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Formal Synthesis of Bioactive Indole Alkaloids Eburnamonine, Eburnaminol, and Vindeburnol

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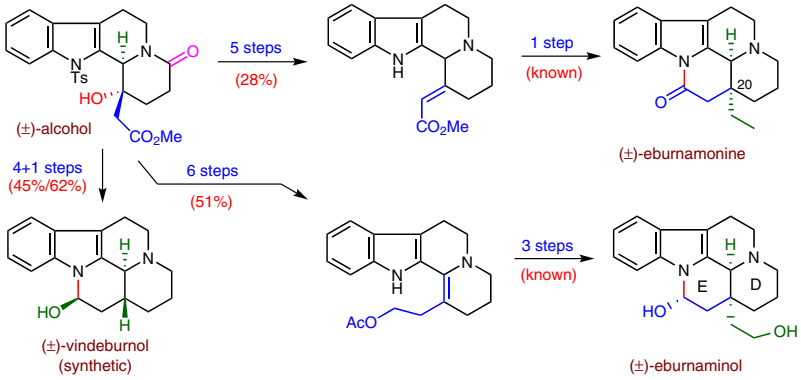

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Abstract Starting from (±)-3-acetoxyglutarimide, diastereoselective formal synthesis of indole alkaloids (±)-eburnamonine, (±)-eburnaminol, and (±)-vindeburnol have been demonstrated via a common intermediate (±)-1-hydroxy-12-tosyl-2,3,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizin-4(1*H*)-one in very good overall yields. The acetoxy group from (±)-3-acetoxyglutarimide was first used to induce the diastereoselectivity and also as a latent source of ketone carbonyl group. The stereoselective eliminations, reductions, and intramolecular cyclizations were the involved key steps.

Key words hexahydroindoloquinolizinone, elimination, reduction, cyclizations, eburnamonine, eburnaminol, vindeburnol

Indole alkaloids are an important class of compounds with a broad range of biological activities, and some of them are in clinical use. Hence they are the target compounds of interest for a large number of synthetic organic chemists (Figure 1).[1] The (+)-eburnamonine from *Hunteria eburnean* is a eumetabolic vasoregulator drug and prolyl oligopeptidase inhibitor; IC_{50} = 8 μM.[2a–d] Eburnaminol from *Kopsia larutensis* belong to the eburnan class of indole alkaloids having an angular pentacyclic ring system with *cis*-geometry containing a quaternary carbon.[2e] Several elegant diastereoselective and enantioselective total syntheses of the above specified indole alkaloids have been reported in the earlier and contemporary literature.[3–6] (–)-Vindeburnol is a potent central vasodilator, which also provides benefit for severe depression.[7a–e] In continuation of our studies on bioactive natural products based on cyclic anhydrides,[8] we herein report the application of well designed (±)-1-hydroxy-12-tosyl-2,3,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizin-4(1*H*)-one (**2**) from 3-acetoxyglutarimide (±)-**1** to accomplish the concise diastereoselective synthesis of structurally interesting indole-based target compounds eburnamonine (Scheme 1), eburnaminol (Scheme 2), and vindeburnol (Scheme 3).

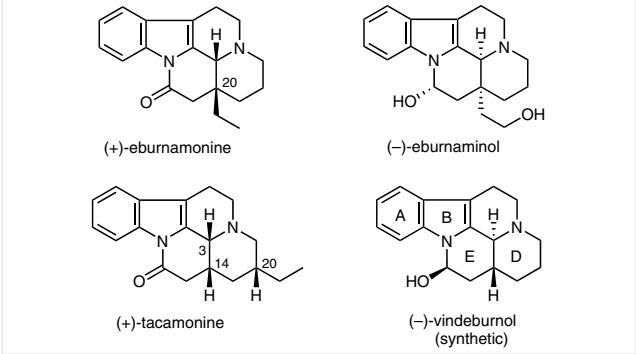
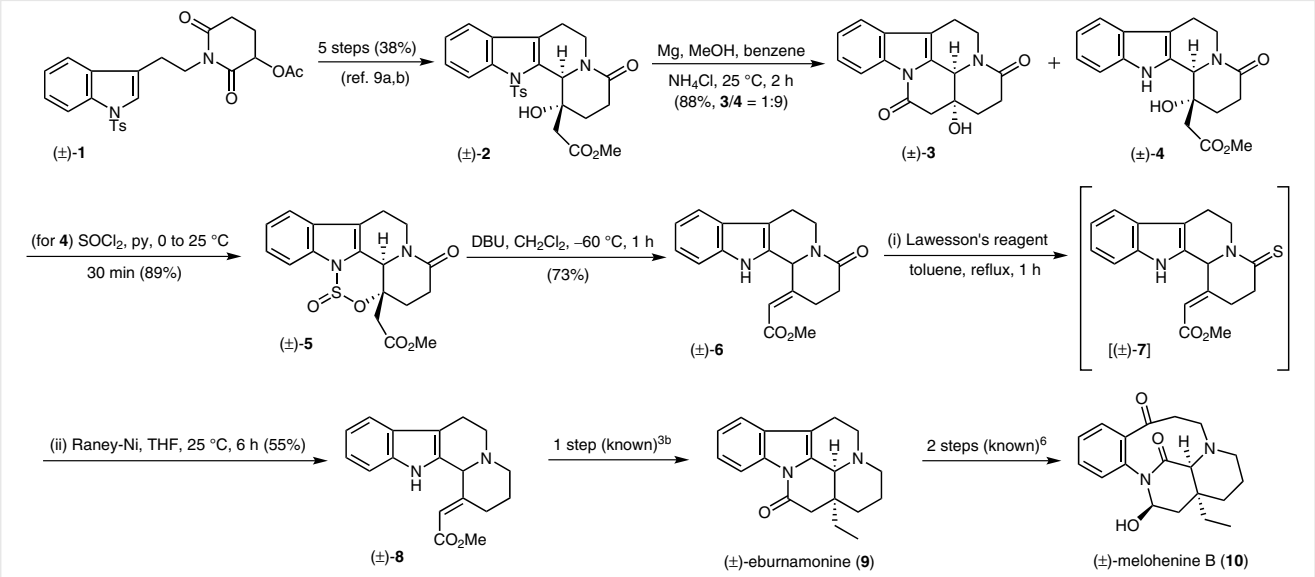


Figure 1 Bioactive indole alkaloids

Preparation of enantiomerically pure starting materials (+)-**2** and (–)-**2** was not feasible due to the inherent acidity of the methine proton in the corresponding ketone starting material.[9a,b] The racemic synthesis of eburnan class of alkaloid eburnamonine was intended from our common precursor (±)-**2**, which was obtained from 3-acetoxyglutarimide (±)-**1**[9c,d] using known procedures in five steps in 38% overall yield.[9a,b] The common precursor (±)-**2** on treatment with magnesium and methanol in the presence of benzene as a cosolvent (MeOH–C_6H_6, 1:1)[10] underwent a smooth N-detosylation and supplied a separable mixture of an in situ cyclized and uncyclized products (±)-**3** and (±)-**4**, respectively, in 88% combined yield in 2 hours (**3**/**4** = 1:9) (Scheme 1). As expected, the lactamization process of (±)-**4** to (±)-**3** with a *cis*-ring fusion was slow due to the 1,2-equatorial-axial orientations of cyclizing groups (Figure 2). Hence it was feasible to obtain the desired (±)-**4** as the major product even after arresting the reaction on complete consump-



Scheme 1 Formal synthesis of (±)-eburnamonine and (±)-melohenine B

tion of starting material. The major product (±)-**4** on treatment with thionyl chloride and pyridine directly provided the corresponding isolable cyclic sulfuramidite (±)-**5** in 89% yield.[11] An increase in reaction time with a hope to directly obtain the desired elimination product (±)-**6** resulted in excessive decomposition of the formed sulfuramidite (±)-**5**. The eliminative cleavage of sulfuramidite (±)-**5** to the corresponding α,β-unsaturated ester (±)-**6** was both base and temperature sensitive. In the presence of DBU, the compound **5** was prone to transform back into the starting material (±)-**4** along with partial decomposition at and above 0 °C. Nonetheless, the compound (±)-**5** on treatment with DBU in dichloromethane at –60 °C stereoselectively formed the thermodynamically more stable desired *E*-isomer (±)-**6** in 73% yield with the release of sulfur dioxide as a leaving group (Figure 3).

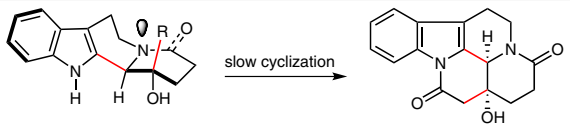


Figure 2 Lactamization leading to *cis*-ring fusion

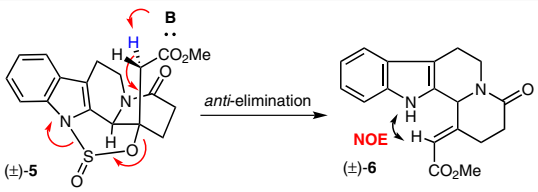


Figure 3 Proposed mechanism for *anti*-elimination

The 2 D NMR studies (see Supporting Information) indicated that the vinylic proton has strong NOE interactions with the proximal proton on indole nitrogen. The lactam (±)-**6** on reaction with the Lawesson reagent[12] was transformed into the expected intermediate thiolactam (±)-**7** (by TLC), which on an immediate column chromatographic filtration followed by Raney nickel mediated desulfurization reaction delivered the α,β-unsaturated ester (±)-**8** in 55% yield over two steps. Starting from the corresponding ethyl ester, the one-step synthesis of (±)-eburnamonine (**9**) via the stereoselective Michael addition of a cuprate from the less hindered α-face in very good yield is known.[3b] The two-step transformation of (±)-**9** to (±)-melohenine B (**10**) through an oxidative ring expansion is also known.[6]

The formal synthesis of yet another two interesting natural products (±)-ebumaminol (**21**) and (±)-larutensine (**22**) was planned from the precursor (±)-**2**, but this time using an intermediate **20**, which does not contain a tetrahedral stereogenic center (Scheme 2). The initially studied Horner–Wadsworth–Emmons (HWE) reaction on ketone (±)-**11** to directly form the corresponding α,β-unsaturated ester was not successful due to steric bulk of proximal *N*-tosyl moiety. The above reaction instead delivered the corresponding relatively more stable air-oxidized product (±)-**12** in 62% yield under refluxing conditions. The product (±)-**12** was formed under inert conditions and proved the higher propensity of (±)-**11** towards the facile air-oxidation process (Figure 4). The tetrabutylammonium fluoride-induced detosylation of compound **11** also resulted in product **12**. In the above-mentioned reactions, N-detosylation, introduction of an angular hydroxyl group, and oxidative dehydrogenation reaction to form the doubly conjugated C=C bond took place in one-pot to provide (±)-**12**. The alternatively performed *p*-

TSA-mediated dehydration of β-hydroxy ester (±)-**2** also resulted in the corresponding unexpected spiro β-lactone (±)-**13** in 85% yield. However, the thionyl chloride induced dehydration of tertiary alcohol (±)-**2** exclusively provided the thermodynamically more stable α,β-unsaturated ester (±)-(*E*)-**15** in 81% yield. An attempted naphthalene radical induced N-detosylation of product (±)-(*E*)-**15** caused the deprotection, but with a ring expansion via the cleavage of more reactive internal carbon–nitrogen single bond to form a 10-membered macrolactam (±)-**14** in 56% yield.[13] Treatment of compound (±)-**15** with magnesium and methanol in the presence of benzene as a cosolvent (MeOH–C_6H_6, 1:1) or on treatment with sodium amalgam in methanol delivered the planned N-detosylation product. However, it was accompanied with a nonstereoselective reduction of α,β-unsaturated C–C double bond resulting in ~1:1 mixture of the corresponding diastereomers of **16** (by ^{1}H NMR analysis). Finally, the catalytic hydrogenation of the C=C bond in the α,β-unsaturated ester (±)-(*E*)-**15** using H_2/PtO_2 was stereoselective and exclusively formed the product (±)-**16** in 98% yield. Plausibly three dimensional features of compound (±)-(*E*)-**15** dictate the site for adsorption of π-lobes on platinum catalyst resulting in a relative *trans*-geometry of the adjacent methine protons. The precursor (±)-**16** on reaction with red-Al directly furnished the desired (±)-amino alcohol **17**, but only in 25 to 30% yield. Alane reduction of (±)-**16** resulted into the desired product (±)-amino alcohol **17** in 84% yield. Both the ester to alcohol and lactam to amine reductions took place in one-pot, while the *N*-tosyl group remained intact. The coupling constant (J = 8 Hz) for angular methine proton in ^{1}H NMR also confirmed the assigned *trans*-stereochemistry of an adjacent methine protons in compound (±)-**17**. The N-detosylation of (±)-**17** followed by selective O-acylation of the formed alcohol (±)-**18** resulted in product (±)-**19** in 85% yield over two steps. The product (±)-**19** on Fujii oxidation[14] [$Hg(OAc)_2$/EDTA·2Na·2H_2O; oxidative dehydrogenation] delivered the known product **20** in 89% yield via formation of the corresponding iminium intermediate followed by an instantaneous intramolecular prototropic shift. We were unable to purify compound **20** by silica gel column chromatography for stability issues. Lounasmaa and Karvinen have reported only the selected signals of IR, ^{1}H NMR, and mass spectra for compound **20**. The obtained spectral data of as such isolated compound **20** were in complete agreement with the assigned structure and the reported data.[4a] Starting from compound **20**, a three-step stereoselective synthesis of (±)-eburnaminol (**21**) through enamine alkylation followed by a reductive intramolecular cyclization and the one-step transformation of (±)-**20** to (±)-larutensine (**22**) via an intramolecular dehydrative cyclization are known.[4a]

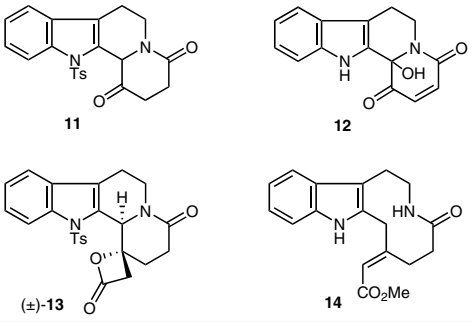
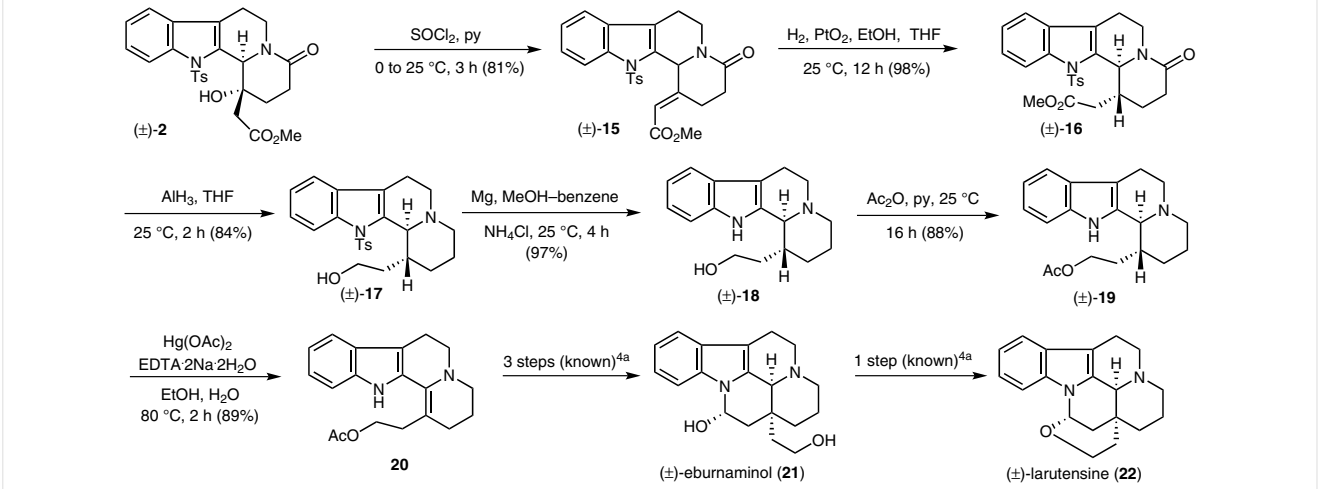


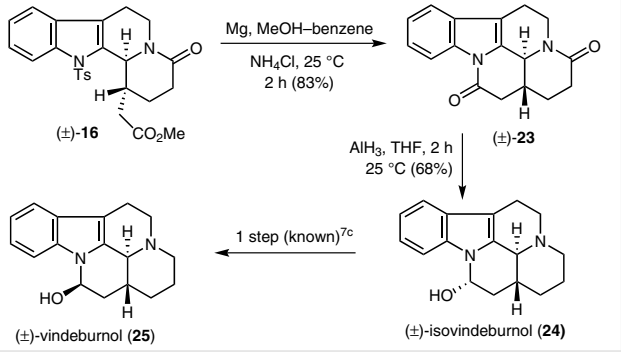
Figure 4 Keto-lactam and some of the exclusively formed unexpected products

Finally the advanced precursor (±)-**16** on reaction with magnesium in methanol plus benzene underwent a smooth N-detosylation followed by a concomitant intramolecular cyclization resulting in lactam (±)-**23** in 83% yield (Scheme 3). The lactamization process of (±)-**16** to (±)-**23** with *trans*-ring fusion was very fast due to the 1,2-equatorial-equato-



Scheme 2 Formal synthesis of (±)-eburnaminol and (±)-larutensine

rial orientations of the cyclizing groups (Figure 5) and hence it was not feasible to stop the reaction at an intermediate stage as described earlier for the corresponding *cis*-ring fusion system shown in Figure 2. The lactam (±)-**23** on alane reduction supplied the kinetically controlled product (±)-isovindeburnol (**24**) in 68% yield. Though the (±)-isovindeburnol (**24**) is known in the literature;[7c] its analytical and spectral data have not been reported. The obtained spectral data for (±)-isovindeburnol (**24**) was in complete agreement with the assigned structure. Acid-catalyzed epimerzation at the *gem*-aminohydrin center of (±)-isovindeburnol (**24**) to deliver the thermodynamically more stable (±)-vindeburnol (**25**) via the dehydration-rehydration pathway is well known in the literature.[7c,8c]



Scheme 3 Diastereoselective formal synthesis of (±)-vindeburnol

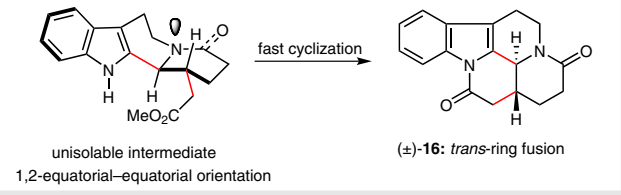


Figure 5 Lactamization leading to *trans*-ring fusion

In summary, we have demonstrated a facile diastereoselective formal synthesis of indole alkaloids via stepwise use of three different oxygen functions in (±)-3-acetoxyglutarimide in a chemo-, regio-, and stereoselective pathway. We feel that our present approach is general and will be useful to synthesize focused mini-library of indole-based structurally interesting and biologically useful architectures for SAR studies.

Melting points are uncorrected. The ^{1}H NMR spectra were recorded on 200 MHz NMR, 400 MHz NMR, and 500 MHz NMR spectrometers using TMS as an internal standard. The ^{13}C NMR spectra were recorded on 200 NMR spectrometer (50 MHz), 400 NMR spectrometer (100 MHz), and 500 NMR spectrometer (125 MHz). Mass spectra were taken on MS-TOF mass spectrometer. 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 and 230–400 mesh). Commercially available PtO_2, Mg foils, DBU, Lawesson's reagent, $AlCl_3$, $LiAlH_4$, Ac_2O, and $Hg(OAc)_2$ were used.

(±)-Methyl 2-(1-Hydroxy-4-oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizin-1-yl)acetate (4)

To stirred solution of *N*-tosyl-protected β-hydroxy ester (±)-**2** (400 mg, 0.83 mmol) in MeOH–benzene mixture (14 mL, 1:1) were sequentially added activated Mg turnings (199 mg, 8.30 mmol) and NH_4Cl (444 mg, 8.30 mmol) at 25 °C under an argon atmosphere. The reaction mixture was stirred for 2 h and the reaction was quenched with sat. aq NH_4Cl (4 mL) and aq 1 N HCl (4 mL). Solvent was removed in vacuo and the residue was dissolved in EtOAc (40 mL). The organic layer was washed with brine (20 mL) and dried (Na_2SO_4). Concentration of organic layer in vacuo, followed by silica gel column chromatographic purification of the resulting residue using EtOAc–PE (8:2) as an eluent afforded the major uncyclized compound (±)-**4** as a white solid (215 mg, 79%) and then the minor cyclized compound (±)-**3** as a colorless gummy solid (22 mg, 9%).

Major Product (±)-4

Mp 202–204 °C.

IR (neat): 3376, 1732, 1603 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.10–2.20 (m, 3 H), 2.40–2.55 (m, 1 H), 2.54 (d, *J* = 16 Hz, 1 H), 2.64–2.89 (m, 4 H), 3.66 (s, 3 H), 4.71 (s, 1 H), 4.82 (br s, 1 H), 5.07–5.13 (m, 1 H), 7.12 (dt, *J* = 8, 2 Hz, 1 H), 7.20 (dt, *J* = 8, 2 Hz, 1 H), 7.37 (d, *J* = 8 Hz, 1 H), 7.52 (d, *J* = 8 Hz, 1 H), 8.90 (br s, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.7, 29.9, 31.9, 35.2, 40.1, 52.2, 61.2, 72.4, 111.2, 111.3, 118.3, 119.5, 122.3, 126.1, 129.5, 136.1, 168.3, 173.5.

MS (ESI): *m*/*z* = 351 [M + Na]$^+$.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{20}N_2O_4Na$: 351.1315; found: 351.1310.

(±)-13a-Hydroxy-1,2,5,6,13,13a-hexahydro-3*H*-indolo[3,2,1-*de*]pyrido[3,2,1-*ij*][1,5]naphthyridine-3,12(4^1*H*)-dione (Minor Product 3)

IR ($CHCl_3$): 3446, 1719, 1634 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 1.50 (dt, *J* = 16, 4 Hz, 1 H), 1.72 (dd, *J* = 12, 4 Hz, 1 H), 2.07 (dd, *J* = 16, 4 Hz, 1 H), 2.55–2.83 (m, 4 H), 2.76 (d, *J* = 16 Hz, 1 H), 3.04 (dt, *J* = 12, 8 Hz, 1 H), 4.71 (dd, *J* = 12, 8 Hz, 1 H), 4.78 (br s, 1 H), 5.88 (s, 1 H), 7.31 (quint, *J* = 8 Hz, 2 H), 7.49 (d, *J* = 8 Hz, 1 H), 8.20 (d, *J* = 8 Hz, 1 H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ = 19.8, 28.2, 29.4, 41.2, 46.5, 59.9, 68.2, 114.2, 115.4, 118.7, 124.1, 124.7, 129.7, 133.2, 133.5, 165.9, 168.6.

MS (ESI): *m*/*z* = 297 [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{17}N_2O_3$: 297.1234; found: 297.1231.

(±)-Methyl (5-Oxido-1-oxo-2,3,10,11-tetrahydro-1*H*-4-oxa-5-thia-5a,11a-diazabenzo[*cd*] fluoranthen-3a(3a1*H*)-yl)acetate (5)

To a stirred solution of (±)-**4** (150 mg, 0.46 mmol) in pyridine (6 mL) was added $SOCl_2$ (0.20 mL, 2.76 mmol) at 0 °C. Ice bath was removed and the reaction mixture was stirred at 25 °C for 30 min. It was then poured into a mixture of EtOAc (10 mL) and crushed ice. The residue

was extracted with EtOAc (3 × 15 mL) and the combined organic layers were washed with brine (25 mL) and dried (Na_2SO_4). Concentration of organic layer in vacuo, followed by silica gel column chromatographic purification of the resulting residue using EtOAc–PE (6:4) as an eluent afforded the cyclic sulfuramidite (±)-**5** as a yellowish white solid (152 mg, 89%); mp 148–150 °C.

IR (neat): 1731, 1649 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 2.06 (d, *J* = 16 Hz, 1 H), 2.35 (q, *J* = 8 Hz, 1 H), 2.60–2.95 (m, 6 H), 3.03 (dt, *J* = 12, 4 Hz, 1 H), 3.69 (s, 3 H), 4.89 (dd, *J* = 12, 4 Hz, 1 H), 5.14 (s, 1 H), 7.30–7.45 (m, 2 H), 7.57 (d, *J* = 8 Hz, 1 H), 7.69 (d, *J* = 8 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.2, 29.8, 30.6, 34.3, 37.8, 52.4, 56.3, 84.4, 112.6, 115.0, 119.5, 123.7, 124.7, 128.6, 129.0, 137.8, 168.1, 168.4.

MS (ESI): *m*/*z* = 397 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{18}N_2O_5SNa$: 397.0829; found: 397.0826.

(±)-Methyl (*E*)-2-(4-Oxo-3,4,6,7,12,12b-Hexahydroindolo[2,3-*a*]quinolizin-1(2*H*)-ylidene)acetate (6)

To a stirred solution of compound (±)-**5** (50 mg, 0.13 mmol) in CH_2Cl_2 (4 mL) was added DBU (0.03 mL, 0.20 mmol) at –60 °C under an argon atmosphere. The reaction mixture was stirred at the same temperature for 1 h. The reaction was quenched with sat. aq NH_4Cl (2 mL) and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with H_2O (15 mL) and brine (15 mL), and dried (Na_2SO_4). Concentration of the dried organic layer in vacuo followed by the silica gel column chromatographic purification of the resulting residue using PE–EtOAc (1:1) as an eluent yielded the conjugated ester (±)-**6** as a brownish yellow solid (30 mg, 73%); mp 171–173 °C.

IR (neat): 3272, 1709, 1625 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 2.32 (dt, *J* = 12, 4 Hz, 1 H), 2.46 (dt, *J* = 16, 4 Hz, 1 H), 2.60–2.70 (m, 1 H), 2.75 (d, *J* = 12 Hz, 1 H), 2.90–3.06 (m, 2 H), 3.80 (s, 3 H), 3.80–3.85 (m, 1 H), 5.03 (q, *J* = 8 Hz, 1 H), 5.31 (s, 1 H), 6.14 (s, 1 H), 7.13 (t, *J* = 8 Hz, 1 H), 7.19 (t, *J* = 8 Hz, 1 H), 7.32 (d, *J* = 8 Hz, 1 H), 7.50 (d, *J* = 8 Hz, 1 H), 7.96 (s, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.7, 23.0, 32.4, 41.4, 51.7, 61.1, 110.9, 111.2, 117.1, 118.5, 120.0, 122.6, 127.4, 129.4, 135.8, 153.1, 165.8, 168.9.

MS (ESI): *m*/*z* = 311 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{19}N_2O_3$: 311.1390; found: 311.1386.

(±)-Methyl (*E*)-2-(3,4,6,7,12,12b-Hexahydroindolo[2,3-*a*]quinolizin-1(2*H*)-ylidene)acetate (8)

To a stirred solution of compound (±)-**6** (10 mg, 0.03 mmol) in anhyd toluene was added Lawesson's reagent (12 mg, 0.03 mmol) at 25 °C under an argon atmosphere. The reaction mixture was refluxed for 1 h and cooled to 25 °C. Toluene was removed in vacuo and the obtained residue was quickly purified by silica gel (230–400 mesh) column chromatography by using PE–EtOAc (6:4) to provide the thiolactam (±)-**7** (8 mg, 0.02 mmol), which was immediately used in the next step. A solution of (±)-**7** in anhyd THF (1 mL) was added dropwise to a stirred solution of freshly prepared Raney nickel (100 mg) suspension in anhyd THF (2 mL) at 25 °C. The reaction mixture was vigorously stirred for 6 h at 25 °C under 1 atmosphere of H_2 pressure and filtered through a pad of Celite by washing with EtOAc (15 mL). Concentration of filtrate under vacuo followed by silica gel (230–400 mesh) column chromatographic purification of the resulting residue using EtOAc–PE (7:3) as an eluent yielded conjugated ester (±)-**8** as a brownish yellow gum (5 mg, 55%).

IR ($CHCl_3$): 3275, 1706, 1645 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 1.75–1.95 (m, 2 H), 2.70–2.82 (m, 2 H), 2.90 (br s, 1 H), 2.95–3.12 (m, 4 H), 3.25–3.35 (m, 1 H), 3.73 (s, 3 H), 4.62 (s, 1 H), 5.89 (s, 1 H), 7.13 (t, *J* = 10 Hz, 1 H), 7.19 (t, *J* = 10 Hz, 1 H), 7.34 (d, *J* = 10 Hz, 1 H), 7.52 (d, *J* = 10 Hz, 1 H), 7.81 (br s, 1 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 18.7, 25.4, 26.6, 49.9, 50.4, 51.3, 63.0, 108.8, 111.1, 116.9, 118.4, 119.7, 122.1, 127.1, 135.9, 166.6.

MS (ESI): *m*/*z* = 297 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{21}N_2O_2$: 297.1598; found: 297.1589.

(±)-12b-Hydroxy-6,7,12,12b-tetrahydroindolo[2,3-*a*]quinolizine-1,4-dione (12)

To a stirred solution of ketone (±)-**11** (50 mg, 0.12 mmol) in THF (2 mL) at 25 °C was added dropwise Bu_4NF (1.0 M in THF, 0.18 mL, 0.18 mmol) and the reaction mixture was stirred for 3 h. The reaction was quenched with sat. aq NH_4Cl (2 mL) and the solvent was removed in vacuo. The residue was dissolved in EtOAc (25 mL) and the organic layer was washed with brine (15 mL), and dried (Na_2SO_4). Concentration of organic layer in vacuo, followed by silica gel column chromatographic purification of the resulting residue using PE–EtOAc (6:4) as an eluent afforded the oxidized compound (±)-**12** as a yellow solid (19 mg, 58%); mp 175–177 °C.

IR (neat): 3284, 1724, 1676 cm^{-1}.

^1H NMR (DMSO-d_6, 400 MHz): δ = 2.05–2.18 (m, 1 H), 2.40–2.55 (m, 1 H), 2.58–2.72 (m, 1 H), 3.03–3.20 (m, 1 H), 6.70 (d, *J* = 12 Hz, 1 H), 6.82 (d, *J* = 12 Hz, 1 H), 6.88 (s, 1 H, D_2O exchangeable), 7.16 (t, *J* = 8 Hz, 1 H), 7.37 (t, *J* = 8 Hz, 1 H), 7.47 (d, *J* = 8 Hz, 1 H), 7.96 (d, *J* = 8 Hz, 1 H), 11.96 (s, 1 H, D_2O exchangeable).

^{13}C NMR (DMSO-d_6, 100 MHz): δ = 27.7, 28.1, 90.0, 104.5, 112.5, 119.4, 119.9, 120.3, 120.8, 125.2, 126.6, 130.2, 137.6, 174.6, 180.8.

MS (ESI): *m*/*z* = 269 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{13}N_2O_3$: 269.0921; found: 269.0915.

(±)-12-Tosyl-2,3,6,7,12,12b-hexahydro-4*H*-spiro[indolo[2,3-*a*]quinolizine-1,2′-oxetane]-4,4′-dione (13)

To a stirred solution of (±)-**2** (20 mg, 0.04 mmol) in anhyd toluene (3 mL) was added anhyd *p*-TSA (8 mg, 0.05 mmol) at 25 °C and the reaction mixture was refluxed for 4.5 h. Toluene was removed in vacuo and the residue was dissolved in EtOAc (15 mL). The organic layer was washed with sat. aq $NaHCO_3$ (10 mL) and brine (10 mL), and dried (Na_2SO_4). Concentration of organic layer in vacuo, followed by silica gel column chromatographic purification of the resulting residue using EtOAc–PE (6:4) as an eluent afforded the spirolactone (±)-**13** as a gummy solid (16 mg, 85%).

IR (neat): 1783, 1698 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 2.27 (s, 3 H), 2.30–2.80 (m, 6 H), 2.84 (d, *J* = 16 Hz, 1 H), 2.95–3.20 (m, 1 H), 3.35–3.55 (m, 1 H), 4.45–4.65 (m, 1 H), 5.59 (s, 1 H), 7.05 (d, *J* = 8 Hz, 2 H), 7.15–7.45 (m, 5 H), 8.08 (d, *J* = 8 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 21.5, 22.5, 28.1, 28.8, 37.2, 45.7, 63.7, 89.1, 117.3, 119.1, 125.4, 126.1, 126.8, 128.6, 129.2, 129.3, 130.9, 131.3, 138.7, 145.3, 170.1, 175.2.

MS (ESI): *m*/*z* = 473 $[M + Na]^+$.

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{24}H_{22}N_2O_5SNa$: 473.1142; found: 473.1145.

(±)-Methyl (*E*)-2-(4-Oxo-12-tosyl-3,4,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizin-1(2*H*)-ylidene)acetate (15)

To a stirred solution of (±)-**2** (600 mg, 1.24 mmol) in pyridine (8 mL) was added $SOCl_2$ (0.45 mL, 6.22 mmol) at 0 °C. Ice bath was removed and the reaction mixture was stirred at 25 °C for 3 h. It was then poured into a mixture of EtOAc (15 mL) and crushed ice. The aqueous layer was extracted with EtOAc (3 × 25 mL) and the combined organic layers were washed with brine (50 mL), and dried (Na_2SO_4). Concentration of organic layer in vacuo, followed by silica gel column chromatographic purification of the resulting residue using EtOAc–PE (1:1) as an eluent afforded the conjugated ester (±)-**15** as a yellowish white solid (468 mg, 81%); mp 150–152 °C.

IR (neat): 1791, 1713, 1652 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.33 (s, 3 H), 2.55–3.00 (m, 5 H), 3.14 (dd, *J* = 18, 8 Hz, 1 H), 3.30–3.45 (m, 1 H), 3.61 (s, 3 H), 4.60–4.70 (m, 1 H), 5.22 (s, 1 H), 5.94 (s, 1 H), 7.18 (d, *J* = 8 Hz, 2 H), 7.32 (t, *J* = 8 Hz, 1 H), 7.40 (t, *J* = 8 Hz, 1 H), 7.47 (d, *J* = 8 Hz, 1 H), 7.57 (d, *J* = 8 Hz, 2 H), 8.19 (d, *J* = 8 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.2, 21.6, 25.7, 31.3, 38.5, 51.1, 56.0, 114.6, 115.3, 118.9, 122.9, 124.2, 125.7, 126.3, 128.7, 129.1, 129.9, 134.6, 136.9, 145.3, 156.8, 166.5, 172.3.

MS (ESI): m/z = 487 [M + Na]$^+$.

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{25}H_{24}N_2O_5SNa$: 487.1298; found: 487.1299.

(±)-Methyl (*E*)-2-(4-Oxo-1,2,3,4,5,6,8,9-octahydro-7*H*-azecino[5,4-*b*]indol-7-ylidene)acetate (14)

To a stirred solution of naphthalene (108 mg, 0.85 mmol) in THF (4 mL) at 25 °C was carefully added a piece of Na metal (12 mg, 0.52 mmol) under an argon atmosphere. The reaction mixture was stirred for 30 min to form a greenish blue solution. THF solution (2 mL) of conjugated ester (±)-**15** (60 mg, 0.13 mmol) was dropwise added to the reaction mixture at –78 °C. After 20 min, the reaction was quenched with sat. aq NH_4Cl (2 mL). The mixture was extracted with EtOAc (3 × 15 mL) and the combined organic layers were washed with brine (25 mL), and dried (Na_2SO_4). Concentration of organic layer in vacuo, followed by silica gel column chromatographic purification of the resulting residue using EtOAc–PE (7:3) as an eluent afforded the macrolactam (±)-**14** as a gummy solid (23 mg, 56%).

IR (neat): 3301, 3262, 1722, 1649 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.10–2.35 (m, 3 H), 2.46 (br s, 1 H), 2.83 (br s, 2 H), 3.22 (br s, 2 H), 3.42 (br s, 1 H), 3.69 (d, *J* = 16 Hz, 1 H), 3.77 (s, 3 H), 5.53 (br s, 1 H), 6.42 (s, 1 H), 7.11 (t, *J* = 8 Hz, 1 H), 7.18 (t, *J* = 8 Hz, 1 H), 7.31 (d, *J* = 8 Hz, 1 H), 7.52 (d, *J* = 8 Hz, 1 H), 8.04 (br s, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 24.1, 30.4, 34.6, 38.9, 40.5, 52.2, 110.8, 110.9, 118.2, 119.4, 121.9, 123.5, 127.3, 132.1, 135.7, 141.9, 172.5, 172.9.

MS (ESI): m/z = 313 [M + H]$^+$.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{18}H_{21}N_2O_3$: 313.1547; found: 313.1547.

(±)-Methyl 4-Oxo-12-tosyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizin-1-yl)acetate (16)

To a stirred solution of conjugated ester (±)-**15** (200 mg, 0.43 mmol) in EtOH and THF mixture (8 mL, 1:1) was added a catalytic amount of PtO_2 (10 mg, 0.04 mmol) at 25 °C. The resulting mixture was stirred under the balloon pressure of H_2 atmosphere for 12 h and filtered through a pad of Celite by washing with EtOAc (40 mL). The mixture was concentrated in vacuo to afford the hydrogenated compound (±)-**16** as a gummy solid (197 mg, 98%).

IR ($CHCl_3$): 1734, 1642 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.73 (t, *J* = 4 Hz, 1 H), 1.78 (t, *J* = 4 Hz, 1 H), 2.27 (s, 3 H), 2.30–2.80 (m, 6 H), 2.96 (dd, *J* = 16, 6 Hz, 1 H), 3.11 (sext, *J* = 6 Hz, 1 H), 3.68 (s, 3 H), 4.96 (dd, *J* = 12, 4 Hz, 1 H), 5.01–5.08 (m, 1 H), 7.04 (d, *J* = 8 Hz, 2 H), 7.20–7.35 (m, 3 H), 7.34 (d, *J* = 8 Hz, 2 H), 8.11 (d, *J* = 8 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 21.5, 21.8, 22.9, 28.8, 36.3, 36.8, 41.4, 51.7, 59.8, 117.2, 118.6, 125.0, 125.5, 126.6, 127.4, 129.2, 131.1, 132.1, 135.4, 138.7, 145.0, 170.9, 172.4.

MS (ESI): m/z = 489 [M + Na]$^+$.

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{25}H_{26}N_2O_5SNa$: 489.1445; found: 489.1444.

(±)-(12-Tosyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizin-1-yl)ethan-1-ol (17)

A flame dried round-bottomed flask was charged with $AlCl_3$ (28 mg, 0.21 mmol) and THF (2 mL) under an argon atmosphere. The stirred reaction mixture was cooled to 0 °C and a suspension of $LiAlH_4$ (24 mg, 0.63 mmol) in THF (2 mL) was added dropwise. After stirring for 10 min at 0 °C, a solution of lactam ester (±)-**16** (100 mg, 0.21 mmol) in THF (4 mL) was added dropwise to the above mixture. It was stirred for 2 h at 25 °C and quenched by the addition of sat. aq Na_2SO_4 (2 mL). The mixture was filtered through Celite and the solid residue was washed with EtOAc (20 mL). The filtrate was dried (Na_2SO_4) and concentrated in vacuo. The silica gel column chromatographic purification of the resulting residue using CH_2Cl_2–MeOH (96:04) as an eluent afforded the alcohol (±)-**17** as a gummy solid (76 mg, 84%).

IR ($CHCl_3$): 3377, 1658, 1600 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.30–1.57 (m, 2 H), 1.73–1.90 (m, 2 H), 1.80–2.00 (m, 1 H), 2.00–2.15 (m, 1 H), 2.24 (s, 3 H), 2.15–2.60 (m, 2 H), 2.65–2.80 (m, 2 H), 2.85–2.95 (br s, 1 H), 3.00–3.22 (m, 2 H), 3.45–3.55 (m, 1 H), 3.55–3.68 (m, 1 H), 3.73 (quint, *J* = 8 Hz, 1 H), 4.56 (d, *J* = 8 Hz, 1 H), 7.06 (d, *J* = 8 Hz, 2 H), 7.18 (t, *J* = 8 Hz, 1 H), 7.20 (t, *J* = 8 Hz, 1 H), 7.25 (d, *J* = 8 Hz, 1 H), 7.44 (d, *J* = 8 Hz, 2 H), 8.04 (d, *J* = 8 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.0, 20.5, 21.5, 29.8, 33.3, 35.8, 43.4, 53.4, 60.0, 60.4, 116.5, 118.4, 120.7, 124.2, 124.5, 126.7, 129.3, 131.3, 133.4, 137.6, 137.7, 144.4.

MS (ESI): m/z = 447 [M + Na]$^+$.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{24}H_{29}N_2O_3S$: 425.1893; found: 425.1893.

(±)-1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-*a*]quinolizin-1-yl)ethan-1-ol (18)

To stirred solution of *N*-tosyl-protected amino alcohol (±)-**17** (75 mg, 0.18 mmol) in MeOH–benzene (4 mL, 1:1) were sequentially added activated Mg turnings (200 mg, 8.30 mmol) and NH_4Cl (200 mg, 3.74 mmol) at 25 °C. The reaction mixture was stirred for 4 h and the reaction was quenched with sat. aq NH_4Cl (5 mL) and aq 1 N HCl (2 mL). Solvent was removed in vacuo and the residue was extracted with EtOAc (3 × 5 mL). The combined organic layer was washed with brine

(10 mL) and dried (Na_2SO_4). Concentration of organic layer in vacuo, followed by silica gel column chromatographic purification of the resulting residue using CH_2Cl_2–MeOH (92:8) as an eluent afforded the *N*-tosyl deprotected amino alcohol (±)-**18** as a brownish white solid (46 mg, 97%); mp 178–180 °C.

IR (Nujol): 3375, 3126 cm^{-1}.

^1H NMR (CD_3OD, 400 MHz): δ = 1.35–1.47 (m, 1 H), 1.55–1.85 (m, 4 H), 1.98–2.10 (m, 1 H), 2.25 (br s, 1 H), 2.75–3.10 (m, 5 H), 3.40–3.50 (m, 1 H), 3.63–3.78 (m, 2 H), 3.88 (d, *J* = 8 Hz, 1 H), 6.98 (t, *J* = 8 Hz, 1 H), 7.06 (t, *J* = 8 Hz, 1 H), 7.31 (d, *J* = 8 Hz, 1 H), 7.40 (d, *J* = 8 Hz, 1 H).

^{13}C NMR (CD_3OD, 100 MHz): δ = 20.76, 20.81, 21.7, 34.2, 36.2, 49.61, 49.64, 60.5, 61.9, 108.1, 112.0, 118.6, 119.8, 122.2, 128.3, 134.8, 137.8.

MS (ESI): *m*/*z* = 271 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{23}N_2O$: 271.1805; found: 271.1797.

(±)-(1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-*a*]quinolizin-1-yl)ethyl Acetate (19)

To a stirred solution of (±)-**18** (40 mg, 0.15 mmol) in pyridine (2 mL) was added Ac_2O (0.30 mL, 3.18 mmol) at 25 °C. After stirring for 16 h, the reaction was quenched with H_2O (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with sat. aq $NaHCO_3$ (15 mL) and brine (15 mL), and dried (Na_2SO_4). Concentration of organic layer in vacuo, followed by silica gel column chromatographic purification of the resulting residue using CH_2Cl_2–MeOH (94:6) as an eluent afforded the ester (±)-**19** as a gummy solid (41.0 mg, 88%).

IR ($CHCl_3$): 3429, 1737 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.65–1.82 (m, 3 H), 1.85–2.05 (m, 3 H), 2.10 (s, 3 H), 2.05–2.18 (m, 1 H), 2.80–3.15 (m, 5 H), 3.35–3.45 (m, 1 H), 3.94–4.05 (m, 1 H), 4.10–4.20 (m, 1 H), 4.25–4.37 (m, 1 H), 7.08 (t, *J* = 8 Hz, 1 H), 7.17 (t, *J* = 8 Hz, 1 H), 7.37–7.45 (m, 2 H), 9.28 (br s, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 19.5, 20.9, 21.0, 28.2, 31.1, 34.4, 49.2, 51.6, 60.0, 62.3, 107.8, 111.3, 118.0, 119.4, 121.9, 126.6, 131.5, 136.4, 171.8.

MS (ESI): *m*/*z* = 313 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{25}N_2O_2$: 313.1911; found: 313.1908.

(±)-2-(2,3,4,6,7,12-Hexahydroindolo[2,3-*a*]quinolizin-1-yl)ethyl Acetate (20)

To a stirred solution of acetate (±)-**19** (25 mg, 0.08 mmol) in EtOH (2 mL) were added a solution containing EDTA disodium salt dihydrate (70 mg, 0.24 mmol) and $Hg(OAc)_2$ (76 mg, 0.24 mmol) in H_2O (3 mL) and the resulting solution was gently heated at 80 °C for 2 h. After cooling, CH_2Cl_2 was added to the reaction mixture and the two-phase mixture was basified to pH 11 with 5% aq ammonia. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with sat. aq $NaHCO_3$ (10 mL) and brine (10 mL), and dried (Na_2SO_4). Filtration and concentration of organic layer in vacuo afforded the enamine (±)-**20** as a brown gummy solid (22 mg, 89%).

IR ($CHCl_3$): 3361, 1728, 1634 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.95–2.02 (m, 4 H), 2.02–2.20 (m, 1 H), 2.18 (s, 3 H), 2.22–2.30 (m, 1 H), 2.77 (dd, *J* = 8, 8 Hz, 1 H), 2.97 (t, *J* = 8 Hz, 2 H), 3.03–3.15 (m, 3 H), 4.24 (dd, *J* = 8, 8 Hz, 2 H), 7.10 (t, *J* = 8 Hz, 1 H), 7.21 (t, *J* = 8 Hz, 1 H), 7.51 (d, *J* = 8 Hz, 1 H), 7.56 (d, *J* = 8 Hz, 1 H), 10.13 (br s, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.1, 21.8, 22.4, 30.0, 33.2, 52.0, 52.2, 63.5, 103.8, 111.5, 111.8, 118.1, 119.1, 122.3, 125.9, 129.3, 135.2, 137.4, 172.9.

MS (ESI): *m*/*z* = 311 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{23}N_2O_2$: 311.1754; found: 311.1750.

(±)-1,2,5,6,13,13a-Hexahydro-3*H*-indolo[3,2,1-*de*]pyrido[3,2,1-*ij*][1,5]naphthyridine-3,12(41*H*)-dione (23)

Activated Mg turnings (62.40 mg, 2.60 mmol) and NH_4Cl (65 mg, 1.22 mmol) were sequentially added to stirred solution of *N*-tosyl protected lactam (±)-**16** (60 mg, 0.13 mmol) in MeOH–benzene (1:1; 4 mL) at 25 °C. The reaction mixture was stirred for 2 h and quenched with sat. aq NH_4Cl (1 mL) and aq 1 N HCl (1 mL). MeOH and benzene were removed in vacuo and the residue was extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine (40 mL) and dried (Na_2SO_4). Concentration of organic layer in vacuo, followed by silica gel (230–400 mesh) column chromatographic purification of the resulting residue using EtOAc–PE (7:3) as an eluent afforded the pentacyclic compound (±)-**23** as a white solid (30 mg, 83%); mp 172–174 °C.

IR ($CHCl_3$): 1709, 1644 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 1.77 (ddd, *J* = 18, 10, 5 Hz, 1 H), 2.03 (dd, *J* = 10, 5 Hz, 1 H), 2.21 (tq, *J* = 10, 5 Hz, 1 H), 2.55 (ddd, *J* = 15, 10, 5 Hz, 1 H), 2.65 (d, *J* = 15 Hz, 1 H), 2.69 (dt, *J* = 15, 5 Hz, 1 H), 2.77–2.84 (m, 2 H), 2.93 (dd, *J* = 15, 5 Hz, 1 H), 2.96–3.05 (m, 1 H), 4.27 (d, *J* = 10 Hz, 1 H), 5.09 (td, *J* = 10, 5 Hz, 1 H), 7.32 (dt, *J* = 10, 5 Hz, 1 H), 7.36 (dt, *J* = 10, 5 Hz, 1 H), 7.46 (d, *J* = 10 Hz, 1 H), 8.36 (d, *J* = 10 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 20.4, 25.9, 32.1, 37.2, 38.2, 38.9, 55.1, 112.6, 116.2, 118.6, 124.3, 125.0, 129.1, 132.1, 135.2, 166.7, 168.3.

MS (ESI): *m*/*z* = 281 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{17}N_2O_2$: 281.1285; found: 281.1281.

(±)-2,3,41,5,6,12,13,13a-Octahydro-1*H*-indolo[3,2,1-*de*]pyrido[3,2,1-*ij*][1,5]naphthyridin-12-ol [Isovindeburnol, (±)-24]

A flame dried round-bottomed flask was charged with $AlCl_3$ (12 mg, 0.09 mmol) and THF (1 mL) under an argon atmosphere. The stirred reaction mixture was cooled to 0 °C and a suspension of $LiAlH_4$ (10 mg, 0.27 mmol) in THF (1 mL) was added dropwise. After stirring for 10 min at 0 °C, a solution of lactam (±)-**23** (25 mg, 0.09 mmol) in THF (2 mL) was added dropwise to the above reaction mixture. Then it was stirred for 2 h at 25 °C and quenched by the addition of sat. aq Na_2SO_4 (2 mL). The mixture was filtered through Celite and the solid residue was washed with EtOAc (3 × 10 mL). The filtrate was dried (Na_2SO_4) and concentrated in vacuo. Silica gel (230–400 mesh) column chromatographic purification of the resulting residue using CH_2Cl_2–MeOH (96:04) as an eluent afforded the isovindeburnol [(±)-**24**] as a brownish solid (16 mg, 68%); mp 246–248 °C (Lit.[7c] mp 254 °C).

IR ($CHCl_3$): 3345, 1720, 1645 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 0.77–0.94 (m, 1 H), 1.10–1.23 (m, 1 H), 1.23–1.34 (m, 1 H), 1.38–1.54 (m, 1 H), 1.57–1.67 (m, 1 H), 1.67–1.80 (m, 1 H), 2.01–2.15 (m, 2 H), 2.15–2.27 (m, 1 H), 2.40–2.60 (m, 1 H), 2.60–2.75 (m, 1 H), 2.86–3.00 (m, 2 H), 3.00–3.10 (m, 1 H), 5.36 (t, *J* = 8 Hz, 1 H), 7.00–7.25 (m, 2 H), 7.43 (d, *J* = 8 Hz, 1 H), 7.67 (d, *J* = 8 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.3, 24.9, 29.5, 35.6, 39.5, 52.4, 54.5, 62.9, 79.0, 105.2, 112.3, 118.2, 120.1, 121.3, 128.6, 134.5, 138.0.

MS (ESI): *m*/*z* = 269 $[M + H]^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{21}N_2O$: 269.1648; found: 269.1645.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588386. NMR spectra of all the synthesized compounds are included.

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