Reductive Pictet−Spengler Cyclization of Nitriles in the Presence of Tryptamine: Synthesis of Indolo[2,3-*a*]quinolizidine, Nazlinine, and Elaeocarpidine

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Preparation of tetrahydro-β-carbolines through catalytic hydrogenation of nitriles in the presence of tryptamine was applied to simple syntheses of indolo[2,3-*a*]quinolizidine (**3**), nazlinine (**4**), and elaeocarpidine (**7**).

One of the easiest syntheses of tetrahydro-β-carbolines is the Pictet−Spengler reaction of tryptamine with aldehydes, or their equivalent α-keto esters and α-keto acids.[1] However, when targeting polyfunctional compounds, the preparation of the starting polyfunctional aldehydes may meet with difficulties. We recently developed an efficient modification of the reaction that involves trapping, by tryptamine, of an iminium ion generated *in situ* by catalytic hydrogenation of a nitrile.[2] With regard to the easier access to polyfunctional nitriles over aldehydes, this modification seemed of interest for the synthesis of some natural products and analogues.

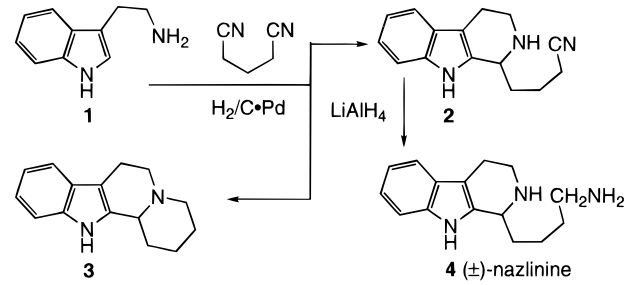
Results and Discussion

Hydrogenation of glutaronitrile in acetic acid in the presence of tryptamine (**1**) yielded 1-(3-cyanopropyl)-tetrahydro-β-carboline (**2**) and indolo[2,3-*a*]quinolizidine (**3**) (Scheme 1).[3] After 48 h, the tricyclic nitrile **2** was isolated in 58% yield while indolo[2,3-*a*]quinolizidine (**3**) began to form (14%). Increasing the reaction time to 72 h raised the yield of **3** to 40% at the expense of **2** (33%). Formation of **3** implies hydrogenation of one nitrile group of glutaronitrile to a protonated imine that is trapped by tryptamine yielding **a** ; elimination of NH_3 to iminium ion **b**; Pictet−Spengler cyclization to **c**; hydrogenation of the second nitrile group to a protonated imine that is trapped as aminal **d**; elimination of NH_3 to iminium ion **e**; and finally, hydrogenation to **3**. No nazlinine (**4**) was detected in the reaction mixture, indicating that the cyclization to **d** was entropically favored over complete hydrogenation of the intermediate (protonated) imine (Scheme 2).

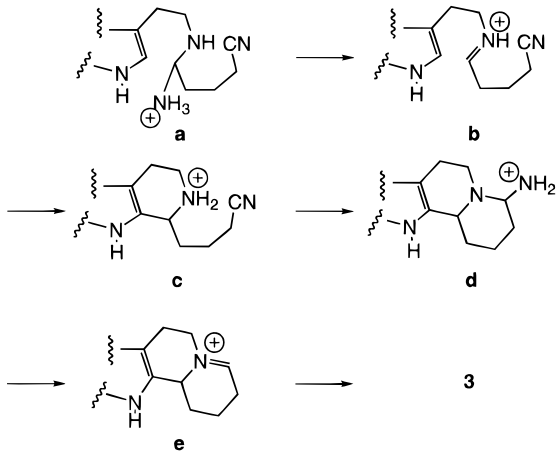
Nazlinine (**4**) is a racemic alkaloid isolated[4] from *Nitraria schoberi*; its structure was elucidated through a biomimetic synthesis[5] from tryptamine and tetrahydropyridine. Lithium aluminum hydride reduction of nitrile **2** expectedly gave (±)-nazlinine (**4**) (79%).

(±)-Elaeocarpidine (**7**) was isolated from *Elaeocarpus* species[6,7] and synthesized by Harley-Mason and Taylor[8] *via* lactam **6**, and by Gribble.[9] Only the depicted relative configuration of elaeocarpidine appears to be possible, for steric reasons. In our hands, lactam **6** was easily prepared (76%) through hydrogenation of *N*-(cyanoethyl)pyrrolidone **5**[10] in the presence of tryptamine

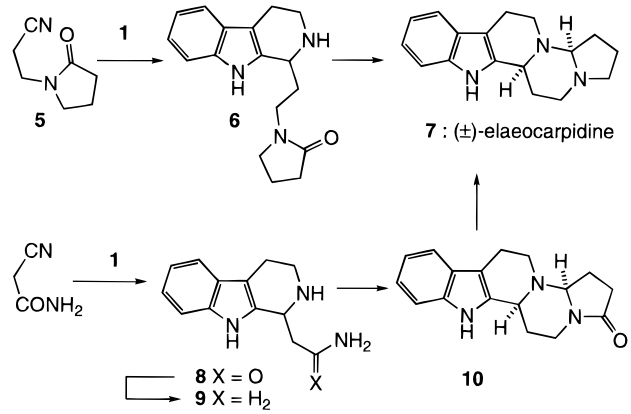
Scheme 1



Scheme 2



Scheme 3



(Scheme 3). Reduction of **6** with DIBAH in THF resulted in cyclization to elaeocarpidine (**7**) (73%). In a second route, cyanoacetamide was hydrogenated in the

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presence of tryptamine to give the tricyclic amide **8** (58%) that was reduced with $LiAlH_4$ in THF to yield the nazlinine analogue **9** (64%). Treatment with methyl 3-formylpropanoate gave lactam **10** (42%) that was at last reduced with $LiAlH_4$ in THF to give **7** (54%).

The above results then illustrate some syntheses of tetrahydro-*β*-carbolines through catalytic hydrogenation of nitriles in the presence of tryptamine, as an efficient substitute to the Pictet−Spengler cyclization.

Experimental Section

General Experimental Procedures. IR spectra were recorded on a Bomem spectrometer, and UV spectra on a Philips Unicam 8700 spectrophotometer. ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were measured on a Brucker AC300 spectrometer with TMS as internal standard. Chemical shifts are reported in ∂ ppm. *J* values are given in. Mass spectra were recorded on an Autospec (VG Instruments). Separations were carried out on TLC plates with Kieselgel 60 PGF_{254} (Merck no. 7749), using CH_2Cl_2/MeOH.

4-(2,3,4,9-Tetrahydro-1H-*β*-carbolin-1-yl)butyronitrile (2). To a solution of tryptamine (800 mg, 5 mmol) in 10 mL of glacial acetic acid were added glutaronitrile (700 mg, 7.5 mmol) and 266 mg of 10% Pd·C in one portion. The mixture was hydrogenated at room temperature and atmospheric pressure for 48 h. The catalyst was removed by filtration through Celite and washed with CH_2Cl_2. The resulting solution was made basic with aqueous NH_3 and then extracted with CH_2Cl_2. The combined CH_2Cl_2 solutions were dried on $MgSO_4$, and the solvent was evaporated. The residue was purified by Si gel chromatography using CH_2Cl_2−MeOH (96:4) as eluent to give 696 mg of **2** (58%) and 159 mg of **3** (14%). **2**: UV (MeOH) λ_{max} 222, 282, 291 nm; IR (film) ν_{max} 3402, 3227, 2933, 2854, 2806, 2247, 1620, 1456, 1352, 1232, 1153, 1116, 742 cm^{-1}; EIMS *m/z* 239 $[M]^+$ (33), 171 (100), 156 (19), 144 (15); ^1H NMR ($CDCl_3$) δ 1.7−1.98 (4H, m), 2.35 (4H, m), 2.7 (2H, m), 2.97−3.01 (1H, dt, *J* = 5.8, 13.5 Hz), 3.24−3.28 (1H, dt, *J* = 5.8, 13.5 Hz), 4.02 (1H, m), 7.08 (1H, t, *J* = 7.6 Hz), 7.13 (1H, t, *J* = 7.6 Hz), 7.31 (1H, d, *J* = 7.6 Hz), 7.47 (1H, d, *J* = 7.6 Hz), 8.52 (1H, s); ^{13}C NMR ($CDCl_3$) δ 16.9, 21.4, 22.4, 33.1, 42.0, 51.6, 108.8, 110.8, 117.9, 119.1, 119.8, 121.4, 127.1, 135.0, 135.6. **3**: UV (MeOH) λ_{max} 231, 282, 290 nm; IR (film) ν_{max} 3398, 3200, 3057, 2937, 2849, 2806, 2760, 1466, 1450, 1346, 1321, 1275, 1211, 1184, 1141, 1109, 738 cm^{-1}; EIMS *m/z* 225 $[M]^+$ (91), 197 (35), 169 (33), 156 (18), 143 (17), 130 (15), 115 (16), 82 (100); ^1H NMR ($CDCl_3$) δ 1.4−1.6 (2H, m), 1.69−1.84 (3H, m), 2.2 (2H, m), 2.33−2.41 (1H, m), 2.59−2.73 (2H, m), 2.95−3.1 (3H, m), 3.2 (1H, m), 7.08 (2H, m), 7.27 (1H, d, *J* = 9 Hz), 7.44 (1H, d, *J* = 9 Hz), 7.98 (1H, s); ^{13}C NMR ($CDCl_3$) δ 21.5, 24.2, 25.6, 29.8, 53.4, 55.6, 60.1, 107.9, 110.6, 117.9, 119.2, 121.1, 127.4, 135.1, 135.9.

Nazlinine (4). To a solution of $LiAlH_4$ (177 mg, 4.66 mmol) in THF (15 mL) was added dropwise with stirring a solution of 222 mg (0.93 mmol) of nitrile **2** in THF. The mixture was heated to reflux for 4 h and cooled to room temperature, and excess hydride was decomposed by addition of moist THF. $MgSO_4$ was added, the THF solution was filtered, and the solid was washed with THF. Evaporation of the THF solution gave an oil, which was chromatographed on an alumina column, to afford 178 mg (79%) of (±)-nazlinine (**4**): UV (MeOH) λ_{max} 222, 272, 279, 289 nm; IR (film) ν_{max} 3352, 3225, 3063, 2926, 1674, 1454, 1435, 1201, 1141, 800, 723 cm^{-1}; EIMS *m/z* 243 $[M]^+$ (30), 197 (11), 185 (24), 171 (100), 154 (15), 144 (26); ^1H NMR ($CDCl_3$) δ 1.4−1.8 (7H, m), 2.54−2.72 (6H, m), 2.94 (1H, m), 3.27 (1H, m), 3.95 (1H, m), 7.07 (2H, m), 7.26 (1H, d, *J* = 8 Hz), 7.43 (1H, d, *J* = 8 Hz), 9.28 (1H, s); ^{13}C NMR ($CDCl_3$) δ 22.4, 22.7, 32.4, 34.3, 41.2, 42.2, 52.3, 108.1, 110.6, 117.6, 118.7, 120.9, 127.2, 135.6, 136.2.

1-[2-(2,3,4,9-Tetrahydro-1*H*-*β*-carbolin-1-yl)ethyl]-pyrrolidin-2-one (6). **6** was prepared according to the procedure utilized for compound **2** using 480 mg (3 mmol) of tryptamine 414 mg (3 mmol) of *N*-(cyanoethyl)-pyrrolidone and 64 mg (0.06 mmol) of 10% Pd·C. After hydrogenation (48 h), compound **6** was isolated as an oil (650 mg, 76%). **6**: UV (MeOH) λ_{max} 226, 282, 290 nm; IR (film) ν_{max} 3406, 3275, 3111, 3055, 2941, 2854, 1666, 1494, 1452, 1315, 1298, 1267, 1163, 1116 cm^{-1}; EIMS *m/z* 283 $[M]^+$ (34), 197 (10), 185 (13), 171 (100), 144 (13); ^1H NMR ($CDCl_3$) δ 1.83 (4H, m), 2.3 (2H, t, *J* = 9 Hz), 2.57 (1H, s), 2.68 (2H, m), 3.0−3.2 (4H, m), 3.35 (1H, m), 3.76 (2H, m), 7.02 (1H, t, *J* = 9 Hz), 7.08 (1H, t, *J* = 9 Hz), 7.33 (1H, d, *J* = 9 Hz), 7.43 (1H, d, *J* = 9 Hz), 10.25 (1H, s); ^{13}C NMR ($CDCl_3$) δ 17.7, 22.1, 30.5, 32.4, 39.5, 40.5, 46.9, 48.6, 107.3, 110.7, 117.3, 118.3, 120.7, 126.8, 135.1, 135.4, 175.6.

2-(2,3,4,9-Tetrahydro-1*H*-*β*-carbolin-1-yl)acetamide (8). Compound **8** was prepared analogously to compound **2** using 160 mg (1 mmol) of tryptamine 101 mg (1.2 mmol) of cyanoacetamide and 21 mg (0.02 mmol) of 10% Pd·C. After hydrogenation (48 h), compound **8** was isolated as a solid (133 mg, 58%). **8**: mp 196−197 °C; UV (MeOH) λ_{max} 280, 232 nm; IR (KBr) ν_{max} 3439, 3214, 3048, 2951, 1677, 1451, 1413, 1314, 1257, 743 cm^{-1}; EIMS *m/z* 229 $[M]^+$ (29), 184 (9), 171 (100), 156 (25), 144 (15), 130 (18), 115 (12); *anal.* C 67.64%, H 6.39%, N 18.08%, calcd for $C_{13}H_{15}N_3O$, C 68.1%, H 6.59%, N 18.32%; ^1H NMR (DMSO) δ 2 .38−2.48 (1H, m), 2.55−2.64 (2H, m), 2.68 (1H, dd, *J* = 4.5, 14.5 Hz), 2.83−2.96 (1H, m), 3.09−3.19 (1H, m), 3.32 (2H, s), 4.3 (1H, dd, *J* = 3.4, 9 Hz), 6.92 (1H, s), 6.94−7.06 (2H, m), 7.29 (1H, d, *J* = 8 Hz), 7.47 (1H, d, *J* = 8 Hz), 7.56 (1H, s); ^{13}C NMR ($CDCl_3$) δ 21.0, 39.0, 41.2, 49.3, 107.9, 111.1, 117.8, 119.0, 121.6, 126.5, 132.8, 135.8, 174.7.

2-(2,3,4,9-Tetrahydro-1*H*-*β*-carbolin-1-yl)ethylamine (9). Compound **9** was obtained by the procedure used for the preparation of **4**, using 1.2 g (32 mmol) of $LiAlH_4$ in 80 mL of THF, and 1.5 g (6.3 mmol) of amide **8**, to afford 894 mg (64%) of amine **9**: UV (MeOH) λ_{max} 224, 279, 290 nm; IR (film) ν_{max} 3394, 3259, 3057, 2937, 1574, 1469, 1319, 740 cm^{-1}; EIMS *m/z* 215 $[M]^+$ (24), 198 (29), 185 (16), 171 (90), 160 (21), 156 (23), 144 (26), 130 (100); ^1H NMR ($CDCl_3$) δ 1.88 (2H, s), 2.6−2.72 (2H, m), 2.8−3.1 (6H, m), 3.16−3.3 (1H, m), 4.05 (1H, t, *J* = 4.5 Hz), 7−7.12 (2H, m), 7.28 (1H, d, *J* = 8 Hz), 7.44 (1H, d, *J* = 8 Hz), 10 (1H, s); ^{13}C NMR ($CDCl_3$) δ 22.1, 35.4, 38.6, 42.1, 52.1, 107.9, 110.9, 117.8, 118.8, 120.9, 127.2, 135.4, 135.6.

Oxoelaeocarpidine (10). A solution of amine **9** (430 mg, 2 mmol) and methyl 3-formylpropionate (500 mg, 4 mmol) in benzene/MeOH (40:2) was left at room temperature under N_2 for 5 h. Then 3 mL of AcOH was added and the reaction mixture was refluxed for 3 h.

The solvents were then evaporated in vacuo, and the residue was basified with aqueous NH_3 and extracted with CH_2Cl_2. The combined organic layers were dried on $MgSO_4$ and evaporated. The residue was purified by Si gel chromatography using CH_2Cl_2−MeOH (93:3) as eluent to give 246 mg (42%) of **10**: mp 294−295 °C; UV (MeOH) λ_{max} 223, 283, 290 nm; IR (KBr) ν_{max} 3273, 2962, 2922, 2845, 2812, 1678, 1454, 1373, 1307, 1267, 1182, 1093, 908, 734 cm^{-1}; EIMS *m/z* 281 $[M]^+$ (100), 252 (13), 224 (8), 197 (19), 171 (83), 156 (25); *anal.* C 72.51%, H 6.33%, N 14.71%, calcd for $C_{17}H_{19}N_3O$, C 72.57%, H 6.8%, N 14.93%; ^1H NMR ($CDCl_3$) δ 1.65 (1H, ddd, J = 4.5, 11, 24 Hz), 1.96 (1H, m), 2.2 (1H, m), 2.4 (4H, m), 2.78 (1H, m), 2.9 (2H, m), 3.15 (1H, dd, J = 4.5, 11 Hz), 3.45 (1H, m), 3.95 (1H, t, J = 7 Hz), 4.2 (1H, dd, J = 4.5, 11 Hz), 7.05 (2H, m), 7.3 (1H, d, J = 8 Hz), 7.45 (1H, d, J = 8 Hz), 9.6 (1H, s); ^{13}C NMR ($CDCl_3$) δ 21.1, 24.0, 27.5, 29.2, 38.3, 45.8, 58.7, 76.4, 107.2, 110.8, 117.6, 118.8, 121.0, 126.5, 132.7, 136.1, 173.4.

Elaeocarpidine (7): (a) The procedure described for the preparation of **4** was repeated using 26 mg (0.69 mmol) of $LiAlH_4$ and 64 mg (0.23 mmol) of compound **10** in 10 mL of THF to afford 33 mg of (±)-elaeocarpidine (**7**) (54%). (b) A solution of **6** (51 mg, 0.18 mmol) in THF (8 mL) was added with 0.6 mL of an 1 M solution of DIBAH in hexane and left for 1 h at room temperature. After addition of wet THF and $MgSO_4$, extraction of the precipitate with THF followed by evaporation afforded a residue (53 mg), which was purified by TLC to afford 35 mg (73%) of compound **7**: mp 195 °C; UV (MeOH) λ_{max} 221, 231, 280, 289 nm; IR (KBr) ν_{max} 3200, 3109, 3055, 2968, 2818, 1452, 1379, 1302, 1184, 1097, 1010, 734 cm^{-1}; EIMS *m/z* 267 $[M]^+$ (100), 252 (10), 239 (43), 225 (29), 210 (25), 197 (22), 169 (62), 154 (34), 143 (18); ^1H NMR ($CDCl_3$) δ 1.7−2.1 (6H, m), 2.3 (2H, m), 2.47 (1H, m), 2.7 (2H, m), 2.93 (1H, m), 3.08 (1H, m), 3.18 (2H, m), 3.34 (1H, m), 7.04 (2H, m), 7.27 (1H, d, J = 8 Hz), 7.43 (1H, d, J = 8 Hz), 8.93 (1H, s); ^{13}C NMR ($CDCl_3$) δ 19.2, 21.5, 28.1, 47.1, 50.1, 51.7, 59.5, 83.5, 107.4, 110.7, 117.7, 118.8, 120.9, 126.9, 134.1, 136.0.

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