

#### 4-Hydroxyproline containing podands as new chiral catalysts for the asymmetric Biginelli reaction

Olga V. Fedorova, Yulia A. Titova, Irina G. Ovchinnikova, Gennady L. Rusinov and Valery N. Charushin

The IR spectra were recorded on a Perkin Elmer Spectrum One IR Fourier transform spectrometer using a diffuse reflectance sampling accessory (DRA). The NMR spectra were recorded on Bruker DRX-400 (400 and 100 MHz) spectrometer in DMSO-*d*<sub>6</sub> at 295 K using TMS and DMSO-*d*<sub>6</sub> ( $\delta_C$  39.5 ppm) as references. The mass analyzer was a Bruker Daltonics MicroTOF-Q II mass spectrometer with an electrospray ionization source. Melting points were measured on a Boetius heating microstage. Optical rotations were measured on a Perkin Elmer 341 polarimeter. The RP-HPLC determination of enantiomeric excess of compound **4** was performed on an Agilent 1200 Series instrument using an YMC-Pack Chiral-NEA-R column (250 × 4.6 mm, 5  $\mu$ m); detection at 254 nm, flow rate 1.0 mL/min; eluent, MeCN–H<sub>2</sub>O 35:65. Retention time of (*S*)-enantiomer was 13.86 min; (*R*)-enantiomer, 16.63 min.

*Podands 2a-c, 3a-c (typical procedure).* To a solution of *N*-Boc protected *trans*-4-hydroxy-*L*-proline (0.45 g, 2 mmol) in CHCl<sub>3</sub> (20 ml) was added Et<sub>3</sub>N (0.25 ml, 2.5 mmol), ethyl chloroformate (0.25 mL, 2.5 mmol) at 0° C under stirring. After 30 min, amino podand **1** (0.7 mmol) in CHCl<sub>3</sub> (10 ml) was added. The reaction mixture was stirred at 25 °C for 7 h. The chloroform solution was washed with 1 M NaHCO<sub>3</sub> (30 ml) and H<sub>2</sub>O (3 × 30 ml). After removal of the solvent, the crude product was stirred in TFA (10 ml) until the deprotection finished. After evaporating TFA, the product **2** was extracted with ethyl acetoacetate and recrystallized from *n*-butanol (for **2a**) or EtOH (for **2b,c**) on ice-cooling, white solids. Salt **2** was dissolved in H<sub>2</sub>O and basified up to the pH 11 by the addition of 1 M NaOH. The product **3** was extracted with CHCl<sub>3</sub> (5 × 25 ml). The CHCl<sub>3</sub> phase was washed with water (30 ml) and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solvent was evaporated and product **3** was purified by recrystallization from MeCN (for **3a**) or THF (for **3b,c**) on ice-cooling, white solids.

(2*S*,2'*S*,4*R*,4'*R*)-*N,N'*-[2,2'-(2,2'-Oxybisethane-2,1-diyl)bis(oxy)bis(2,1-phenylene)]bis(4-hydroxypyrrolidine-2-carboxamide) × 2 CF<sub>3</sub>CO<sub>2</sub>H **2b**: [α]<sub>D</sub><sup>20</sup> = -17.50 (c = 0.5, H<sub>2</sub>O). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ: 2.08 (m, 2H, H(C-3)), 2.39 (m, 2H, H(C-3)), 3.15 (d, 2H, H(C-5)), 3.36 (d.d, 2H, H(C-5)), 3.88 (m, 4H, OCH<sub>2</sub>), 4.20 (m, 4H, OCH<sub>2</sub>), 4.46 (m, 2H, H(C-4)), 4.67 (d.d, 2H, H(C-2)), 5.61 (br.s, 2H, OH), 6.97 (d.t, 2H, Ph), 7.10 – 7.18 (m, 4H, Ph), 7.75 (d.d, 2H, Ph), 8.88 (br.s, 2H, H(N-1)), 9.72 (br.s, 2H, H(N-1)), 9.84 (s, 2H, NH). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>), d: 39.60 (2 C), 53.71 (2 C), 58.47 (2 C), 68.21 (2 C), 69.01 (2 C), 69.14 (2 C), 113.19 (2 C), 116.05, 118.44, 120.64 (2 C), 123.59 (2 C), 126.01 (2 C), 126.09 (2 C), 150.08 (2 C), 157.76, 158.01, 167.15 (2 C). IR (film, v/cm<sup>-1</sup>): 3298, 3091, 2934, 2760, 2628, 1667, 1600, 1553, 1498, 1452, 1431, 1408, 1337, 1321, 1285, 1267, 1229, 1186, 1129, 1083, 1060, 1034, 959, 926, 835, 801, 745, 722, 671.

(2*S*,2'*S*,4*R*,4'*R*)-*N,N'*-[2,2'-[2,2'-(Ethane-1,2-diylbis(oxy))bis(ethane-2,1-diyl)]bis(oxy)bis(2,1-phenylene)]bis(4-hydroxypyrrolidine-2-carboxamide) × 2 CF<sub>3</sub>CO<sub>2</sub>H **2c**: [α]<sub>D</sub><sup>20</sup> = -10.82 (c = 0.5, H<sub>2</sub>O). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ: 2.02 (m, 2H, H(C-3)), 2.41 (m, 2H, H(C-3)), 3.16 (d, 2H, H(C-5)), 3.37 (d.d, 2H, H(C-5)), 3.61 (s, 4H, OCH<sub>2</sub>), 3.79 (t, 4H, OCH<sub>2</sub>), 4.16 (m, 4H, OCH<sub>2</sub>), 4.48 (m, 2H, H(C-4)), 4.67 (d.d, 2H, H(C-2)), 5.61 (br.s, 2H, OH), 6.96 (t, 2H, Ph), 7.09 – 7.17 (m, 4H, Ph), 7.76 (d, 2H, Ph), 8.91 (br.s, 2H, H(N-1)), 9.72 (br.s, 2H, H(N-1)), 9.82 (s, 2H, NH). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>), d: 39.65 (2 C), 53.69 (2 C), 58.49 (2 C), 68.24 (2 C), 68.93 (2 C), 69.21 (2 C), 70.01 (2 C), 113.19 (2 C), 116.05, 118.44, 120.64 (2 C), 123.61 (2 C), 126.02 (2 C), 126.18 (2 C), 150.15 (2 C), 158.13, 158.38, 167.22 (2 C). IR (film, v/cm<sup>-1</sup>): 3380, 3311, 3079, 2935, 2728, 2596, 1687, 1658, 1608, 1552, 1493, 1463, 1453, 1424, 1405, 1353, 1317, 1288, 1267, 1252, 1198, 1136, 1087, 1060, 1035, 997, 974, 922, 830, 802, 745, 719, 657.

(2*S*,2'*S*,4*R*,4'*R*)-*N,N'*-[2,2'-(Ethane-1,2-diylbis(oxy))bis(2,1-phenylene)]bis(4-hydroxypyrrolidine-2-carboxamide) **3a**: yield 0.32 g (67%), m.p. 164-166 °C, [α]<sub>D</sub><sup>20</sup> = +5.430 (c = 0.5, EtOH). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ: 1.53 (m, 2H, H(C-3)), 1.96 (d.d, 2H, H(C-3)), 2.25 (d, 2H, H(C-5)), 2.39 (d, 2H, H(C-5)), 3.13 (s, 2H, H(N-1)), 3.79 (t, 2H, H(C-2)), 3.92 (m, 2H, H(C-4)), 4.41 (m, 4H, OCH<sub>2</sub>), 4.57 (d, 2H, OH), 6.93 (t, 2H, Ph), 7.04 (t, 2H, Ph), 7.10 (d, 2H, Ph), 8.23 (d, 2H, Ph), 10.27 (s, 2H, NH). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>), d: 39.60 (2 C), 54.33 (2 C), 60.11 (2 C), 67.63 (2 C), 71.47 (2 C), 111.89 (2 C), 118.47 (2 C), 120.80 (2 C), 123.33 (2 C), 127.56 (2 C), 147.61 (2 C), 173.03 (2 C). IR (film, v/cm<sup>-1</sup>): 3483, 3381, 3276, 3069, 2932, 2868, 1681, 1657, 1599, 1530, 1485, 1452, 1415, 1324, 1290, 1253, 1203, 1118, 1102, 1063, 953, 927, 881, 823, 800, 780, 745, 609. HRMS (ESI), *m/z*: 471.2245 [M + H]<sup>+</sup> (calc.

for  $C_{24}H_{31}N_4O_6^+$ ,  $m/z$ : 471.2244). Found (%): C, 61.39; H, 6.55; N, 12.08. Calc. for  $C_{24}H_{30}N_4O_6$  (%): C, 61.26; H, 6.43; N, 11.91.

(2*S*,2'*S*,4*R*,4'*R*)-*N,N'*-[2,2'-(2,2'-Oxybisethane-2,1-diyl)bis(oxy)bis(2,1-phenylene)]bis(4-hydroxypyrrolidine-2-carboxamide) **3b**: yield 0.3 g (68%), m.p. 143-145 °C,  $[\alpha]_D^{20} = -0.486$  (c = 0.5, EtOH).  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 1.75 (m, 2H, H(C-3)), 2.05 (m, 2H, H(C-3)), 2.73 (d.d, 2H, H(C-5)), 2.83 (d, 2H, H(C-5)), 3.46 (br.s, 2H, H(N-1)), 3.90 (t, 2H, H(C-2)), 3.96 (t, 4H, OCH<sub>2</sub>), 4.16 (m, 2H, H(C-4)), 4.20 (t, 4H, OCH<sub>2</sub>), 4.69 (d, 2H, OH), 6.92 (d.t, 2H, Ph), 7.00 (d.t, 2H, Ph), 7.05 (d, 2H, Ph), 8.28 (d.d, 2H, Ph), 10.32 (s, 2H, NH).  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ ), d: 39.62 (2 C), 54.88 (2 C), 60.23 (2 C), 68.71 (2 C), 69.75 (2 C), 71.60 (2 C), 111.91 (2 C), 118.36 (2 C), 120.73 (2 C), 123.32 (2 C), 127.56 (2 C), 147.33 (2 C), 173.23 (2 C). IR (film,  $\nu/cm^{-1}$ ): 3361, 3065, 2929, 2869, 1659, 1598, 1531, 1482, 1447, 1327, 1289, 1248, 1208, 1136, 1117, 1059, 1044, 948, 920, 881, 822, 744, 667, 604. HRMS (ESI),  $m/z$ : 515.2499  $[M + H]^+$  (calc. for  $C_{26}H_{35}N_4O_7^+$ ,  $m/z$ : 515.2506). Found (%): C, 60.59; H, 6.71; N, 10.77. Calc. for  $C_{26}H_{34}N_4O_7$  (%): C, 60.69; H, 6.66; N, 10.89.

(2*S*,2'*S*,4*R*,4'*R*)-*N,N'*-{2,2'-[2,2'-(Ethane-1,2-diylbis(oxy))bis(ethane-2,1-diyl)]bis(oxy)bis(2,1-phenylene)}bis(4-hydroxypyrrolidine-2-carboxamide) **3c**: yield 0.28 g (67%), m.p. 147-149 °C,  $[\alpha]_D^{20} = -3.206$  (c = 0.5, EtOH).  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 1.76 (m, 2H, H(C-3)), 2.05 (m, 2H, H(C-3)), 2.77 (d.d, 2H, H(C-5)), 2.87 (d, 2H, H(C-5)), 3.42 (br.s, 2H, H(N-1)), 3.69 (s, 4H, OCH<sub>2</sub>), 3.80 (t, 4H, OCH<sub>2</sub>), 3.90 (t, 2H, H(C-2)), 4.15 (t, 4H, OCH<sub>2</sub>), 4.18 (m, 2H, H(C-4)), 4.69 (d, 2H, OH), 6.91 (t, 2H, Ph), 6.97 – 7.04 (m, 4H, Ph), 8.26 (d.d, 2H, Ph), 10.29 (s, 2H, NH).  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ ), d: 39.64 (2 C), 54.84 (2 C), 60.14 (2 C), 68.34 (2 C), 69.09 (2 C), 70.35 (2 C), 71.49 (2 C), 112.03 (2 C), 118.41 (2 C), 120.66 (2 C), 123.26 (2 C), 127.55 (2 C), 147.33 (2 C), 173.06 (2 C). IR (film,  $\nu/cm^{-1}$ ): 3348, 3068, 2935, 2873, 1661, 1597, 1520, 1483, 1449, 1328, 1289, 1248, 1206, 1117, 1059, 956, 937, 886, 848, 799, 746, 605. HRMS (ESI),  $m/z$ : 559.2770  $[M + H]^+$  (calc. for  $C_{28}H_{39}N_4O_8^+$ ,  $m/z$ : 559.2762). Found (%): C, 60.71; H, 6.73; N, 10.67. Calc. for  $C_{28}H_{38}N_4O_8$  (%): C, 60.20; H, 6.86; N, 10.03.