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**Supplementary Material**

# Total Synthesis of *cis* and *trans* -3-Hydroxy-D-proline and of (+)-Detoxinine

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**General Methods.** All reactions were performed in dried and purified solvents and monitored by TLC plates (Merck 5554). Preparative column chromatography was performed on Merck silica gel 60 F-254, mesh 230-400 with typically 10-30 g of silica gel per gram substance. NMR-spectra were recorded in $CDCl_3$ with TMS as internal standard. Optical rotations were determined at 22°C in $CHCl_3$ (unless otherwise stated) at 589 nm.

**(2*R*,3*R*)-3-*O*-*tert*-Butyldiphenylsilyl-1,2-*O*-isopropylidene-5-hexene-1,2,3-triol (7b).** $[\alpha]_D^{20}$ = -17.8 (c = 0.4, $CHCl_3$); $^1$H-NMR (250 MHz): δ = 1.06 (s, 9H), 1.24 (s, 3H), 1.32 (s, 3H), 1.54-1.68 (m, 1H), 1.72-1.84 (m, 2H), 3.52 ($m_c$, 1H), 3.64 (mc, 1H), 3.80 (dd, $J_1$ = 7.5 Hz, $J_2$ = 7.5 Hz, 1H), 3.90 (dd, $J_1$ = 8.7 Hz, $J_2$ = 7 Hz, 3.96 (mc, 1H), 4.14 ($m_c$, 1H), 7.32-7.44 (m, 6H), 7.64-7.72 (m, 4H); $^{13}$C-NMR (63 MHz): δ = 19.43, 24.88, 26.13, 26.98, 30.82, 35.33, 59.09, 65.36, 68.34, 71.40, 77.68, 109.24, 127.47, 127.56, 129.70, 133.65, 135.89; IR (film, KBr): ν = 3437 s(br.), 3072 w, 3049 w, 2983 m, 2958 m, 2932 s, 2890 s, 2858 s, 1740 w, 1590 w, 1473 m, 1427 s, 1371 m, 1370 m, 1258 m, 1214 m, 1112 s, 1079 s(br.), 860 m, 822 s, 740 s, 703 vs, 611 s, 510 vs, 489 m $cm^{-1}$; MS (80 eV, EI, 120 °C), m/z (%): 399 (3.7), 357 (18.5), 339 (11.1), 313 (9.2), 299 (48.2), 281 (5.8), 269 (28.4), 255 (13.0), 239 (7.7), 225

(29.9), 221 (100), 199 (99.7), 197 (18.9), 193 (15.3), 191 (43.0), 183 (29.1), 177 (28.0), 143 (18.5), 139 (26.6), 135 (29.8), 117 (11.6); $C_{24}H_{34}O_4Si$ (414.6157) calcd C 69.52, H 8.27; found C 68.98, H 8.33.

**(2*R*,3*R*)-5-Azido-3-*O*-*tert*-butyldiphenylsilyl-1,2-*O*-isopropylidene-pentane-1,2,3-triol (9b).** $[\alpha]_D^{20}$ = -9.5 (c = 1.1, $CHCl_3$); $^1$H-NMR (250 MHz): δ = 1.10 (s, 9H), 1.26 (s, 3H), 1.36 (s, 3H); 1.62-1.88 (m, 2H), 3.16-3.40 (m, 2H), 3.88 (dd, $J_1$ = 7.7 Hz, $J_2$ = 6.3 Hz, 1H), 3.94 ($m_c$, 2H), 4.16 (dd, $J_1$ = 12.5 Hz, $J_2$ = 5.8 Hz, 1H), 7.36-7.50 (m, 6H), 7.68-7.76 (m, 4H); $^{13}$C-NMR (63 MHz): δ = 19.43, 24.88, 26.13, 26.98, 32.33, 49.09, 66.34, 67.34, 71.42, 77.62, 109.29, 127.44, 127.11, 129.34, 133.63, 135.81; IR (film, KBr): ν = 3072 m, 3050 w, 2985 m, 2959 s, 2932 s, 2892, 2859 m, 2096 vs, 1590 w, 1472 m, 1462 w, 1428 s, 1380 m, 1370 m, 1264 m, 1212 m, 1112 vs(br.), 1076 s(br.), 998 m, 822 s, 740 s, 702 vs, 611 s, 509 s $cm^{-1}$; MS (80 eV, EI, 100 °C), m/z (%): 424 (3.5), 396 (2.4), 382 (89.3), 338 (6.9), 317 (10.9), 296 (49.5), 267 (17.3), 252 (48.4), 225 (37.1), 199 (100), 107 (24.2), 183 (56.4), 135 (31.6); $C_{24}H_{33}N_3O_3Si$ (439.6285) calcd C 65.57, H 7.57, N 9.56; found C 65.43, H 7.31, N 9.39.

**(2*R*,3*R*)-5-Azido-1-*O*-*tert*-butyldimethylsilyl-3-*O*-*tert*-butyldiphenylsilyl-pentane-1,2,3-triol (10b).** $[\alpha]_D^{20}$ = -7.3 (c = 1.6, $CHCl_3$); $^1$H-NMR (250 MHz): δ = 0.04 (s, 3H), 0.05 (s, 3H), 0.88 (s, 9H), 1.10 (s, 9H), 1.70 ($m_c$, 1H), 1.92 ($m_c$, 1H), 2.46 (d, $J$ = 5.5 Hz, 1 H; $D_2O$-exchange pos.), 3.14 (t, $J$ = 6.8 Hz, 1H), 3.16 (t, $J$ = 7.5 Hz, 1H), 3.56-3.70 (m, 3H), 3.96-4.04 (m, 1H), 7.36-7.48 (m, 6H), 7.68-7.75 (m, 4H); $^{13}$C-NMR (63 MHz): δ = -5.49, 18.10, 19.45, 25.77, 26.98, 32.31, 47.83, 63.45, 70.84, 73.21, 127.66, 127.69, 129.83, 129.86, 132 98, 133.54, 135.75, 135.80; MS (80 eV, EI, 120 °C), m/z (%): 498 (1.2), 470 (1.5), 456 (43.1), 428 (16.3), 350 (16.3), 306 (14.0), 296 (24.6), 225 (15.5), 218 (14.8), 211 (15.1), 199 (100), 183 (24.3), 135 (59.3), 73 (67.9); $C_{27}H_{43}N_3O_3Si_2$ (513.820) calcd C 63.11, H 8.43, N 8.18; found C 63.43, H 8.34, N 8.39.

**(2*R*,3*R*)-5-Azido-1-*O*-*tert*-butyldimethylsilyl-3-*O*-*tert*-butyldiphenylsilyl-2-*O*-methyl-sulfonyl-pentane-1,2,3-triol (11b).** $[\alpha]_D^{20}$ = +1.1 (c = 1.0, $CHCl_3$); $^1$H-NMR (270 MHz): δ = 0.04 (s, 3 H; Si-$CH_3$), 0.05 (s, 3 H; Si-$CH_3$), 0.88 (s, 9 H; TBS-*tert* -butyl), 1.08 (s, 9 H;

TPS-*tert*-butyl), 1.70 ($m_c$, 1 H; 4-H); 1.92 ($m_c$, 1 H; 4-H), 2.94 (s, 3 H; mes-$CH_3$), 3.06-3.26 (m, 2 H; 5-H), 3.84-3.96 (m, 2 H; 1-H), 4.10 ($m_c$, 1 H; 3-H), 4.54 ($m_c$, 1 H; 2-H), 7.36-7.48 (m, 6 H; aromatic-H), 7.64-7.72 (m, 4 H; aromatic-H); H,H-COSY-90 (270 MHz); crosspeaks: δx/δy = 1.70/1.92, 1.70/3.16, 1.70/4.10, 1.92/3.16, 1.92/4.10, 3.90/4.54, 4.10/4.54; $^{13}$C-NMR (63 MHz): δ = -5.62, -5.58, 18.13, 19.32, 25.72, 26.85, 31.51, 38.11, 47.53, 61.81, 69.84, 77.20, 84.22, 127.72, 127.79, 129.97, 130.04, 132.49, 132.87, 135.70, 135.77; IR (film, KBr): ν = 2985 m, 2959 s, 2932 s, 2096 vs, 1425 vs, 1380 m, 1370 m, 1150 vs, 822 s, 740 s, 700 vs, 609 s, 506 s cm$^{-1}$. MS (80 eV, EI, 150 °C), m/z (%): 548 (2.8), 534 (3.2), 506 (86.3), 410 (24.6), 351 (12.4), 331 (10.4), 296 (12.1), 277 (100), 240 (9.3), 199 (34.2), 183 (16.7), 135 (43.9), 73 (33.1); $C_{28}H_{45}N_3O_5SSi_2$ (591.9176) calcd C 56.82, H 7.66, N 7.10; found C 56.32, H 7.42 N 7.44.

**(2*S*,3*R*)-*N*-*tert*-Butoxycarbonyl-2-hydroxymethyl-3-*tert*-butyldiphenylsiloxy-pyrrolidine (13b).** $[\alpha]_D^{20}$ = -7.2 (c = 1.3, $CHCl_3$); $^1$H-NMR (250 MHz): δ = 1.06 (s, 9H), 1.48 (s, 9H), 1.60-1.74 (m, 1H), 1.74-1.92 (m, 1H), 3.10-3.22 (m, 1H), 3.36 ($m_c$, 1H), 3.76-3.96 (m, 2H), 4.08 ($m_c$, 1H), 4.22 ($m_c$, 1H), 4.33-4.43 (m, 1H), 7.36-7.52 (m, 6H), 7.64-7.72 (m, 4H); $^{13}$C-NMR (63 MHz): δ = -5.60, 14.14, 18.21, 19.26, 22.62, 25.82, 26.84, 32.55, 43.73, 59.32, 60.38, 66.47, 71.34, 72.77, 127.69, 128.33, 129.64, 133.33, 135.65, 154.42; IR (film, KBr): ν = 3437 s(br.), 3071 m, 3049 w, 2960 m, 2931 m, 2891 s, 2858 s, 1697 vs(br.), 1674 vs(br.), 1589 w, 1473 s, 1427 s, 1407 vs(br.), 1367 s, 1255 m, 1174 vs, 1112 vs, 1041 s, 822 s, 740 s, 702 vs, 610 s, 509 s cm$^{-1}$; MS (80 eV, EI, 200 °C), m/z (%): 454 (0.4), 424 (0.6), 398 (1.3), 382 (4.8), 342 (100), 324 (8.4), 290 (7.1), 199 (29.6), 135 (9.3), 91 (14.2), 57 (19.3); $C_{26}H_{37}NO_4Si$ (455.6681) calcd C 68.53, H 8.18, N 3.07; found C 68.22, H 7.78 N 2.88.

**(2*R*,3*R*)-*N*-*tert*-Butyloxycarbonyl-3-*tert*-butyldiphenylsiloxy-pyrrolidine-2-carboxylic acid (24).** Alcohol **13b** (4.3 g, 9.4 mmol), dissolved in acetone (100 ml) was treated dropwise with *Jones* reagent (freshly prepared from $CrO_3$ (2 g), $H_2SO_4$ (2.7 g) and $H_2O$ (12 ml)) under vigorous stirring at 0 °C until a lasting orange-colouring was visible. 2-Propanol (1 ml) was added, and the mixture was filtered through celite and washed with acetone/HOAc 20:1. The solvents were evaporated, and the residue was purified by flash column chromatography

($CH_2Cl_2$/ MeOH/HOAc 94:5:1) to give **24** (3.9 g, 83%) as colorless viscous oil: $[\alpha]_D^{20}$ = +2.5 (c = 1.9, $CHCl_3$); $^1$H-NMR ([$D_6$]DMSO 500 MHz, 130 °C): δ = 1.07 (s, 9H), 1.40 (s, 9H), 1.80-1.92 (m, 2H), 3.45 (ddd, $J_1$ = 10 Hz, $J_2$ = 8.7 Hz, $J_3$ = 3 Hz, 1H), 3.55 (ddd, $J_1$ = 10.5 Hz, $J_2$ = 8.7 Hz, $J_3$ = 7.5 Hz, 1H), 4.22 (s, 1H), 4.58 (dt, $J_1$ = 3 Hz, $J_2$ = 2.8 Hz, 1H), 7.38-7.47 (m, 6H), 7.64-7.68 (m, 4H), 10.65 (s, 1H); $^{13}$C-NMR ([$D_6$]DMSO, 126 MHz, 130 °C $CDCl_3$): δ = 18.09, 26.06, 26.17, 27.47, 27.56, 32.01, 43.67, 67.36, 67.60, 75.66, 78.29, 127.00, 127.11, 129.13, 132.72, 132.83, 134.51, 134.58, 153.11, 170.66; IR (film, KBr): ν = 3441 m(br.), 3068 m, 3058 s, 3031 m, 2928 s, 2894 s, 2858 s, 1712 vs(br.), 1428 vs, 1361 s, 1113 s, 1054 s, 999 m, 925 m, 703 vs, 608 s, 505 s $cm^{-1}$; MS (80 eV, EI, 80 °C), m/z (%): 469 (0.1), 454 (0.2), 425 (0.6), 412 (3.1), 368 (2.5), 356 (100), 338 (5.4), 324 (2.2), 312 (78.4), 290 (7.7), 266 (9.8), 255 (6.8), 234 (8.5), 199 (37.0), 57 (17.0); $C_{26}H_{35}NO_5Si$ (469.6517) calcd C 66.49, H 7.51, N 2.98; found C 66.21, H 7.72 N 2.84.

***trans*-(2*R*,3*R*)-3-Hydroxyproline (25).** (0.5 g, 1.1 mmol) was dissolved in $CH_2Cl_2$ (50 ml), treated with $CF_3CO_2H$ (5 ml) and refluxed for 5 h. The solvents were evaporated and the residual solid was filtered through cellite washed with EtOAc/acetone 5:1 (100 ml) and with MeOH/$H_2O$ 2:1 (400 ml). The MeOH/$H_2O$-solution was evaporated to dryness and treated several times with aq. ion exchange resin (Dowex 50W·4). Recrystallization from aq. ethanol gave **25** (120 mg, 83%) as a colorless powder: m.p. 229-236 °C (decomp.) (lit.[11c], m.p. 232 °C); $[\alpha]_D^{20}$ = +18.4 (c = 1.2, $H_2O$) (lit.[11c], +18.8 (c = 0.14, $H_2O$); $^1$H-NMR ($D_2O$, 270 MHz): δ = 1.94-2.16 (m, 2H), 3.38-3.42 (m, 2H), 3.96 (s(br.), 1H), 4.56 (m, 1 H); $^{13}$C-NMR ( $D_2O$, 68 MHz): δ = 31.68, 44.72, 70.04, 74.22, 171.83; IR (film, KBr): ν = 3250 s, 3080 m, 2850 m, 1629 vs, 1580 s, 1470 s, 1410 m, 1380 m, 1290 m, 1107 m, 869 s $cm^{-1}$; MS (80 eV, EI, 250 °C), m/z (%): 86 (100), 74 (12.7), 69 (44.6), 57 (6.6); $C_5H_9NO_3$ (131.0582) calcd C 45.80, H 6.92, N 10.68; found C 45.51, H 6.66, N 10.29.