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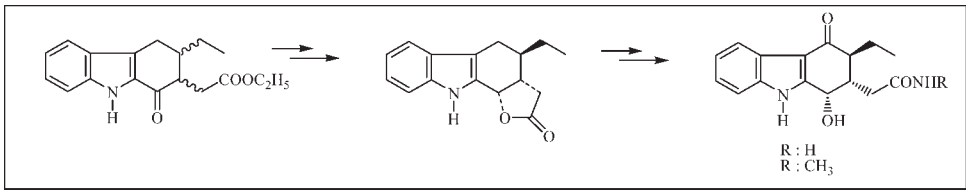

In this study, a new synthetic route for the synthesis of 1-hydroxy-4-oxo-1,2,3,4-tetrahydrocarbazole derivatives **12** and **13** from lactone **11** is described. Unfortunately, cyclization of compounds **12** and **13** to their respective azocino[4,3-*b*]indole derivatives **14** and **15** was unsuccessful.

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INTRODUCTION

Recently we reported the total synthesis of (±)-epidasycarpidone [1] based on the acid catalyzed D-ring cyclization of the appropriate 4-oxo-1,2,3,4-tetrahydrocarbazol derivative. 4-Oxotetrahydrocarbazole with a functionalized ethyl side chain plays an important role in the synthesis of the hexahydroazocino[4,3-*b*]indole frame work [2–5]. In the present work, the synthesis of 2-ethyl-substituted 4-oxo-tetrahydrocarbazole derivatives is described. These intermediates, such as **12** and **13**, could be useful starting materials for the synthesis of uleine alkaloids.

RESULTS AND DISCUSSION

For the synthesis of 4-oxotetrahyrocarbazole derivatives, we started from the diastereomers **1**, which were reported previously [1]. Diastereomers like 1-oxo-2-substituted-2,3,4,9-tetrahydrocarbazole were converted into the racemic trans form by treatment with sodium methoxide [6,7]. However, the diastereomer of **1** was transformed into the racemic trans keto acid **2** by using 15% potassium hydroxide in methanol-water (3:1) at room temperature (Scheme 1). Synthesis of racemic trans ester **3** was achieved under mild conditions by stirring compound **2** for 4 h in DMSO using K_2CO_3 and ethyl iodide. The GC-MS analysis of the isolated ester shows only a single isomer, whose spectral data were identical to those of the trans ester **3** reported in the literature [8]. Treatment of trans ketoester **3** or ketoacid **2** with $NaBH_4$ in THF-CH_3OH (1:1) at room temperature yielded the corresponding alcohols **4** and **5**, which underwent acid-catalyzed ring closure to produce lactone **10** (Scheme 2).

Compound **10** was oxidized to the corresponding 4-oxo-lactone **11** by treatment with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone at 0°C [9].

Subsequent opening of lactone **11** with ammonia and methylamine at room temperature in THF-MeOH afforded amides **12** and **13**.

Unfortunately, cyclization of compounds **12** and **13** under a variety of conditions failed. Compounds **14** and **15** were never detected [2–5] (Scheme 3).

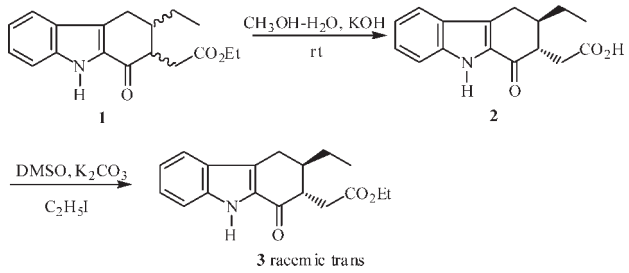
At this point, we decided to reduce alcohol **12** to compound **16**. Treatment of **12** with Et_3SiH and $TiCl_4$ in CH_2Cl_2, however, afforded compound **17** [10] (Scheme 4).

In conclusion, starting from compound **1** and using common intermediates **11**, we obtained the racemic trans amides **12** and **13**. Unfortunately, all attempts to convert amides **12** and **13** to the corresponding tetracyclic lactams **14** and **15** were unsuccessful and reduction of alcohol **12** into compound **16** also failed.

EXPERIMENTAL

^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded with a Bruker instrument DPX-400, 400-MHz High-Performance Digital FT-NMR Spectrometer using $CDCl_3$

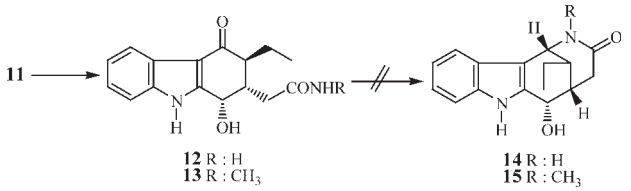
Scheme 1



and DMSO as solvents and tetramethylsilane (TMS) as an internal standard at 25°C. Chemical shifts are expressed in terms of parts per million (δ) and the coupling constants are given in Hz. IR spectra were recorded using a Mattson 1000 FTIR spectrometer. Melting points were determined in a capillary tube on a Gallenkamp apparatus and are uncorrected. Reactions were monitored by thin layer chromatography (silica gel 60 F254). Purification of solvents was performed according to standard methods.

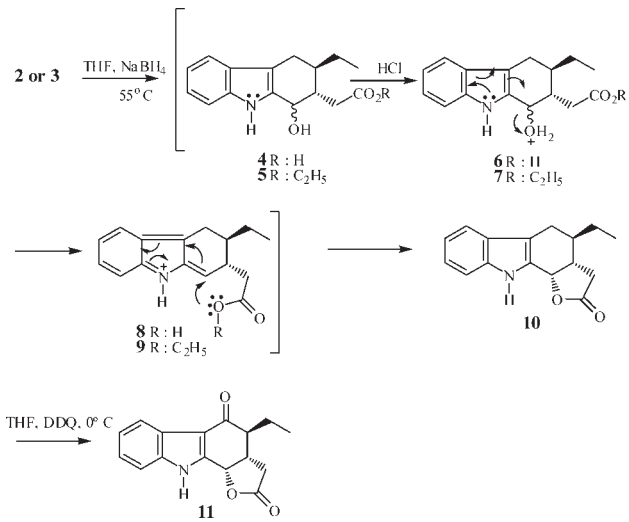
2-(3-Ethyl-1-oxo-1,2,3,4,9-tetrahydrocarbazole-2-yl)-2-acetic acid (2). A solution of 5.00 g (16.72 mmol) of compound 1 in 20 mL tetrahydrofurane and 100 mL 15% potassium hydroxide solution (methanol-water (1:1) was stirred for 4 h. The organic solvent was evaporated under vacuum. The residue was acidified slowly with 100 mL of 10% hydrochloric acid. The mixture was cooled to 0°C and the precipitate was filtered. The product was washed with water and ether and recrystallized from ethyl acetate to yield 4.38 g (96%) of compound 2; m.p. 229–231°C. R_f = 0.69 (EtOAc/methanol, 20:1); IR (potassium bromide): ν 3283, 2959, 2912, 1706, 1639 cm^{-1}; ^1H NMR (dimethyl sulfoxide-d_6): δ 0.96–0.99 (t, 3H, CH_2CH_3, J = 7.37 Hz), 1.40–1.49 (m, 1H), 1.60–1.66 (m, 1H), 2.22–2.35 (m, 1H), 2.65–2.71 (m, 3H), 2.73–2.80 (m, 1H), 3.18 (dd, 1H, J = 4.46 and 16.48 Hz), 7.07–7.10 (m, 1H, aromatic proton), 7.25–7.32 (m, 1H, arom. H), 7.39–7.42 (d, 1H, arom. H, J = 8.30 Hz), 7.69–7.71 (d, 1H, arom H, J = 7.80 Hz), 11.72 (s, 1H, N—H), 12.13 (bs, 1H, OH); APT NMR (dimethyl sulfoxide-d6): δ 11.0 (CH_3), 25.2 (CH_2), 25.4 (CH_2), 31.8 (CH_2), 41.8 (CH), 49.0 (CH), 113.2 (CH), 120.1 (CH), 121.6 (CH), 125.8 (C), 126.6 (CH), 126.7 (C), 130.8 (C), 137.6 (C), 173.8 (C=O, acid), 191.1 (C=O, ketone); MS: m/z 271 (M^+), 253 (M^+-H_2O), 225 (M^+-CO_2H), 78 (M^+-$C_{10}H_{11}NO_3$); *Anal.* Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.78; H, 6.36; N, 5.17.

Scheme 3

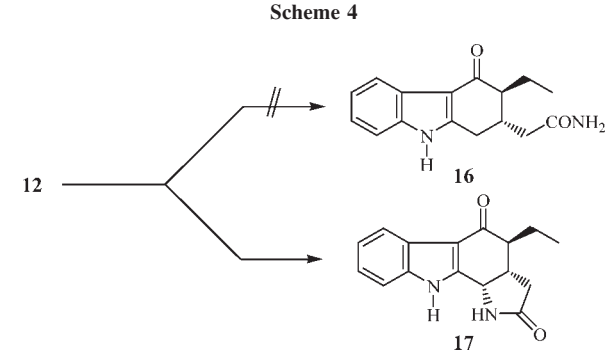


Ethyl(3-ethyl-1-oxo-1,2,3,4,9-tetrahydro-1*H*-carbazole-2-yl)-2-acetate (3). A solution of 2.00 g (7.37 mmol) of compound **2** in 20 mL of DMSO, 2.00 g potassium carbonate (14.47 mmol) and 5.00 g iodoethane (32.05 mmol) was stirred for 3 h at room temperature. The residue was poured into water and extracted with dichloromethane. The organic layer was dried with anhydrous magnesium sulfate and the solvent was removed. The residue was purified by chromatography using silica gel and dichloromethane/ethyl acetate (15:1). The product was recrystallized from ether to yield 2.07 g (94%) of compound 3; mp 158°C.R_f = 0.47 (dichloromethane/EtOAc, 15:1); IR (potassium bromide): ν 3283, 2964, 1705, 1641, 1545, 1431, 1334, 810, 750 cm^{-1}; ^1H NMR (deuteriochloroform): δ 1.10 (t, 3H, J = 7.43 Hz), 1.34 (t, 3H, J = 7.13 Hz), 1.55–1.61 (m, 1H), 1.74–1.80 (m,1H), 2.34-2.36 (m, 1H), 2.77–2.94 (m, 3H), 3.03–3.07 (m, 1H), 3.29 (dd, 1H, J = 16.62 and 4.60 Hz), 4.22–4.28 (q, 2H), 7.19–7.23 (m, 1H), 7.41–7.45 (m, 1H), 7.52 (d, 1H, J = 8.36 Hz), 7.72 (d, 1H, J = 8.03 Hz), 9.41 (s, 1H); APT NMR (deuteriochloroform): δ 10.8 (CH_3), 14.2 (CH_3), 25.5 (CH_2), 26.1 (CH_2), 32.3 (CH_2), 42.4 (CH), 48.9 (CH), 60.6 (CH_2), 112.6 (CH), 120.4 (CH), 121.2 (CH), 125.8 (C), 127.0 (CH), 127.7 (C), 130.3 (C), 138.33 (C), 172.6 (C=O, ester), 191.4 (C=O, ketone); MS: m/z 299 (M^+), 270 (M^+-C_2H_5), 254 (M^+-OC_2H_5), 225 (M^+—$CO_2C_2H_5$). Anal. Calcd for $C_{16}H_{17}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.25; H, 7.10; N, 4.70.

Scheme 2



Scheme 4



4-Ethyl-3,3a,4,5-tetrahydro-10*H*-furo[2,3-α]carbazol -2(10bH)-one (10). A solution of 1.00 g (31.75 mmol) of compound **2** in 20 mL tetrahydrofuran was treated with 2.00 g of sodium borohydride and the mixture was refluxed for 2 h. The reaction mixture was poured into a solution of 50 mL of 10% hydrochloric acid and cooled to 0°C. Then, the precipitate was filtered and the product was recrystallized from ether to yield 0.85 g (90%) of compound **10**; m.p. 202°C. R_f = 0.57 (EtOAc); IR (potassium bromide): ν 3371, 2959, 2857, 1762 cm^{-1}; ^1H NMR (dimethyl sulfoxide-d_6): δ 1.04–1.08 (t, 3H, CH_2CH_3, J = 7.46), 1.32–1.44 (m, 1H), 1.62–1.73 (m, 1H), 1.77–1.86 (m, 1H), 2.46–2.52 (dd, 1H, J = 7.79 and 16.20 Hz), 2.61–2.66 (dd, 1H, J = 4.10 and 16.47 Hz), 2.69–2.82 (m, 2H), 3.04–3.09 (dd, 1H, J = 4.94 and 16.18 Hz), 5.55–5.56 (d, 1H, J = 5.95 Hz), 7.14–7.17 (m, 1H, aromatic proton), 7.24–7.28 (m, 1H, aromatic proton), 7.38-7.40 (d, 1H, aromatic proton, J = 8.73 Hz), 7.58–7.60 (d, 1H, aromatic proton, J = 7.88 Hz), 8.28 (s, 1H, N—H); APT NMR (dimethyl sulfoxide-d_6): δ 11.6 (CH_3), 23.4 (CH_2), 25.8 (CH_2), 33.4 (CH_2), 36.5 (CH), 40.2 (CH), 73.8 (CH), 111.4 (CH), 113.5 (C), 119.2 (CH), 119.8 (CH), 123.4 (CH), 126.22 (C), 128.0 (C), 137.2 (C), 176.5 (C=O, lactone); MS: m/z 255 (M^+), 196 (M^+-CH_3CO_2H), 140 (M^+—- CH_3CO_2H—C_4H_8), 78 (M^+—$C_{10}H_{11}NO_2$); Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 7.33; H, 6.76; N, 5.53.

4-Ethyl-3,3a,4,10-tetrahydro-3*H*-furo[2,3-α]carbazol-2,5 (10*H*,10b*H*)-dione (11). To a solution of 1.00 g (3.92 mmol) of compound **10** in 20 mL tetrahydrofuran (10% water) was added dropwise 1.78 g (7.84 mmol) of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone in 5 mL tetrahydrofuran at 0°C. The reaction mixture was stirred for 12 h at room temperature. Then, the solution was poured into 5% potassium carbonate solution and extracted with ethyl acetate. The organic layer was dried with anhydrous magnesium sulfate and the solvent was removed. The residue was purified by chromatography using silica gel and ethyl acetate. The product was recrystallized from ether to yield 0.95 g (90%); of compound **11**. m.p. 237°C. R_f = 0.79 (EtOAc); IR (potassium bromide): ν 3195, 2964, 2888, 1781, 1644 cm^{-1}; ^1H NMR (dimethyl sulfoxide-d_6): δ :0.92–0.95 (t, 3H, CH_2CH_3, J = 7.30 Hz), 1.58–1.65 (m, 1H), 1.74–1.80 (m, 1H), 2.41–2.51 (m, 3H), 2.83–2.89 (dd, 1H, J = 8.21 and 16.43 Hz), 6.05 (d, 1H, J = 6.75 Hz), 7.21–7.31 (m, 2H, aromatic proton), 7.50 (d, 1H, aromatic proton, J = 7.95 Hz), 8.06 (d, 1H, aromatic proton, J = 7.61 Hz), 12.39 (s, 1H, N-H); APT NMR (dimethyl sulfoxide-d_6): δ 12.0 (CH_3), 24.1 (CH_2), 34.0 (CH_2), 39.4 (CH), 49.9 (CH), 71.9 (CH), 111.9 (C), 112.8 (CH), 122.6 (CH), 122.8 (CH), 123.9 (C), 124.4 (CH), 137.6 (C), 142.7 (C), 175.9 (C=O, lactone), 193.6 (C=O, ketone); MS: m/z 269 (M^+), 223 (M^+—CO_2H), 167 (M^+—CO_2H—C_4H_8), 78 (M^+—$C_{10}H_9NO_3$); *Anal*. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.33; H, 5.58; N 5.23.

2-(3-Ethyl-1-hydroxy-4-oxo-1,2,3,4,9-tetrahydro-1*H*-carbazol-2-yl)-acetamide (12). A solution of 1.00 g (37.17 mmol) of compound 11 in 30 mL of methanol and 30 mL of 25% ammonia solution was stirred for 4 h at room temperature. The residue was poured into water and cooled to 0°C. The precipitate was filtered. The product was washed with water and ether and recrystallized from methanol to yield 0.85 g (80%) of compound 12; m.p. 160–161°C. R_f = 0.27 (EtOAc/methanol, 20:1); IR (potassium bromide): ν 3379, 2953–2868, 1624 cm^{-1}; ^1H NMR (dimethyl sulfoxide-d_6): δ 0.91–0.95 (t, 3H, CH_2CH_3, J = 7.17 Hz), 1.56–1.64 (m, 1H), 1.75–1.83 (m, 1H), 1.94–2.09 (m, 1H), 2.31–2.34 (m, 2H), 2.79–2.83 (dd, 1H, J = 4.50 and 4.19 Hz), 5.26-5.27 (d, 1H,„J = 4,43 Hz), 5,95 (s,1H, OH), 6.83 (s, 1H, NH), 7.13–7.20 (m, 2H, aromatic proton), 7.32 (s, 1H, NH), 7.42–7.44(d, 1H, aromatic proton, J = 8.01 Hz), 7.95–7.97 (d, 1H, aromatic proton, J = 7.50 Hz), 11.97 (s, 1H, N—H); APT NMR (dimethyl sulfoxide-d_6): δ 12.2 (CH_3), 22.5 (CH_2), 33.9 (CH_2), 42.4 (CH), 52.3 (CH), 62.8 (CH), 109.7 (C), 112.6 (CH), 120.9 (CH), 120.1 (CH), 123.1 (CH), 125.1 (C), 136.9 (C), 151.5 (C), 174.1 (C=O, amid), 194.7 (C=O, ketone); MS: m/z 285 (M^+), 268 (M^+—OH), 251 (M^+—OH—NH_3), 223 (M^+—OH—NH_3—CO), 78 (M^+—$C_{10}H_{11}N_2O_3$); *Anal*. Calcd for $C_{16}H_{17}N_2O_3$: C, 67.35; H, 6.01; N, 9.82. Found: C, 67.38; H, 5.96; N, 9.87.

***N*-Methyl-2-(3-Ethyl-1-hydroxy-4-oxo-1,2,3,4,9-tetrahydro-1*H*-carbazol-2-yl)-acetamide (13).** A solution of 1.00 g (37.17 mmol) of compound **11** in 30 mL of methanol and 30 mL of 40% methylamine was stirred for 4 h at room temperature. The residue was poured into the water and cooled to 0°C. The precipitate was filtered. The product was washed with water and ether and recrystallized from methanol to yield 0.69 g (62%) of compound **13**; m.p. 161°C R_f = 0.24 (EtOAc/methanol, 20:1); IR (potassium bromide): ν 3254, 2965, 2932, 1655, 1630 cm^{-1}; ^1H NMR (dimethyl sulfoxide-d6): δ 0.91–0.94 (t, 3H, CH_2CH_3, J = 7.30 Hz), 1.55–1.62 (m, 1H), 1.73–1.82 (m, 1H), 1.93–2.01 (m, 1H), 2.29–2.33 (m, 1H), 2.50 (d, NCH_3, J = 6.80 Hz), 2.82–2.85 (m, 1H,), 5.24–5.26 (t, 1H, J = 5,28 Hz), 5.90 (d, 1H, OH, J = 5,79 Hz), 7.13–7.21 (m, 2H, aromatic proton), 7.43 (d, 1H, aromatic proton, J = 7.78 Hz), 7,77 (s, 1H, NH), 7.96 (d, 1H, aromatic proton, J = 7.10 Hz), 11.89 (s, 1H, N—H); APT NMR (dimethyl sulfoxide-d_6): δ 12.2 (CH_3), 22.49 (CH_2), 26.0 (CH_3), 34.3 (CH_2), 42.5 (CH), 52.2 (CH), 62.9 (CH), 109.7 (C), 112.6 (CH), 120.9 (CH), 122.1 (CH), 123.1 (CH), 125.0 (C), 136.9 (C), 151.4 (C), 172.3 (C=O, amid), 194.69 (C=O, ketone); MS: *m/z* 269 (M^+—NH_2CH_3), 241 (M^+—CO—NH_2CH_3), 224 (M^+—OH—CO—NH_2CH_3); *Anal*. Calcd for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.33. Found: C, 67.95; H, 6.73; N, 9.30.

4-Ethyl-1,3a,4,10b-tetrahydropyrrolo[2,3-α]carbazole-2,5 (3*H*,10*H*)-dione (17). A solution of 1.00 *g* (3.50mmol) of compound **12** in 20 mL tetrahydrofuran was cooled to -78°C. After addition of 0.45 mL (6.48 mmol) $TiCl_4$ and 2.2 mL (14.25 mmol) triethylsilane, the resulting mixture was stirred for 2 h and poured into water. Then, the precipitate was filtered and the product was recrystallized from ether to yield 0.48 g (54%) of compound **17**; m.p. 183°C (dec.). R_f = 0.19 (EtOAc/methanol, 20:1); IR (potassium bromide): ν 3239, 2965, 2931, 1655, 1630 cm^{-1}; ^1H NMR (dimethyl sulfoxide-d_6): δ :0.92–0.96 (t, 3H, CH_2CH_3, J = 7.28 Hz), 1.55–1.60 (m, 1H), 1.70–1.76 (m, 1H), 1.92–2.07 (m, 2H), 2.30–233 (m, 1H), 2.80–2.83 (m, 1H), 5.24 (d, 1H, J = 4.92 Hz), 6.74 (s, 1H, N—H), 7.10–7.17 (m, 2H, aromatic proton), 7.28 (s, 1H, N—H), 7.40 (d, 1H, aromatic proton, J = 7.60 Hz), 7.94 (d, 1H, aromatic proton, J = 7.96 Hz); APT NMR (dimethyl sulfoxide-d_6): δ 12.4 (CH_3), 23.0 (CH_2), 33.9 (CH_2), 42.2 (CH), 52.2 (CH), 62.7 (CH), 110.0 (C), 112.6 (CH), 120.9 (CH), 121.9 (CH), 122.9 (C), 125.1 (CH), 137.2 (C), 142.5 (C), 174.1 (C=O, lactam), 195.1 (C=O, ketone); MS: *m/z* 211 (M^+—CH_2CON), 182 (M^+—C_2H_5—CH_2CON), 167

(M^+—$C_3H_6CO_2N$); *Anal*. Calcd for $C_{16}H_{16}NO_2$: C, 75.57; H, 6.34; N, 5.51. Found: C, 75.62; H, 6.36; N 5.48.

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REFERENCES AND NOTES

[1] Uludag, N.; Hokelek, T.; Patir, S. J Heterocycl Chem 2006, 43, 585.

[2] Magnus, P.; Sear, N.-L.; Kim, C. S.; Vicker, N. J Org Chem 1992, 57,70.

[3] Uludag, N.; Patir, S. J Heterocycl Chem 2007, 44, 1317.

[4] Patir, S.; Rosemmund, P.; Götz, P.-H. Heterocycles 1996, 43, 15.

[5] Patir, S. Liebigs Ann 1995, 1561.

[6] Monika, H.-S.; Blechert, S. Angew Chem Int Ed Engl 1997, 36, 13.

[7] Jiricek, J.; Blechert, S. J Am Chem Soc 2004, 126, 3534.

[8] Kaynak, F.-B.; Özbey, S.; Uludag, N.; Patir, S. Acta Crystallogr 2004, E60, 120.

[9] Oikawa, Y.; Yanemitsu, O. J Org Chem 1977, 42, 1213.

[10] Amat, M.; Coll, M.-D.; Bosch, J. Tetrahedron 1995, 51, 10759.