# Stereoselective Total Synthesis of *cis*- and *trans*-3-Hydroxypipecolic Acid

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## Supporting Information II

**Experimental procedure and characterization data for compounds 6, 3A, 12, 4, 14, 15 and 17.**

**(2*R*,3*R*)-2-(*tert*-Butoxycarbonylamino)-1,3-bis(*tert*-butyldimethylsilyloxy)-hept-6-ene (6).** To a solution of the aminodiol derivative **3** (580 mg, 1.6 mmol) in anhydrous $CH_2Cl_2$ (7 mL), catalytic DMAP and imidazole (218 mg, 3.2 mmol) were added sequentially under nitrogen atmosphere with stirring. The solution was cooled to 0 °C, and TBDMSCl (366 mg, 2.4 mmol) in $CH_2Cl_2$ (3 mL) was added slowly. The cooling bath was removed, and the reaction mixture was heated at 40–50 °C for 18 h. A second batch of TBDMSCl (180 mg, 1.2 mmol) in $CH_2Cl_2$ (2 mL) and imidazole (125 mg, 1.8 mmol) were added to the reaction mixture, and stirring was continued at the same temperature overnight. The reaction was then quenched by addition of water (15 mL), the organic layer was separated, and the aqueous layer was extracted with $CH_2Cl_2$ (2 x 25 mL). The combined organic extracts were washed with brine, dried over $Na_2SO_4$, and concentrated. The residual oil was purified by flash column chromatography (EtOAc /hexane = 5:95 to 15:85) to afford the di-TBDMS-protected product **6** (610 mg, 95%, based on recovered starting material) as a light yellow viscous liquid, along with recovery of some unreacted starting material **3** (85 mg): $[\alpha]^{25}{}_{D}$ -9 (c 1.2, $CHCl_3$); IR (neat) 1710 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ

0.06 and 0.08 (2s, 12H), 0.91 (s, 18H), 1.49 (s, 9H), 1.54–1.62 (m, 2H), 2.04–2.20 (m, 2H), 3.43–3.47 (m, 1H), 3.57–3.71 (m, 2H), 3.96–4.11 (m, 1H), 4.76 (d, *J*=8.6 Hz, 1H), 4.95–5.06 (m, 2H), 5.77–5.89 (m, 1H); $^{13}$C NMR (100.6 MHz, $CDCl_3$) δ –4.9, –4.4, –3.9, 18.5, 26.0, 26.2, 28.8, 29.2, 30.1, 30.2, 33.5, 33.8, 54.0, 55.1, 61.9, 69.1, 79.4, 115.2, 138.3, 138.5, 156.2; HRMS calcd for $C_{24}H_{52}N_2O_4Si_2$ *m*/*z* (M+H) 474.3435, found 474.3422.

**Conversion of the *syn*-Amino Alcohol 3 to the Corresponding Oxazolidinone Derivative 3A.** To an ice-cooled solution of the amino alcohol **3** (200 mg. 0.56 mmol) in anhydrous THF (5 mL) was added potassium *t*-butoxide (1 M solution in THF, 2.7 mL, 2.7 mmol) dropwise. The reaction mixture was allowed to attain room temperature, and stirring was continued overnight. The reaction was quenched by addition of saturated aqueous $NH_4Cl$ solution (5 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine and dried over $Na_2SO_4$. Removal of solvent under vacuum and purification of the crude residue by flash column chromatography (EtOAc/ hexane = 3:7) afforded the oxazolidinone **3A** as a colorless oil (127.5 mg, 80%): $[\alpha]^{25}_D$ 53.8 (c 1.98, $CHCl_3$); IR (neat) 3276, 1753 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 0.07 (s, 6H), 0.89 (s, 9H), 1.68–1.79 (m, 1H), 1.82–1.94 (m, 1H), 2.13–2.32 (m, 2H), 3.51–3.65 (m, 3H), 4.32–4.36 (m, 1H; {d, *J*=4.53 Hz, after decoupling from H–1'; please see supporting information, page S9}), 4.98–5.15 (m, 2H), 5.80–5.91 (m, 1H), 6.37 (br s, 1H); $^{13}$C NMR (100.6 MHz, $CDCl_3$) δ –5.3, 18.3, 25.9, 29.0, 34.4, 59.1, 65.0, 79.0, 116.0, 137.1, 159.6; HRMS calcd. for $C_{14}H_{28}NO_3Si$ *m*/*z* (M + H) 286.1838, found 286.1857.

***N*-Benzyloxycarbonyl-(4*S*)-2,2-dimethyl-4-(1'-oxo-4'-pentenyl)-1,3-oxazolidine (12).** To an ice-cooled solution of the Weinreb amide **11**[16] (1.29 g, 4 mmol) in 10 mL of anhydrous THF was added dropwise a solution of 3-butenylmagnesium bromide (10 mmol) (prepared from Mg (0.48

g, 0.02 g atom) and 4-bromo-1-butene (1.35 g, 10 mmol)) in ether (15 mL) and stirred at the same temperature for 3 h. The reaction was quenched by careful addition of an aqueous 10% HCl solution (25 mL) and was stirred for 5 min. The resulting solution was extracted with ethyl acetate (3 x 30 mL), and the combined extract was washed sequentially with water and brine, dried over anhydrous $Na_2SO_4$, and concentrated under vacuum. Purification of the oily residue by flash column chromatography (ethyl acetate/hexane = 1:15) afforded the ketone **12** (0.926 g, 73%) as a colorless oil: $[\alpha]^{25}_D$ 55 (c 1.1, $CHCl_3$); IR (neat) 1713, 1651 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) (mixture of rotamers) δ 1.48 and 1.57 (2s, 3H), 1.65 and 1.70 (2s, 3H), 2.13–2.39 (m, 2H), 2.41–2.68 (m, 2H), 3.91–3.99 (m, 1H), 4.10–4.20 (m, 1H), 4.38–4.57 (m,1H), 4.88–5.23 (m, 4H), 5.60–5.88 (m, 1H), 7.22–7.40 (m, 5H); $^{13}C$ NMR (125.8 MHz, $CDCl_3$) (mixture of rotamers) δ 23.7, 24.9, 25.2, 26.1, 27.0, 27.1, 38.0, 38.5, 64.9, 65.3, 65.4, 65.9, 67.0, 67.7, 94.9, 95.6, 115.3, 115.4, 128.0, 128.1, 128.3, 128.5, 128.6, 135.9, 136.7, 136.9, 151.9, 153.1; HRMS calcd for $C_{18}H_{24}NO_4$ *m/z* (M + H) 318.1705, found 286.1687.

**Hydrolysis of 13 to the Diol 4.** To a solution of the oxazolidine **13** (800 mg, 2.5 mmol) in 90% aqueous MeOH (10 mL) was added Dowex-50W ion-exchange resin (2.6 g), and the mixture was stirred at 50 °C for 24 h. The resin was removed by filtration and washed with methanol, and the combined filtrate was concentrated in vacuo to give 648 mg (93%) of the diol **4** as a light yellow, low melting solid: $[\alpha]^{25}_D$ –12 (c 1.1, $CHCl_3$); IR (neat) 3301, 1684; $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.64–1.74 (m, 2H), 2.11–2.32 (m, 2H), 2.44–2.50 (m, 2H, exchangeable with $D_2O$), 3.62 (br s, 1H), 3.81-3.87 (m, 2H), 3.99–4.07 (m, 1H), 5.02–5.14 (m, 4H), 5.64 (br s, 1H), 5.79–5.92 (m, 1H), 7.32–7.40 (m, 5H); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) δ 30.6, 33.8, 55.7, 62.7, 67.4, 73.8, 115.8, 128.5, 128.6, 129.0, 136.7, 138.3, 156.9; HRMS calcd for $C_{15}H_{22}NO_4$ *m/z* (M + H) 280.1549, found 280.1552.

**(2*R*,3*S*)-2-(*tert*-Butoxycarbonylamino)-1,3-bis(*tert*-butyldimethylsilyloxy)-hept-6-ene (14).** Using the diol **4** (678 mg, 2.43 mmol), we followed the same procedure as that for compound **6**. After purification, the di-TBDMS-protected diol **14** (1.15 g, 94%) was obtained as a light yellow oily liquid: $[\alpha]^{25}_{D}$ –7 (c 1, $CHCl_3$); IR (neat) 3350, 1730 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 0.08 and 0.09 (2s, 12H), 0.92 (s, 18H), 1.51–1.72 (m, 2H), 2.04–2.29 (m, 2H), 3.68–3.93 (m, 4H), 4.91–5.15 (m, 5H), 5.75–5.89 (m, 1H), 7.24–7.30 (m, 5H); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) δ –5.1, –4.9, –4.6, –4.4, 18.5, 26.3, 29.2, 30.2, 33.0, 56.0, 61.8, 67.0, 71.3, 115.0, 128.4, 128.6, 128.9, 137.1, 138.9, 156.5; HRMS calcd for $C_{27}H_{50}NO_4Si_2$ *m/z* (M + H) 508.3278, found 508.3287.

**Conversion of 14 to the Piperidinol Derivative 15.** Starting from the aminodiol derivative **14** (200 mg, 0.39 mmol), we followed the same procedure as that for compound **7**. After purification, the cyclic carbinolamine **15** (174 mg, 87%) was obtained as a light yellow oil: IR (neat) 3435, 1684 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) (mixture of anomers): δ –0.03–0.14 (m, 12H), 0.83–0.97 (m, 18H), 1.43–1.53 (m, 1H), 1.56–1.71 (m, 1H), 2.06–2.19 (m, 2H), 3.53–3.69 (m, 1H), 3.76–3.87 (m, 1H), 4.05–4.23 (m, 3H), 5.06–5.30 (m, 2H), 5.71–5.82 (m, 1H), 7.29–7.43 (m, 5H); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) (mixture of anomers) δ –5.2, –5.1, –4.6, 18.4, 18.5, 21.5, 22.5, 24.5, 25.2, 26.2, 26.3, 59.4, 60.1, 64.2, 64.6, 65.9, 67.6, 74.2, 74.4, 128.1, 128.2, 128.4, 128.6, l28.8, 136.8, 137.1, 156.0, 157.2; calcd for $C_{26}H_{48}NO_5Si_2$ *m/z* (M + H) 510.3071, found 510.3063.

**Oxidation of 16 to (2*S*,3*S*)-*N*-*tert*-butoxycarbonyl-3-(*tert*-butyldimethylsilyloxy)pipecolic Acid (17).** Starting from the piperidine derivative **16** (178 mg, 0.47 mmol), we followed the same procedure as that for compound **9**. Flash column chromatography afforded the pure carboxylic acid derivative **17** (122 mg, 66%) as a low melting solid: $[\alpha]^{25}_{D}$ –5.5 (c 1.05, $CHCl_3$);

IR (neat) 3435, 1701, 1649 $cm^{-1}$; $^{1}H$ NMR (400 MHz, $CDCl_3$) (mixture of rotamers) δ 0.03–0.16 (m, 6H), 0.87–0.90 (m, 9H), 1.17–1.58 (m, 2H), 1.65–1.79 (m, 1H), 1.90–2.09 (m, 1H), 2.91–3.16 (m, 1H), 4.05–4.25 (m, 1H), 4.45 (br d, *J*=12.4 Hz, 1H), 4.84 and 4.96 (2s, 1H), 5.09–5.26 (m, 2H), 7.30–7.41 (m, 5H), 10.4 (br s, 1H); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) δ –4.8, –4.6, 18.4, 18.6, 26.1, 29.1, 41.7, 42.0, 61.4, 61.6, 66.2, 67.8, 128.1, 128.3, 128.8, 136.9, 137.0, 156.6, 157.4, 175.5; HRMS calcd for $C_{20}H_{32}NO_5Si$ *m/z* (M + H) 394.2050, found 394.2034.