 mmol) in dry DMF (1.5 mL) were added K_2CO_3 (0.075 g, 0.54 mmol) and allyl bromide (0.04 mL, 0.54 mmol) at 0 °C under nitrogen atmosphere. The reaction mixture was then stirred at 10 °C for 3 h. After completion of the reaction (TLC), it was poured into water (5 mL) and extracted with EtOAc (2×10 mL). The combined organic layers were washed with brine (5 mL) and dried over anhydrous Na_2SO_4. The crude diastereomeric mixture thus obtained after evaporation of the solvent was separated and purified by repeated silica gel column chromatography using petroleum ether/EtOAc (9:1) as eluent to afford **30α** (0.033 g, 32%) and **30β** (0.032 g, 31%) as pale yellow foams.

Compound **30α**: R_f 0.60 (20% EtOAc/petroleum ether); $[\alpha]_D^{24}$ −49.8 (*c* 1.1, $CHCl_3$); IR (neat): ν_{max} 3343, 2931, 2882, 1461 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.60 (br s, 1H), 7.49 (d, *J*=7.6 Hz, 1H), 7.28 (d, *J*=7.8 Hz, 1H), 7.20–7.01 (m, 2H), 6.02–5.86 (m, 1H), 5.58–5.40 (m, 2H), 5.19–5.05 (m, 2H), 4.78 and 4.72 (ABq, J_1=J_2=5.9 Hz, 2H), 3.72 (d, *J*=9.4 Hz, 2H), 3.58 (d, *J*=9.6 Hz, 1H), 3.48 (s, 3H), 3.27–3.11 (m, 3H), 3.05 (dd, J_1=7.6, J_2=5.0 Hz, 1H), 2.88–2.78 (m, 1H), 2.59–2.45 (m, 1H), 1.98–1.76 (m, 2H), 1.80 (d, *J*=5.0 Hz, 3H), 1.66–1.53 (m, 1H), 1.55–1.42 (m, 1H), 0.87 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 137.3, 136.5, 136.0, 135.8, 127.3, 123.8, 121.0, 118.9, 117.9, 116.8, 110.6, 106.8, 97.3, 72.1, 56.2, 55.6, 53.0, 43.9, 43.3, 42.7, 29.1, 18.6, 16.7, 8.2; HRMS: [M+H] found 383.2699. $C_{24}H_{34}N_2O_2$+H requires 383.2699.

Compound **30β**: R_f 0.65 (20% EtOAc/petroleum ether); $[\alpha]_D^{24}$ +16.2 (*c* 1.1, $CHCl_3$); IR (neat): ν_{max} 3408, 2931, 2882, 1464 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.12 (br s, 1H), 7.48 (d, *J*=7.5 Hz, 1H), 7.28 (d, *J*=7.8 Hz, 1H), 7.18–7.03 (m, 2H), 6.03–5.86 (m, 1H), 5.45–5.32 (m, 2H), 5.10 (d, *J*=12.4 Hz, 2H), 4.73 (s, 2H), 3.86 (dd, J_1=7.0, J_2=3.6 Hz, 1H), 3.70 (d, *J*=1.6 Hz, 2H), 3.44 (s, 3H), 3.35–3.08 (m, 3H), 3.06 (dd, J_1=13.8, J_2=5.0 Hz, 1H), 2.90–2.78 (m, 1H), 2.48 (dd, J_1=15.8, J_2=4.0 Hz, 1H), 2.07 (dd, J_1=14.6, J_2=7.2 Hz, 1H), 1.74 (d, *J*=5.2 Hz, 3H), 1.69 (dd, J_1=14.6, J_2=3.8 Hz, 1H), 1.49 (q, *J*=7.4 Hz, 2H), 0.85 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 137.2, 136.8, 136.1, 135.6, 127.3, 123.7, 121.1, 119.0, 117.9, 117.0, 110.5, 106.9, 97.1, 71.9, 56.3, 55.4, 52.9, 43.12, 43.07, 41.6, 29.4, 18.5, 16.4, 8.0; HRMS: [M+H] found 383.2697. $C_{24}H_{34}N_2O_2$+H requires 383.2699.

*4.1.19. (2S,13bS)-2-Ethyl-2-((methoxymethoxy)methyl)-2,5,7,8,13,13b-hexahydro-1H-azepino[1′,2′:1,2]pyrido[3,4-b]indole (**33α**) and (2S,13 bR)-2-ethyl-2-((methoxymethoxy)methyl)-2,5,7,8,13,13b-hexahydro-1H-azepino[1′,2′:1,2]pyrido[3,4-b]indole (**33β**).* To a stirred solution of the diene **30**β (0.034 g, 0.09 mmol) in dry CH_2Cl_2 (5 mL) was added Grubbs second generation catalyst (0.004 g, 5 mol %) under argon atmosphere and the reaction mixture was heated to reflux and stirred for 4 h. After completion of the reaction (TLC), most of the solvent was evaporated off and the crude residue thus obtained was purified by silica gel column chromatography using petroleum ether/EtOAc (6:4) as eluent to afford **33β** (0.02 g, 67%) as a yellow foam.

Compound **33β**: R_f 0.40 (40% EtOAc/petroleum ether); $[\alpha]_D^{24}$ −7.9 (*c* 1.2, $CHCl_3$); IR (neat): ν_{max} 3411, 2929, 1462, 1044 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.83 (br s, 1H), 7.49 (d, *J*=7.6 Hz, 1H), 7.32 (d, *J*=7.8 Hz, 1H), 7.22–7.03 (m, 2H), 5.87–5.72 (m, 1H), 5.56 (d, *J*=11.5 Hz, 1H), 4.58 and 4.54 (ABq, J_1=J_2=6.4 Hz, 2H), 4.30 (d, *J*=7.3 Hz, 1H), 3.53 (dd, J_1=16.5, J_2=4.3 Hz, 1H), 3.46 and 3.38 (ABq, J_1=J_2=9.2 Hz, 2H), 3.36 (s, 3H), 3.31–3.16 (m, 2H), 3.07–2.82 (m, 2H), 2.65 (d, *J*=14.8 Hz, 1H), 2.12 (dd, J_1=14.3, J_2=4.0 Hz, 1H), 2.11–1.92 (m, 2H), 1.99–1.84 (m, 1H), 0.99 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 136.6, 135.9, 135.5, 128.8, 127.3, 121.3, 119.3, 118.0, 110.7, 108.4, 96.7, 73.9, 55.3, 55.1, 52.0, 51.1, 43.0, 37.8, 27.1, 19.5, 8.5; HRMS: [M+H] found 341.2226$C_{21}H_{28}N_2O_2$+H requires 341.2229.

*Similarly reaction with **30α** afforded the compound **33α*** in 71% yield. R_f 0.45 (40% EtOAc/petroleum ether); $[\alpha]_D^{24}$ −13.0 (*c* 1.5, $CHCl_3$); IR (neat): ν_{max} 3334, 2931, 1458, 1047 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.20 (br s, 1H), 7.49 (d, *J*=7.6 Hz, 1H), 7.31 (d, *J*=7.8 Hz, 1H), 7.19–7.04 (m, 2H), 5.89–5.74 (m, 1H), 5.44 (d, *J*=11.5 Hz, 1H), 4.74 and 4.71 (ABq, J_1=J_2=6.2 Hz, 2H), 4.34 (d, *J*=8.7 Hz, 1H), 3.84 (d, *J*=9.4 Hz, 1H), 3.52 (d, *J*=9.4 Hz, 1H), 3.55–3.44 (m, 1H), 3.45 (s, 3H), 3.21 (dd, J_1=15.7, J_2=6.2 Hz, 1H), 3.18–3.04 (m, 1H), 2.98–2.82 (m, 2H), 2.76–2.62 (m, 1H), 2.12–1.91 (m, 2H), 1.71–1.55 (m, 1H), 1.59–1.44 (m, 1H), 0.91 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 136.08, 136.00, 135.95, 128.6, 127.1, 121.2, 119.1, 118.0, 110.6, 108.2, 97.1, 73.0, 55.4, 54.5, 51.64, 51.56, 43.9, 36.8, 31.8, 20.0, 8.2; HRMS: [M+H] found 341.2229. $C_{21}H_{28}N_2O_2$+H requires 341.2229.

*4.1.20. (2R,13bS)-2-Ethyl-2-((methoxymethoxy)methyl)-2,3,4,5,7,8,13, 13b-octahydro-1H-azepino[1′,2′:1,2]pyrido[3,4-b]indoleazapines (**34α**) and (2R,13bR)-2-ethyl-2-((methoxymethoxy)methyl)-2,3,4,5,7, 8,13,13b-octahydro-1H-azepino[1′,2′:1,2]pyrido[3,4-b]indole (**34β**).* To a stirred solution of the alkene **33α** (0.032 g, 0.09 mmol) in dry MeOH (2 mL) was added pre-activated palladium on charcoal (10% w/w, 0.01 g) under nitrogen atmosphere. The reaction mixture was then stirred under hydrogen atmosphere (under hydrogen balloon) and was stirred at room temperature for 1 h. After completion of the reaction (TLC), it was immediately filtered through a short pad of Celite and the Celite pad was washed with EtOAc (10 mL). The solvent was evaporated off and the crude residue thus obtained was purified by column chromatography on deactivated neutral alumina using petroleum ether/EtOAc (7:3) as eluent to afford **34α** (0.024 g, 75%) as a yellow oil. Compound **34α**: R_f 0.60 (20% MeOH/EtOAc); $[\alpha]_D^{24}$ −67.4 (*c* 0.5, $CHCl_3$); IR (neat): ν_{max} 3341, 2928, 2855, 1462, 1047 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.58 (br s, 1H), 7.47 (d, *J*=7.5 Hz, 1H), 7.31 (d, *J*=7.1 Hz, 1H), 7.19–7.04 (m, 2H), 4.59 (s, 2H), 3.70 (d, *J*=7.6 Hz, 1H), 3.34 and 3.25 (ABq, J_1=J_2=9.2 Hz, 2H), 3.34 (s, 3H), 3.24–3.06 (m, 2H), 3.15 (td, J_1=12.4, J_2=4.8 Hz, 2H), 2.98–2.84 (m, 1H), 2.69 (d, *J*=17.7 Hz, 1H), 2.62 (td, J_1=11.0, J_2=6.8 Hz, 1H), 2.51 (t, *J*=11.4 Hz, 1H), 2.03–1.58 (m, 5H), 1.53–1.41 (m, 1H), 0.97 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 136.3, 136.1, 127.2, 121.4, 119.3, 118.0, 110.6, 109.2, 96.7, 73.5, 60.4, 55.4, 55.2, 53.1, 42.5, 39.0, 34.7, 29.6, 24.6, 21.3, 8.2; HRMS: [M+H] found 343.2383. $C_{21}H_{30}N_2O_2$+H requires 343.2386.

Similarly reaction of **33**β *afforded the compound* **34**β in 79% yield. R_f 0.60 (20% MeOH/EtOAc) $[\alpha]_D^{24}$ +27.6 (*c* 1.1, $CHCl_3$); IR (neat): ν_{max} 3328, 2926, 2852, 1464, 1046 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.79 (br s, 1H), 7.48 (d, *J*=7.6 Hz, 1H), 7.30 (d, *J*=7.8 Hz, 1H), 7.20–7.01 (m, 2H), 4.79 and 4.74 (ABq, J_1=J_2=5.7 Hz, 2H), 3.70 (d, *J*=7.5 Hz, 1H), 3.53 (s, 2H), 3.52 (s, 3H), 3.20 (dd, J_1=11.8, J_2=5.2 Hz, 1H), 3.15–3.02 (m, 1H), 2.99–2.89 (m, 1H), 2.73 (d, *J*=14.9 Hz, 1H), 2.57 (td, J_1=11.0, J_2=3.7 Hz, 1H), 2.48 (t, *J*=11.8 Hz, 1H), 2.21 (d, *J*=15.5 Hz, 1H), 1.98–1.59 (m, 4H), 1.47–1.22 (m, 3H), 0.88 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 137.0, 136.3, 126.9,

121.0, 118.9, 117.9, 110.5, 108.2, 97.4, 74.5, 61.6, 55.6, 55.2, 53.0, 42.3, 39.1, 32.8, 30.4, 23.8, 21.7, 8.0; HRMS: [M+H] found 343.2384. $C_{21}H_{30}N_2O_2$+H requires 343.2386.

*4.1.21. ((2R,13bS)-2-Ethyl-2,3,4,5,7,8,13,13b-octahydro-1H-azepino [1′,2′:1,2]pyrido[3,4-b]indol-2-yl)methanol (**29α**) and ((2R,13bR)-2-ethyl-2,3,4,5,7,8,13,13b-octahydro-1H-azepino[1′,2′:1,2]pyrido[3,4-b] indol-2-yl)methanol (**29β**).* The following procedure for **29α** is representative. To a stirred solution of the −MOM ether **34α** (0.023 g, 0.07 mmol) in MeOH (1.5 mL) was added 6 N HCl (1.5 mL) at 0 °C. The reaction mixture was then warmed up to room temperature and stirred for 3 h at room temperature. After completion of the reaction (TLC), it was quenched by addition of solid $NaHCO_3$ and filtered through a short pad of Celite and the Celite pad was washed with EtOAc (10 mL). The solvent was evaporated off and the crude residue thus obtained was purified by column chromatography on deactivated neutral alumina using EtOAc/MeOH (8:2) as eluent to afford **29α** (0.012 g, 60%) as a yellow oil.

Compound **29α**: R_f 0.40 (20% MeOH/EtOAc); $[\alpha]_D^{24}$ +40.1 (*c* 0.7, $CHCl_3$); IR (neat): ν_{max} 3291, 2926, 2855, 1462 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.22 (br s, 1H), 7.47 (d, *J*=7.5 Hz, 1H), 7.29 (d, *J*=7.7 Hz, 1H), 7.19–7.03 (m, 2H), 3.99 (d, *J*=8.5 Hz, 1H), 3.60 (s, 2H), 3.21–2.53 (m, 6H), 2.11 (dd, J_1=14.0, J_2=2.4 Hz, 1H), 1.93–1.76 (m, 2H), 1. 76 (dd, J_1=15.0, J_2=9.3 Hz, 1H), 1.55–1.40 (m, 2H), 1.32 (q, *J*=7.5 Hz, 2H), 0.87 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 136.1, 135.9, 127.0, 121.3, 119.2, 118.0, 110.7, 108.1, 68.4, 56.2, 54.7, 52.1, 40.5, 40.2, 34.8, 32.4, 25.3, 20.2, 8.0; HRMS: [M+H] found 299.2127. $C_{19}H_{26}N_2O$+H requires 299.2123.

Compound **29β**: white solid; yield: 57%. R_f 0.40 (20% MeOH/EtOAc); $[\alpha]_D^{24}$ −63.0 (*c* 0.3, $CHCl_3$); mp 191–192 °C, [lit:[8j] mp 230–232 °C]; IR (KBr): ν_{max} 3432, 2924, 2855, 1458 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.61 (br s, 1H), 7.47 (d, *J*=7.6 Hz, 1H), 7.30 (d, *J*=7.6 Hz, 1H), 7.19–7.04 (m, 2H), 3.75 (d, *J*=8.0 Hz, 1H), 3.39 and 3.36 (ABq, J_1=J_2=10.8 Hz, 2H), 3.14 (dd, J_1=9.4, J_2=5.0 Hz, 2H), 3.02–2.84 (m, 1H), 2.78–2.61 (m, 2H), 2.55 (td, J_1=10.6, J_2=2.3 Hz, 1H), 2.05–1.85 (m, 2H), 1.85 (dd, J_1=15.1, J_2=8.6 Hz, 1H), 1.80–1.58 (m, 2H), 1.54 (qd, J_1=7.5, J_2=3.2 Hz, 2H), 1.58–1.38 (m, 1H), 0.95 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 136.2, 136.0, 127.1, 121.4, 119.4, 118.0, 110.7, 109.0, 68.6, 60.1, 56.4, 53.4, 42.1, 40.1, 34.5, 30.3, 25.0, 21.2, 8.2; HRMS: [M+H] found 299.2125. $C_{19}H_{26}N_2O$+H requires 299.2123.

*4.1.22. (−)-Quebrachamine (**3**).* To a stirred solution of the alcohol **29α** and **29β** (0.019 g, 0.06 mmol) in pyridine (0.5 mL) was added methanesulfonyl chloride (0.04 mL) at 0 °C under nitrogen atmosphere and the reaction mixture was stirred at the same temperature for 4 h. After completion of the reaction (TLC), evaporated excess methanesulfonyl chloride and pyridine were removed at room temperature. The resulting residue was washed with diethyl ether (2×2 mL), treated with water (0.2 mL) and 10% NH_4OH (0.4 mL) with cooling at 0 °C and extracted with $CHCl_3$ (2×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4. Evaporation of the solvent in vacuo afforded a gummy residue, which was dissolved in dry $CHCl_3$ (1.5 mL) and refluxed under N_2 atmosphere for 3 h. Evaporation of the solvent in vacuo afforded the quaternary salt as a yellow hygroscopic solid.

To a three neck round bottom flask fitted with a Dewar condenser and NH_3 outlet was transferred the crude quaternary salt in absolute EtOH (1 mL). After transferring liquid NH_3 (5 mL) into the flask, freshly cut small sodium pieces were added till the blue colour persisted for 20 min. The reaction was quenched by the addition of solid NH_4Cl and excess NH_3 was allowed to evaporate. The residue was dissolved in water, extracted with CH_2Cl_2 (2×10 mL), washed with brine and dried over anhydrous K_2CO_3. The solvent was evaporated off and the crude residue thus obtained was purified by silica gel column chromatography using petroleum ether/EtOAc (6:4) as eluent to afford **3** (0.004 g, 22%) as a white solid. R_f 0.60 (40% EtOAc/petroleum ether); $[\alpha]_D^{24}$ −93.0 (*c* 0.1, $CHCl_3$), [lit:[9d] $[\alpha]_D^{24}$ −99.0 (*c* 0.27, $CHCl_3$)]; mp (139–142 °C), [lit:[9d] mp (144–146 °C)]; IR (KBr): ν_{max} 3426, 2925, 1629, 1245 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.72 (br s, 1H), 7.48 (d, *J*=6.8 Hz, 1H), 7.28 (d, *J*=7.1 Hz, 1H), 7.14–7.01 (m, 2H), 3.25 (d, *J*=11.9 Hz, 1H), 2.92 (dd, J_1=11.5, J_2=4.5 Hz, 1H), 2.86 (dd, J_1=4.3, J_2=2.8 Hz, 1H), 2.79–2.63 (m, 2H), 2.51–2.39 (m, 1H), 2.42 (dd, J_1=4.4, J_2=2.8 Hz, 1H), 2.33 (td, J_1=11.5, J_2=4.5 Hz, 1H), 2.25 (td, J_1=11.5, J_2=3.2 Hz, 1H), 1.93 (dd, J_1=13.7, J_2=7.7 Hz, 1H), 1.67–1.51 (m, 2H), 1.54 and 1.46 (ABq, J_1=J_2=19.3 Hz, 2H), 1.31–1.17 (m, 2H), 1.21–1.06 (m, 2H), 0.85 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 139.9, 134.8, 128.9, 120.1, 118.6, 117.4, 110.0, 108.7, 56.7, 55.1, 53.2, 37.1, 34.7, 33.4, 32.0, 22.7, 22.4, 22.0, 7.8; HRMS: [M+H] found 283.2175. $C_{19}H_{26}N_2$+H requires 283.2174.

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Supplementary data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.tet.2013.04.097.

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