A novel Supramolecular Palladium Catalyst for the Asymmetric Reduction of Imines in Aqueous Media

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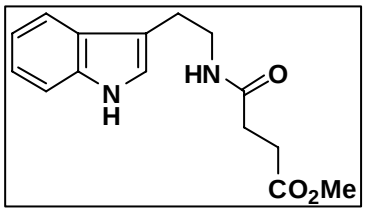
Supporting Information

General Information

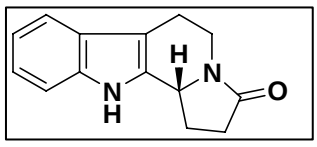
Chemicals were used as purchased unless otherwise noticed. Tetrahydrofuran (THF) was distilled from sodium/benzophenone immediately prior to use. Methanol was distilled from magnesium and catalytic amount of iodine. Dichloromethane, acetonitrile, benzene and triethylamine were distilled from calcium hydride immediately prior to use. Phosphorous oxychloride was distilled immediately prior to use. *N*,*N*-Dimethylformamide (DMF) was distilled from calcium hydride under reduced pressure below 70 ºC. The reaction progress was monitored by thin layer chromatography on silica gel (aluminum foils) and spotted under UV light (254 nm), followed by staining with ethanolic 25% phosphomolibdic solution or aqueous $KMnO_4$. Purification by column chromatography was carried out with silica gel (70-230 or 230-400 Mesh).
^{1}H-NMR spectra were measured at 250 or 300 MHz and the ^{13}C-NMR spectra at 62.5 or 75 MHz, in $CDCl_3$ or CD_3OD at room temperature. Chemical shifts (δ) were reported in ppm and the coupling constants (^3J) in Hertz (Hz). Signal multiplicity was assigned as singlet (s), doublet (d), double doublet (dd), triplet (t), double triplet (dt), quartet (q), quintuplet (qt), multiplet (m) and broad (br). Infrared spectra were measured as films in NaCl cell and the wavenumber is expressed in cm^{-1}. Melting points are not corrected.

Harmicine.



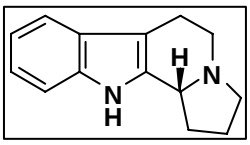
Methyl 4-{[2-(1H-indol-3-yl)ethyl]amino}-4-oxobutanoate (4). To a solution of tryptamine (0.500 g, 3.10 mmol) in acetone (10 mL) was added succinic anhydride (0.315 g, 3.10 mmol) dissolved in acetone (5 mL). The reaction mixture was stirred 12 h at rt. The solvent was removed under reduced pressure and methanol (10 mL) was added, followed by the addition of thionyl chloride (1.0 mL, 14 mmol) at 0ºC. The reaction was allowed to reach rt and stirred 16 h. The solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel (hexane/ethyl acetate 50%). Methyl ester **4** (780 mg, 2.85 mmols) in 92% yield as a white solid (m.p.: 102-103 °C, lit.[1] 101-102 °C). IR (film): 3340, 2856, 1725, 1652. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 2.39 (t, *J* 6.8 Hz, 2H); 2.64 (t, *J* 6.9 Hz, 2H); 2.98 (t, *J* 7.2 Hz, 2H); 3.57 (t, *J* 7,5 Hz, 2H); 3.65 (s, 3H); 5.30 (br s, 1H); 7,04-7.18 (m, 3H); 7.35 (d, *J* 7.8 Hz, 1H); 7.58 (d, *J* 7.8 Hz, 1H); 8.30 (br s, 1H). ^{13}C-RMN (62.5 MHz, $CDCl_3$), δ: 25.2 (CH_2); 29.2 (CH_2); 30.9 (CH_2); 39.8 (CH_2); 51.7 (CH_3); 111.2 (CH); 112.7 (C_0); 118.6 (CH); 119.3 (CH); 122.0 (CH); 122.1 (CH); 127.2 (C_0); 136.3 (C_0); 171.3 (C_0); 173.4 (C_0).

General procedure for β-CD mediated reduction of imines. An equimolar amount of imine (0.5 mmol) was added to a suspension of dried β-CD (0.5 mmol) in 2.5 mL of aqueous sodium bicarbonate solution (0.2 mol/L). The mixture was stirred at room temperature overnight and the resulting slurry lyophilized to give a cream powder that was used without further purification. Then, the imine-CD complex was resuspended in 4.0 mL of H_2O:CH_2Cl_2 (1:1), and $PdCl_2$ (0.15 mmol) was added at once followed by Et_3N (0.36 mmol). The temperature was dropped to 0 ^{o}C and Et_3SiH (2.0 mmol) added dropwised. The mixture was stirred at 0 °C for 2 h. The mixture was basified to pH 9, extracted with CH2Cl2 and purified by flash chromatography to afford the respective amines using AcOEt:MeOH:NH_4OH (95:5:1) as eluent.



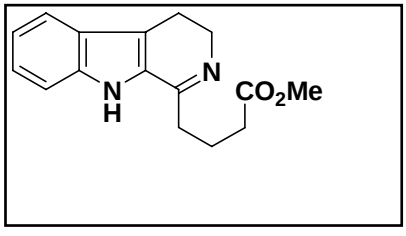
1,2,5,6,11,11b-Hexahydro-indolizino[8, 7-b]indol-3-one (3f). An equimolar amount of imine **1f** (0.5 mmol) was added to a suspension of dried β-CD (0.5 mmol) in 2.5 mL of aqueous sodium bicarbonate solution (0.2 mol/L). The mixture was stirred at room temperature overnight and the resulting slurry lyophilized to give a cream powder that was used without further purification. Then, the imine-CD complex was resuspended in 4.0 mL of H_2O:CH_2Cl_2 (1:1), and $PdCl_2$ (0.15 mmol) was added at once followed by Et_3N (0.36 mmol). The temperature was dropped to 0 ^{o}C and Et_3SiH (2.0 mmol) added dropwised. The mixture was stirred at 0 °C for 2 h. The mixture was acidified with HCl (1.0 mol/L) to pH 3, and stirred for additionally 1 h. Then the mixture was extracted with CH_2Cl_2, dried with Na_2SO_4, and rotaevaporated. The crude mixture was purified by column chromatography on silica gel (chloroform/methanol 9:1 v/v) to afford **3f** (0.410 mg, 1.60 mmol) in 95% yield as a brown viscous unstable oil, and 85% *ee* by HPLC analysis (Welch-01, hexane/2-propanol/diethylamine = 80: 20: 0.1, 1.0 mL/min, 254 nm, minor isomer 4.1 min, major isomer 4.5 min). m.p.: 250 ^{o}C; lit[12h]: 251-252 ºC. Specific optical rotation: $[\alpha]^{20}_{D}$ = +234 (c=1.0, $CHCl_3$); lit[2]: $[\alpha]^{20}_{D}$ = +249,5 (c=1.0, $CHCl_3$). FTIR (film): 3260, 2950, 2847, 1669, 1455, 742. ^{1}H-NMR (250 MHz, CD_3OD) δ: 1.86-2.01 (m, 1H); 2.38-2.48

(m, 1H); 2.56-2.68 (m, 2H); 2.75-2.79 (m, 2H); 3.00-3.25 (m, 1H); 4.38-4.46 (m, 1H); 4.96-5.01 (m, 1H); 7.00 (dt, *J* 1.2 and 7.0 Hz, 1H); 7.08 (dt, *J* 1.2 and 7.0 Hz, 1H); 7.28-7.32 (m, 1H); 7.39-7.42 (m, 1H). ^{13}C-RMN (62.5 MHz, CD_3OD) δ: 22.2 (CH_2); 27.0 (CH_2); 32.7 (CH_2); 39.1 (CH_2); 56.4 (CH); 107.6 (C_0); 112.2 (CH); 119.0 (CH); 120.2 (CH); 122.7 (CH); 128.2 (C_0); 135.0 (C_0); 138.3 (C_0); 176.1 (C_0).



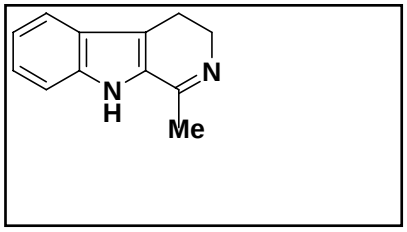
(+)-Harmicine (5). A flame dried round-bottomed flask was charged with $AlCl_3$ (0.05 g, 0.38 mmol) and THF (3.0 mL) under nitrogen atmosphere. The mixture was cooled at 0 ^oC and a 2,4M THF soln. of $LiAlH_4$ (0.55 mL, 1.33 mmol) was added. After stirring 10 min. at 0 ^oC, a soln. of lactam **3f** (0.15 g, 0.66 mmol) in THF (3.0 mL) was added via canula. The reaction mixture was stirred 30 min. at rt, quenched by the addition of satd. aq. NH_4Cl (0.1 mL) and poured into satd. aq. $NaHCO_3$ (20 mL). After extraction with ethyl acetate (2X15 mL), the organic phase was washed with brine (2X15 mL) and dried with $MgSO_4$. The crude product was purified by column chromatography on silica gel (chloroform/methanol 9:1 v/v) to afford (+)-harmicine **3** (0.126 g, 0.59 mmol) in 90% yield as yellow solid. (m.p. 160-161 ^oC; lit.[3] 161-164 ºC). Specific optical rotation: $[\alpha]^{20}_D$ = +105 (c 0.5, $CHCl_3$); lit[ii]: $[\alpha]^{20}_D$ = +101,9 (c 0.5, $CHCl_3$). FTIR (film): 3255, 2950, 2854, 1452, 738. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 1.80-2.00 (m, 3H); 2.24-2.32 (m, 1H); 2.60-2.66 (m, 1H); 2.80-3.15 (m, 4H); 3.30-3.37 (m, 1H); 4.25-4.30 (m, 1H); 7.10 (m, 2H); 7.31 (d, *J* 7.3 Hz, 1H); 7.43 (d, *J* 7.0 Hz, 1H); 8.6 (br, 1H). ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ: 17.8 (CH_2); 23.4 (CH_2); 29.4 (CH_2); 45.9 (CH_2); 49.2 (CH_2); 56.9 (CH); 107.8 (C_0); 110.7 (CH); 118.1 (CH); 119.4 (CH); 121.4 (CH); 127.3 (C_0); 135.3 (C_0); 135.9 (C_0).

Methyl 5-{[2-(1*H*-indol-3-yl)ethyl]amino}-5-oxopentanoate (6). To a soln. of tryptamine (0.200 g, 1.25 mmol) in CH_2Cl_2 (5 mL) was added a soln. of glutaric anhydride (0.142 g, 1.25 mmol) in CH_2Cl_2 (0.5 mL). The reaction mixture was let to react at rt under magnetic stirring and after 20 min. the solvent was removed under reduced pressure. The residue was dissolved in methanol (2.0 mL) and thionyl chloride (0.1 mL, 1.4 mmol) and the mixture was stirred 3 h at rt. The solvent was removed under reduced pressure and the crude product was purified by column chromatography on sílica gel (hexane/ethyl acetate 50%) to afford **6** in 96% yield as a white solid (m.p: 102-103 °C; lit[4]: 104-105 °C). FTIR (film): 2945, 1733, 1650, 1553, 1435, 1220, 747. ^{1}H-RMN (300 MHz, CD_3OD) δ: 1.86 (qt., *J*=7.5 Hz, 2H); 2.19 (t, *J*=7.2 Hz, 2H); 2.30 (t, *J*=7.2 Hz, 2H); 2.94 (t, *J*=7.2 Hz, 2H); 3.48 (q, *J*=7.5 Hz, 2H); 3.65 (s, 3H); 6.98-7.11 (m, 3H); 7.33 (d, *J*=8.1Hz, 1H), 7.56 (d, *J*= 8.1Hz, 1H). ^{13}C-RMN (75 MHz, CD_3OD) δ: 22.3 (CH_2); 26.4 (CH_2); 34.0 (CH_2); 36.2 (CH_2); 41.5 (CH_2); 52.2 (CH_3); 112.3 (CH); 113.4 (C_0); 119.4 (CH); 119,.7 (CH); 122.4 (CH); 123.5 (CH); 128.9 (C_0); 138.3 (C_0); 175.3 (C_0); 1754 (C_0). HRMS (ESI): calcd. for $[C_{15}H_{22}N_5^+ + H]^+$: 289.1552; found. 289.1567.

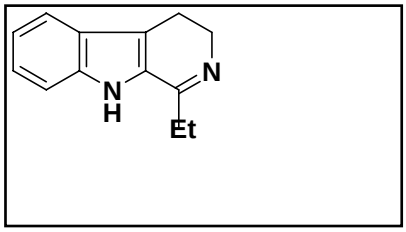


To a soln. of **6** (0.290 g, 1.0 mmol) in toluene (7 mL) and acetonitrile (3 mL) was added $POCl_3$ (0.3 mL, 3 mmol) dropwise and the reaction mixture was then refluxed for 5 h. The reaction mixture was then cooled to rt and it was concentrated under vacuum. The crude reaction mixture was dissolved in CH_2Cl_2 (20 mL),

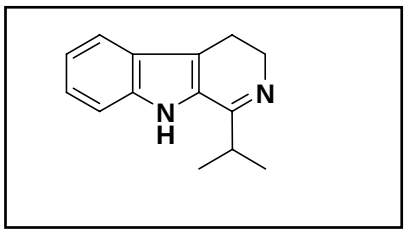
washed with aq. 1 M $NaHCO_3$ (15 mL). The organic phase was dried over $MgSO_4$ and evaporated under reduced pressure. ^{1}H RMN (400 MHz, $CDCl_3$) δ: 2.00-2.05 (2H, m); 2.48 (2H, br t, J = 6.4 Hz); 2.69 (2H, br t, J = 7.9 Hz); 2.87 (2H, t, J = 8,5 Hz); 3.7 (3H, s); 3.87 (2H, br t, J = 8.5 Hz); 7.13 (1H, dt, J = 8.2 , 0.9 Hz); 7.26 (1H, dt, J = 8.2 , 0.9 Hz); 7.44 (1H, d, J = 8.2 Hz); 7.57 (1H, d, J = 8.2 Hz); 9.9 (1H, s). ^{13}C RMN (100 MHz, $CDCl_3$) δ: 19.3 (CH_2), 22.0 (CH_2), 32.8 (CH_2), 34.8 (CH_2), 48.0 (CH_2), 51.8 (CH_3); 112.2 (C_0); 116,6 (C_o); 119.8 (CH); 120.0 (CH); 124.4 (CH); 125.3 (C_0); 128.4 (C_0); 136.9 (C_0); 160.9 (C_0); 174.96 (C_0).



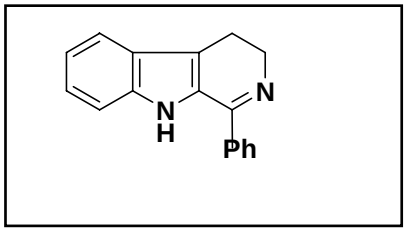
1-Methyl-4,9-dihydro-3*H*-*β*-carboline (1a): ^{1}H RMN (400 MHz, $CDCl_3$) δ: 2.38 (3H, s); 2.88 (2H,br t, J = 8.4 Hz); 3.89 (2H, dt, J = 8.4 , 1.1 Hz); 7.14 (1H, dt, J = 8.1 , 0.7 Hz); 7.26 (1H, dt, J = 8.1 , 0.7 Hz); 7.39 (1H, br d, J = 8.1 Hz); 7.60 (1H, br d, J = 8.1 Hz); 9.38 (1H, br s, NH). ^{13}C RMN (100 MHz, $CDCl_3$) δ: 19.5 (CH_2); 22.1 (CH_3); 48.20 (CH_2); 111.9 (CH); 116.3 (C_0); 119.9 (CH); 120.2 (CH); 124.3 (CH); 125.4 (C_0); 129.1 (C_0); 136.4 (C_0); 157.8 (C_0). HRMS (70 eV): calcd. for $C_{12}H_{12}N_2$ *m/z* 184.1000; found 184.1007.



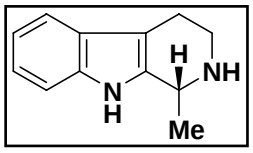
1-ethyl-4,9-dihydro-3*H*-*β*-carboline (1b): cream solid; m.p. 165-167 ºC; ^{1}H RMN (400 MHz, $CDCl_3$) δ: 1.30 (3H t, *J* = 7.4 Hz); 2.74 (2H q, *J* = 7.4 Hz); 2.91 (2H t, *J* = 8.4 Hz); 3.89 (2H, t, *J* = 8.4 Hz); 7.10-7.63 (4H m); 8.81 (br s, 1H). ^{13}C RMN (100 MHz, $CDCl_3$) δ: 10.9 (CH_3); 19.3 (CH_2); 28.4 (CH_2); 48.2 (CH_2); 111.9 (CH); 116.8 (C_0); 120.0 (CH); 120.3 (CH); 124.4 (CH); 125.6 (C_0); 128.6 (C_0); 136.6 (C_0); 161.7 (C_0). HRMS (ESI) for $[C_{13}H_{14}N_2 + H]^+$: calcd. 199.1230, found: 199.1222.



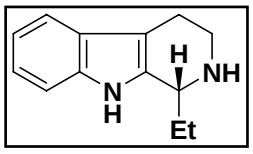
1-Isopropyl-4,9-dihydro-3*H*-*β*-carboline (**1c**): To a solution of tryptamine (0.191 g, 1.19 mmol) and propenoic acid (0.136 g, 1.19 mmol) in CH_2Cl_2 (12.0 mL) at 0 °C were added DCC (0.177 g, 1.31 mmol) and DMAP (0.251 g, 1.31 mmol). The reaction mixture was stirred at room temperature for 10 h, then washed with 5% aqueous HCl (3 x 15.0 mL), 5% aqueous $NaHCO_3$ (20.0 mL), H_2O (20.0 mL), brine (20.0 mL), and dried (Na_2SO_4). The solvents were removed and the resulting amide was reacted directly without purification with $POCl_3$ (242 μL) in dry benzene (9.25 mL) and the mmixture was heated to reflux for 2 h, cooled to room temperature, and then concentrated. The resulting orange viscous oil was purified by chromatography ($CHCl_3$/MeOH, 10%) to afford a cream solid in 86% yield, which was characterized as the imine. M.p. 163-166 ºC. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.28 (br s, 3H); 1.31 (br s, 3H); 2.85 (t, *J* 8.3 Hz, 2H); 3.02 (m, 1H); 3.88 (t, *J* 8.3 Hz, 2H); 7.13-7.62 (m, 4H); 8.54 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 19.3 (CH_2); 20.3 (2x CH_3); 28.7 (CH_2); 33.2 (CH); 48.1 (CH_2); 111.8 (CH); 117.2 (C_0); 119.9 (CH); 120.2 (CH); 124.4 (CH); 125.6 (C_0); 128.2 (C_0); 136.5 (C_0); 165.1 (C_0). FT-IR (KBr film, cm^{-1}): 3438, 1621, 1601, 1506, 750. HRMS (70 eV): $C_{14}H_{17}N_2$ *m/z* 213.1386, found: 213.1375.



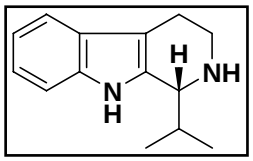
1-Phenyl-4,9-dihydro-3*H*-*β*-carboline (1e): ^{1}H NMR (400 MHz, d_6-DMSO), δ: 2.88 (t, *J* = 7.8 Hz, 2H); 3.90 (t, *J* = 7.8 Hz, 2H); 7.07-7.10 (m, 1H); 7.17-7.21 (m, 1H); 7.40-7.65 (m, 5H); 7.73-7.78 (m, 2H); 11.00 (br s, 1H). HRMS (70 eV): $C_{17}H_{14}N_2$ *m/z* 246.1157, found: 246.1150. The spectrometric data is in accordance with reference Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 4916-4917.



(*R*)-1-Methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (2a): $[\alpha]_D$ +51 (*c* = 1.0, MeOH), (lit. (*R*)-isomer, $[\alpha]_D$ +53.5 (*c* = 2.08, EtOH), N. Uematsu, A. Fujii, S. Hashiguchi, T. Ikariya and R. Noyori, *J. Am. Chem. Soc.*, 1996, **118**, 4916-4917), 90% *ee* by HPLC analysis (Chiralcel OD, hexane/2-propanol/diethylamine = 80: 20: 0.1, 1.0 mL/min, 254 nm, minor isomer 8.8 min, major isomer 5.9 min). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.46 (3H, d, J = 6,7 Hz); 1.80 (1H, br s); 2.88-2.83 (2H, m); 3.05 (1H, ddd, J = 13.1, 9.2, 5.2 Hz); 3.37 (1H, ddd, J = 13.1, 5.2, 3.7 Hz); 4.19 (1H, tq, J =6.7, 2.0 Hz); 7.09 (1H, dt, J = 7.3, 0.9 Hz); 7.15 (1H, dt, J = 7.3, 0.9 Hz); 7.31 (1H, d, J = 7.3 Hz); 7,48 (1H, d, J = 7.3 Hz); .78 (1H, br s). HRMS (EI): calcd. for $C_{14}H_{18}N_2$ 214.1466, found: 214.1458.

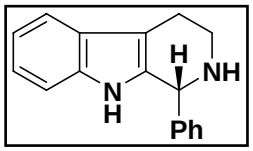


(*R*)-1-Ethyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (2b): $[\alpha]_D$ +52.0 (*c* = 1.0, MeOH), (lit. (S)-isomer, $[\alpha]_D$ –62.6 (CH_3COCH_3), C. Gremmen, B. Willemse, M. J. Wanner and G.-J. Koomen, *Org. Lett.*, **2000**, *2*, 1955-1958), 83% *ee* by HPLC analysis (ChiralPack OD, hexane/2-propanol/diethylamine = 80: 20: 0.1, 1.0 mL/min, 254 nm, major isomer 8.9 min, minor isomer 11.0 min). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.10 (t, *J* = 7.1 Hz, 3H); 1.67-1.75 (m, 1H); 1.85-2.07 (m, 1H); 2.72-2.78 (m, 2H); 3.00-3.06 (m, 1H); 3.34-3.40 (m, 1H); 4.00-4.04 (m, 1H); 7.06-7.19 (m, 2H); 7.32 (d, *J* = 7.2 Hz, 1H); 7.49 (d, *J* = 7.6 Hz, 1H); 7.77 (br s, 1H). The spectrometric data is in accordance with references Zhang, X.; Jiang W.; Sui Z. *J. Org. Chem.* **2003**, *68*, 4523-4526 and (a) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558-10559. (b) Gremmen, C.; Willemse, B.; Wanner, M. J.; Koomen, G.-J. *Org. Lett.* **2000**, *2*, 1955-1958.).

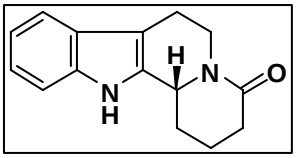


(R)-1-Isopropyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (2c): amine as a creamy solid. $[\alpha]_D$ +65 (c 1.0, MeOH), 70% *ee* by HPLC analysis (ChiralPack OD, hexane/2-propanol/diethylamine = 80: 20: 0.1, 0.8 mL/min, 254 nm, major isomer 6.0 min, minor isomer 8.0 min). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.91 (d, *J*= 7.2 Hz, 3H); 1.14 (d, *J*= 7.2 Hz, 3H); 2.16-2.28 (m, 1H); 2.72-2.77 (m, 2H); 2.93-3.03 (m, 1H); 3.42-3.45 (m, 1H); 4.00-4.04 (m, 1H); 7.10-7.15 (m, 2H); 7.31 (dd, *J*= 1.4, 7.3 Hz, 1H); 7.50 (dd, *J*= 1.4, 7.3 Hz, 1H); 7.85 (br s, 1H). HRMS (EI): calcd. for $C_{14}H_{18}N_2$ 214.1466, found: 214.1458. FT-IR (KBr film, cm^{-1}): 1466, 3471. The spectrometric data is in accordance with references: (a) Shankaraiah, N.; da Silva, W. A.; Andrade, C. K. Z.; Santos, L. S. *Tetrahedron Lett.* **2008**, *49*, 4289–4291. (b) Zhang, X.; Jiang W.; Sui Z. *J. Org. Chem.* **2003**, *68*, 4523-4526. (c) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem.*

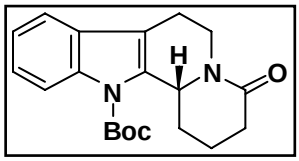
Soc. **2004**, *126*, 10558-10559. (d) Gremmen, C.; Willemse, B.; Wanner, M. J.; Koomen, G.-J. *Org. Lett.* **2000**, *2*, 1955-1958.).



(*R*)-1-Phenyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (2e): $[\alpha]_D$ –4.1 (*c* = 1.0, $CHCl_3$), (lit. (*R*)-isomer, $[\alpha]_D$ –3.9 (*c* = 1.03, $CHCl_3$), N. Uematsu, A. Fujii, S. Hashiguchi, T. Ikariya and R. Noyori, *J. Am. Chem. Soc.*, 1996, **118**, 4916-4917), 90% *ee* by HPLC analysis (ChiralPack OD, hexane/2-propanol/diethylamine = 80: 20: 0.1, 1.0 mL/min, 254 nm, minor isomer 15.8 min, major isomer 19.9 min). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 2.83-2.95 (m, 2H); 3.07-3.16 (m, 1H); 3.33-3.39 (m, 1H); 5.17 (s, 1H); 7.10-7.19 (m, 3H); 7.30-7.37 (m, 5H); 7.56-7.60 (m, 1H); 7.66 (br s, 1H). HRMS (EI): calcd. for $C_{17}H_{16}N_2$ 248.1314, found: 248.1320. The spectrometric data is in accordance with reference Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 4916-4917.



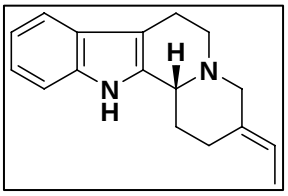
2,3,6,7,12,12b-Hexahydroindolo[2,3-*a*]quinazolin-4(1*H*)-one (3g). Following the general procedure for β-CD mediated reduction and imine **1g**, the crude mixture was purified by column chromatography on silica gel ($CHCl_3$: MeOH, 9:1 v/v) to afford a **3g** as a viscous oil in 80% yield and 90% *ee* determined by HPLC analysis (Welk-01 Column, hexane:2-propanol, 85:15,1.0 mL/min, 254 nm, major isomer 4.2 min, minor isomer 5.1 min). $[\alpha]^{20}_D$ +279 (c 1, $CHCl_3$). FTIR (film): 3260, 2950, 2847, 1616, 1455, 742. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.75-1.96 (m, 3H); 2.35-2.62 (m, 3H); 2.74-2.81 (m, 3H); 4.76-4.80 (m, 1H); 5.12-5.23 (m, 1H); 7.10-7.20 (m, 2H); 7.34 (d, *J*=8.1 Hz, 1H); 7.50 (d, *J*=7.2 Hz, 1H); 8.35 (s, br, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 19.3 (CH_2); 21.0 (CH_2); 29.0 (CH_2); 32.4 (CH_2); 40.2 (CH_2); 54.4 (CH); 109.3 (C_0); 110.9 (CH); 118.3 (CH); 119.7 (CH); 122.0 (CH); 126.8 (C_0); 133.3 (C_0); 136.2 (C_0); 169.3 (C_0).



***Tert*-butil 4-oxo-1,3,4,6,7,12b-hexahydroindolo[2,3-*a*]quinazoline-12(2*H*)-carboxylate (7).** Lactam **3g** (0.190 g, 0.80 mmol) was dissolved in THF (10 mL) and triethylamine was added (0.30 mL, 2.0 mmol). After stirring 10 min. at rt, $(Boc)_2O$ (0.270 g, 1.20 mmol) and DMAP (0.025 g, 0.20 mmol) and the reaction mixture was stirred 4 h at rt. After evaporation of the solvent under reduced pressure, the crude was successively washed with aq. satd. NH_4Cl (2X10 mL), aq. satd. $NaHCO_3$ (2X10 mL) and brine (10 mL). The crude product was purified by column chromatography under silica gel (hexanes/ethyl acetate 2:3 v/v) to afford **7** (0.260 g, 1.92 mmol) in 96% yield as a pale brown oil. Specific optical rotation: $[\alpha]_D$= +289 (c=1,8, CH_2Cl_2); lit [12c]: $[\alpha]_D$ = +328 (c=2.0, CH_2Cl_2). FTIR (film): 3050, 1735, 1639. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.40-1.46 (m, 1H); 1.66 (s, 9H); 1.90-1.95 (m, 2H); 2.38-2.48 (m, 1H); 2.60-2.67 (m, 2H); 2.70-2.81 (m, 2H); 2.82-2.84 (m, 1H); 5.10-5.17 (m, 2H); 7.22-7.31 (m, 2H); 7.42-7.45 (m, 1H); 8.06-8.08 (m, 1H). ^{13}C-RMN (75 MHz, $CDCl_3$) δ: 19.3 (CH_2); 21.5 (CH_2); 28.1 (3XCH_3); 30.1 (CH_2); 31.9 (CH_2); 39.0 (CH_2); 56.0 (CH); 84.2 (C_0); 115.4 (CH); 118.2 (CH); 122.9 (CH); 124.5 (CH); 128.5 (C_0); 135.1 (C_0); 136.7 (C_0); 150.1 (C_0); 169.8 (C_0).

***Tert*-Butyl (3*E*)-3-ethylidene-4-oxo-1,3,4,6,7,12b-hexahydroindolo[2,3-a]quinazoline-12(2*H*)-carbolylate (8).** To a soln. of diisopropylamine (0.20 mL, 1.35 mmol) in anhydrous THF (1.0 mL) was added *n*-butyllithium (1.8 M soln in THF, 1.05 mL, 1.35 mmol) at 0 °C and under a nitrogen atmosphere. After 15 min., the mixture was cooled to -78 °C and a soln. of **7** (0.210 g, 0.62 mmol) in THF (2 mL) was added via canula. The reaction mixture was stirred 30 min. at -78°C when freshly distilled acetaldehyde (0.35 mL, 6.3 mmol) was added via syringe. The reaction mixture was stirred 30 min. at -78°C, followed by stirring 16 h at rt. The reaction was quenched upon addition of satd. Aq. NH_4Cl (10 mL) and the aqueous phase was extracted with ethyl acetate (2X20 mL). The combined organic phase was dried over $MgSO_4$, the solvent was evaporated under reduced pressure to afford a viscous yellow oil which was dissolved in CH_2Cl_2 (3 mL). Under a nitrogen atmosphere, the soln. was cooled at -40 °C and mesyl chloride (80 μL, 1.0 mmol) was added Et_3N (0.20 mL). After stirring 30 min. at –40 °C, the reaction was warmed up to rt and stirred 3 h. The solvent was evaporated under reduced pressure and the residue was dissolved in THF (5 mL) and DBN (0.25 mL, 2.0mmol) was added. After stirring 16 h at rt, the solvent was removed and the residue was dissolved in CH_2Cl_2 (3 mL) and washed with satd. aq. NH_4Cl (2X20 mL). The organic phase was dried with $MgSO_4$, the solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel (hexanes/ethyl acetate 60:40 v/v) to afford **8** as a pale brown oil (0.152 g, 0,41), in 67% yield. Specific optical rotation: $[\alpha]^{20}_D$ = +136 (c=2, CH_2Cl_2); lit[12c]: $[\alpha]_D$ = 140.4 (c=2.0, CH_2Cl_2) . FTIR (film): 1738, 1598. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.45-1.51 (m, 1H); 1.68 (s, 9H); 1.75 (d, *J*=8.0, 3H); 2.38-2.48 (m, 1H); 2.56-2.63 (m, 1H); 2.69-2.90 (m, 4H); 5.11-5.21 (m, 2H); 6.97-7.03 (m, 1H); 7.21-7.31 (m, 2H); 7.42-7.44 (m, 1H); 8.03-8.06 (m, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 13.6 (CH_3); 21.5 (CH_2); 23.3 (CH_2); 28.2 (3XCH_3); 30.2 (CH_2); 39.0 (CH_2); 55.1 (CH); 84.2 (C_0); 115.5 (CH); 118.1 (CH); 118.2 (CH); 122.9 (CH); 124.5 (CH); 128.5 (C_0); 129.2 (C_0); 134.2 (C_0); 134.9 (C_0); 136,6 (C_0); 150,1 (C_0); 164,8 (C_0).

(3*E*)- 3-ethylidene-2,3,6,7,12b-hexahydroindolo[2,3-*a*]quinolizin-4(1*H*)-one. To a soln. of **8** (0.075 g, 0.20 mmol) in aq. MeOH (5 mL, 3:1 v/v was added K_2CO_3 (0.276 g, 2.0 mmol) and the mixture was refluxed for 12 h. The reaction mixture was evaporated under reduced pressure CH_2Cl_2 (15 mL) was added. The organic phase was washed with brine (2X10 mL), dried over $MgSO_4$ and the residue was purified by column chromatography on silica gel (ethyl acetate) to afford (0.057 g, 0.18 mmol) in 93% yield as a yellow solid. M.p. 199-201 °C (lit [12c]= 198-202 °C). Specific optical rotation: $[\alpha]^{20}_D$ +80 (c 1, CH_2Cl_2); lit[12c]: $[\alpha]_D$ = 77.2 (c=1.0, CH_2Cl_2). FTIR (film): 3320, 1746. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.72-1.82 (m, 1H); 1.77 (dd, *J*=8 e 4.0 Hz, 3H); 2.31-2.41 (m, 1H); 2.50-2.58 (m, 1H); 2.77-2.97 (m, 4H); 4.81-4.84 (m, 1H); 5.18-5.25 (m, 2H); 7.19 (m, 2H); 7.31-7.34 (m, 1H); 7.49-7.51 (m, 1H); 8.57 (m, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 13.7 (CH_3); 21.0 (CH_2); 22.6 (CH_2); 28.9 (CH_2); 40.6 (CH_2); 53.9 (CH); 109.3 (CH); 111.0 (CH); 118.3 (C_0); 119.6 (CH); 122.0 (CH); 126.7 (CH); 129.2 (C_0); 133.3 (C_0); 134.1 (CH); 136.3 (C_0); 164.7 (C_0).



(+)-Deplancheine 9. A flame dried round-bottomed flask was charged with $AlCl_3$ (0.114 g, 0.85 mmol) and THF (3.0 mL) under nitrogen atmosphere. The mixture was cooled at 0 ^oC and a 2,4M THF soln. of $LiAlH_4$ (1.25 mL, 3.0 mmol) was added. After stirring 10 min. at 0 ^oC, a soln. of lactam (0.400 g, 1.50 mmol) in THF (3.0 mL) was added via canula. The reaction mixture was stirred 30 min. at rt, quenched by the addition of satd. aq. NH_4Cl (0.1 mL) and poured into satd. aq. $NaHCO_3$ (20 mL). After extraction with ethyl acetate (2X15 mL), the organic phase was washed with brine (2X15 mL) and dried with $MgSO_4$. The crude product was purified through a pad of silica gel (hexane/ethyl acetate 40%) to afford (+)-deplancheine **5** (0.363 g, 1.44 mmol) in 96% yield as yellow solid (139-140 °C; lit [12c]= 139,5-140,5 °C). Specific optical rotation: $[\alpha]^{20}_D$ +54 (c 1, $CHCl_3$); lit [12c]: $[\alpha]_D$ = +52 (c 1, $CHCl_3$). FTIR (film,): 3438, 3035. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.52-1.61 (m, 1H); 1.66 (d, *J*= 7.2 Hz, 3H); 1.97-2.02 (m, 1H); 2.14-2.19 (m, 1H); 2.62-2.73 (m, 2H); 2.81-2.84 (m, 1H); 3.00-3.11 (m, 3H); 3.30-3.35 (m, 1H); 3.39-3.41 (m, 1H); 5.48 (q, *J*=7.5 Hz, 1H); 7.08-7.17 (m, 2H); 7.32-7.35 (m, 1H); 7.47-7.50 (m, 1H); 7.92 (s, br, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 12.8 (CH_3); 21.7 (CH_2); 26.0 (CH_2); 30.5 (CH_2); 53.0 (CH_2); 60.1 (CH); 63.5 (CH_2); 108.3 (C_0); 110.6 (CH); 118.1 (CH); 119.3 (2XCH); 121.3 (CH); 127.5 (C_0); 134.1 (C_0); 134.8 (C_0); 136.1 (C_0).

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