The Stereoselective Synthesis of Functionalized *trans*-2,5-Disubstituted Tetrahydrofurans

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Supporting Information

Contents:

General Procedure for the Addition of Titanium(IV) Enolates 3a-e to Lactol 2. To a solution of $TiCl_4$ (1.1 mmol) in CH_2Cl_2 (2.5 mL) at -23°C was added a solution of oxazolidinone **3a-e** (1.0 mmol) in CH_2Cl_2 (2.0 mL) followed by the addition of diisopropylethylamine (1.1 mmol) after 5 min. The reaction mixture was stirred at -23°C for 1 h and then a solution of lactol **2** (1.1 mmol) in CH_2Cl_2 (2.5 mL) was added dropwise. The reaction mixture was stirred at -23°C for 1 h, and then quenched with satd. aq. NH_4Cl (4 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 3 mL), the combined organic phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was taken up in CH_3CN (10 mL) and aq. HF 40% was added dropwise until total deprotection (TLC control). Then the reaction mixture was quenched with satd. aq. $NaHCO_3$ (5 mL). The aqueous phase was extracted with Et_2O (3 x 3 mL), the combined organic phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel to afford the adducts.

3-{(2'*S*)-2-[(2*S*,5*S*)-5-(*tert*-Butyldiphenylsiloxymethyl)-tetrahydro-2-furanyl]-propanoyl}-1,3-oxazolan-2-one (5a). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.96 (s, 9H), 1.04 (d, *J*=6.8 Hz, 3H), 1.53-1.63 (m, 1H), 1.68-1.75 (m, 1H), 1.93-1.98 (m, 1H), 2.00-2.05 (m, 1H), 3.49 (dd, *J*=5.1, 10.5 Hz, 1H), 3.54 (dd, *J*=5.1, 10.5 Hz, 1H), 3.88 (dq, *J*=6.8, 9.3 Hz, 1H), 3.89-4.00 (m, 2H), 4.06 (quint, *J*=6.0 Hz, 1H), 4.12 (dt, *J*=6.3, 9.3 Hz, 1H), 4.18-4.29 (m, 2H), 7.18-7.35 (m, 6H), 7.58-7.62 (m, 4H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 13.9, 19.2, 26.7, 27.9, 29.9, 42.5, 42.7, 61.7, 66.4, 79.6, 81.5, 127.6, 129.5, 133.6, 135.6, 153.4, 175.8; IR (film) 1699, 1780 cm^{-1}; LRMS (EI) *m/z* 199 (100%, $[C_{12}H_{11}OSi]^+$), 424 (33, $[M-C_4H_9]^+$); HRMS (EI) *m/z* calcd for $C_{23}H_{26}NO_5Si$ $[M-C_4H_9]^+$ 424.15802, found 424.15821; $[\alpha]_D$ +16.6 (*c* 1.54, CH_2Cl_2).

3-{(2'*R*)-2-[(2*S*,5*S*)-5-(*tert*-Butyldiphenylsiloxymethyl)-tetrahydro-2-furanyl]-propanoyl}-1,3-oxazolan-2-one (4a). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.27 (d, *J*=6.8 Hz, 3H), 1.62-1.70 (m, 1H), 1.83-1.92 (m, 1H), 1.94-2.03 (m, 1H), 2.05-2.11 (m, 1H), 3.65 (d, *J*=4.7 Hz, 2H), 3.92 (quint, *J*=6.8 Hz, 1H), 3.94-4.02 (m, 2H), 4.09-4.14 (m, 1H), 4.21-4.26 (m, 1H), 4.29-4.38 (m, 2H), 7.36-7.41 (m, 6H), 7.67-7.70 (m, 4H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 13.2, 19.0, 26.6, 27.6, 29.7, 41.9, 42.6, 61.7, 66.3, 79.5, 80.3,

127.8, 129.7, 133.8, 135.8, 153.5, 175.8; IR (film) 1699, 1778 cm^{-1}; LRMS (EI) *m/z* 199 (100%, $[C_{12}H_{11}OSi]^+$), 424 (60, $[M\text{-}C_4H_9]^+$); HRMS (EI) *m/z* calcd for $C_{23}H_{26}NO_5Si$ $[M\text{-}C_4H_9]^+$ 424.15803, found 424.15864; $[\alpha]_D$ –6.5 (*c* 1.30, CH_2Cl_2).

(4*R*)-4-Benzyl-3-{(2'*S*)-2-[(2*S*,5*S*)-5-hydroxymethyltetrahydro-2-furanyl]-propanoyl}-1,3-oxazolan-2-one (5b). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.13 (d, *J*=6.8 Hz, 3H), 1.70-1.82 (m, 2H), 1.95-2.10 (m, 2H), 2.10-2.18 (m, 1H), 2.84 (dd, *J*=9.2, 13.6 Hz, 1H), 3.26 (dd, *J*=3.3, 13.6 Hz, 1H), 3.49 (dd, *J*=5.5, 11.4 Hz, 1H), 3.66 (dd, *J*=3.3, 11.4 Hz, 1H), 4.04 (dq, *J*=6.8, 9.3 Hz, 1H), 4.13-4.23 (m, 3H), 4.28-4.33 (m,1H), 4.69-4.75 (m, 1H), 7.22-7.36 (m, 5H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 13.7, 27.1, 29.9, 37.5, 42.7, 55.2, 64.7, 65.7, 79.4, 81.6, 127.3, 128.9, 129.6, 135.4, 153.4, 176.0; IR (film) 3467, 1693, 1776 cm^{-1}; LRMS (EI) *m/z* 101 (100%, $[C_5H_9O_2]^+$), 333 (43, $[M]^+$); HRMS (EI) *m/z* calcd for $C_{18}H_{23}NO_5$ $[M]^+$ 333.15762, found 333.15714; $[\alpha]_D$ –50.3 (*c* 1.10, CH_2Cl_2); m.p.: 151.5-152.5°C.

(4*S*)-4-Benzyl-3-{(2'*R*)-2-[(2*S*,5*S*)-5-hydroxymethyltetrahydro-2-furanyl]-propanoyl}-1,3-oxazolan-2-one (4c). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.27 (d, *J*=6.8 Hz, 3H), 1.66-1.85 (m, 2H), 1.94-2.08 (m, 1H), 2.09-2.18 (m, 1H), 2.33 (br s, 1H), 2.74 (dd, *J*=9.5, 13.2 Hz, 1H), 3.28 (dd, *J*=2.9, 13.2 Hz, 1H), 3.51 (dd, *J*=6.2, 11.7 Hz, 1H), 3.67 (dd, *J*=3.7, 11.7 Hz, 1H), 3.98 (quint, *J*=6.8 Hz, 1H), 4.08-4.23 (m, 3H), 4.27 (q, *J*=6.8 Hz, 1H), 4.66-4.73 (m, 1H), 7.22-7.37 (m, 5H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 13.3, 27.2, 29.8, 37.8, 41.9, 55.2, 64.8, 65.9, 79.7, 80.3, 127.4, 128.9, 129.5, 135.3, 153.3, 175.4; IR (film) 3467, 1693, 1776 cm^{-1}; LRMS (EI) *m/z* 302 (100%, $[M\text{-}CH_3O]^+$), 333 (10, $[M]^+$); HRMS (EI) *m/z* calcd for $C_{18}H_{23}NO_5$ $[M]^+$ 333.15762, found 333.15752; $[\alpha]_D$ +57.3 (*c* 0.52, CH_2Cl_2); m.p.: 91.4-93.2°C.

(4*S*)-4-Benzyl-3-{(2'*R*)-2-[(2*R*,5*S*)-5-hydroxymethyltetrahydro-2-furanyl]-propanoyl}-1,3-oxazolan-2-one (6c). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.17 (d, *J*=6.8 Hz, 3H), 1.71-1.79 (m, 1H), 1.83 (br s, 1H), 1.90-2.03 (m, 2H), 2.08-2.15 (m, 1H), 2.84 (dd, *J*=9.0, 13.4 Hz, 1H), 3.27 (dd, *J*=3.4, 13.4 Hz, 1H), 3.47 (dd, *J*=3.9, 12.0 Hz, 1H), 3.73 (dd, *J*=2.9, 12.0 Hz, 1H), 4.02 (dq, *J*=6.8, 9.3 Hz, 1H), 4.08-4.15 (m, 2H), 4.16-4.22 (m, 2H), 4.70-4.74 (m, 1H), 7.26-7.35 (m, 5H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.0, 27.0, 30.5, 37.4, 42.6, 55.6,

65.1, 65.7, 79.9, 83.0, 127.4, 129.0, 129.5, 135.4, 154.0, 176.1; IR (film) 3467, 1693, 1776 cm^{-1}; LRMS (EI) *m/z* 302 (100%, $[M\text{-}CH_3O]^+$), 333 (08, $[M]^+$); HRMS (EI) *m/z* calcd for $C_{18}H_{23}NO_5$ $[M]^+$ 333.15762, found 333.15775; $[\alpha]_D$ +62.3 (*c* 0.41, CH_2Cl_2); m.p.: 105.2-106.3°C.

(4*R*)-4-Benzyl-3-{2-[(2*S*,5*S*)-5-hydroxymethyltetrahydro-2-furanyl]-acetyl}-1,3-oxazolan-2-one (4/5d). To a solution of a 10:1 mixture of **5e/7e** (0.398 g, 1.00 mmol) in CH_2Cl_2 (2.0 mL) was added a catalitic amount (0.100 mmol) of AIBN. The reaction was stirred for 1 h at 80°C and Bu_3SnH (0.323 mL, 1.20 mmol) was added. After 1 h at 80°C it was cooled at room temperature and was added satd. aq. NH_4Cl (2 mL) and 10% KF aq. (2 mL). The mixture was stirred 1 h and 5 mL of Et_2O was added.. The layers were separated, the aqueous phase was extracted with Et_2O (3 x 3 mL), the combined organic phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was diluted with AcOEt (5 mL), filtered and the solvent was removed under reduced pressure. Silica gel chromatography (50% AcOEt in hexanes, v/v) of the crude product afforded a 10:1 mixture of **4/5d:6/7d** (0.267 g, 0.84 mmol) in 84% yield, as a colorless oil. The major diastereoisomer **4/5d** was isolated and characterized. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.55-1.76 (m, 3H), 1.85-2.04 (m, 1H), 2.09-2.18 (m, 1H), 2.73 (dd, *J*=9.2, 13.5 Hz, 1H), 2.96 (dd, *J*=5.1, 16.5 Hz, 1H), 3.24 (dd, *J*=2.9, 13.5 Hz, 1H), 3.30 (dd, *J*=8.1, 16.5 Hz, 1H), 3.45 (dd, *J*=5.9, 11.7 Hz, 1H), 3.62 (dd, *J*=3.3, 11.7 Hz, 1H), 4.08-4.18 (m, 3H), 4.45-4.53 (m, 1H), 4.59-4.67 (m, 1H), 7.13-7.29 (m, 5H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 27.1, 32.0, 37.8, 41.5, 55.1, 64.8, 66.1, 75.1, 79.2, 127.3, 128.9, 129.5, 135.1, 153.5, 170.9; IR (film) 3444, 1778, 1699 cm^{-1}; LRMS (EI) *m/z* 288 (100%, $[M\text{-}CH_3O]^+$), 319 (06, $[M]^+$); HRMS (EI) *m/z* calcd for $C_{17}H_{21}NO_5$ $[M]^+$ 319.14197, found 319.14191; $[\alpha]_D$ –41.2 (*c* 1.65, CH_2Cl_2).

(4*R*)-4-Benzyl-3-{(2'*S*)-2'-bromo-2-[(2*S*,5*S*)-5-hydroxymethyltetrahydro-2-furanyl]-propanoyl}-1,3-oxazolan-2-one (5e). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.79-1.89 (m, 2H), 2.01-2.11 (m, 2H), 2.30-2.38 (m, 1H), 2.93 (dd, *J*=8.4, 13.6 Hz, 1H), 3.24 (dd, *J*=2.9, 13.6 Hz, 1H), 3.52 (dd, *J*=5.5, 11.7 Hz, 1H), 3.69 (dd, *J*=3.3, 11.7 Hz, 1H), 4.14-4.32 (m, 3H), 4.70-4.77 (m, 2H), 5.61 (d, *J*=9,5 Hz, 1H), 7.23-7.36 (m, 5H); ^{13}C-NMR (75 MHz,

$CDCl_3$) δ 26.9, 30.2, 37.4, 43.7, 55.5, 64.6, 66.1, 79.7, 80.9, 127.6, 129.1, 129.6, 134.8, 152.9, 168.6; IR (film) 3448, 1778, 1603 cm^{-1}; LRMS (EI) *m/z* 91 (100%, $[C_7H_7]^+$), 397 (06, $[M]^+$); HRMS (EI) *m/z* calcd for $C_{17}H_{20}BrNO_5$ $[M]^+$ 397.05248, found 397.05240; $[\alpha]_D$ –121.5 (*c* 1.05, CH_2Cl_2); m.p.: 150.1-150.7°C.

General Procedure for the Reduction of N-Acyloxazolidinones. To a suspension of $LiBH_4$ (5.0 mmol) in THF (10.0 mL) at 0°C under argon, was added dropwise a solution of acyloxazolidinone (1.0 mmol) in THF (2.0 mL) and MeOH (4.0 mmol). The cooling bath was removed and the reaction was let to stir 3 h at room temperature. The reaction was then quenched with 1M aqueous solution of sodium potassium tartarate (5 mL) and stirred until both layers were clear. The mixture was poured into ether and water, the layers were separated and the aqueous phase was extracted with Et_2O (3 x 1 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude products was purified by flash chromatography on silica gel to afford the diols and the oxazolidinones.

(2'*R*)-2-[(2*S*,5*S*)-5-Hydroxymethyltetrahydro-2-furanyl]-propan-1-ol [(2'*R*, 2*S*, 5*S*)-8]. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.82 (d, *J*=6.8 Hz, 3H), 1.61-1.79 (m, 3H), 1.94-1.99 (m, 1H), 2.10-2.15 (m, 1H), 2.40 (br s, 2H), 3.51 (dd, *J*=5.9, 11.7 Hz, 1H), 3.62-3.69 (m, 3H), 3.82 (dt, *J*=5.6, 8.8 Hz, 1H), 4.13-4.18 (m, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 13.2, 26.8, 31.5, 40.6, 64.7, 68.3, 79.8, 85.3; IR (film) 3363, 1036 cm^{-1}; LRMS (EI) *m/z* 57 (100%, $[C_3H_5O]^+$), 129 (76, $[M\text{-}CH_3O]^+$); HRMS (EI) *m/z* calcd for $C_7H_{13}O_2$ $[M\text{-}CH_3O]^+$ 129.09155, found 129.09182; $[\alpha]_D$ +12.2 (*c* 0.35, CH_2Cl_2).

(2'*S*)-2-[(2*S*,5*S*)-5-Hydroxymethyltetrahydro-2-furanyl]-propan-1-ol [(2'*S*, 2*S*, 5*S*)-8]. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.92 (d, *J*=7.0 Hz, 3H), 1.63-1.83 (m, 2H), 1.88-2.02 (m, 3H), 2.55 (br s, 2H), 3.49 (dd, *J*=6.2, 11.7 Hz, 1H), 3.57 (dd, *J*=4.8, 11.0 Hz, 1H), 3.64 (dd, *J*=2.9, 11.7 Hz, 1H), 3.68 (dd, *J*=7.3, 11.0 Hz, 1H), 4.07-4.16 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 11.8, 27.3, 28.1, 38.3, 64.8, 65.9, 79.8, 82.1; IR (film) 3363, 1036 cm^{-1}; LRMS (EI) *m/z* 101 (100%, $[C_5H_9O_2]^+$), 129 (75, $[M\text{-}CH_3O]^+$); HRMS (EI) *m/z* calcd for $C_7H_{13}O_2$ $[M\text{-}CH_3O]^+$ 129.09155, found 129.09137; $[\alpha]_D$ +22.4 (*c* 0.38, CH_2Cl_2).

(2'*S*)-2-[(2*R*,5*S*)-5-Hydroxymethyltetrahydro-2-furanyl]-propan-1-ol [(2'*S*, 2*R*, 5*S*)-8]. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.84 (d, *J*=7.1 Hz, 3H), 1.60-1.70 (m, 1H), 1.71-1.82 (m, 2H), 1.85-1.94 (m, 1H), 2.00-2.09 (m, 1H), 2.45 (br s, 2H), 3.50 (dd, *J*=5.1, 11.7 Hz, 1H), 3.58-3.67 (m, 2H), 3.70-3.79 (m, 2H), 4.03-4.10 (m, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 13.6, 26.1, 30.7, 40.6, 64.9, 68.3, 80.0, 86.0; IR (film) 3384, 1036 cm^{-1}; LRMS (EI) *m/z* 57 (100%, $[C_3H_5O]^+$), 129 (71, $[M\text{-}CH_3O]^+$); HRMS (EI) *m/z* calcd for $C_7H_{13}O_2$ $[M\text{-}CH_3O]^+$ 129.09155, found 129.09181; $[\alpha]_D$ –21.3 (*c* 0.20, CH_2Cl_2).

2-[(2*S*,5*S*)-5-Hydroxymethyltetrahydro-2-furanyl]-ethan-1-ol [(2*S*,5*S*)-9]. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.50-1.76 (m, 6H), 1.88-2.06 (m, 2H), 3.43 (dd, *J*=6.1, 11.4 Hz, 1H), 3.58 (dd, *J*=3.3, 11.4 Hz, 1H), 3.73 (t, *J*=5.5 Hz, 2H), 4.07-4.14 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 27.2, 32.4, 37.4, 61.5, 64.9, 79.2, 79.4; IR (film) 3363, 1053 cm^{-1}; LRMS (EI) *m/z* 101 (100%, $[M\text{-}C_2H_5O]^+$), 115 (03, $[M\text{-}CH_3O]^+$); HRMS (EI) *m/z* calcd for $C_6H_{11}O_2$ $[M\text{-}CH_3O]^+$ 115.07590, found 115.07421; $[\alpha]_D$ -21.3 (*c* 0.20, CH_2Cl_2).