A Flexible Approach to (*S*)-5-Alkyl-tetramic acid Derivatives: Application to the Asymmetric Synthesis of (+)-Preussin and Protected (3*S*, 4*S*)-AHPPA

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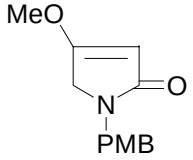
General Information

Optical rotations were recorded on a Perkin-Elmer 341 automatic polarimeter. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Varian unity +500 spectrometer. Unless otherwise noted, ^{1}H-NMR spectra were registered in $CDCl_3$, and chemical shifts are expressed in parts per million (δ) relative to internal Me_4Si. IR spectra were recorded on a Nicolet Avatar 360 FT-IR spectrophotometer. Mass spectra were recorded by Bruker Dalton Esquire 3000 plus and Finnigan Mat-LCQ (ESI direct injection). HRFABMS spectra were recorded on a Bruker APEX-FTMS apparatus. Elemental analyses were performed using a Vario RL analyzer. Melting points were determined on a Yanaco MP-500 melting point apparatus and are uncorrected.

Tetrahydrofuran was distilled prior to use from sodium benzophenone ketyl. Methylene chloride was distilled from phosphorus pentoxide. Silica gel (zhifu, 300-400 mesh) from Yantai silica gel factory (China) was used for column chromatography, eluting (unless otherwise stated) with ethyl acetate/petroleum ether (PE) (60-90 °C) mixture.

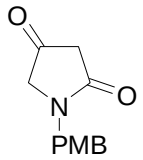
4-Methoxy-1-(4-methoxybenzyl)-2,5-dihydro-1*H*-2-azolone (11)



To a refluxing solution of 4-methoxybenzylamine (4.68 g, 34.2 mmol) in MeCN (17.5 mL) were added dropwise methyl (*E*)-4-chloro-3-methoxy-2-butenoate **10** (4.5 g, 27.4 mmol) in MeCN (17.5 mL) and a solution of Et_3N (3.06 g, 30.25 mmol) in MeCN (3.0 mL) in parallel. After completed the additions, the reflux was maintained for 4 h. The mixture was then chilled with an ice-bath, and the precipitate was filtered. The residue was washed with MeCN (30 mL), and the combined filtrates were concentrated under reduced pressure. The residue was dissolved in H_2O (15 mL), acidified with conc. HCl until pH 3. The resulting mixture was extracted with CH_2Cl_2. The combined extracts were concentrated under reduced pressure to give a residue, which was subjected to column chromatography on silica gel (EtOAc / PE = 3/1) to provided **11** (4.524 g, 75.4 %) as a white solid. Mp 63-65 °C; IR (KBr) ν_{max}: 2936, 1682, 1513, 1455, 1353, 1264 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.68 (s, 2H), 3.77 (s, 3H), 3.80 (s, 3H), 4.50 (s, 2H), 5.07 (s, 1H), 6.85 (d, *J*= 8.6 Hz, 2H), 7.17 (d, *J*= 8.6 Hz, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 173.35, 171.99, 158.93, 129.42, 129.23, 114.00, 94.19, 58.04, 55.22, 49.72, 44.70; MS (m/z): 256.0 (M+Na^{+}, 100), 234.0

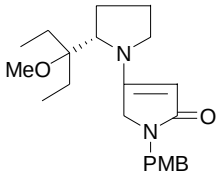
(M+H$^+$, 23); Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 67.15; H, 6.62; N, 5.90.

1-(4-Methoxybenzyl)-pyrrolidine-2,4-dione (12)



To 500 mg (2.09 mmol) of finely pulverized **11** was added a 37% HCl solution (5 mL). The resulting solution was stirred at rt for 5 h, then extracted with CH_2Cl_2. The combined CH_2Cl_2 layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by chromatography on silica gel (EtOAc/PE= 1/1) to give **12** (432 mg, 75 %) as a pale yellow oil. IR (KBr) ν_{max}: 2921, 1774, 1692, 1514, 1248, 1177, 1030 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.09 (s, 2H), 3.72 (s, 2H), 3.80 (s, 3H), 4.57 (s, 2H), 6.85 (d, *J*= 8.6 Hz, 2H), 7.20 (d, *J*= 8.6 Hz, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 203.3, 168.6, 159.5, 129.8, 127.0, 114.3, 56.6, 55.3, 45.4, 41.7; MS (m/z): 242 (M+Na$^+$, 44), 220 (M+H$^+$, 100); Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.92; H, 6.09; N, 6.55.

4-[(*S*)-2-(1-Methoxy-1-ethylpropyl)pyrrolidin-1-yl]-1-(4-methoxybenzyl)-2,5-dihydro-1*H*-2-azolone (9)

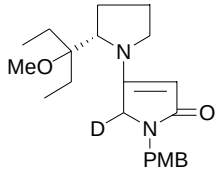


A solution of **12** (470 mg, 2.29 mmol), (*S*)-2-(1-methoxy-1-ethylpropyl)-pyrrolidine **13** (392 mg, 2.29 mmol), and a catalytic amount of PPTS in benzene (5 mL) was heated to reflux for 24 h with continuing elimination of water using a Dean-Stark apparatus. After removal of the solvent under reduced pressure, the resulting residue was purified by column chromatography on silica gel (EtOAc : PE=3:1) to give **9** (427 mg, 50.1 %) as a colorless oil. $[\alpha]_D^{20}$ -27.8 (*c* 1.2, $CHCl_3$); IR (KBr) ν_{max}: 2971, 2936, 1666, 1596, 1512, 1457, 1393, 1246, 1174, 1081, 1030 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.9 (m, 6H, CH_3), 1.40-2.02 (m, 8H, CH_2), 3.09 (s, 3H, OCH_3), 3.11-3.16 (m, 1H), 3.22-3.28 (m, 1H), 3.62 (m, 1H), 3.68 (d, *J*= 16.9 Hz, 1H), 3.80 (s, 3H), 4.00 (d, *J*= 16.9 Hz, 1H), 4.50 (s, 2H), 4.75 (s, 1H), 6.85 (d, *J*= 8.6 Hz, 2H), 7.18 (d, *J*= 8.6 Hz, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 174.2, 162.7, 158.7, 130.4, 129.1, 113.9, 90.4, 81.5, 65.8, 55.2, 50.7, 49.3, 44.9, 27.0, 26.2, 23.9, 8.1, 7.4; HRMS (ESI) calcd for $[C_{22}H_{32}N_2O_3+H]^+$: 373.2486; found: 373.2480.

Representative procedure for the alkylation of (*S*)-9.

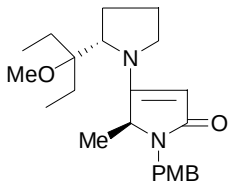
To a solution of (*S*)-**9** (120 mg, 0.323 mmol) in THF [5.5 mL, containing 0.28 mL (1.62 mmol) of HMPA as a co-solvent] was added dropwise *t*-BuLi (0.26 mL, 0.39 mmol, 1.5 M in pentane) at –78 ºC. After being stirred for 1 h, methyl iodide (0.2 mL, 3.23 mmol) was added and the stirring continued for an additional 7 h. The reaction was quenched by saturated ammonium chloride (2 mL). The resulting mixture was extracted with ether, and the organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by column chromatography on silica gel to give **14b** (109 mg, 87.4 %) as a single regio and diastereomer.

(5R*S*)-4-[(*S*)-2-(1-Methoxy-1-ethylpropyl)pyrrolidin-1-yl]-1-(4-methoxybenzyl)-5-deutero-2,5-dihydro-1*H*-2-azolone (14a)



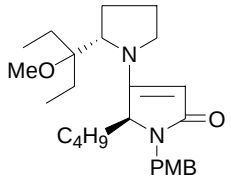
14a: Colorless oil. Yield: 78 %. $[\alpha]_D^{20}$ -26.1 (*c* 2.0, $CHCl_3$); IR (KBr) ν_{max}: 2928, 1665, 1590, 1512, 1392, 1245, 1033 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.83 (m, 6H), 1.40-2.10 (m, 8 H), 3.10 (s, 3 H), 3.12-3.17 (m, 1H), 3.22-3.29 (m, 1H), 3.60-3.64 (m, 1 H), 3.68 (s, 1H), 3.79 (s, 3H), 4.51 (s, 2 H), 4.80 (s, 1 H), 6.83 (d, *J*= 8.6 Hz, 2H), 7.18 (d, *J*= 8.6 Hz, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 174.3, 162.7, 158.7, 130.5, 129.2, 113.9, 90.5, 81.5, 65.8, 55.3, 50.6, 49.4, 44.9, 27.0, 26.2, 24.0, 8.2, 7.5; MS (m/z): 396 ($M+Na^+$, 20), 374 ($M+H^+$, 100); HRMS calcd for $[C_{22}H_{31}DN_2O_3+H]^+$: 374.2548; found: 374.2539.

(5*S*)-4-[(*S*)-2-(1-Methoxy-1-ethylpropyl)pyrrolidin-1-yl]-1-(4-methoxybenzyl)-5-methyl-2,5-dihydro-1*H*-2-azolone (14b)



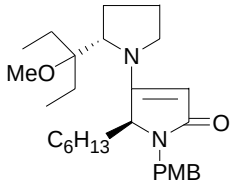
14b: Colorless oil. Yield: 87.4 %. $[\alpha]_D^{20}$ +30.2 (*c* 1.1, $CHCl_3$); IR (KBr) ν_{max}: 2932, 1666, 1592, 1511, 1388, 1245, 1032 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.85 (m, 6H), 1.25 (d, *J*= 6.3 Hz, 3H), 1.36-2.08 (m, 8H), 3.10-3.17 (m, 1H), 3.2 (s, 3H), 3.26-3.33 (m, 1H), 3.68 (m, 1H), 3.78 (s, 3H), 3.80-3.87 (m, 1H), 3.92 (d, *J*= 15.3 Hz, 1H), 4.88 (s, 1H), 5.08 (d, *J*= 15.3 Hz, 1H), 6.85 (d, *J*= 8.5 Hz, 2H), 7.18 (d, *J*= 8.5 Hz, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 172.6, 168.4, 158.7, 130.3, 129.1, 113.9, 91.4, 81.5, 66.1, 55.7, 55.2, 51.2, 50.2, 42.2, 26.6, 25.8, 24.7, 17.0, 8.4, 7.8; HRMS (ESI) calcd for $[C_{23}H_{34}N_2O_3+H]^+$: 387.2642; found: 387.2635.

(5*S*)-4-[(*S*)-2-(1-Methoxy-1-ethylpropyl)-1-pyrrolidinyl]-1-(4-methoxybenzyl)-5-



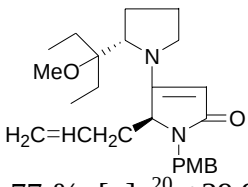
14c: Colorless oil. Yield: 71%. $[\alpha]_D^{20}$ +29.7 (*c* 1.1, $CHCl_3$); IR (KBr) ν_{max}: 2957, 2922, 1663, 1591, 1509, 1407, 1242, 1026 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.85 (m, 9H), 1.08-2.06 (m, 14H), 3.13-3.19 (m, 1H), 3.21 (s, 3H), 3.28-3.35 (m, 1H), 3.64-3.73 (m, 1H), 3.79 (s, 3H), 3.85 (d, *J*= 15.2 Hz, 1H), 3.93 (m, 1H), 4.95 (s, 1H), 5.11 (d, *J*= 15.2 Hz, 1H), 6.82 (d, *J*= 8.5 Hz, 2H), 7.18 (d, *J*= 8.5 Hz, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 173.4, 166.6, 158.8, 130.3, 129.2, 113.9, 93.1, 81.5, 66.4, 59.4, 55.3, 51.7, 50.1, 42.53, 28.4, 26.6, 25.7, 24.9, 24.7, 24.0, 22.6, 14.0, 8.4, 7.8; HRMS (ESI) calcd for $[C_{26}H_{40}N_2O_3+H]^+$: 429.2642; found: 429.2635; Anal. Calcd for $C_{26}H_{40}N_2O_3$: C, 72.86; H, 9.41; N, 6.54. Found: C, 73.06; H, 9.42; N, 6.60.

(5*S*)-4-[(*S*)-2-(1-Methoxy-1-ethylpropyl)pyrrolidin-1-yl]-1-(4-methoxybenzyl)-5-methyl-2,5-dihydro-1*H*-2-azolone (14d)



14d: Colorless oil. Yield: 69 %. $[\alpha]_D^{20}$ +38.8 (*c* 1.9, $CHCl_3$); IR (KBr) ν_{max}: 2931, 1667, 1593, 1512, 1382, 1246, 1174, 1090 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.85 (m, 9H), 1.08-2.06 (m, 18H), 3.12-3.18 (m, 1H), 3.20 (s, 3H), 3.26-3.34 (m, 1H), 3.63-3.70 (m, 1H), 3.8 (s, 3H), 3.84 (d, *J*= 15.2 Hz, 1H), 3.88-3.94 (m, 1H), 4.94 (s, 1H), 5.09 (d, *J*= 15.2 Hz, 1H), 6.82 (d, *J*= 8.5 Hz, 2H), 7.18 (d, *J*= 8.5 Hz, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 173.3, 166.6, 158.7, 130.3, 129.3, 113.9, 93.2, 81.5, 66.4, 59.4, 55.3, 51.7, 50.2, 42.5, 31.8, 29.2, 28.7, 26.7, 25.7, 25.0, 24.7, 22.5, 21.8, 14.1, 8.5, 7.8; Anal. Calcd for $C_{28}H_{44}N_2O_3$: C, 73.64; H, 9.71; N, 6.13. Found: C, 73.28; H, 9.74; N, 6.38.

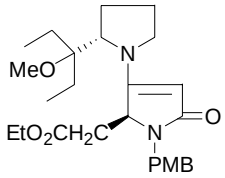
(5*S*)-4-[(*S*)-2-(1-Methoxy-1-ethylpropyl)pyrrolidin-1-yl]-1-(4-methoxybenzyl)-5-allyl-2,5-dihydro-1*H*-2-azolone (14e)



14e: Pale yellow oil. Yield: 77 %. $[\alpha]_D^{20}$ +39.9 (*c* 1.2, $CHCl_3$); IR (KBr) ν_{max}: 2929, 1667, 1592, 1512, 1379, 1246, 1175 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.86 (m,

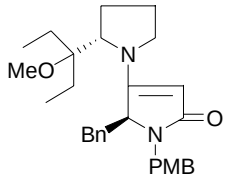
6H), 1.20-2.10 (m, 8H), 2.38-2.48 (m, 1H), 2.58-2.70 (m, 1H), 3.16 (m, 1H), 3.20 (s, 3H), 3.64-3.73 (m, 1H), 3.80 (s, 3H), 3.88 (d, *J*= 15.3 Hz, H), 3.94 (m, 1H), 4.93 (s, 1H), 5.10 (m, 2H), 5.17 (d, *J*= 15.3 Hz, 1H), 5.60 (m, 1H), 6.82 (d, *J*= 8.5 Hz, 2H), 7.18 (d, *J*= 8.5 Hz, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 173.1, 166.3, 158.7, 157.3, 138.9, 131.4, 129.2, 118.7, 113.9, 110.9, 93.0, 92.8, 86.0, 81.6, 66.5, 58.8, 58.8, 56.4, 55.2, 51.6, 50.5, 42.5, 41.9, 33.5, 26.6, 25.7, 24.9, 24.5, 8.5, 7.8; MS (m/z): 435 ($M+Na^+$, 16), 413 ($M+H^+$, 100); HRMS calcd for $[C_{25}H_{36}N_2O_3+H]^+$: 413.2799; found: 413.2797.

(5*S*)-4-[(*S*)-2-(1-Methoxy-1-ethylpropyl)pyrrolidin-1-yl]-1-(4-methoxybenzyl)-5-ethyoxylcarboxylethyl-2,5-dihydro-1*H*-2-azolone (14f)



14f: Pale yellow oil. Yield: 84.2 %. $[\alpha]_D^{20}$ +11.8 (*c* 0.7, $CHCl_3$); IR (KBr) ν_{max}: 2925, 1733, 1671, 1596, 1377, 1246, 1174, 1033 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$, two rotamers, M: m= 11: 1) δ : 0.85 (m, 6H), 1.24 (t, *J*=7.2 Hz, 3H), 1.26-2.08 (m, 8H), 2.42-2.52 (dd, *J*= 15.5, 7.2 Hz, 1H, M), 2.54-2.60 (dd, *J*= 15.5, 8.8 Hz, 1H, m), 2.65-2.71 (dd, *J*= 15.5, 5.2 Hz, 1H, m), 2.76-2.84 (d, brd, *J*= 15.5 Hz, 1H, M), 3.16-3.22 (m, 1H), 3.23 (s, 3H), 3.28-3.36 (m, 1H), 3.66-3.76 (m, 1H), 3.80 (s, 3H), 4.12 (q, *J*= 7.2 Hz, 2H), 4.13 (m, 1H), 4.36-4.42 (m, 1H), 4.92 (d, *J*= 15.4 Hz, 1H, M and m overlapped), 4.98 (s, 1H), 6.82 (d, *J*= 8.5 Hz, 2H), 7.20 (d, *J*= 8.5 Hz, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ (two rotamers): 173.2, 170.7, 166.5, 158.7, 130.4, 129.1, 114.0, 113.8, 93.9, 92.9, 81.6, 66.3, 61.2, 61.0, 60.4, 58.3, 57.3, 56.5, 55.2, 53.4, 51.5, 50.4, 43.4, 43.0, 38.1, 35.6, 26.6, 25.9, 24.9, 24.7, 14.2, 14.1, 8.6, 7.9; HRMS (ESI) calcd for $[C_{26}H_{38}N_2O_5+H]^+$: 459.2853; found: 459.2853.

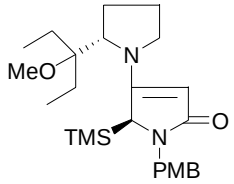
(5*S*)-4-[(*S*)-2-(1-Methoxy-1-ethylpropyl)pyrrolidin-1-yl]-1-(4-methoxybenzyl)-5-benzyl-2,5-dihydro-1*H*-2-azolone (14g)



14g: Colorless oil. Yield: 85.4 %. $[\alpha]_D^{20}$ +66.8 (*c* 1.1, $CHCl_3$); IR (KBr) ν_{max}: 2926, 2856, 1698, 1512, 1248, 1113 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$, two rotamers, M: m= 2.1: 1) δ: 0.85 (m, 6H), 1.20-2.10 (m, 8H), 2.66-2.71 (m, 2H, m), 2.75 (dd, *J*= 15.1, 7.5 Hz, 2H, M), 3.15 (s, 3H), 3.20-3.34 (m, 2H), 3.50 (d, *J*= 15.1 Hz, 1H), 3.63 (m, 1H), 3.75 (s, 3H), 4.05 (m, 1H), 4.90 (s, 1H), 5.12 (d, *J*= 15.1 Hz, 1H), 6.72 (d, *J*=7.7 Hz, 2H), 6.80 (d, *J*=7.7 Hz, 2H), 7.15-7.35 (m, 5H); ^{13}C-NMR (125 MHz,

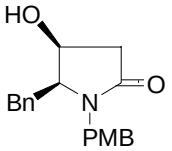
$CDCl_3$) δ (two rotamers): 173.5, 167.1, 158.6, 136.9, 129.9, 129.2, 128.5, 126.9, 113.7, 93.1, 81.6, 66.4, 60.3, 55.1, 51.6, 50.6, 43.2, 38.0, 26.5, 25.6, 24.8, 24.2, 8.6, 7.8; MS (m/z): 485 ($M+Na^+$, 22), 463 ($M+H^+$, 100); HRMS calcd for $[C_{29}H_{38}N_2O_3+H]^+$: 463.2955; found: 463.2960.

(5*S*)-4-[(*S*)-2-(1-Methoxy-1-ethylpropyl)pyrrolidin-1-yl]-1-(4-methoxybenzyl)-5-trimethylsilyl-2,5-dihydro-1*H*-2-azolone (14h)



14h: Pale yellow oil. Yield: 45%. $[\alpha]_D^{20}$ -13.1 (*c* 0.8, $CHCl_3$); IR (KBr) ν_{max}: 2920, 1652, 1597, 1463, 1398, 1239, 1090, 836 (s) cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.22 (s, 9H), 0.83 (m, 6H), 1.40-2.10 (m, 8 H), 3.09 (s, 3 H), 3.10-3.18 (m, 1H), 3.22-3.29 (m, 1H), 3.60-3.66 (m, 1 H), 3.70 (d, *J*= 17.0 Hz, 1H), 3.78 (s, 3H), 4.50 (dd, *J*= 15.9 Hz, 2 H), 4.79 (s, 1H), 6.77 (d, *J*=8.6 Hz, 2H), 7.20 (d, *J*=8.6 Hz, 2H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 174.2, 163.6, 162.8, 134.6, 130.5, 129.9, 127.9, 109.7, 90.6, 81.5, 65.8, 55.1, 50.8, 50.7, 49.4, 45.2, 29.7, 27.0, 26.3, 26.2, 24.0, 8.2, 7.5, -1.0; MS (m/z): 445 ($M+H^+$, 100); HRMS calcd for $[C_{25}H_{40}SiN_2O_3+H]^+$: 445.2881; found: 445.2879.

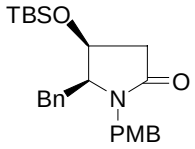
(4*S*, 5*S*)-5-Benzyl-4-hydroxy-1-(4-methoxybenzyl)-2-pyrrolidinone (16)



To a solution of **14g** (727 mg, 1.57 mmol) in THF (50 mL) was added a solution of 10 % HCl (20 mL). After stirred at 30 ºC for 26 h, the mixture was extracted with ethyl acetate and the combined extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was dissolved in a mixed solvent system (CH_2Cl_2,11.5 mL; AcOH, 1.2 mL), then cooled to 0 ºC and stirred vigorously, into which was added portion-wise $NaBH_4$ (141 mg, 3.7 mmol). After stirred for 3.5 h, a cold saturated solution of $NaHCO_3$ (3 mL) was added. The resulting mixture was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated in vacuo. The crude was purified by column chromatography on silica gel (EtOAc / PE=1/1) to give (4*S*, 5*S*)-**16** (400 mg, 82 %) and (4*R*, 5*S*)-**16** as an un-separable mixture in a ratio of 20:1 (deduced from **17**). (4*S*, 5*S*)-**16**: White solid. Mp 144.5-145.5 ºC; $[\alpha]_D^{20}$ -75.7 (*c* 0.7, $CHCl_3$); IR (KBr) ν_{max}: 2926, 2856, 1698, 1512, 1248, 1113 cm^{-1}; ^{1}H-NMR (500 MHz, CD_3CN) δ: 2.28 (dd, *J*= 16.5, 3.7 Hz, 1 H), 2.56 (dd, *J*= 16.5, 6.1 Hz, 1 H), 2.97 (dd,

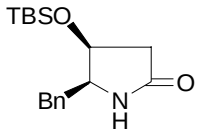
J= 13.4, 5.5 Hz, 1 H), 3.04 (dd, *J*= 13.4, 8.6 Hz, 1 H), 3.33 (d, *J*= 5.5 Hz, 1 H, D_2O exchangeable), 3.70 (ddd, *J*= 9.2, 6.1, 3.7 Hz, 1H), 3.83 (s, 3H), 3.97 (d, *J*= 15.3 Hz, 1H), 4.15 (m, 1 H), 4.85 (d, *J*= 15.3 Hz, 1H), 6.94 (d, *J*= 8.6 Hz, 2H), 7.16 (d, *J*= 8.6 Hz, 2H), 7.20-7.38 (m, 5H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 173.4, 159.0, 137.4, 129.2, 129.2, 128.7, 128.4, 126.7, 114.1, 66.1, 62.8, 55.3, 43.6, 40.3, 32.9; MS (m/z): 334 ($M+Na^+$, 100), 311 ($M+H^+$, 19); Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.31; H, 6.75; N, 4.50. Found: C, 73.24; H, 6.80; N, 4.67.

(4*S*, 5*S*)-5-Benzyl-4-(*tert*-butyldimethylsilyoxy)-1-(4-methoxybenzyl)-2-pyrrolidinone (17)



To a mixture of **16** (400 mg, 1.29 mmol), imidazole (175 mg, 2.57 mmol) and a catalytic amount of DMAP in anhydrous CH_2Cl_2 (8 mL) was added a solution of *tert*-butyldimethylchlorosilane (387 mg, 2.57 mmol) in anhydrous CH_2Cl_2 (4 mL). After being stirred at rt overnight, an aqueous solution of $NaHCO_3$ (10 mL) was added. The organic layer was separated, and washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The crude was purified by column chromatography on silica gel (EtOAc / PE=1/5) to give **17** (514 mg, 90 %) as a colorless oil. $[\alpha]_D^{20}$ -31.6 (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max}: 2926, 2856, 1698, 1512, 1248, 1113 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: -0.03 (s, 3H), 0.03 (s, 3H), 0.90 (s, 9H), 2.37 (dd, *J*= 16.3, 7.4 Hz, 1 H), 2.49 (dd, *J*= 16.3, 7.1 Hz, 1 H), 2.81 (dd, *J*= 14.3, 7.1 Hz, 1 H), 3.08 (dd, *J*= 14.3, 5.8 Hz, 1 H), 3.48 (d, *J*= 14.9 Hz, 1 H), 3.70 (ddd, *J*= 7.1, 7.1, 5.8 Hz, 1H), 3.78 (s, 3H), 4.32 (ddd, *J*= 7.4, 7.1, 7.1 Hz, 1H), 4.93 (d, *J*= 14.9 Hz 1H), 6.80 (d, *J*= 8.6 Hz, 2H), 6.90 (d, *J*= 8.6 Hz, 2H), 7.15-7.35 (m, 5H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 172.3, 158.9, 138.4, 129.4, 129.2, 128.6, 128.5, 126.5, 113.9, 67.9, 62.3, 55.2, 43.8, 39.5, 33.8, 25.7, 18.0, -4.5, -5.1; MS (m/z): 426 ($M+H^+$, 100); HRMS calcd for $[C_{25}H_{35}NO_3Si+H]^+$: 426.2459; found: 426.2457.

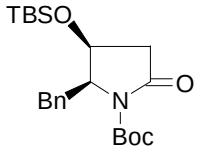
(4*S*, 5*S*)-5-Benzyl-4-(*tert*-butyldimethylsilyloxy)-2-pyrrolidinone (18)



To a solution of **17 (**389 mg, 0.915 mmol) in a mixed CH_3CN (11.4 mL) and H_2O (3.8 mL) solvent system was added ceric ammonium nitrate (2.0 g, 3.66 mmol) in one portion. After stirred at rt for 25 min., H_2O (10 mL) was added and the mixture was extracted with EtOAc (30 mL × 3). The combined organic layers were washed successively with saturated aqueous $NaHCO_3$ (5 mL × 3) and brine (5 mL). The organic phase was dried over anhydrous Na_2SO_4, filtrated and concentrated. The crude was purified by chromatography on silica gel (EtOAc / PE= 1/1) to give **18**

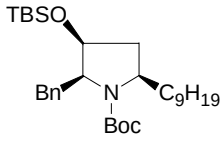
(202 mg, 74.6 %) as a colorless oil. $[\alpha]_D^{20}$ -64 (*c* 1.1, $CHCl_3$); IR (KBr) ν_{max}: 3389, 2927, 1702, 1255, 1149, 1082 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.10 (s, 6H), 0.95 (s, 9H), 2.34 (dd, *J*= 16.7, 4.5 Hz, 1 H), 2.56 (dd, *J*= 16.7, 6.6 Hz, 1 H), 2.74 (dd, *J*= 13.8, 10.8 Hz, 1 H), 2.89-2.96 (dd, *J*= 13.8, 3.7 Hz, 1 H), 3.85 (ddd, *J*= 10.8, 5.4, 3.7 H, 1H), 4.56 (ddd, *J*= 6.6, 5.4, 4.5 Hz, 1 H), 5.40 (s, 1H), 7.18-7.35 (m, 5H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 174.8, 138.2, 129.0, 128.9, 126.7, 69.3, 60.7, 40.3, 36.2, 25.7, 18.1, -4.6, -5.0; MS (m/z): 306 ($M+H^+$, 100); Anal. Calcd for $C_{17}H_{27}SiNO_2$: C, 66.84; H, 8.91; N, 4.59. Found: C, 67.11; H, 9.11; N, 4.76.

(4*S*, 5*S*)-5-Benzyl-4-(*tert*-butyldimethylsilyloxy)-1-(*tert*-butyloxycarbonyl)-2-pyrrolidinone (19)



To a cooled (0 ºC) solution of **18** (202 mg, 0.66 mmol) in CH_2Cl_2 (4 mL) were added successively a catalytic amount of DMAP, Et_3N (0.18 mL, 1.32 mmol), and di(*tert*-butyl)dicarbonate (289 mg, 1.32 mmol). The mixture was allowed to stirr at rt overnight. After being diluted with H_2O (3 mL), the resulting mixture was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried, filtered and concentrated. The crude was purified by chromatography on silica gel (EtOAc / PE=1/10) to give **19** (261 mg, 97.3 %) as a white solid. Mp 82.5-84.5 ºC; $[\alpha]_D^{20}$ +34.3 (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max}: 2956, 2930, 1791, 1758, 1715, 1357, 1295, 1150 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.02 (s, 6H), 0.88 (s, 9H), 1.45 (s, 9H), 2.25 (dd, *J*= 16.8, 10.3 Hz, 1 H), 2.44 (dd, *J*= 16.8, 7.7 Hz, 1 H), 2.94 (dd, *J*= 14.1, 5.1 Hz, 1 H), 3.18 (dd, *J*= 14.1, 5.7 Hz, 1 H), 4.42-4.47 (ddd, *J*= 7.5, 5.7, 5.1 Hz, 1 H), 4.49-4.55 (ddd, *J*= 10.3, 7.7, 7.5 Hz, 1 H), 7.15-7.35 (m, 5H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 171.0, 149.6, 137.7, 130.1, 128.3, 126.5, 83.0, 66.9, 62.2, 40.4, 34.0, 27.9, 25.8, 18.1, -4.8, -5.0; MS (m/z): 348 (88), 391 (100), 404 ($M+H^+$, 51), 426 (19); Anal. Calcd for $C_{22}H_{35}NO_4Si$: C, 65.19; H, 8.64; N, 3.46. Found: C, 65.35; H, 8.74; N, 3.70.

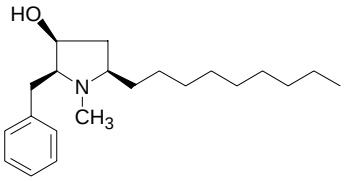
(2*S*, 3*S*, 5*R*)-2-Benzyl-3-(*tert*-butyldimethylsilyloxy)-1-(*tert*-butyloxycarbonyl)-5-(*n*-nonyl)-pyrrolidine (20)



The transformation of **19** to **20** was achieved by reported procedure,[2,3] which afforded **20** (48 mg, 75 %) as a colorless oil. $[\alpha]_D^{20}$ -48.6 (*c* 1.1, $CHCl_3$). IR (KBr) ν_{max}: 2927, 2856, 1693, 1454, 1388, 1141, 1090 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$, two rotamers) δ: -0.06-0.10 (m, 6H), 0.84-0.96 (m, 12 H), 1.06-1 .52 (m, 23 H), 1.55-1.65 (m, 2H), 1.97 (m, 2H, rotamer 1), 2.12-2.32 (m, 2H, rotamer 2), 2.46-2.60 (m, 1 H), 2.70-2.82 (m, 2 H, rotamer 1), 3.00 (dd, *J*= 13.6, 4.7 Hz, 2H, rotamer 2), 3.48-3.71 (m, 1 H),

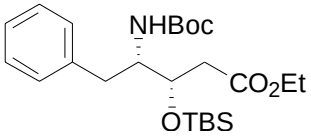
3.96-4.08 (m, 1H), 4.12-4.20 (m, 2 H), 4.25 (dd, *J*= 16.7, 7.1 Hz, 2 H), 7.10-7.30 (m, 5 H); ^{13}C-NMR (125 MHz, $CDCl_3$, two rotamers) δ: 154.9, 140.1, 129.9, 128.0, 125.6, 78.9, 71.4, 62.3, 55.7, 38.0, 37.2, 35.9, 31.9, 29.7, 29.5, 29.3, 28.0, 26.5, 25.85, 22.7, 18.1, 14.1, -4.7, -5.0; MS (ESI): 540 ($M+Na^+$, 74), 518 ($M+H^+$, 100), 404 (83).

(2*S*, 3*S*, 5*R*)- 2-Benzyl-1-methyl-5-(*n*-nonyl)-3-pyrrolidinol (Preussin, 5)



To a solution of **20** (34 mg, 0.084 mmol) in dry THF (0.85 mL) was added $LiAlH_4$ (32 mg, 0.84 mmol) in one portion. The resulting reaction mixture was stirred at 60 ºC for 28 h. After being diluted with 2 mL of Et_2O, $Na_2SO_4{\cdot}10H_2O$ was added to quench the reaction. After filtration and removal of the solvent under reduced pressure, the crude was purified by chromatography on silica gel (EtOAc / PE= 1/5) to give preussin (**5**) (24 mg, 90 %) as a colorless oil. $[\alpha]_D^{20}$ +21.9 (*c* 1.3, $CHCl_3$) [natural **5**, $[\alpha]^{25}_D$ +22.0 (*c* 1.0, $CHCl_3$)]; IR (KBr) ν_{max}: 3435, 2925, 2854, 1455, 1457, 1391, 1174 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.88 (t, *J*= 6.91 Hz, 3 H), 1.16-1.38 (m, 15 H), 1.38-1.46 (m, 1 H), 1.72 (m, 1 H), 2.11 (m, 1 H), 2.18 (m, 1 H), 2.26 (m, 1H), 2.33 (s, 3H), 2.80-2.92 (m, 2 H), 3.8 (m, 1 H),7.15-7.35 (m, 5 H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 139.5, 129.4, 128.4, 126.1, 73.5, 70.5, 65.7, 39.3, 38.7, 35.1, 33.7, 31.9, 29.9, 29.6, 29.6, 29.3, 26.3, 22.7, 14.1; MS (m/z): 318 ($M+H^+$, 100); HRMS calcd for $[C_{21}H_{35}NO+H]^+$: 318.2791; found: 318.2786.

(3*S*, 4*S*)-4-*tert*-Butyloxycarbonylamino-3-hydroxy-5-phenylpentanoic acid ethyl ester (21)



To a solution of **19** (10 mg, 0.025 mmol) in dry THF (0.1 mL) was added a catalytic amount of potassium cyanide and EtOH (0.1 mL). The mixture was stirred at rt for 16 h. The solvent was removed under reduced pressure and the crude was purified by column chromatography on silica gel (EtOAc / PE= 1/12) to give **21** (6 mg, 91 %) as a colorless oil. $[\alpha]_D^{20}$ -23.4 (*c* 0.7, MeOH); IR (KBr) ν_{max}: 2956, 2930, 2857, 1737, 1703, 1366, 1253, 1174 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$, two rotamers, M and m) δ: 0.02 (s, 3H), 0.07 (s, 3H), 0.92 (s, 9 H), 1.23 (t, *J*= 6.9 Hz, 3H), 1.35 (s, 9 H), 2.47 (dd, *J*= 15.9, 6.0 Hz 1 H, M), 2.51-2.59 (dd, *J*= 15.9, 6.0 Hz 1 H, m), 2.68-2.77 (m, 2 H, m), 2.78-2.90 (m, 2 H, M), 3.80-3.87 (m, 1H, m), 3.92-3.99 (m, 1H, M), 4.12 (q, *J*= 6.9Hz, 2H, M), 4.18-4.28 (m, 2H, m), 4.55 (brs, 1H, m), 4.62-4.68 (m, 1H, M), 7.15-7.35 (m, 5 H); ^{13}C-NMR (125 MHz, $CDCl_3$, two rotamers) δ: 171.2, 155.5, 138.2, 129.1, 128.3, 126.2, 79.1, 69.8, 60.5, 55.4, 39.9, 38.5, 28.3, 25.9, 18.1, 14.1,

-4.4, -4.7; HRMS calcd for $[C_{21}H_{35}NO+H]^+$: 318.2827; found: 318.2829. **S10**