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Total Synthesis of (±)/(+)-Subincanadine E and Determination of Absolute Configuration

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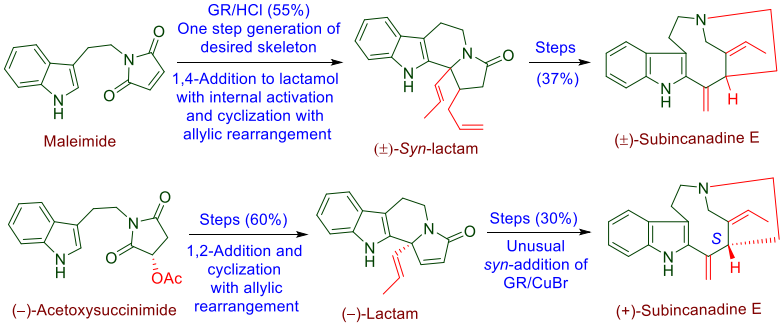


ABSTRACT: A facile synthesis of (±)-subincanadine E has been described from tryptamine based maleimide. 1,2-Addition of Grignard reagent to maleimide, internal activation of formed lactamol for in situ 1,4-addition of Grignard reagent and associated position specific allylic rearrangement in diastereoselective Pictet–Spengler cyclization were the key steps. Enantioselective first total synthesis of naturally occurring cytotoxic (+)-subincanadine E has also been accomplished from (*S*)-acetoxysuccinimide via an unusual *syn*-addition of cuprate to the *α*,*β*-unsaturated lactam. *Sinister* absolute configuration has been assigned to (+)-subincanadine E on the basis of total synthesis. (*S*)-Acetoxy group in the succinimide precursor was initially employed to impart regio- and stereoselectivity and then as a suitable leaving group to generate the desired conjugated lactam.

■ INTRODUCTION

The structurally interesting and biologically important cytotoxic alkaloids subincanadines A–G were isolated in 2 to 14 mg quantities from 100 grams bark of the Brazilian medicinal plant *Aspidosperma subincanum* by Ohsaki and co-workers in 2002 (Figure 1).[1,2] (+)-Subincanadine E is also named as pericine and it was first isolated from *Picralima nitida* by Stöckigt and co-workers in

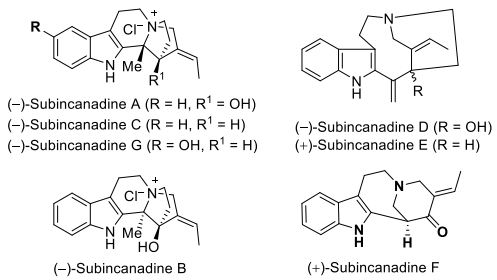


Figure 1. Potent cytotoxic alkaloids subincanadines A–G.[1,11]

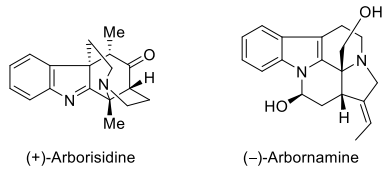
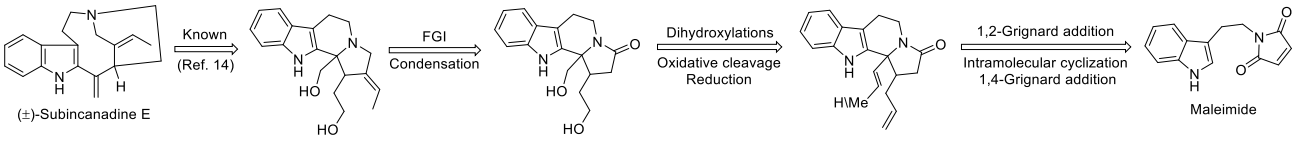


Figure 2. Biogenetic precursor (+)-subincanadine E (pericine) derived novel natural products.

1982.[3,4] Recently, Kam and co-workers have proposed that the (*S*)-pericine is a common biogenetic precursor of two structurally unprecedented monoterpenoid indole alkaloids (+)-arborisidine and (–)-arbornamine (Figure 2).[5] (+)-Subincanadine E endures unique structural architecture and in vitro exhibits potent cytotoxicity against murine lymphoma L1210 cells ($IC_{50,}$ 0.3 μg/mL) & human epidermoid carcinoma KB cells ($IC_{50,}$ 4.4 μg/mL).[1] A few new synthetic routes to the target compounds from figure 1 have been reported in recent literature.[6–14] Zhai and co-workers in 2014 reported the first total synthesis of (±)-subincanadine E.[14] Development of new synthetic approaches for (+)/(–)-subincanadine E is essential from its exceptional structural features, promising biological activity and establishment of stereochemistry point of view. Retrosynthetically, corresponding tryptamine derived maleimide would be the potential precursor for total synthesis of (±)-subincanadine E (Scheme 1). Conceptually the starting maleimide bears suitable functional groups for sequential 1,2- and 1,4-addition of Grignard reagent followed by intramolecular Pictet–Spengler cyclization to provide the desired tetracyclic hexahydroindolizinoindolone. Condensation of above stated well protected lactam with acetaldehyde to generate the exocyclic carbon–carbon double bond and essential functional group interconversions would deliver the known advanced diol intermediate leading to the target

compound. Moreover (*R*)- and (*S*)-acetoxysuccinimides may also serve as appropriate starting materials for enantioselective synthesis of (+)- and (–)-subincanadines E. In continuation of our studies on the use of cyclic anhydrides to synthesize bioactive natural products;[15–19] we herein report synthesis of (±)-subincanadine E and natural isomer (+)-subincanadine E from the readily available corresponding imides as starting materials (Schemes 1–5).

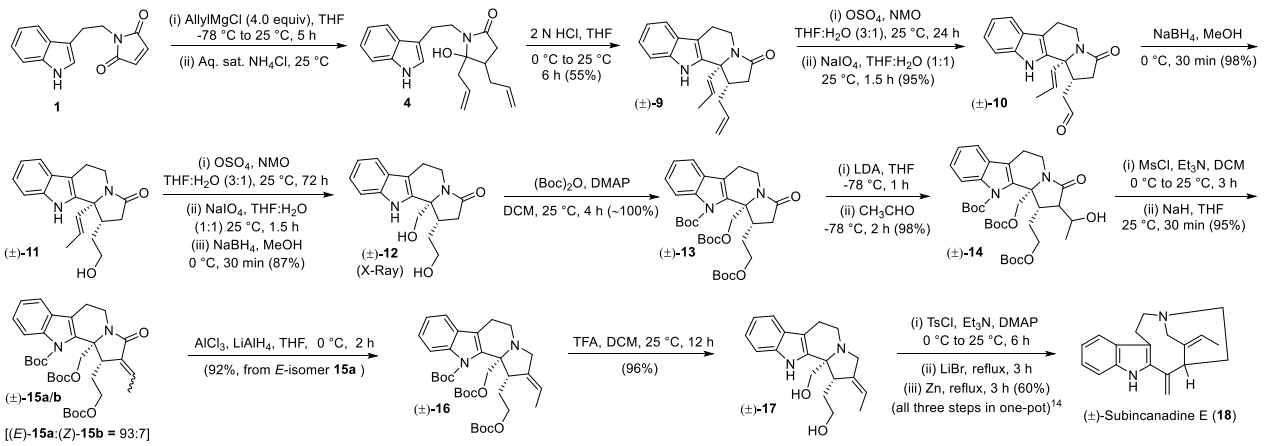


Scheme 1. Concise Retrosynthetic Analysis of (±)-Subincanadine E

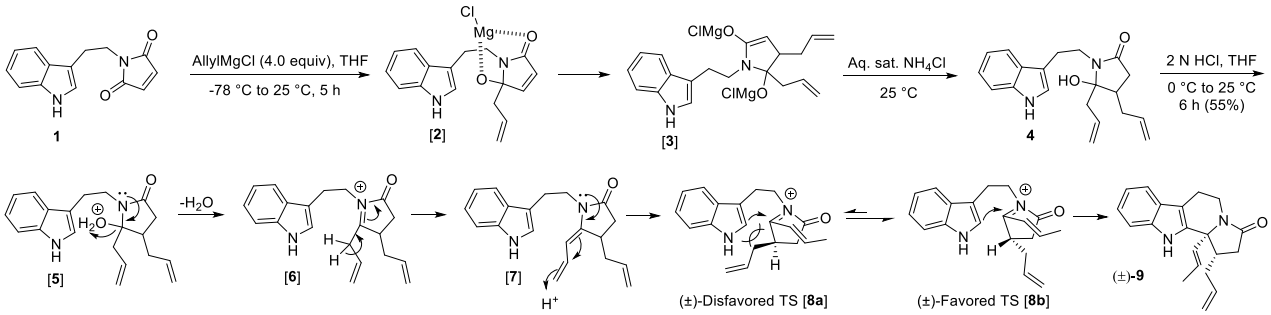
■ RESULTS AND DISCUSSION

One-pot reaction of maleimide **1** with four equivalents of allylmagnesium chloride at –78 °C followed by acidification with hydrochloric acid at 25 °C directly delivered the two allyl groups introduced and one of the double bond rearranged cyclized product (±)-**9** in ~20% yield (Scheme 2). Remarkably, two different types of coupling reactions of Grignard reagent with maleimide **1** and acid catalyzed diastereoselective intramolecular cyclization involving position specific allylic rearrangement took place in one-pot. Quenching of the above described Grignard reaction with saturated aqueous ammonium chloride to obtain the intermediate product (±)-**4** and its immediate reaction with 2 N HCl provided the desired product (±)-**9** in 55% yield. The plausible mechanisms for reactions of Grignard reagent with maleimide and acid catalyzed intramolecular Pictet−Spengler cyclization involving position specific allylic rearrangement have been depicted in scheme 3. On the basis of control experiments described in scheme 4; the 1,2-addition of Grignard reagent to maleimide **1** takes place first and forms the magnesium complex **2**, which internally activates lactam moiety for in situ 1,4-addition of Grignard reagent and delivers the lactamol **4**.[20] Lactamol **4** on treatment with 2 N HCl underwent amide nitrogen driven dehydration

to form the diene intermediate **7**, which on selective rearrangement of the double bond followed by diastereoselective intramolecular cyclization directly resulted in the essential product (±)-**9**. The in situ allylic rearrangement was eventually useful to appropriately tailor the carbon chain at an angular position. Mechanistically above mentioned intramolecular Pictet−Spengler cyclization takes place via flat iminium ion intermediate and the incoming nucleophile approaches from less hindered side in the favored intermediate **8b** resulting in *syn*-product (±)-**9**.[7,21]



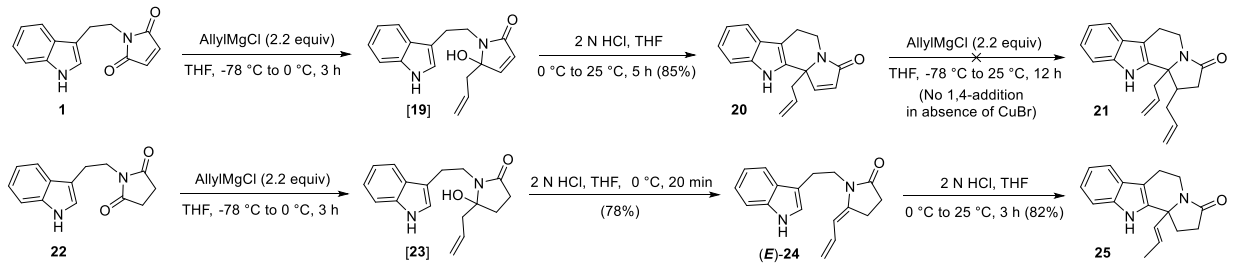
Scheme 2. Synthesis of (±)-Subincanadine E via Grignard Additions, Allylic Rearrangement, Pictet–Spengler Cyclization, Condensation and Ring Expansion Route



Scheme 3. Plausible Mechanisms for Couplings of Grignard Reagent with Maleimide and Intramolecular Cyclization Involving Position Specific Allylic Rearrangement

Reaction of maleimide **1** with 2.20 equivalents of allylmagnesium chloride at –78 °C exclusively formed the lactomol intermediate **19** (Scheme 4). The sensitive lactamol **19** on immediately performed acid induced intramolecular cyclization furnished the corresponding *α,β*-unsaturated indolizinoindolone **20** in 85% yield, without an allylic rearrangement. The

indolizinoindolone **20** did not undergo 1,4-addition of Grignard reagent in absence of CuBr due to the lack of substrate/reagent activation. The witnessed in situ allylic rearrangement was specific to the succinimide derived lactamols and it was feasible to isolate an exclusively formed diene intermediate **24**[22] in the model transformation of succinimide **22** to indolizinoindolone **25**. The exclusive formation of relatively more stable diene (*E*)-**24** could be attributed to the effective conjugation of lone pair on nitrogen atom.



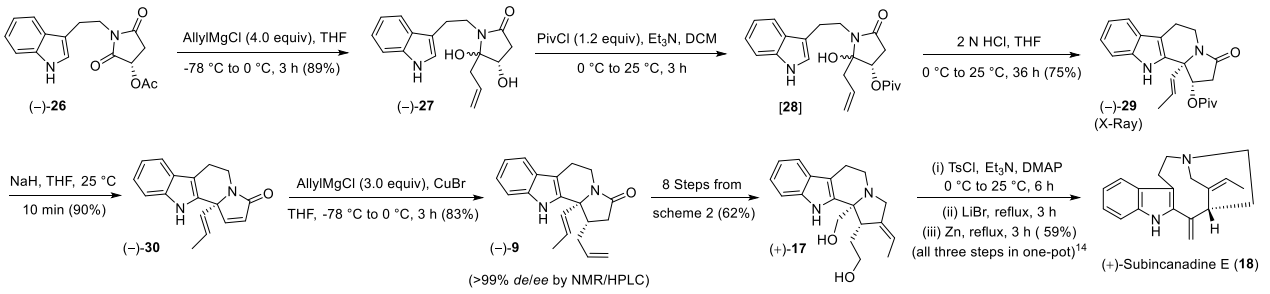
Scheme 4. Model Studies on Grignard Addition to Imides, Allylic Rearrangement, Isolation of the Proposed Diene Intermediate and Intramolecular Cyclizations

Direct transformation of two different types of carbon–carbon double bonds in compound (±)-**9** via dihydroxylation, oxidative cleavage and reduction to the corresponding product (±)-diol **12** was low yielding. The stepwise transformations of terminal and internal olefins in compound (±)-**9** initially provided primary alcohol (±)-**11** in 93% yield and then the desired (±)-diol **12** in 87% yield (Scheme 2). The structure of advanced intermediate (±)-diol **12** was unambiguously established by X-ray crystallographic data and it also confirmed the formation of *syn*-product (±)-**9** in the above mentioned Pictet−Spengler cyclization. Boc-protection of indole nitrogen atom and two primary alcohol units in compound (±)-**12** provided the required product (±)-**13** in quantitative yield. Condensation of (±)-lactam **13** with acetaldehyde followed by mesylation of the formed alcohol and stereoselective elimination of mesylate delivered the column chromatographically separable mixture of *α,β*-unsaturated lactam (±)-**15a** as a major product in 88% yield and (±)-**15b** as a minor product in 7% yield, over three steps. As expected the vinylic proton of a major *E*-isomer (±)-**15a** was more deshielded (6.56 ppm) compared to the corresponding minor *Z*-isomer (±)-**15b** (5.82

ppm) due to the five membered *peri*-intraction with a *γ*-lactam carbonyl. Alane-reduction of a lactam carbonyl in compound (±)-**15** to (±)-amine **16** in 92% yield followed by trifluoroacetic acid induced deprotection of three Boc-groups furnished the known (±)-diol **17** in 96% yield. A one-pot three-step transformation of (±)-diol **17** under Zhai and co-workers conditions[14] delivered the desired (±)-subincanadine E (**18**) in 60% yield. The analytical and spectral data obtained for (±)-diol **17** and (±)-subincanadine E (**18**) were in complete agreement with the reported data.[1,14]

Finally we planned the enantioselective synthesis of (+)/(–)-subincanadine E (**18**) from (*S*)-acetoxysuccinimide **26**[23] (Scheme 5). As expected, Grignard reagent regioselectively attacked on the more reactive imide carbonyl of (*S*)-acetoxysuccinimide **26** and directly delivered the corresponding deacylated single diastereomer (–)-**27** in 89% yield. Acid-catalyzed Pictet–Spengler cyclization of (–)-hydroxy-lactamol **27** was not diastereoselective and provided nearly 1:1 mixture of the corresponding diastereomers in 73% yield.[24] (–)-Hydroxy-lactamol **27** on treatment with pivaloyl chloride and triethylamine selectively formed the corresponding sterically hindered lactamol intermediate **28** in quantitative yield; which was used for the next step without purification and characterization for stability issues. Acid-catalyzed Pictet–Spengler cyclization of lactamol **28** was stereoselective and exclusively provided the expected double bond rearranged cyclized *syn*-product (–)-**29** in 75% yield. The structure of product (–)-**29** was also established by X-ray crystallographic data and it confirmed the *syn*-relationship between the angular alkenyl chain and *O*-pivaloyl group. Base-induced elimination of pivaloyl group in compound (–)-**29** resulted in the *α*,*β*-unsaturated lactam **30** in 90% yield. The addition of allyl-cuprate to (–)-lactam **30** was highly diastereoselctive, but unexpectedly resulted in the *syn*-product (–)-**9** in 83% yield with >99% *de*/*ee* (by ^{1}H NMR/HPLC). The analytical and spectral data obtained for *syn*-product (–)-**9** were in complete agreement with the earlier obtained data for *syn*-product (±)-**9** from scheme 2. Such type of *syn*-addition precedence is known in the literature, however genesis of

stereoselection still remains an unanswered question.[25,26] The *syn*-product (–)-**9** was transformed to (+)-diol **17** in 62% overall yield by repeating 8-steps from scheme 2. One-pot three-step transformation of (+)-diol **17** under Zhai and co-workers conditions[14] delivered the desired (+)-subincanadine E (**18**) in 59% yield. The analytical and spectral data obtained for (+)-subincanadine E (**18**) were in complete agreement with the reported data[1,14] including specific rotations {natural[1] $[\alpha]^{23}_{D}$ +39.0 (*c* 1.0 MeOH), synthetic **18** $[\alpha]^{25}_{D}$ +42.3 (*c* 0.12 MeOH)}. Enantioselective first total synthesis of (+)-subincanadine E (**18**) was accomplished from (*S*)-acetoxysuccinimide **26** with 18% overall yield and *Sinister* configuration has been assigned to the natural product.



Scheme 5. Enantioselective Synthesis (+)-Subincanadine E from (*S*)-Acetoxysuccinimide via an Unanticipated *Syn*-addition of the Cuprate

■ CONCLUSION

In summary, from the readily available maleimide/succinimide we have described new efficient approach to (±)/(+)-subincanadine E and established its absolute configuration. The 1,4-addition of Grignard reagent to the internally activated lactamol, witnessed position selective allylic rearrangements in succinimide derived lactamols and stereoselective *syn*-addition of cuprate to the unsaturated lactam are noteworthy. Our present synthetic strategy is flexible and will pave efficient enantioselective routes to subincanadines A–G and focused mini-library of their unnatural congeners and derivatives for SAR studies.

■ EXPERIMENTAL SECTION

General Description. Melting points are uncorrected. The ^{1}H NMR spectra were recorded on 200 MHz NMR, 400 MHz NMR and 500 MHz NMR spectrometers using solvent residue signal as an internal standard [^{1}H NMR: $CDCl_3$ (7.27), CD_3OD (3.31), DMSO-d_6 (2.50); ^{13}C NMR: $CDCl_3$ (77.00), CD_3OD (49.00), DMSO-d_6 (39.51)]. The ^{13}C NMR spectra were recorded on 200 NMR (50 MHz), 400 NMR (100 MHz) and 500 NMR (125 MHz) spectrometers. HRMS (ESI) were taken on Orbitrap (quadrupole plus ion trap) and TOF mass analyzer. The IR spectra were recorded on an FT-IR spectrometer. Column chromatographic separations were carried out on silica gel (60−120 mesh and 230−400 mesh). Commercially available starting materials and reagents were used.

1-Allyl-11b-[(*E*)-prop-1-en-1-yl]-1,2,5,6,11,11b-hexahydro-3*H*-indolizino(8,7-*b*)indol-3-one (9). To a stirred solution of compound **1**[27] (2.00 g, 8.33 mmol) in dry THF (40 mL) was added solution of allylmagnesium chloride in THF (2 M, 16.06 mL, 33.33 mmol) in a dropwise mode at −78 °C under argon atmosphere. The reaction mixture was stirred for 1 h at same temperature and then allowed to reach 25 °C. It was further stirred for 4 h and the reaction was quenched with saturated aqueous NH_4Cl solution at 0 °C. The reaction mixture was concentrated in vacuo and the obtained residue was dissolved in EtOAc (80 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo afforded lactamol **4** which was directly used for the next step. To a stirred solution of lactamol **4** in THF (25 mL) was added 2 N HCl (1.50 mL) at 0 °C and the reaction mixture was stirred for 6 h allowing to reach 25 °C. The reaction was quenched with saturated aqueous $NaHCO_3$ at 0 °C and the aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by purification of the obtained residue by column chromatography (silica gel, 60–120 mesh, EtOAc–PE, 30:70) afforded single

diastereomer (±)-**9** as a yellow solid (1.40 g, 55%). Mp 83−85 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.73 (d, J = 6.1 Hz, 3H), 2.27–2.48 (m, 2H), 2.48–2.63 (m, 3H), 2.75–3.00 (m, 3H), 4.46 (dd, J = 12.2 and 4.9 Hz, 1H), 5.24–5.33 (m, 2H), 5.35–5.45 (m, 1H), 5.61 (d, J = 15.9 Hz, 1H), 5.87–6.00 (m, 1H), 7.13 (t, J = 7.3 Hz, 1H), 7.21 (t, J = 7.3 Hz, 1H), 7.36 (d, J = 7.9 Hz, 1H), 7.50 (d, J = 7.3 Hz, 1H), 8.18 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.7, 21.4, 34.8, 35.3, 37.1, 44.4, 65.9, 108.6, 111.0, 117.7, 118.5, 119.8, 122.2, 126.4, 127.5, 129.0, 134.6, 135.8, 137.1, 171.6; ESIMS (m/z) 307 $[M+H]^+$; HRMS (ESI) calcd for $C_{20}H_{23}N_2O$ 307.1805, found 307.1802; IR ($CHCl_3$) ν_{max} 3284, 1681 cm^{-1}.

11b-Allyl-1,2,5,6,11,11b-hexahydro-3*H*-indolizino(8,7-*b*)indol-3-one (20). To a stirred solution of compound **1**[27] (300 mg, 1.25 mmol) in dry THF (10 mL) was added a solution of allylmagnesium chloride in THF (2 M, 1.37 mL, 2.75 mmol) in a dropwise mode at −78 °C under argon atmosphere. The reaction mixture was stirred for 1.5 h at same temperature and then it was allowed to reach 0 °C in next 1.5 h. The reaction was quenched with saturated aqueous NH_4Cl solution at 0 °C. The reaction mixture was concentrated in vacuo and the obtained residue was dissolved in EtOAc (50 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of organic layer in vacuo afforded lactamol **19**; which was directly used for the next step. To a stirred solution of lactamol **19** in THF (10 mL) was added 2 N HCl (0.30 mL) at 0 °C and the reaction mixture was stirred for 5 h allowing to reach 25 °C. The reaction was quenched with saturated aqueous $NaHCO_3$ at 0 °C and the reaction mixture was extracted with EtOAc (3 × 15 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by purification of the obtained residue by column chromatography (silica gel, 60–120 mesh, PE–EtOAc, 50:50) afforded compound (±)-**20** as a yellow solid (280 mg, 85%). Mp 191−193 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.70–2.96 (m,

4H), 3.32 (td, *J* = 12.5 and 5.5 Hz, 1H), 4.62 (dd, *J* = 13.4 and 6.1 Hz, 1H), 5.12–5.22 (m, 2H), 5.64–5.77 (m, 1H), 6.21 (d, *J* = 6.1 Hz, 1H), 7.13 (t, *J* = 7.3 Hz, 1H), 7.21 (t, *J* = 7.3 Hz, 1H), 7.35 (t, *J* = 5.5 Hz, 1H), 7.36 (d, *J* = 6.1 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 8.47 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.8, 35.9, 41.9, 67.0, 107.9, 111.1, 118.8, 119.8, 119.9, 122.4, 126.5, 126.8, 131.0, 132.9, 136.3, 150.1, 171.6; ESIMS (*m*/*z*) 265 $[M+H]^+$; HRMS (ESI) calcd for $C_{17}H_{17}N_2O$ 265.1335, found 265.1337; IR ($CHCl_3$) ν_{max} 3459, 1678 cm^{-1}.

(*E*)-1-[2-(1*H*-Indol-3-yl)ethyl]-5-allylidenepyrrolidin-2-one (24). To a stirred solution of compound **22**[27] (500 mg, 2.10 mmol) in dry THF (15 mL) was added a solution of allylmagnesium chloride in THF (2 M, 2.10 mL, 4.20 mmol) in a dropwise mode at −78 °C under argon atmosphere. The reaction mixture was stirred for 1.5 h at same temperature and then allowed to reach 0 °C in next 1.5 h. The reaction was quenched with saturated aqueous NH_4Cl solution. The reaction mixture was concentrated in vacuo and the obtained residue was dissolved in EtOAc (50 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo afforded lactamol **23**; which was directly used for the next step. To a stirred solution of lactamol **23** in THF (12 mL) was added 2 N HCl (0.50 mL) at 0 °C and the reaction mixture was stirred for 20 min. The reaction was quenched with saturated aqueous $NaHCO_3$ at 0 °C and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by purification of the obtained residue by column chromatography (silica gel, 60–120 mesh, PE–EtOAc, 50:50) afforded compound **24** as a white solid (428 mg, 78%). Mp 105−107 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.40–2.60 (m, 2H), 2.70–2.90 (m, 2H), 3.04 (t, *J* = 8.2 Hz, 2H), 3.83 (t, *J* = 7.7 Hz, 2H), 4.98 (d, *J* = 10.2 Hz, 1H), 5.08 (d, *J* = 16.8 Hz, 1H), 5.60 (d, *J* = 11.0 Hz, 1H), 6.30–6.55 (m, 1H), 7.08 (d, *J* = 2.2 Hz, 1H), 7.05–7.30 (m, 2H), 7.36 (d, *J* = 7.1 Hz, 1H), 7.68 (d, *J* = 7.1 Hz, 1H), 8.23 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.7, 22.5, 28.6, 40.7,

102.6, 111.2, 112.5, 112.8, 118.5, 119.4, 121.96, 122.00, 127.4, 131.6, 136.2, 142.5, 175.7; ESIMS (*m*/*z*) 289 $[M+Na]^+$; HRMS (ESI) calcd for $C_{17}H_{18}N_2ONa$ 289.1311, found 289.1314; IR ($CHCl_3$) ν_{max} 3423, 1681, 1601 cm^{-1}.

(*E*)-11b-(Prop-1-en-1-yl)-1,2,5,6,11,11b-hexahydro-3*H*-indolizino(8,7-*b*)indol-3-one (25). To a stirred solution of compound **24** (400 mg, 1.50 mmol) in THF (10 mL) was added 2 N HCl (0.50 mL) at 0 °C and the reaction mixture was stirred for 3 h allowing to reach 25 °C. The reaction was quenched with saturated aqueous $NaHCO_3$ at 0 °C and the reaction mixture was extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by purification of the obtained residue by column chromatography (silica gel, 60–120 mesh, PE–EtOAc, 40:60) afforded compound **25** as a white solid (328 mg, 82%). Mp 177−179 °C; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.70 (d, *J* = 6.8 Hz, 3H), 2.25 (q, *J* = 10.9 Hz, 1H), 2.39–2.51 (m, 2H), 2.69 (dt, *J* =17.4 and 9.5 Hz, 1H), 5.80 (dd, *J* = 15.4 and 5.2 Hz, 1H), 2.85–2.94 (m, 1H), 3.09 (td, *J* = 16.9 and 5.5 Hz, 1H), 4.44 (dd, *J* = 13.1 and 6.1 Hz, 1H), 5.42 (qd, *J* = 15.4 and 6.4 Hz, 1H), 5.70 (d, *J* = 15.3 Hz, 1H), 7.14 (t, *J* = 7.6 Hz, 1H), 7.20 (t, *J* = 7.4 Hz, 1H), 7.36 (d, *J* = 7.8 Hz, 1H), 7.51 (d, *J* = 7.8 Hz, 1H), 8.63 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.4, 21.1, 30.4, 32.1, 34.9, 63.3, 108.0, 111.0, 118.4, 119.6, 122.0, 126.5, 127.3, 131.2, 134.9, 136.2, 173.2; ESIMS (*m*/*z*) 267 $[M+H]^+$; HRMS (ESI) calcd for $C_{17}H_{19}N_2O$ 267.1492, found 267.1494; IR ($CHCl_3$) ν_{max} 3419, 1677 cm^{-1}.

(–)-(4*S*)-1-[2-(1*H*-Indol-3-yl)ethyl]-5-allyl-4,5-dihydroxypyrrolidin-2-one (27). To a stirred solution of compound (–)-**26**[23] (2.00 g, 6.66 mmol) in dry THF (30 mL) was added a solution of allylmagnesium chloride in THF (2 M, 13.33 mL, 26.66 mmol) in a dropwise mode at –78 °C under argon atmosphere. The reaction mixture was allowed to reach 0 °C in next 3 h and then quenched with saturated aqueous NH_4Cl solution. The reaction mixture was concentrated in vacuo

and the obtained residue was dissolved in EtOAc (80 mL). The organic layer was washed with brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by purification of the obtained residue by column chromatography (silica gel, 230–400 mesh, MeOH–DCM, 2:98) afforded compound (–)-**27** as foam (1.70 g, 89%). $[\alpha]^{25}_{D}$ –18.7 (*c* 0.2 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.33–2.44 (m, 2H), 2.55 (dd, *J* = 14.6 and 7.3 Hz, 1H), 2.69 (dd, *J* = 17.7 and 6.7 Hz, 1H), 3.00 (d, *J* = 4.9 Hz, 1H), 3.03–3.12 (m, 1H), 3.13–3.22 (m, 1H), 3.33–3.44 (m, 1H), 3.61 (s, 1H), 3.66–3.77 (m, 1H), 4.16 (br s, 1H), 5.07–5.20 (m, 2H), 5.58–5.74 (m, 1H), 7.04 (s, 1H), 7.14 (t, *J* = 7.4 Hz, 1H), 7.20 (t, *J* = 7.9 Hz, 1H), 7.36 (d, *J* = 7.9 Hz, 1H), 7.71 (d, *J* = 7.9 Hz, 1H), 8.08 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.7, 39.0, 40.3, 41.3, 68.8, 91.0, 111.3, 113.1, 118.9, 119.4, 120.1, 122.0, 122.2, 127.3, 131.3, 136.2, 172.4; ESIMS (*m*/*z*) 323 $[M+Na]^+$; HRMS (ESI) calcd for $C_{17}H_{20}N_2O_3Na$ 323.1366, found 323.1363; IR ($CHCl_3$) ν_{max} 3619, 3478, 3352, 1678 cm^{-1}.

(–)-(1*S*,11b*R*)-3-Oxo-11b-[(*E*)-prop-1-en-1-yl]-2,3,5,6,11,11b-hexahydro-1*H*-indolizino(8,7-*b*)indol-1-yl Pivalate (29). To a stirred solution of lactamol (–)-**27** (1.70 g, 5.66 mmol) in CH_2Cl_2 (25 mL) were slowly added Et_3N (1.93 mL, 14.16 mmol) and pivCl (1.10 mL, 8.49 mmol) at 0 °C. The reaction mixture was stirred for 3 h allowing reach 25 °C and the reaction was quenched with water. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layer was washed with aqueous $NaHCO_3$, brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo and the obtained vacuum dried *O*-pivaloyl lactamol **28** was directly used for the next step. To a stirred solution of lactamol **28** in THF (20 mL) was added 2 N HCl (2.00 mL) at 0 °C and the reaction mixture was stirred for 36 h allowing to reach 25 °C. The reaction was quenched with saturated aqueous $NaHCO_3$ at 0 °C and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by purification of the obtained

residue by column chromatography (silica gel, 60–120 mesh, EtOAc–PE, 20:80) afforded single diastereomer (–)-**29** as a solid (1.50 g, 75%). Mp 171−173 °C; $[\alpha]^{25}_{D}$ –59.3 (*c* 0.25 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.30 (s, 9H), 1.67 (d, *J* = 7.3 Hz, 3H), 2.73 (dd, *J* = 15.2 and 4.9 Hz, 1H), 2.82–2.99 (m, 3H), 3.06 (td, *J* = 12.2 and 4.9 Hz, 1H), 4.45 (dd, *J* = 12.8 and 6.1 Hz, 1H), 5.30–5.45 (m, 2H), 5.52 (d, *J* = 15.9 Hz, 1H), 7.12 (t, *J* = 7.3 Hz, 1H), 7.22 (t, *J* = 7.3 Hz, 1H), 7.45 (d, *J* = 7.9 Hz, 1H), 7.49 (d, *J* = 7.9 Hz, 1H), 9.57 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.7, 20.7, 27.2, 35.2, 36.5, 39.0, 68.3, 73.2, 109.3, 111.5, 118.3, 119.5, 122.3, 126.3, 127.8, 131.4, 132.8, 135.7, 169.3, 179.6; ESIMS (*m*/*z*) 367 $[M+H]^+$; HRMS (ESI) calcd for $C_{22}H_{27}N_2O_3$ 367.2016, found 367.2011; IR ($CHCl_3$) ν_{max} 3390, 1684, 1612 cm^{-1}.

(–)-(*S*,*E*)-11b-(Prop-1-en-1-yl)-5,6,11,11b-tetrahydro-3*H*-indolizino(8,7-*b*)indol-3-one (30). To a stirred suspension of NaH (410 mg, 10.24 mmol) in dry THF (25 mL) was slowly added the solution of compound (–)-**29** (1.50 g, 4.098 mmol) in THF (10 mL) in dropwise mode at 25 °C. The reaction was monitored by TLC and quenched with aqueous NH_4Cl after 10 min. The reaction mixture was concentrated in vacuo and the obtained residue was dissolved in EtOAc (50 mL). The organic layer was washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by purification of the obtained residue by column chromatography (silica gel, 60–120 mesh, PE–EtOAc, 50:50) afforded compound (–)-**30** as a white solid (972 mg, 90%). Mp 211−213 °C; $[\alpha]^{25}_{D}$ –298.4 (*c* 0.2 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.69 (d, *J* = 6.1 Hz, 3H), 2.80 (dd, *J* = 15.5 and 5.5 Hz, 1H), 2.86–2.99 (m, 1H), 3.24 (td, *J* = 12.2 and 4.3 Hz, 1H), 4.54 (dd, *J* = 13.1 and 6.7 Hz, 1H), 5.46 (d, *J* = 15.2 Hz, 1H), 5.51–5.62 (m, 1H), 6.18 (d, *J* = 6.1 Hz, 1H), 7.13 (t, *J* = 7.9 Hz, 1H), 7.20 (t, *J* = 7.9 Hz, 1H), 7.36 (d, *J* = 7.9 Hz, 1H), 7.37 (d, *J* = 6.1 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 8.64 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.7, 21.9, 35.1, 68.2, 109.2, 111.0, 118.8, 119.8, 122.5, 126.4, 126.5, 128.6, 130.6, 131.1, 136.3, 149.7, 170.8 ; ESIMS

(*m*/*z*) 265 $[M+H]^+$; HRMS (ESI) calcd for $C_{17}H_{17}N_2O$ 265.1335, found 265.1337; IR ($CHCl_3$) ν_{max} 3462, 1677 cm^{-1}.

(–)-(1*S*,11b*R*)-1-Allyl-11b-[(*E*)-prop-1-en-1-yl]-1,2,5,6,11,11b-hexahydro-3*H*-indolizino(8,7-*b*)indol-3-one (9). To a stirred solution of compound (–)-**30** (900 mg, 3.40 mmol) in dry THF (25 mL) containing CuBr (48 mg, 0.34 mmol) was added a solution of allylmagnesium chloride (2 M in THF, 5.10 mL, 10.22 mmol) in a dropwise mode at −78 °C under argon atmosphere. The reaction mixture was allowed to reach 0 °C in 3 h and the reaction was quenched with saturated aqueous NH_4Cl solution. The reaction mixture was concentrated in vacuo and the obtained residue was dissolved in EtOAc (40 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by purification of the obtained residue by column chromatography (silica gel, 60–120 mesh, EtOAc–PE, 30:70) afforded compound (–)-**9** as a white solid (865 mg, 83%). Mp 83−85 °C; $[\alpha]^{25}_D$ –87.0 (*c* 0.22 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.73 (d, *J* = 6.1 Hz, 3H), 2.27–2.48 (m, 2H), 2.48–2.63 (m, 3H), 2.75–3.00 (m, 3H), 4.46 (dd, *J* = 12.2 and 4.9 Hz, 1H), 5.24–5.33 (m, 2H), 5.35–5.45 (m, 1H), 5.61 (d, *J* = 15.9 Hz, 1H), 5.87–6.00 (m, 1H), 7.13 (t, *J* = 7.3 Hz, 1H), 7.21 (t, *J* = 7.3 Hz, 1H), 7.36 (d, *J* = 7.9 Hz, 1H), 7.50 (d, *J* = 7.3 Hz, 1H), 8.18 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.7, 21.4, 34.8, 35.3, 37.1, 44.4, 65.9, 108.6, 111.0, 117.7, 118.5, 119.8, 122.2, 126.4, 127.5, 129.0, 134.6, 135.8, 137.1, 171.6; ESIMS (*m*/*z*) 307 $[M+H]^+$; HRMS (ESI) calcd for $C_{20}H_{23}N_2O$ 307.1805, found 307.1802; IR ($CHCl_3$) ν_{max} 3284, 1681 cm^{-1}.

(–)-2-{(1*R*,11b*S*)-3-Oxo-11b-[(*E*)-prop-1-en-1-yl]-2,3,5,6,11,11b-hexahydro-1*H*-indolizino(8,7-*b*)indol-1-yl}acetaldehyde (10). To a stirred solution of compound (–)-**9** (800 mg, 2.61 mmol) in THF:H_2O (3:1, 25 mL) was added NMO (50% in water, 3.05 mL, 13.07 mmol) and catalytic amount of OsO_4 (0.20 mL, 0.5 M solution in *t*-BuOH) at 25 °C and the reaction mixture

was stirred for 24 h. The reaction was quenched with saturated solution of $Na_2S_2O_3$ and further stirred for 30 min. Aqueous layer was extracted in EtOAc (3 × 30 mL) and the combined organic layer was washed with brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo and the obtained diol was directly used for next step. To a stirred solution of obtained diol in THF:H_2O (1:1, 30 mL) was added $NaIO_4$ (1.25 gm, 5.88 mmol) at 25 °C in three equal lots and the reaction was monitored on TLC. The reaction mixture diluted with EtOAc (50 mL) after 1.5 h and the organic layer was washed with brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by purification of the obtained residue by column chromatography (silica gel, 60–120 mesh, EtOAc–PE, 40:60) afforded compound (–)-**10** as a solid (764 mg, 95%). Mp 97−99 °C; $[\alpha]^{25}_{D}$ –94.2 (*c* 0.1 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.70 (d, *J* = 6.1 Hz, 3H), 2.25 (dd, *J* = 16.8 and 9.5 Hz, 1H), 2.67–2.98 (m, 4H), 2.98–3.20 (m, 3H), 4.44 (dd, *J* = 12.8 and 5.7 Hz, 1H), 5.38–5.50 (m, 2H), 7.12 (t, *J* = 7.3 Hz, 1H), 7.21 (t, *J* = 7.3 Hz, 1H), 7.44 (d, *J* = 8.1 Hz, 1H), 7.49 (d, *J* = 7.7 Hz, 1H), 9.67 (s, 1H), 9.83 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.6, 21.0, 35.5, 36.2, 37.2, 47.2, 66.1, 108.3, 111.4, 118.4, 119.6, 122.2, 126.4, 128.4, 130.0, 135.1, 136.0, 171.0, 202.0; ESIMS (*m*/*z*) 309 $[M+H]^+$; HRMS (ESI) calcd for $C_{19}H_{21}N_2O_2$ 309.1598, found 309.1590; IR ($CHCl_3$) ν_{max} 3376, 3020, 1725, 1677, 1601 cm^{-1}.

(–)-(1*S*,11b*R*)-1-(2-Hydroxyethyl)-11b-[(*E*)-prop-1-en-1-yl]-1,2,5,6,11,11b-hexahydro-3*H*-indolizino(8,7-*b*)indol-3-one (11). To a stirred solution of aldehyde (–)-**10** (740 mg, 2.40 mmol) in MeOH (15 mL) was added the $NaBH_4$ (133 mg 3.60 mmol) at 0 °C in two equal lots and reaction mixture was stirred for 30 min. The reaction was quenched with aqueous NH_4Cl and the reaction mixture was concentrated in vacuo. The obtained residue was dissolved in EtOAc (40 mL) and the organic layer was washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by purification of the obtained residue by column chromatography (silica gel, 230–400 mesh, DCM–MeOH, 2:98) afforded compound (–)-**11** as a

solid (739 mg, 98%). Mp 110−112 °C; $[\alpha]^{25}_{D}$ –212.1 (*c* 0.13 $CHCl_3$); ^{1}H NMR (CD_3OD, 500 MHz) δ 1.65–1.80 (m, 1H), 1.73 (d, *J* = 5.4 Hz, 3H), 2.25–2.35 (m, 1H), 2.39 (dd, *J* = 15.1 and 11.9 Hz, 1H), 2.45–2.55 (m, 1H), 2.59 (dd, *J* = 15.3 and 7.7 Hz, 1H), 2.70–2.83 (m, 2H), 2.96 (td, *J* = 11.6 and 5.8 Hz, 1H), 3.55–3.65 (m, 1H), 3.65–3.75 (m, 1H), 4.30–4.37 (m, 1H), 5.31–5.40 (m, 1H), 5.72 (d, *J* = 16.0 Hz, 1H), 7.00 (t, *J* = 7.6 Hz, 1H), 7.09 (t, *J* = 7.3 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.41 (d, *J* = 7.7 Hz, 1H); ^{13}C NMR (CD_3OD, 125 MHz) δ 17.8, 22.4, 34.1, 36.2, 37.7, 43.9, 61.5, 68.0, 108.2, 112.3, 119.0, 120.1, 122.7, 127.7, 129.0, 129.6, 136.2, 138.2, 174.7; ESIMS (*m*/*z*) 311 $[M+H]^+$; HRMS (ESI) calcd for $C_{19}H_{23}N_2O_2$ 311.1754, found 311.1749; IR ($CHCl_3$) ν_{max} 3333, 1666 cm^{-1}.

(+)-(1*S*,11b*S*)-1-(2-Hydroxyethyl)-11b-(hydroxymethyl)-1,2,5,6,11,11b-hexahydro-3*H*-indolizino(8,7-*b*)indol-3-one (12). To a stirred solution of compound (–)-**11** (700 mg, 2.25 mmol) in THF:H_2O (3:1, 25 mL) was added NMO (50% in water, 2.60 mL, 11.29 mmol) and catalytic amount of OsO_4 (0.15 mL, 0.50 M solution in *t*-BuOH) at 25 °C and reaction mixture was stirred for 72 h. The reaction was quenched with saturated solution of $Na_2S_2O_3$ and further stirred for 30 min. Aqueous layer was extracted with EtOAc (3 × 40 mL) and the combined organic layer was washed with brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo and the obtained vacuum dried triol was directly used for next step. To a stirred solution of obtained triol in THF:H_2O (1:1, 35 mL) was added $NaIO_4$ (2.10 gm, 10.17 mmol) at 25 °C in three equal lots. The reaction mixture was diluted with EtOAc (60 mL) after 1.5 h and the organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The obtained aldehyde was immediately used for the next reaction without any purification. To a stirred solution of aldehyde in MeOH (15 mL) was added the $NaBH_4$ (171 mg, 4.63 mmol) at 0 °C. The reaction was quenched with aqueous NH_4Cl after 30 min and reaction mixture was concentrated in vacuo. The obtained residue was dissolved in EtOAc (50 mL) and the organic layer was washed with brine

and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by purification of the obtained residue by column chromatography (silica gel, 230–400 mesh, MeOH–DCM, 7:93) afforded compound (+)-**12** as a solid (589 mg, 87%). Mp 117−119 °C; $[\alpha]^{25}_D$ +382.6 (*c* 0.21 MeOH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.80–1.95 (m, 1H), 2.22–2.47 (m, 4H), 2.52–2.65 (m, 1H), 2.74 (dd, *J* = 15.3 and 4.9 Hz, 1H), 3.05 (td, *J* = 12.5 and 4.9 Hz, 1H), 3.37–3.47 (m, 1H), 3.50–3.60 (m, 1H), 3.69 (dd, *J* = 11.6 and 4.9 Hz, 1H), 3.85 (dd, *J* = 11.6 and 6.1 Hz, 1H), 4.28 (dd, *J* = 12.8 and 6.1 Hz, 1H), 4.58 (t, *J* = 5.5 Hz, 1H), 5.16 (t, *J* = 5.5 Hz, 1H), 6.98 (t, *J* = 7.3 Hz, 1H), 7.07 (t, *J* = 7.3 Hz, 1H), 7.34 (d, *J* = 7.9 Hz, 1H), 7.40 (d, *J* = 7.9 Hz, 1H), 10.82 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 21.3, 31.8, 34.6, 37.6, 40.9, 59.7, 62.4, 65.1, 106.4, 111.4, 117.9, 118.7, 121.1, 126.2, 135.5, 136.2, 171.9; ESIMS (*m*/*z*) 301 $[M+H]^+$; HRMS (ESI) calcd for $C_{17}H_{21}N_2O_3$ 301.1547, found 301.1542; IR ($CHCl_3$) ν_{max} 3500, 3284, 1670, 1628 cm^{-1} .

(–)-*tert*-Butyl (1*S*,11b*S*)-1-{2-[(*tert*-Butoxycarbonyl)oxy]ethyl}-11b-{[(*tert*-butoxycarbonyl)oxy]methyl}-3-oxo-1,2,3,5,6,11b-hexahydro-11*H*-indolizino(8,7-*b*)indole-11-carboxylate (13). To a stirred solution of diol (+)-**12** (210 mg, 0.70 mmol) in CH_2Cl_2 was added $(Boc)_2O$ (0.535 mL, 2.45 mmol) and catalytic amount of DMAP (17 mg, 0.14 mmol) and the reaction mixture was stirred at 25 °C for 4 h. Reaction was quenched with water and aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by purification of the obtained residue by column chromatography (silica gel, 60–120 mesh, EtOAc–PE, 15:85) afforded compound (−)-**13** as a solid (418 mg, 99%). Mp 72−74 °C; $[\alpha]^{25}_D$ −116.3 (*c* 1.0 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.42 (s, 9H), 1.47 (s, 9H), 1.72 (s, 9H), 1.95 (sept, *J* = 6.7 Hz, 1H), 2.38 (dd, *J* = 17.1 and 6.7 Hz, 1H), 2.55–2.80 (m, 4H), 2.93 (sept, *J* = 6.7 Hz, 1H), 3.37 (td, *J* = 12.8 and 5.5 Hz, 1H), 4.01–4.10 (m, 1H), 4.11–4.20 (m, 1H), 4.44 (dd, *J* = 13.7 and 7.3 Hz, 1H), 4.90 (d, *J* = 12.2 Hz, 1H), 5.12 (d, *J* = 12.2 Hz, 1H), 7.24 (t, *J* = 7.3 Hz, 1H), 7.32 (t, *J* = 7.3 Hz,

1H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.92 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.0, 27.6, 27.7, 28.2, 31.2, 34.5, 37.5, 37.6, 66.0, 66.1, 67.7, 81.9, 82.3, 84.8, 115.6, 118.6, 119.0, 122.9, 125.3, 128.4, 135.0, 136.0, 150.4, 153.2, 153.6, 173.8; ESIMS (*m*/*z*) 601 $[M+H]^+$; HRMS (ESI) calcd for $C_{32}H_{45}N_2O_9$ 601.3120, found 601.3113; IR ($CHCl_3$) ν_{max} 1738, 1678, 1600 cm^{-1}

(–)-*tert*-Butyl (1*S*,11b*S*)-1-{2-[(*tert*-Butoxycarbonyl)oxy]ethyl}-11b-{[(*tert*-butoxycarbonyl) oxy]methyl}-2-(1-hydroxyethyl)-3-oxo-1,2,3,5,6,11b-hexahydro-11*H*-indolizino(8,7-*b*)indole-11-carboxylate (14). Freshly prepared solution of LDA in THF (1 M, 0.50 mL, 0.50 mmol) was added to a stirred solution of compound (−)-**13** (200 mg, 0.33 mmol) in THF (10 mL) in a dropwise mode at −78 °C under argon atmosphere. The reaction mixture was stirred for 1 h at −78 °C and solution of acetaldehyde (75 μL, 1.33 mmol) in THF (3 mL) was slowly added to the reaction mixture. The reaction was quenched after 2 h by using aqueous NH_4Cl and the reaction mixture was concentrated in vacuo. The obtained residue was dissolved in EtOAc (50 mL) and the organic layer was washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by purification of the obtained residue by column chromatography (silica gel, 60–120 mesh, EtOAc–PE, 30:70) afforded compound (−)-**14** as a solid (210 mg, 98%). Mp 63−65 °C; $[\alpha]^{25}_D$ –111.4 (*c* 0.3 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.98 (d, *J* = 6.1 Hz, 3H), 1.37 (s, 9H), 1.40 (s, 1H), 1.47 (s, 9H), 1.73 (s, 9H), 1.92 (sept, *J* = 6.9 Hz, 1H), 2.37 (dd, *J* = 8.2 and 3.4 Hz, 1H), 2.55–2.72 (m, 3H), 2.90–3.00 (m, 1H), 3.44 (sext, *J* = 5.7 Hz, 2H), 3.71 (s, 1H), 4.05–4.15 (m, 1H), 4.18–4.25 (m, 1H), 4.44 (dd, *J* = 13.3 and 6.9 Hz, 1H), 4.93 (d, *J* = 5.0 Hz, 1H), 7.26 (t, *J* = 7.7 Hz, 1H), 7.32 (t, *J* = 7.3 Hz, 1H), 7.41 (d, *J* = 7.6 Hz, 1H), 7.96 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.1, 20.5, 27.6, 27.8, 28.3, 30.4, 35.3, 39.6, 53.9, 65.4, 66.5, 66.9, 68.7, 81.9, 82.3, 85.0, 116.0, 118.2, 118.5, 123.0, 125.2, 128.5, 134.8, 135.6, 150.2, 153.0, 153.5, 176.6; ESIMS (*m*/*z*) 645 $[M+H]^+$; HRMS (ESI) calcd for $C_{34}H_{49}N_2O_{10}$ 645.3382, found 645.3365; IR ($CHCl_3$) ν_{max} 3556, 1736, 1667 cm^{-1}.

(–)-*tert*-Butyl (1*S*,11b*S*,*E*/*Z*)-1-{2-[(*tert*-Butoxycarbonyl)oxy]ethyl}-11b-{[(*tert*-butoxycarbonyl)oxy]methyl}-2-ethylidene-3-oxo-1,2,3,5,6,11b-hexahydro-11*H*-indolizino(8,7-*b*)indole-11-carboxylate (15a/b). To a stirred solution of alcohol (–)-**14** (150 mg, 0.232 mmol) in CH_2Cl_2 (8 mL) was slowly added Et_3N (95 μL, 0.697 mmol) and MsCl (26 μL, 0.348 mmol) at 0 °C. The reaction mixture was stirred for 3 h and allowed to reach 25 °C. The reaction was quenched with water and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layer was washed with aqueous $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated in vacuo. The obtained mesylate was directly used for next step without any purification. To a stirred suspension of NaH (20 mg, 0.498 mmol) in dry THF (10 mL) was slowly added the solution of *O*-mesylate in THF (5 mL) in dropwise mode at 25 °C. The reaction was quenched with aqueous NH_4Cl after 30 min and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by purification of the obtained residue by column chromatography (silica gel, 230–400 mesh, EtOAc–PE, 20:80) afforded compound (−)-**15b** as a solid (10 mg, 6.86%) and (−)-**15a** as a solid (128 mg, 87.79%). **15a:** Mp 77−79 °C; $[\alpha]^{25}_{D}$ –124.3 (*c* 0.2 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.28 (s, 9H), 1.48 (s, 9H), 1.70 (d, *J* = 6.7 Hz, 3H), 1.75 (s, 9H), 1.88–1.98 (m, 1H), 2.37–2.50 (m, 1H), 2.61 (dd, *J* = 16.5 and 5.5 Hz, 1H), 2.99 (ddd, *J* = 11.3, 10.7 and 6.7 Hz, 1H), 3.59 (td, *J* = 12.2 and 5.5 Hz, 1H), 3.78 (dd, *J* = 10.1 and 4.9 Hz, 1H), 3.97 (q, *J* = 8.0 Hz, 1H), 4.15–4.24 (m, 1H), 4.45 (dd, *J* = 13.4 and 7.3 Hz, 1H), 4.80 (d, *J* = 11.6 Hz, 1H), 5.22 (d, *J* = 11.6 Hz, 1H), 6.56 (q, *J* = 7.3 Hz, 1H), 7.22 (t, *J* = 7.9 Hz, 1H), 7.29 (t, *J* = 7.3 Hz, 1H), 7.39 (d, *J* = 7.3 Hz, 1H), 7.95 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.7, 19.8, 27.4, 27.7, 28.2, 29.1, 36.0, 39.3, 64.7, 65.5, 67.6, 81.6, 82.0, 84.6, 115.9, 118.3, 118.8, 122.7, 124.8, 128.7, 131.1, 134.0, 134.3, 135.5, 150.2, 152.9, 153.5, 170.9; ESIMS (*m*/*z*) 627 $[M+H]^+$; HRMS (ESI) calcd for $C_{34}H_{47}N_2O_9$ 627.3276, found 627.3268;

IR ($CHCl_3$) ν_{max} 1734, 1682 cm^{-1}. **15b:** Mp 73−74 °C; $[\alpha]^{25}_D$ –111.3 (*c* 0.1 $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.31 (s, 9H), 1.49 (s, 9H), 1.73 (s, 9H), 1.78–1.90 (m, 1H), 2.15 (d, *J* = 7.3 Hz, 3H), 2.40–2.51 (m, 1H), 2.63 (dd, *J* = 16.5 and 4.9 Hz, 1H), 3.00 (ddd, *J* = 16.2, 10.7 and 7.3 Hz, 1H), 3.40 (d, *J* = 11.6 Hz, 1H), 3.50 (td, *J* = 11.6 and 5.5 Hz, 1H), 4.02–4.12 (m, 1H), 4.22–4.32 (m, 1H), 4.46 (dd, *J* = 13.4 and 7.3 Hz, 1H), 4.83 (d, *J* = 11.6 Hz, 1H), 5.08 (d, *J* = 11.6 Hz, 1H), 5.82 (q, *J* = 7.3 Hz, 1H), 7.22 (t, *J* = 6.7 Hz, 1H), 7.29 (t, *J* = 7.3 Hz, 1H), 7.40 (d, *J* = 7.3 Hz, 1H), 7.95 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.6, 20.1, 27.5, 27.8, 28.3, 28.9, 35.3, 42.7, 64.4, 65.0, 67.2, 81.7, 82.0, 84.6, 116.0, 118.4, 118.8, 122.8, 124.9, 128.8, 131.8, 134.8, 135.1, 135.6, 150.2, 153.1, 153.6, 170.1; ESIMS (*m*/*z*) 627 $[M+H]^+$; HRMS (ESI) calcd for $C_{34}H_{47}N_2O_9$ 627.3276, found 627.3266; IR ($CHCl_3$) ν_{max} 1736, 1681 cm^{-1}.

(–)-*tert*-Butyl (1*S*,11b*S*,*E*)-1-{2-[(*tert*-Butoxycarbonyl)oxy]ethyl}-11b-{[(*tert*-butoxycarbonyl)oxy]methyl}-2-ethylidene-1,2,3,5,6,11b-hexahydro-11*H*-indolizino(8,7-*b*)indole-11-carboxylate (16). The solution of $AlCl_3$ (42 mg, 0.319 mmol) in THF (5 mL) was added dropwise to a stirred suspension of LAH (35 mg, 0.958 mmol) in THF (15 mL) at 0 °C under argon atmosphere. The reaction mixture was stirred for 30 min and solution of lactam (−)-**15a** (100 mg, 0.159 mmol) in THF (10 mL) was added dropwise at 0 °C. The reaction mixture was stirred for 1.5 h at 0 °C and the reaction was quenched with saturated aqueous Na_2SO_4 at 0 °C. Reaction mixture was diluted with EtOAc (20 mL), filtered through Celite pad and dried over Na_2SO_4. The organic layer was concentrated in vacuo and purification of the obtained residue by column chromatography (silica gel, 230–400 mesh, PE–EtOAc, 25:75) afforded amine (−)-**16** as a solid (90 mg, 92%). Mp 67−69 °C; $[\alpha]^{25}_D$ −37.4 (*c* 0.3 $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.27 (s, 9H), 1.43 (d, *J* = 6.7 Hz, 3H), 1.48 (s, 9H), 1.73 (s, 9H), 1.85–2.00 (m, 1H), 2.16 (sext, *J* = 12.8 Hz, 1H), 2.49 (dd, *J* = 17.1 and 5.5 Hz, 1H), 3.00–3.25 (m, 3H), 3.50–3.60 (m, 1H), 3.69 (d, *J* = 12.2 Hz, 2H), 4.02 (q, *J* = 7.9 Hz, 1H), 4.17–4.25 (m, 1H), 4.58 (d, *J* = 11.0 Hz, 1H), 5.09 (q, *J*

= 7.3 Hz, 1H), 5.24 (d, *J* = 11.0 Hz, 1H), 7.15–7.30 (m, 2H), 7.44 (d, *J* = 7.3 Hz, 1H), 7.99 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0, 15.8, 27.5, 27.8, 27.9, 28.3, 41.0, 43.3, 52.9, 65.4, 67.4, 70.9, 81.37, 81.40, 84.0, 115.8, 117.2, 118.0, 118.3, 122.2, 124.1, 129.3, 135.0, 136.2, 139.1, 150.5, 153.3, 153.7; ESIMS (*m*/*z*) 613 $[M+H]^+$; HRMS (ESI) calcd for $C_{34}H_{49}N_2O_8$ 613.3483, found 613.3481; IR ($CHCl_3$) ν_{max} 1734 cm^{-1}.

(+)-2-[(1*S*,11b*S*,*E*)-2-Ethylidene-11b-(hydroxymethyl)-2,3,5,6,11,11b-hexahydro-1*H*-indolizino(8,7-*b*)indol-1-yl]ethan-1-ol (17). To a stirred solution of compound (−)-**16** (75 mg, 0.122 mmol) in CH_2Cl_2 (5 mL) was added TFA (0.188 mL, 2.44 mmol) at 0 °C. The ice bath was removed after 30 min and the reaction mixture was further stirred for 12 h at 25 °C. On complete consumption of starting material (by TLC) the reaction was quenched by adding saturated aqueous $NaHCO_3$ at 0 °C. Aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layer was washed with brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo and the obtained TFA salt of amine was dissolved in DCM (5 mL). The salt was neutralized with 4 N NaOH and aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo and followed by purification of the obtained residue by column chromatography (silica gel, 230–400 mesh, MeOH–DCM, 10:90) afforded compound (+)-**17** as a solid (36 mg, 96%). Mp 186−187 °C; $[\alpha]^{25}_D$ +29.6 (*c* 0.32 MeOH); ^{1}H NMR (CD_3OD, 400 MHz) δ 1.49 (d, *J* = 6.7 Hz, 3H), 1.85 (sext, *J* = 6.7 Hz, 1H), 2.10 (sext, *J* = 6.7 Hz, 1H), 2.53 (dd, *J* = 15.9 and 5.5 Hz, 1H), 3.00–3.10 (m, 1H), 3.17 (dd, *J* = 14.0 and 6.1 Hz, 1H), 3.24–3.50 (m, 3H), 3.57–3.77 (m, 3H), 3.87 (d, *J* = 10.4 Hz, 1H), 4.04 (d, *J* = 10.4 Hz, 1H), 5.17 (q, *J* = 7.3 Hz, 1H), 6.96 (t, *J* = 7.9 Hz, 1H), 7.04 (t, *J* = 7.3 Hz, 1H), 7.29 (d, *J* = 7.9 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (CD_3OD, 125 MHz) δ 14.8, 16.3, 32.5, 43.7, 44.5, 54.1, 61.2, 66.2, 68.3, 107.9,

111.9, 118.2, 118.7, 119.4, 122.0, 128.2, 137.1, 137.8, 140.5; ESIMS (*m*/*z*) 313 $[M+H]^+$; HRMS (ESI) calcd for $C_{19}H_{25}N_2O_2$ 313.1919, found 313.1908; IR (Nujol) ν_{max} 3422, 3267 cm^{-1}.

(+)-(6*S*,*E*)-5-Ethylidene-7-methylene-1,4,5,6,7,8-hexahydro-2*H*-3,6-ethanoazonino(5,4-*b*)indole (Subincanadine E, 18). To a stirred solution of compound (+)-**17** (16 mg, 0.051 mmol) in THF (7 mL) was added Et_3N (83 μL, 0.614 mmol), DMAP (6.20 mg, 0.051 mmol) and *p*-TsCl (58 mg, 0.307 mmol) at 0 °C. The reaction mixture was stirred for 6 h and allowed to reach 25 °C. On the complete consumption of starting material, LiBr (52 mg, 0.614 mmol) was added and the mixture was refluxed for 3 h. The reaction mixture was allowed to reach 25 °C and zinc dust (80 mg, 1.228 mmol) was added to the reaction mixture. The reaction mixture was again refluxed for 3 h under argon atmosphere. The reaction mixture was concentrated in vacuo and to the obtained residue was added saturated solution of $NaHCO_3$. The reaction mixture was extracted with EtOAc (3 × 10 mL) and the combined organic layer was dried over Na_2SO_4. Concentration of organic layer in vacuo followed by column chromatography (silica gel, 230–400 mesh, MeOH–DCM, 10:90) of the obtained residue provided (+)-subincanadine E (**18**) as a white solid (8 mg, 59%). Mp 143−144 °C; $[\alpha]^{25}_D$ +42.3 (*c* 0.12 MeOH), {lit.[1] $[\alpha]^{23}_D$ +39.0 (*c* 1.0 MeOH)}; ^{1}H NMR (CD_3OD, 400 MHz) δ 1.75–1.92 (m, 1H), 1.83 (d, *J* = 6.7 Hz, 3H), 2.41 (sept, *J* = 7.4 Hz, 1H), 3.11 (td, *J* = 12.1 and 6.1 Hz, 1H), 3.21 (d, *J* = 17.7 Hz, 1H), 3.30–3.45 (m, 2H), 3.69 (d, *J* = 13.4 Hz, 1H), 3.89 (t, *J* = 15.2 Hz, 1H), 3.97 (d, *J* = 15.2 Hz, 1H), 4.15–4.30 (m, 2H), 5.57 (s, 1H), 5.59 (s, 1H), 6.09 (q, *J* = 7.3 Hz, 1H), 7.05 (t, *J* = 7.3 Hz, 1H), 7.15 (t, *J* = 7.3 Hz, 1H), 7.36 (d, *J* = 7.9 Hz, 1H), 7.48 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 14.1, 21.0, 26.4, 42.4, 46.9, 53.5, 59.1, 109.3, 112.1, 118.9, 120.6, 120.7, 123.6, 129.1, 129.2, 132.1, 137.0, 137.5, 143.3; ESIMS (*m*/*z*) 313 $[M+H]^+$; HRMS (ESI) calcd for $C_{19}H_{23}N_2$ 279.1856, found 279.1857; IR (Nujol) 3403 cm^{-1}.

■ ASSOCIATED CONTENT

* Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

^{1}H NMR, ^{13}C NMR and DEPT spectra of all compounds. HPLC plots of compound (±)-**9**/(–)-**9**.

The X-ray crystallographic data of compounds **12** and **29** (CIF).

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Notes

The authors declare no competing financial interest.

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