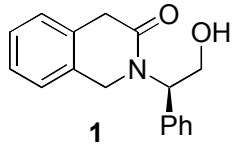
Supporting information

Diastereoselective Protonation of Lactam Enolates Derived from (R)-Phenylglycinol. A Novel Asymmetric Route to 4-Phenyl-1, 2, 3, 4-Tetrahydroisoquinolines

Nicolas Philippe, Vincent Levacher*, Georges Dupas, Guy Quéguiner and Jean Bourguignon

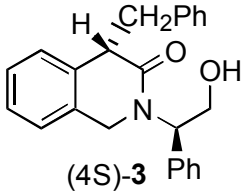
General section. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl under N_2. Other solvents were used without further purification. Flash column chromatography was performed either with a 32-63 mesh silica gel or alumina oxide neutral (50-180 μm). Thin-layer chromatography was effected on silica gel 60 F_{254}. Optical rotation were determined with a Perkin-Elmer 341 polarimeter using 10 cm cells. NMR spectra were taken in $CDCl_3$ on either a 200, 300 or 400 MHz spectrophotometer. The ^1H and ^{13}C NMR chemical shifts are reported in ppm downfield from tetramethylsilane.



1

***N*-[(R)-2-hydroxy-1-phenylethyl]-1,4-dihydroisoquinolin-3-one (1).** To a solution of HBr (3.96 g, 49.3 mmol) in dry EtOH (30 mL) was added portionwise isochroman-3-one (2 g, 13.7 mmol) at 0°C. After being stirred at room temperature for 48 h, EtOH was evaporated to dryness affording 3.1 g of ethyl 2-(bromomethyl)phenylacetate **2** as a brown oil. The crude product was taken on to the next step without further purification: ^1H NMR (200 MHz, $CDCl_3$) δ 7.45-7.15 (m, 4H), 4.62 (s, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.81 (s, 2H), 1.25 (t, *J* = 7.1 Hz, 3H). To a stirred solution of ethyl 2-(bromomethyl)phenylacetate **2**

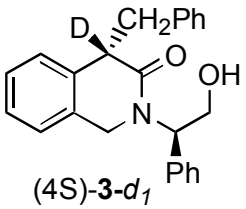
(3 g, 16.7 mmol) in EtOH (20 mL) was added (R)-(-)-2-amino-2-phenylethanol (1.8 g, 13.1 mmol) and K_2CO_3 (4 g, 30 mmol). The resulting solution was stirred at room temperature for 48 h and stirred for an additional 24 h at reflux. The reaction mixture was quenched with water (50 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic phases were dried ($MgSO_4$) and evaporated. Flash chromatography (Alumina; eluent: EtOAc/EtOH 95/5) afforded 2.76 g (62%) of **1** as a white amorphous solid. mp 102°C; $[\alpha]^{19}_D$ = -39.2 ($CHCl_3$, c=0.503), IR (neat) 3300, 2884, 1647 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33-7.16 (m, 8H), 7.00 (d, *J* = 7.5 Hz, 1H), 5.89 (dd, *J* = 8.7 and 5.4 Hz, 1H), 4.40 (d, *J* = 15.5 Hz, 1H), 4.23 (dd, *J* = 11.7 and 5.4 Hz, 1H), 4.14 (dd, *J* = 11.7 and 8.7 Hz, 1H), 4.11 (d, *J* = 15.5 Hz, 1H), 3.68 (s, 2H), 2.61 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 136.5, 132.2, 131.9, 128.8, 127.8, 127.5, 127.0, 126.6, 125.1, 61.9, 58.5, 46.8, 38.3; Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.42; H, 6.59; N, 5.27.



(4S)-**3**

(4S*)-*N*-[(R)-2-hydroxy-1-phenylethyl]-4-benzyl-1,4-dihydroisoquinolin-3-one [(4S)-3]. To a solution of **1** (1 g, 3.74 mmol) in dry THF (40 mL) cooled to -78°C was added dropwise a solution of LHMDS in THF (5.84 mL, 1.6M, 9.35 mmol) under argon. The reaction mixture was stirred at this temperature for 30 min and benzyl bromide (1.33 mL, 11.2 mmol) was added over a period of 5 min. The solution was stirred for a further 3 h. The reaction mixture was treated with a saturated solution of NH_4Cl (40 mL) and the solution was allowed to reach room temperature. After phase separation, the aqueous phase was extracted with CH_2Cl_2 (3 x 40 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under vacuum. The diastereoisomeric excess (de>97%) was deduced by analysis of ^1H NMR spectra and confirmed by HPLC analysis of the crude product. [chromatographic conditions: column C18 (250 x 4.6; 5 μm); UV detection (λ=210nm); eluent: CH_3CN/H_2O (70/30); flow rate: 1 mL/min; temperature: 22 °C; injection: 20 μL (1 mg of sample in 20 mL

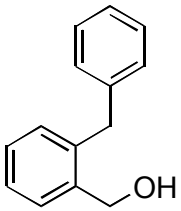
of eluent)]. Purification of the crude product by flash chromatography on alumina (eluent: CH_2Cl_2/EtOH 9.5/0.5) afforded 1.1 g (80%) of (4S)-**3**: mp 97°C; IR (neat) 3225, 1612 cm^{-1}; $[\alpha]^{19}_D$ = -37.3 (CH_2Cl_2, c=0.496); ^1H NMR (300 MHz, $CDCl_3$) δ 7.39-6.90 (m, 12H), 6.75 (d, *J* = 8.9 Hz, 2H), 5.69 (dd, *J* = 7.3 and *J*= 5.5 Hz, 1H), 4.12 (m, 2H), 3.93 (appt, *J* = 5.5 Hz, 1H), 3.92 (d, *J* = 16.0 Hz, 1H), 3.33 (d, *J* = 16.0 Hz, 1H), 3.24 (dd, *J* = 13.1 and *J*= 6.6 Hz, 1H), 3.14 (dd, *J* = 13.1 and *J*= 4.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 137.1, 136.0, 134.7, 131.5, 129.5, 128.7, 128.2, 128.0 (x2), 127.6, 127.4, 126.7, 126.5, 125.0, 62.0, 59.8, 49.3, 47.2, 40.6; Anal. Calcd for $C_{24}H_{23}NO_2$: C, 80.64; H, 6.49; N, 3.92. Found: C, 80.42; H, 6.47; N, 3.90.



(4S)-**3**-*d*$_1$

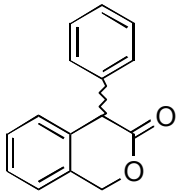
(4S*)-*N*-[(R)-2-hydroxy-1-phenylethyl]-4-deuterio-4-benzyl-1,4-dihydroisoquinolin-3-one [(4S)-3-*d*$_1$]. To a solution of (4S)-**3.** (250 mg, 0.70 mmol) in dry THF (40 mL) was added dropwise butyllithium in hexane (0.84 mL, 2.5M, 2.7 mmol) at -78°C. After stirring at this temperature for 30 min, EtOD (1 mL) was added dropwise at -78°C and the solution was allowed to reach room temperature over a period of 2 hours. The reaction mixture was quenched with a saturated solution of NH_4Cl (10 mL). After evaporation of THF, the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The resulting organic phase was dried ($MgSO_4$) and evaporated affording (4S)-**3**-*d*$_1$ as a pale yellow oil (**3**-*d*$_1$./**3** 95/5). Diastereomeric excess (de=90%) was determined par HPLC [chromatographic conditions: : column C18 (250 x 4.6; 5 µm); UV detection (λ=210nm); eluent: CH_3CN/ H_2O (70/30); flow rate: 1 mL/min; temperature: 22 °C; injection: 20 µL (1 mg of sample in 20 mL of eluent)]. The crude product was subjected to column chromatography on alumina (eluent: CH_2Cl_2/EtOH 9.5/0.5) to afford (4S)-**3**-*d*$_1$ in 90% yield as a white solid: mp 97°C; IR (neat) 3225, 1612 cm^{-1}; ^1H NMR (300

MHz, $CDCl_3$) δ 7.39-6.90 (m, 12H), 6.75 (d, *J* = 8.9 Hz, 2H), 5.69 (dd, *J* = 7.3 and *J*= 5.5 Hz, 1H), 4.12 (m, 2H), 3.93 (d, *J* = 16.0 Hz, 1H), 3.33 (d, *J* = 16.0 Hz, 1H), 3.24 (d, *J* = 13.1 Hz, 1H), 3.14 (d, *J* = 13.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 137.1, 136.0, 134.7, 131.5, 129.4, 128.7, 128.2, 128.0 (x2), 127.6, 127.4, 126.7, 126.5, 125.0, 62.0, 59.8, 49.3, 47.2, 40.6; Anal Calcd for $C_{24}H_{22}DNO_2$: C, 80.42; H/D, 6.75; N, 3.91. Found: C, 80.35; H/D, 6.47; N, 3.85.



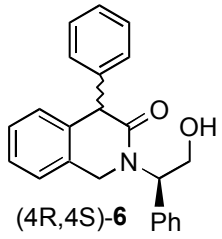
4

(2-benzylphenyl)methanol (4). Iodine (11.95 g, 47 mmol) in THF (40 mL) at 0°C was added dropwise under argon to a solution of sodium borohydride (4.36 g, 115 mmol) in dry THF (150 mL). After 5 min, 2-(phenylmethyl)benzoic acid (10 g, 47 mmol) was added and the mixture was stirred under reflux overnight. After cooling the solution to 0°C, methanol (40 mL) was added dropwise. The resulting mixture was stirred at room temperature for a further 30 min. Solvents were evaporated to dryness and 20% aqueous KOH (150 mL) was then added to the residue. The solution was stirred for 4 h at room temperature and then extracted with CH_2Cl_2 (3 x 60 mL). The combined CH_2Cl_2 layers were dried ($MgSO_4$) and evaporated under vacuum. The crude product was purified by chromatography on silica gel (eluent: CH_2Cl_2) to yield 8.4 g (90%) of **4** as a colorless oil: IR (neat) 3328, 2920 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.50-7.40 (m, 1H), 7.35-7.10 (m, 8H), 4.65 (s, 2H), 4.10 (s, 2H), 1.6 (brs, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 140.3, 136.7, 136.3, 130.3, 128.6, 128.4, 128.0, 127.7, 126.6, 126.0, 62.7, 38.2; Anal Calcd for $C_{14}H_{14}O$: C, 84.81; H, 7.12. Found: C, 84.72; H, 7.06.



5

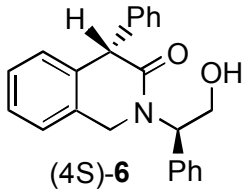
4-phenylisochroman-3-one (5). To a solution of 2-benzylphenylmethanol **4** (8.4 g, 42.37 mmol) in dry Et_2O (150 mL) cooled to -78°C was added dropwise under N_2 a solution of butyllithium in hexane (42.4 mL, 2.5 M, 105.9 mmol). The solution was stirred for 24 h at room temperature. The solution was then treated with methyl chloroformate (6.5 mL, 84.74 mmol) at -78°C and stirred for 3 h at this temperature. After addition of aq 2N HCl (70 mL) and phase separation, the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried ($MgSO_4$) and the solvent evaporated under vacuum. The residue was chromatographed on a silica gel column (eluent: Et_2O/EtOAc 3/7) affording 4.54 g (54%) of a white solid: mp 98°C; IR (neat) 2987, 2895, 2848, 1736 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.45-7.10 (m, 9H), 5.25 (s, 2H), 5.05 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.0, 134.2, 133.9, 131.8, 128.85, 128.75, 128.1, 127.8, 127.7, 127.6, 124.8, 69.4, 51.6; Anal. Calcd for $C_{15}H_{12}O_2$: C, 80.34; H, 5.39. Found: C, 80.42; H, 5.46.



(4R,4S)-**6**

***N*-[(R)-2-hydroxy-1-phenylethyl]-4-phenyl-1,4-dihydroisoquinolin-3-one [(4R,4S)-6].** A solution of 4-phenylisochroman-3-one **5** (2 g, 8.9 mmol) and HBr (2.6 g, 32 mmol) in dry EtOH (20 mL) was stirred at room temperature for 48 h. After evaporation of EtOH under vacuum, R-(-)-2-amino-2-phenylethanol (1.35 g, 9.8 mmol) and potassium carbonate (4.9 g, 35.6 mmol) was added to the residue. After addition of EtOH (20 mL), the

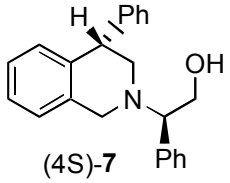
resulting solution was stirred for 48 h at room temperature, then for 24 h at reflux. After evaporation of EtOH, the residue was dissolved in CH_2Cl_2 (30 mL) and water (50 mL). After phase separation, the resulting aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL). The organic phases were dried ($MgSO_4$) and the solvent evaporated under vacuum affording 3.5 g of a thick orange oil. The crude product was purified by chromatography on silica gel (eluent: CH_2Cl_2/EtOH 98/2) to give 1.7 g (55%) of the desired lactam (4R,4S)-**6** as a colorless oil. ^1H NMR spectrum analysis showed that lactam (4R,4S)-**6** was obtained as a 50:50 epimeric mixture. Both epimers could be analyzed by HPLC [chromatographic conditions: Chiralcel OD (250 x 4.6; 10 µm); UV detection (λ=230nm); eluent: hexane / 2-propanol (90/10); flow rate: 1 mL / min; temperature: 20 °C; injection: 20 µL (0.5 mg of sample in 10 mL of eluent); (R,R)-diastereoisomere: 17.73 min, (S,R)-diastereoisomere: 20.52 min]: IR (neat) 3392, 1629 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.55-7.02 (m, 28H), 5.79 (dd, *J* = 8.5 and *J* = 5.2 Hz, 1H), 5.72 (appt, *J* = 6.5 Hz, 1H), 5.01 (s, 1H), 4.98 (s, 1H), 4.41 (d, *J* = 15.7 Hz, 1H), 4.23-4.05 (m, 7H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.6, 171.55, 138.1, 137.8, 136.5, 135.4, 135.2, 132.0, 131.8, 128.55, 128.50 (x2), 128.45, 127.90 (x2), 127.75, 127.60 (x2), 127.55, 127.50, 127.2, 127.05, 127.00, 126.90, 126.60, 125.25, 61.5, 61.1, 58.4, 58.3, 53.7, 53.4, 46.5, 45.9; Anal. Calcd for $C_{23}H_{21}NO_2$: C, 80.44; H, 6.16; N, 4.08. Found: C, 80.31; H, 6.24; N, 3.98.



(4S)-**6**

(4S*)-*N*-[(R)-2-hydroxy-1-phenylethyl]-4-phenyl-1,4-dihydroisoquinolin-3-one [(4S)-6]. To a solution of the epimeric mixture of compound (4R,4S)-**6** (200 mg, 0.58 mmol) in dry THF (8 mL) cooled to -78°C was added under argon a solution of butyllithium in hexane (0.7 mL, 2.5 M, 1.74 mmol). After stirring at this temperature for 30 min, a saturated aqueous solution of NH_4Cl (10 mL) was added dropwise and the solution was stirred at -78°C for a further 3 h. The solution was allowed to reach room temperature. The aqueous

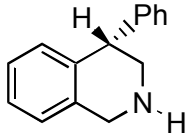
phase was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated. Diastereomeric excess (97%) was measured by HPLC analysis (chromatographic conditions are described above) and by analysis of the ^1H NMR spectrum of the crude product. The crude product was then chromatographed on silica gel (eluent: CH_2Cl_2/EtOH 98/2) yielding 184 mg (92%) of the desired product (4S)-**6**: mp 99°C; $[\alpha]^{19}_D$ = -45 (CH_2Cl_2, c=0.98); IR (neat) 3423, 3029, 2946, 1628 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.35-7.05 (m, 14H), 5.72 (appt, *J* = 6.5 Hz, 1H), 4.98 (s, 1H), 4.23-4.15 (m, 3H), 4.08 (d, *J* = 16.0 Hz, 1H), 2.65 (brs, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.1, 137.8, 136.3, 135.3, 132.1, 128.8, 128.7, 128.2, 128.0, 127.9, 127.8, 127.7, 127.3, 127.1, 125.4, 62.0, 59.6, 53.8, 47.3; Anal. Calcd for $C_{23}H_{21}NO_2$: C, 80.44; H, 6.16; N, 4.08. Found: C, 80.62; H, 6.41; N, 4.01.



(4S)-**7**

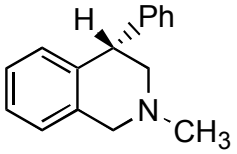
(4S*)-*N*-[(R)-2-hydroxy-1-phenylethyl]-4-phenyl-1,2,3,4-tetrahydroisoquinoline [(4S)-7]. To a solution of sodium borohydride (540 mg, 14.6 mmol) in dry THF (30 mL) was added dropwise under argon a solution of iodine (740 mg, 5.8 mmol) in THF (20 mL) at 0°C. The mixture was kept for additional 5 min, compound (4S)-**6** was then added and the mixture was stirred under reflux overnight. After cooling the solution to 0°C, methanol (15 mL) was added dropwise and the resulting mixture was stirred at room temperature for a further 30 min. Solvents were evaporated to dryness and 20% aqueous NaOH (60 mL) was then added to the residue. The solution was stirred for 4 h at room temperature and then extracted with CH_2Cl_2 (3 x 40 mL). The organic layer was washed with 1N aqueous HCl (10 mL). The resulting acidic aqueous phase was washed with Et_2O (3x10 mL). After neutralization with 2M NaOH (pH=6-7), the aqueous phase was extracted with CH_2Cl_2 (3x20 mL). The combined CH_2Cl_2 layers were dried ($MgSO_4$) and evaporated under vacuum to yield 1.32 g (69%) of (4S)-**7** (de>97%) as a thick colorless oil: IR (neat) 3041, 2928 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.41-7.02 (m, 13H), 6.89 (d, *J* = 8.0 Hz,

1H), 4.27 (appt, *J* = 4.85 Hz, 1H), 3.90-3.75 (m, 4H), 3.66-3.52 (m, 1H), 2.95 (dd, *J* = 11.5 and 5.5 Hz, 1H), 2.79 (dd, *J* = 11.5 and 4.5 Hz, 1H); ^{13}C NMR (60 MHz, $CDCl_3$) δ 145.2, 136.6, 135.4, 135.2, 129.7, 128.8, 128.7, 128.3, 128.2, 127.9, 126.5, 126.3 (x2), 126.1, 69.1, 60.4, 54.3, 52.6, 45.7; Anal. Calcd for $C_{23}H_{23}NO$: C, 83.86; H, 7.04; N, 4.25. Found: C, 83.61; H, 7.12; N, 4.27.



(4S)-**8**

(4S*)-4-phenyl-1,2,3,4-tetrahydroisoquinoline (8). To a solution of compound (4S)-**7** (400 mg, 1.2 mmol) in MeOH (10 mL) was added 20 % $Pd(OH)_2$ (150 mg) and 1N aqueous HCl (1 mL). The resulting solution was stirred for 12 h under a hydrogen atmosphere. The catalyst was filtrated through Celite and washed with MeOH (2 x 15 mL). After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 (20 mL). The CH_2Cl_2 phase was extracted with 1N aqueous HCl (30 mL) and the resulting aqueous phase was washed with Et_2O (2 x 15 mL) to extract 2-phenylethanol. The aqueous layer was made basic with 2N aqueous NaOH (pH=6-7) and extracted with CH_2Cl_2 (2 x 30 mL). Drying ($MgSO_4$) and evaporation of the solvent yielded 165 mg (65%) of **8**: IR (neat) 3306, 2937 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.34-7.08 (m, 8H), 6.90 (d, *J* = 7.0 Hz, 1H), 4.15 (m, 3H), 3.42 (dd, *J* = 13.0 Hz and 5.4 Hz, 1H), 3.16 (dd, 13.0 Hz and 6.5 Hz, 1H), 1.83 (brs, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 140.1, 135.5, 129.2, 129.0, 128.9, 127.9 (x2), 127.6, 127.2, 126.4, 47.8, 44.5, 41.6; Anal. Calcd for $C_{15}H_{15}N$: C, 86.08; H, 7.22; N, 6.69. Found: C, 85.93; H, 7.10; N, 6.62.



(4S)-**9**

(4S*)-*N*-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline (9). A solution of **8** (50 mg, 0.24 mmol) and paraformaldehyde (373 mg, 11.95 mmol) in MeOH (10 mL) was stirred at reflux for 1 h. After cooling to room temperature, 20% $Pd(OH)_2$ (140 mg) was added and the

solution was stirred under hydrogen atmosphere for 16 h. The catalyst was filtered though a plug of Celite and washed with MeOH (2 x 20 mL). Solvent was evaporated under vacuum affording 533 mg (95%) of compound **9** (ee>97%). The enantiomeric excess was determined by chiral HPLC using the following chromatographic conditions. [Column: Chiracel OD (250 x 4.6; 10 μm); UV detection (λ=230nm); Eluent: hexane / 2-propanol (90/10); Flow rate: 1 mL / min; Temperature: 22 °C; Injection: 20 μL (0.5 mg of sample in 10 mL of hexane); (S)-enantiomere: 4.3 min, (R) enantiomere: 5.5 min]; $[\alpha]^{22}_{D}$ = 17.2 (MeOH, c= 0.80) [lit.[15] $[\alpha]^{24}_{D}$ = 16.7 (100% e.e.) (MeOH, c=0.72)]; IR (neat) 3059, 2937 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.39-7.04 (m, 8H), 6.93 (d, *J* = 7.55 Hz, 1H), 4.36 (appt, *J* = 7.0 Hz, 1H), 3.80 (d, *J* = 15.0 Hz, 1H), 3.62 (d, *J* = 15.0 Hz, 1H), 3.10 (dd, *J* = 11.5 and 5.0 Hz, 1H), 2.61 (dd, *J* = 11.5 and 8.5 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.9, 137.0, 135.1, 129.3, 129.0, 128.3, 126.4, 126.2, 126.1, 125.9, 61.8, 58.5, 46.0, 45.9. Anal. Calcd for $C_{16}H_{17}N$: C, 86.05; H, 7.67; N, 6.27. Found: C, 86.20; H, 7.65; N, 6.40.