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A novel synthetic route for the total synthesis of (±)-uleine

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ABSTRACT

In this study, a new synthetic route for the total synthesis of (±)-uleine is described. The important step in the synthesis of this alkaloid consists of an intramolecular cyclization of the D ring of the azocino[4,3-*b*]indole skeleton. Reduction of (*N*-methyl){3-β-ethyl-4-oxo-2,3,4,9-tetrahydrospiro[1*H*-carbazole-1,2′(1,3)dithiolane]-2-yl}-2-acetamide with borane yielded the corresponding (*N*-methyl){3-β-ethyl-4-hydroxy-2,3,4,9-tetrahydrospiro[1*H*-carbazole-1,2′(1,3)dithiolane]-2-yl}-2-acetamide, which underwent acid-catalyzed ring closure to produce azocino[4,3-*b*]indole core. Finally, the synthesis of (±)-uleine was completed through several steps from the azocino[4,3-*b*]indole core.

1. Introduction

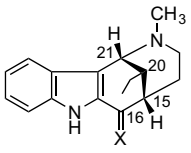
Recently, we reported a new synthetic strategy for the total synthesis of the alkaloid (±)-epidasycarpidone[1] by an acid-catalyzed ring closure of racemic *cis* 3-ethyl-4-oxo-2,3,4,9-tetrahydrocarbazole derivative **3**. Herein, we report an extension of this approach leading to the total synthesis of (±)-uleine (Fig. 1). Uleine was first isolated from *Aspidosperma ulei Mgf*[2] and its correct structure was proposed by Buchi et al.[3] Most of the approaches previously reported for the synthesis of alkaloids of the uleine group start either from 2(4-piperidinylmethyl)-indole,[4–9] 3-(2-iperidinylmethyl) indole[10–21] or with Fischer indolization of 2-azabicyclo [3.3.1]nonane.[22] Furthermore, in an another synthetic strategy, a 1-oxo-tetrahydo-carbazole derivative was used as a key intermediate.[23,24]

2. Results and discussions

The preparation of the starting material, racemic *trans* 3-ethyl-4-oxo-2,3,4,9-tetrahydrocarbazole derivative **5** has been previously described.[1] The hydrolysis of ketoester **5** resulting in acid **6** was carried out by treatment with 15% potassium hydroxide in methanol–water (4:1) at room temperature. The required amide **7** was prepared by the reaction of **6** with triethylamine and ethyl chloroformate in chloroform, followed by the addition of 40% methylamine in water. For the closure of the D ring, it was necessary to reduce the 4-position of the ketoamide **7**.

In previous work,[1] we reported the reduction of *cis* 3-ethyl-4-oxo-2,3,4,9-tetrahydrocarbazole derivative **3** with $NaBH_4$ to furnish the corresponding alcohol and its subsequent conversion to the tetracylic compound **4**. However, the *trans* ketoamide **7** could not be reduced with $NaBH_4$[25] or R_4NBH_4[26] derivative to the corresponding alcohol **8**. Ketone **7** appears to be very hindered. Therefore, we decided to use a borane complex as reducing[27] agent to reduce the hindered ketone **7** to the corresponding alcohol **8** (Scheme 1).

Thus, treatment of ketoamide **7** with borane–dimethylsulfide complex in tetrahydrofuran at ambient temperature provided alcohol **8**, which upon acidification with CF_3COOH, formed compound **10**. Under these reaction conditions, the indole double bond was also reduced. Treatment of compound **10** with DDQ furnished the desired tetracyclic compound **11** in good yield. The stereochemistry of the *epi* compound **4** was confirmed by single crystal X-ray analysis.[1] The stereochemical assignment of the ethyl side chain of the bridge carbon C-12 of compound **11** was confirmed by 2D NMR spectroscopy (COSY, HSQC) and NOESY experiments (Scheme 2).



1 X: O Dasycarpidone
2 X: CH_2 Uleine

Figure 1. Structure of uleine type alkaloids.

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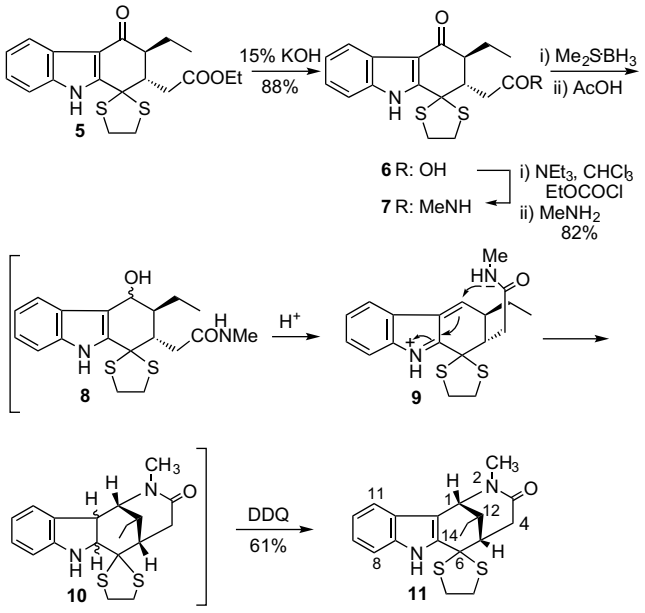
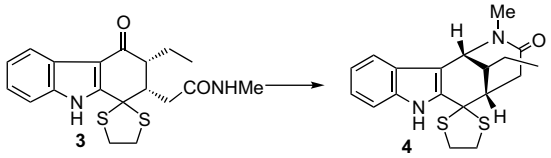
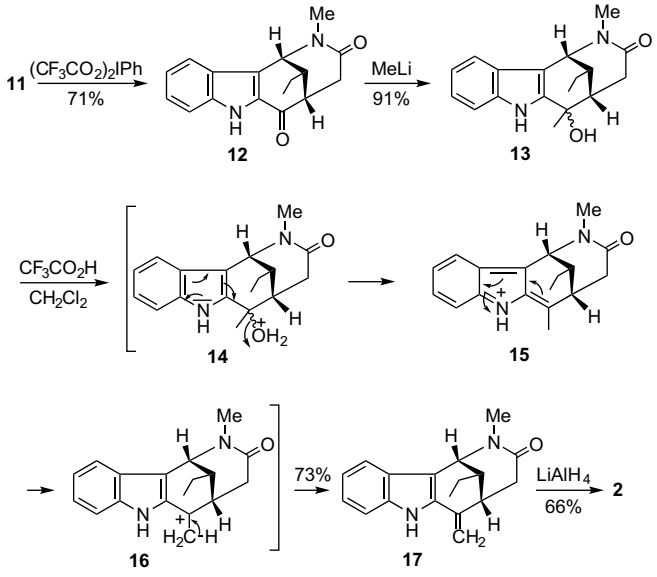


Scheme 1. Synthetic route to azocino[4,3-*b*]indole framework.



Scheme 2. Synthetic route to the *epi* tetracyclic skeleton.

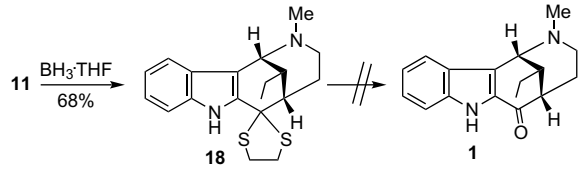
Removal of the protecting group of compound **11** was accomplished by treatment with [bis(trifluoroacetoxy)iodo] benzene[28] in acetonitrile–water (9:1). In order to convert **12** into compound **17**, the C-16 methylene unit was required. Initial attempts to convert the keto group of **12** into the corresponding compound **17** using methyltriphenyl phosphonium bromide[6] were unsuccessful. The reason for this result is probably the steric hindrance of ketone **12**. Consequently, compound **12** was transformed into alcohol **13** by



Scheme 3. Synthetic route to (±)-uleine.

treatment with methyllithium[10] yielding a single epimer in 91%. The dehydration of alcohol **13** with trifluoroacetic acid produced compound **17**. For the formation of **17** from **13**, we suggested possible mechanism as shown in Scheme 3. Finally, the reduction of lactam **17** with $LiAlH_4$ in tetrahydrofuran led to the alkaloid (±)-uleine **2**,[29] which was identical to the natural product reported in the literature.[30,31,23a]

Our next goal was to achieve the synthesis of (±)-dasycarpidone from tetracyclic intermediate **11**. For this purpose, compound **11** was reduced with borane–dimethylsulfide complex[8] to (ethylenedisulfonyl) dasycarpidone derivative **18**. Unfortunately, all attempts to remove the protecting group[28,32] from the compound **18** to produce (±)-dasycarpidone **1** failed (Scheme 4).



Scheme 4. Removal of protecting group.

3. Conclusions

In summary, starting from **3** we completed the construction of dasycarpidone skeleton **11** in an acceptable yield and the total synthesis of (±)-uleine **2**. Further applications of this method can be extended to the syntheses of the other alkaloids of the uleine group.

4. Experimental

4.1. General

^1H NMR spectra were recorded on a BRUKER 500 spectrometer operating at 500 MHz. Spectra were recorded in $CDCl_3$ and DMSO-d_6, using the solvent as internal standard at 500 MHz for ^1H and ^{13}C at 25 °C. Chemical shifts are expressed in terms of parts per million (δ) and the coupling constants are given in hertz. IR spectra were recorded by using Mattson 1000 FT-IR spectrometer. Mass spectra were determined by an Agilent 5973 model of GC–MS. Melting points were determined in a capillary tube on an Electro thermal IA 9000 apparatus and are uncorrected. Reactions were monitored by thin layer chromatography (silica gel 60 F_{254}). Solvents were purified according to the standard methods. All synthetic compounds were in their racemic form.

4.2. {3-β-Ethyl-4-oxo-2,3,4,9-tetrahydrospiro[1*H*-carbazole-1,2(1,3)dithiolane]-2-yl}-2-acetic acid (6)

Ketoester **5** (5.0 g, 12.8 mmol) was dissolved in (15 mL) of tetrahydrofuran and (50 mL) of 20% potassium hydroxide (methanol–water 1:1) was added. The mixture was stirred at room temperature for 4 h and then was poured into solution (250 mL) of cold 10% hydrochloric acid. The precipitate was filtered, dried and recrystallized from diethyl ether to obtain compound **6** (4.1 g, 88%) as a white solid. Mp: 153 °C; [Found: C, 59.82; H, 5.26; N, 3.90. $C_{18}H_{19}NO_3S_2$ requires: C, 59.81; H, 5.30; N, 3.87%.] ν_{max} (KBr) 3450, 3252, 1703, 1622, 1500, 754 cm^{-1}; δ_H (500 MHz, $CDCl_3$+DMSO-d_6) 0.90 (3H, t, J=7.2 Hz, $-CH_3$), 1.64–1.74 (1H, m), 2.19–2.27 (1H, m), 2.52–2.59 (2H, m), 3.02 (1H, dd, J=3.9, 17.0 Hz), 3.24–3.40 (1H, m), 3.52–3.70 (3H, m, $-NCH_3$), 3.82–3.90 (1H, m), 7.23–7.33 (2H, m), 7.55 (1H, d, J=7.9 Hz), 8.06 (1H, d, J=7.6 Hz), 11.91 (1H, s), 12.36 (1H, s); δ_C (75 MHz, DMSO-d_6, APT) 10.2, 20.6, 37.1, 41.8, 45.5, 53.7, 67.9,

110.1, 112.7, 121.2, 122.6, 124.0, 124.6, 128.7, 154.1, 174.2, 192.5; *m*/*z* (EI) 361 (100, M^+), 333 (36), 300 (21), 268 (67), 219 (78), 191 (25), 185 (35), 159 (44%).

4.3. (*N*-Methyl){3-β-ethyl-4-oxo-2,3,4,9-tetrahydrospiro[1*H*-carbazole-1,2′(1,3)dithiolane]-2-yl}-2-acetamide (7)

Acid **6** (1.9 g, 5.2 mmol) was dissolved in (40 mL) of anhydrous chloroform and triethylamine (1.01 g, 10 mmol) was added into the solution. The mixture was cooled and maintained at −5 °C. Ethyl chloroformate (1.08 g, 10 mmol) was next added dropwise and the subsequent mixture was maintained −5 °C for 3 h. Methylamine solution (40%, 10 mL) was then added and the reaction mixture was stirred for 3 h. The mixture was washed with (50 mL) of 10% hydrochloric acid and the organic layer was dried over magnesium sulfate and evaporated. The residue was purified by silica gel chromatography using ethyl acetate to produce amide **7** (1.6 g, 82%). Mp: 158 °C; [Found: C, 60.92; H, 5.94; N, 7.56. $C_{19}H_{22}N_2O_2S_2$ requires: C, 60.93; H, 5.92; N, 7.48%.] ν_{max} (KBr) 3329, 3186, 2926, 1659, 1637, 1579, 1454, 758 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.93 (3H, t, *J*=7.3 Hz, –CH_3), 1.68–1.78 (1H, m), 2.06–2.24 (2H, m), 2.50 (1H, q, *J*=6.1 Hz), 2.75 (3H, d, *J*=4.7 Hz), 2.89 (1H, dd, *J*=15.3, 3.3 Hz), 3.35–3.47 (4H, m), 3.50–3.64 (1H, m), 5.46 (1H, d, *J*=3.4 Hz), 7.17–7.44 (3H, m), 8.14 (1H, t, *J*=4.4 Hz), 8.75 (s, 1H); δ_C (75 MHz, $CDCl_3$+DMSO-d_6, APT) 15.2, 27.0, 30.8, 44.4, 46.2, 50.2, 59.5, 72.1, 115.5, 116.0, 126.0, 126.9, 128.2, 129.6, 133.0, 141.3, 157.8, 177.0, 198.6; *m*/*z* (EI) 374 (65, M^+), 283 (100), 255 (41), 219 (45), 159 (26%).

4.4. 12-Ethyl-2-methyl-6,6-ethylenedithio-1,2,3,4,5,6-hexahydro-1,5-methano-azocino[4,3-*b*]indole-3-one (11)

Borane–dimethylsulfide complex (2 mL) was added to a solution of amide **7** (2.0 g, 5.34 mmol) in 20 mL of anhydrous tetrahydrofuran and stirred for 3 h at room temperature. After being cooled to 0 °C, 10 mL of acetic acid was added. The mixture was poured into (50 mL) of 10% sodium hydroxide solution and the organic layer was extracted with ethyl acetate. The organic layer was then evaporated. The residue was dissolved in 20 mL of tetrahydrofuran and treated with DDQ. The mixture was stirred for 3 h at ambient temperature and the solvent was evaporated. The crude residue was dissolved in dichloromethane and washed with 10% potassium carbonate solution. The organic layer was dried over anhydrous magnesium sulfate and evaporated. The residue was purified by silica gel chromatography using ethyl acetate–acetone–triethylamine (75:25:7) to produce compound **11** (1.18 g, 61%). Mp: 208 °C; [Found: C, 63.66; H, 5.93; N, 7.83. $C_{19}H_{22}N_2OS_2$ requires: C, 63.65; H, 6.19; N, 7.81%.] ν_{max} (KBr) 3296, 2964, 1632, 1548, 752 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.97 (3H, t, *J*=7.3 Hz, H-14), 1.35–1.46 (1H, m, H-13), 1.63–1.73 (1H, m, H-13), 2.47 (1H, t, *J*=7.3 Hz, H-12), 2.65–2.83 (2H, m, H-4 and H-5), 3.00 (3H, s, N–CH_3), 3.03–3.33 (3H, m, –S–CH_2 and H-4), 3.36–3.51 (2H, m, –CH_2S), 4.31 (1H, d, *J*=1.8 Hz, H-1), 7.03 (1H, t, *J*=7.1 Hz, H-10), 7.11 (1H, t, *J*=8.1 Hz, H-9), 7.25 (1H, d, *J*=8.1 Hz, H-8), 7.48 (1H, d, *J*=7.8 Hz, H-11), 8.51 (1H, s, N–H); δ_C (75 MHz, $CDCl_3$, APT) 11.6 (C-14), 23.3 (C-13), 33.5 (N–CH_3), 38.6 (–S–CH_2), 39.1 (–CH_2–S–), 40.1 (C-4), 43.9 (C-12), 45.1 (C-5), 52.7 (C-1), 65.8 (C-6), 110.4 (C-8), 112.1, 117.3 (C-11), 119.1 (C-10), 122.0 (C-9), 125.3, 132.1, 135.5, 168.5 (C-3); *m*/*z* (EI) 358 (100, M^+), 330 (72), 298 (35), 240 (35), 240 (53), 209 (85), 180 (52), 167 (38%).

4.5. 12-Ethyl-2-methyl-1,2,3,4,5,6-hexahydro-1,5-methano-azocino-[4,3-*b*]indole-3,6-dione (12)

[Bis(trifluoroacetoxy)iodo]benzene (2.99 g, 6.97 mmol) was added to a solution of the thioketal **11** (1.0 g, 2.79 mmol) in (40 mL) of acetonitril–water (9:1) and was stirred at room temperature for 2 h. The mixture was then poured into (50 mL) of 10% potassium carbonate solution and extracted with dichloromethane. The organic layer was dried over anhydrous magnesium sulfate and evaporated. The residue was chromatographed on silica gel using chloroform–acetone (4:1) to produce ketone **12** (0.56 g, 71%). Mp: 290 °C (decomposition); [Found: C, 72.36; H, 6.39; N, 9.93. $C_{17}H_{18}N_2O_2$ requires: C, 72.32; H, 6.43; N, 9.92%.] ν_{max} (KBr) 3199, 2925, 1665, 1630, 744 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.96 (3H, t, *J*=7.4 Hz), 1.36–1.51 (2H, m), 2.60–2.69 (2H, m), 2.96–3.10 (2H, m), 3.14 (3H, s), 4.67 (1H, d, *J*=1.7 Hz), 7.23 (1H, t, *J*=7.4 Hz), 7.40 (1H, t, *J*=7.3 Hz), 7.52 (1H, d, *J*=8.4 Hz), 7.75 (1H, d, *J*=8.1 Hz), 10.09 (1H, s); δ_C (75 MHz, $CDCl_3$, APT) 11.8, 24.2, 34.6, 36.2, 46.4, 46.6, 54.5, 113.3, 120.6, 121.6, 125.3, 127.0, 127.4, 128.7, 138.4, 168.4, 191.5; *m*/*z* (EI) 282 (100, M^+), 253 (66), 208 (28), 196 (45), 183 (23), 167 (31), 154 (12), 139 (11), 130 (12), 115 (11), 77 (9%).

4.6. 12-Ethyl-2,6-dimethyl-6-hydroxy-1,2,3,4,5,6-hexahydro-1,5-methano-azocino[4,3-*b*]indole-3-one (13)

Methyllithium (7.5 mL of 3 M solution in tetrahydrofuran) was added to a cooled solution of compound **12** (1.0 g, 3.54 mmol) in (20 mL) of anhydrous tetrahydrofuran under an argon atmosphere at 0 °C. After stirring at room temperature for 30 min without heating, the reaction mixture was poured into 50 mL 10% of sodium hydroxide solution and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and evaporated. The residue was crystallized from diethyl ether to obtain alcohol **13** (0.96 g, 91%). Mp: 225 °C; [Found: C, 72.44; H, 7.45; N, 9.41. $C_{18}H_{22}N_2O_2$ requires: C, 72.46; H, 7.43; N, 9.39%.] ν_{max} (KBr) 3354, 3150, 2966, 1597, 1488, 742 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.93 (3H, t, *J*=7.2 Hz), 1.26–1.37 (2H, m), 1.72 (1H, br s), 2.28 (1H, d, *J*=7.2 Hz), 2.45 (1H, t, *J*=7.7 Hz), 2.59 (1H, dd, *J*=18.8, 7.3 Hz), 2.96 (3H, s), 3.06–3.14 (1H, m), 4.35 (1H, s), 7.09 (1H, t, *J*=7.3 Hz), 7.16 (1H, t, *J*=7.2 Hz), 7.41 (1H, d, *J*=8.0 Hz), 7.53 (1H, d, *J*=7.8 Hz), 9.88 (1H, s); δ_C (75 MHz, $CDCl_3$, APT) 12.4, 24.7, 29.5, 34.3, 35.3, 43.8, 45.5, 54.1, 69.3, 111.3, 111.7, 118.3, 119.6, 122.0, 126.0, 136.4, 136.7, 170.9.

4.7. 12-Ethyl-6-methyliden-1,2,3,4,5,6-hexahydro-1,5-methano-azocino[4,3-*b*]indole-3-one (17)

Trifluoroacetic (5 mL) acid was added to a solution of alcohol **13** (0.8 g, 2.68 mmol) in (50 mL) of dichloromethane and stirred for 2 h at room temperature. The reaction mixture was poured into (50 mL) of 10% sodium hydroxide solution and extracted with dichloromethane. The organic layer was dried over magnesium sulfate and evaporated. The residue was crystallized from diethyl ether–ethyl acetate to give compound **17** (0.55 g, 73%). Mp: 260 °C; [Found: C, 77.13; H, 7.18; N, 10.01. $C_{18}H_{20}N_2O$ requires: C, 77.11; H, 7.19; N, 9.99%.] ν_{max} (KBr) 3152, 2968, 1608, 1466, 1394, 1333, 1238, 740 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.94 (3H, t, *J*=7.4 Hz), 1.26–1.33 (2H, m), 1.62 (1H, br s), 2.35–2.39 (1H, m), 2.48 (1H, d, *J*=17.8 Hz), 2.94–3.06 (m, 2H), 3.11 (s, 3H), 4.48 (d, *J*=1.22 Hz, 1H), 5.07 (1H, s), 5.28 (1H, s), 7.14 (1H, t, *J*=7.2 Hz), 7.22 (1H, t, *J*=7.1 Hz), 7.34 (1H, d, *J*=8.1 Hz), 7.61 (1H, d, *J*=8.1 Hz), 8.39 (1H, s); δ_C (75 MHz, $CDCl_3$, APT) 11.9, 23.6, 34.6, 39.9, 40.9, 43.2, 54.7, 107.7, 111.1, 114.1, 118.5, 120.3, 123.4, 127.0, 131.4, 136.7, 138.5, 170.3; *m*/*z* (EI) 280 (100, M^+), 222 (53), 208 (46), 194 (38), 180 (41), 167 (15), 44 (12%).

4.8. (±)-Uleine (2)

Lactam **17** (0.25 g, 0.89 mmol) was added to a suspension of $LiAlH_4$ (0.30 g, 7.90 mmol) in (30 mL) of anhydrous tetrahydrofuran under an argon atmosphere and was heated for 3 h at reflux. The reaction mixture was cooled to 0 °C, diluted with methanol and poured into (50 mL) of a 10% sodium hydroxide solution. After extracting with dichloromethane, the organic layer was dried and evaporated. The residue was purified by silica gel chromatography

using methanol to give (±)-uleine (**2**) (0.156 g, 66%). Mp: 79–98 °C; ν_{max} (KBr) 3142, 2929, 1628, 1602, 1460, 1441, 1315, 738 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.8 (3H, t, *J*=7.42 Hz, H-18), 1.14 (2H, m, H-19), 1.71 (1H, dd, *J*=13.4, 2.82 Hz, H-14), 2.02–2.11 (3H, m, H-3, H-14, H-20), 2.31 (3H, s, H-5), 2.48 (1H, dd, *J*=8.6, 3.56 Hz, H-3), 2.70 (1H, d, *J*=2.3 Hz, H-15), 4.10 (1H, d, *J*=2.0 Hz, H-21), 5.01 (1H, s, H-17), 5.27 (1H, s, H-17), 7.12 (1H, t, *J*=7.4 Hz, H-10), 7.20 (1H, t, *J*=7.1 Hz, H-11), 7.36 (1H, d, *J*=8.0 Hz, H-12), 7.58 (1H, d, *J*=7.8 Hz, H-9), 8.23 (1H, s, N–H); δ_C (75 MHz, $CDCl_3$, APT) 11.8 (C-18), 24.4 (C-19), 34.8 (C-14), 39.6 (C-15), 44.4 (C-5), 46.3 (C-20), 46.3 (C-3), 56.5 (C-21), 106.6 (C-17), 107.9 (C-7), 110.7 (C-12), 119.6 (C-9), 119.8 (C-10), 122.7 (C-11), 129.4 (C-8), 135.1 (C-2), 136.6 (C-13), 138.8 (C-16); *m*/*z* (EI) 266 (100, M^+), 237 (58), 223 (31), 209 (76), 194 (76), 180 (64), 167 (25), 44 (20%). HRMS: (EI) M^+, found: 266.1783. $C_{18}H_{22}N_2$ requires: 266.1783.

4.9. 12-Ethyl-2-methyl-6,6-ethylenedithio-1,2,3,4,5,6-hexahydro-1,5-methano-2-azocino[4,3-*b*]indole (18)

$BH_3 \cdot SMe_2$ (2 mL) complex was added to a solution of lactam **11** (1.0 g, 2.79 mmol) in (20 mL) of anhydrous tetrahydrofuran under an argon atmosphere and heated for 2 h at reflux. The reaction mixture was then poured into (50 mL) of a 10% sodium hydroxide solution and extracted with dichloromethane. The organic layer was dried over magnesium sulfate and evaporated. The residue was crystallized from diethyl ether–petroleum ether (1:1) to produce compound **18** (0.66 g, 68%). Mp: 186 °C; [Found: C, 66.26; H, 7.04; N, 8.15. $C_{19}H_{24}N_2S_2$ requires: C, 66.23; H, 7.02; N, 8.13%.] ν_{max} (KBr) 3383, 2957, 1456, 1313, 1167, 742 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.9 (3H, t, *J*=7.27 Hz), 1.1–1.2 (2H, m), 1.4–1.5 (m, 2H), 1.58 (1H, br s), 2.4–2.4 (2H, m), 2.5 (3H, s), 2.5–2.6 (1H, m), 2.71 (1H, dd, *J*=11.4, 3.7 Hz), 3.32 (1H, t, *J*=7.2 Hz), 3.44–3.51 (2H, m), 3.56–3.67 (2H, m), 4.18 (1H, s), 7.18 (1H, t, *J*=7.4 Hz), 7.25 (1H, t, *J*=7.9 Hz), 7.39 (1H, d, *J*=8.0 Hz), 7.53 (1H, d, *J*=7.7 Hz), 8.47 (s, 1H); δ_C (75 MHz, $CDCl_3$, APT) 11.9, 24.8, 28.3, 40.1, 40.5, 41.0, 44.4, 51.6, 53.3, 62.0, 64.9, 106.7, 111.3, 118.9, 120.7, 123.2, 128.2, 136.2, 138.1; *m*/*z* (EI) 344 (100, M^+), 301 (18), 283 (59), 251 (28), 233 (25), 213 (100), 180 (63), 44 (23%).

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