Anti Selective Aldol Reactions with Titanium Enolates of N-Glycolyloxazolidinethiones

Michael T. Crimmins* and Patrick J. McDougall

Venable and Kenan Laboratories of Chemistry, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, 27599

crimmins@email.unc.edu

Supporting Information

For oxazolidinethione auxiliary synthesis see: Crimmins, M.T.; King, B.W.; Tabet, E.A.; Chaudhary, K. *J. Org. Chem.* **2001**, 66, 894-902.

General Procedure for substrate synthesis (4,5,6). To a dry round-bottom flask containing 100 mL CH₂Cl₂ was added 53.6 mmol of the alkoxy acetic acid and 0.207 mL (2.68 mmol) of DMF. The solution was cooled to 0° C followed by dropwise addition of 29.5 mL (59 mmol) oxalyl chloride (2.0 M in CH₂Cl₂). The reaction was allowed to warm to room temperature and stirred for 1 hour. Evaporation of most of the solvents gave the unpurified acyl chloride. To a separate dry flask was added 5.18 g (26.8 mmol) oxazolidinethione **2** in 200 mL THF. The solution was cooled to -78° C followed by dropwise addition of 20.1 mL (32.2 mmol) of n-butyllithium (1.6 M in hexanes). The solution was allowed to stir for 15 min at -78° C followed by the dropwise addition of the acyl chloride. The reaction was allowed to warm to room temperature and stirred for 1.5 hrs. The reaction was quenched with saturated NaHCO₃ and extracted twice with EtOAc. The combined organic layers were dried over Na₂SO₄ and concentrated. Purification of the residue by column chromatography afforded the acylated substrate. Yields ranged from 60-80%. (Compound **4** could also be recrystallized from Et₂O/Hex for enhanced purity.)

(4S)-3-allyloxyacetyl-4-benzyl-1,3-oxazolidine-2-thione (**4**)

[α]_D²² +107° (c = 0.90, CH₂Cl₂); IR (CH₂Cl₂) 3065, 2988, 2687, 2308, 1714, 1424, 1366, 1328, 1266, 1024 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 7.37-7.22 (m, 5H), 5.99 (ddt, J = 17.2, 10.4, 5.6 Hz, 1H), 5.40-5.35 (m, 1H), 5.30-5.26 (m, 1H), 5.12-4.93 (m, 3H), 4.42-4.37 (m, 2H), 4.22-4.17 (m, 2H), 3.32 (dd, J = 13.2, 3.2 Hz, 1H), 2.82 (dd, J = 13.6, 10.0 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ 184.7, 171.0, 134.6, 133.8, 129.4, 129.0, 127.5, 118.2, 72.47, 71.39, 59.76, 37.51.

(4S)-3-benzoyloxyacetyl-4-benzyl-1,3-oxazolidine-2-thione (**5**)

[α]_D²² +96.7° (c = 0.55, CH₂Cl₂); IR (CH₂Cl₂) 3056, 2989, 2688, 2308, 1713, 1422, 1355, 1322, 1198 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 7.43-7.19 (m, 10H), 5.06 (dd, J = 37.6,

18.0 Hz, 2H), 4.68 (s, 2H), 4.39_4.32 (m, 2H), 3.29 (dd, $J = 13.2, 3.2$ Hz, 1H), 2.84_2.76 (m, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) _ 184.7, 171.0, 137.2, 135.0, 129.4, 129.1, 128.5, 128.1, 128.0, 127.5, 73.56, 71.53, 71.40, 59.79, 37.56.

(4S)-3-methoxyacetyl-4-benzyl-1,3-oxazolidine-2-thione (6)

$[\alpha]_{\text{D}}^{22} + 114^\circ$ ($c = 0.95$, CH_2Cl_2); IR (CH_2Cl_2) 3056, 2993, 2935, 2308, 1715, 1368, 1329, 1198 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) _ 7.34_7.18 (m, 5H), 5.03_4.88 (m, 3H), 4.38_4.36 (m, 2H), 3.50 (s, 3H), 3.27 (dd, $J = 13.2, 3.2$ Hz, 1H), 2.79 (dd, $J = 13.6, 10.0$ Hz, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) _ 184.7, 170.9, 134.9, 129.3, 129.0, 127.5, 73.96, 71.42, 59.71, 59.45, 37.52.

Anti-aldol data analysis

Due to difficulties in separating anti_aldol products from starting material, aldol adducts **7a-g** and **8a-b** were reduced to their corresponding 1,3_diols for analysis.

General reduction procedure. To a solution containing a mixture of 0.058 mmol of the starting material and 0.140 mmol aldol product and 5 mL diethyl ether at 0°C was added 0.011 mL (0.277 mmol) methanol and 0.139 mL (0.277 mmol) of lithium borohydride (2 M in THF). After stirring for 1 hour the reaction was quenched with Na^+/K^+ tartrate, warmed to room temperature, and allowed to stir for 1.5 hrs. The organic layer was extracted with ethyl acetate and separated. The aqueous layer was saturated with NaCl and extracted multiple times with dichloromethane. The organic layers were combined, dried over Na_2SO_4 , and concentrated. Purification of the residue by column chromatography afforded the diol. Yields ranged from 83-97%.

(2S, 3R)-2-allyloxybutan-1,3-diol: Diol of 7a

$[\alpha]_{\text{D}}^{22} + 5.8^\circ$ ($c = 0.36$, CH_2Cl_2); IR (CH_2Cl_2) 3586, 3053, 2984, 2308, 1424, 1266, 1096 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) _ 5.88 (ddt, $J = 17.2, 10.0, 6.0$ Hz, 1H), 5.27_5.21 (m, 1H), 5.20_5.17 (m, 1H), 4.09_4.02 (m, 2H), 3.96_3.85 (m, 1H), 3.78_3.68 (m, 2H), 3.19 (dt, $J = 4.8, 4.4$ Hz, 1H), 3.01 (bs, 1H), 2.88 (bs, 1H), 1.18 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) _ 134.6, 117.4, 82.20, 71.14, 67.97, 61.13, 18.91.

(2S, 3R)-2-allyloxyhexan-1,3-diol: Diol of 7b

$[\alpha]_{\text{D}}^{26} + 9.5^\circ$ ($c = 1.2$, CH_2Cl_2); IR (CH_2Cl_2) 3586, 3049, 2961, 2876, 2308, 1424, 1085 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) _ 5.90 (ddt, $J = 17.2, 10.4, 5.6$ Hz, 1H), 5.29_5.23 (m, 1H), 5.18_5.15 (m, 1H), 4.11_4.05 (m, 2H), 3.82_3.70 (m, 3H), 3.25 (dt, $J = 4.8, 4.0$ Hz, 1H), 2.64 (bs, 2H), 1.56_1.34 (m, 4H), 0.91 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) _ 134.6, 117.4, 81.35, 71.49, 70.85, 61.00, 35.07, 19.09, 13.97.

(2S, 3R)-2-allyloxyoctan-1,3-diol: Diol of 7c

$[\alpha]_{\text{D}}^{26} + 6.5^\circ$ ($c = 1.7$, CH_2Cl_2); IR (CH_2Cl_2) 3590, 2934, 2864, 1467, 1378, 1081 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) _ 5.90 (ddt, $J = 17.2, 10.4, 6.0$ Hz, 1H), 5.28_5.23 (m, 1H), 5.18_5.15 (m, 1H), 4.11_4.05 (m, 2H), 3.78_3.74 (m, 3H), 3.25 (dt, $J = 4.8, 4.0$ Hz, 1H), 2.69_2.64 (m, 2H), 1.49_1.42 (m, 3H), 1.36_1.26 (m, 5H), 0.90_0.84 (m, 3H); ^{13}C NMR

(CDCl₃, 100 MHz) _ 134.6, 117.4, 81.33, 71.78, 70.86, 61.00, 32.93, 31.77, 25.58, 22.53, 13.96.

(2S, 3R)-2-allyloxy-4-methylpentan-1,3-diol: Diol of 7d

$[\alpha]_D^{26}$ -3.0° (c = 0.26, CH₂Cl₂); IR (CH₂Cl₂) 3594, 3049, 2964, 2876, 2308, 1606, 1471, 1081 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) _ 5.90 (ddt, *J* = 17.2, 10.4, 6.0 Hz, 1H), 5.29_5.23 (m, 1H), 5.19_5.15 (m, 1H), 4.11_4.02 (m, 2H), 3.81_3.73 (m, 2H), 3.50 (dd, *J* = 5.2, 1.2 Hz, 1H), 3.43_3.38 (m, 1H), 2.57 (bs, 2H), 1.83_1.75 (m, 1H), 1.00 (d, *J* = 6.8 Hz), 0.89 (d, *J* = 6.8 Hz); ¹³C NMR (CDCl₃, 100 MHz) _ 134.5, 117.5, 79.18, 76.32, 70.61, 60.89, 29.65, 19.09, 17.90.

(2S, 3R)-2-allyloxy-pent-4-ene-1,3-diol: Diol of 7e

$[\alpha]_D^{25}$ +16.1° (c = 0.60, CH₂Cl₂); IR (CH₂Cl₂) 3690, 3601, 3053, 2988, 2887, 2687, 2308, 1606, 1424, 1266, 1108, 1042 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) _ 5.93_5.85 (m, 2H), 5.39_5.17 (m, 4H), 4.38_4.33 (m, 1H), 4.17_4.08 (m, 2H), 3.79_3.70 (m, 2H), 3.40_3.36 (m, 1H), 2.56 (m, 1H), 2.27_2.24 (m, 1H); ¹³C NMR (CDCl₃, 100 MHz) _ 136.7, 134.5, 117.6, 116.4, 81.08, 72.76, 71.19, 61.36.

(2S, 3R)-2-allyloxy-hex-4-ene-1,3-diol: Diol of 7f

$[\alpha]_D^{26}$ -1.6° (c = 0.50, CH₂Cl₂); IR (CH₂Cl₂) 3598, 3057, 2988, 2687, 2308, 1424, 1266 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) _ 5.96_5.86 (m, 1H), 5.81_5.72 (m, 1H), 5.54_5.47 (m, 1H), 5.30_5.25 (m, 1H), 5.20_5.16 (m, 1H), 4.29_4.26 (m, 1H), 4.17_4.08 (m, 2H), 3.77_3.68 (m, 2H), 3.36 (dd, *J* = 4.8, 4.8 Hz, 1H), 2.38 (bs, 1H), 2.23 (bs, 1H), 1.71 (d, *J* = 4.0 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz) _ 134.6, 129.6, 128.7, 117.5, 81.41, 72.87, 71.27, 61.54, 17.80.

(2S, 3R)-2-allyloxy-1-phenylpropan-1,3-diol: Diol of 7g

IR (CH₂Cl₂) 3598, 2930, 2887, 2370, 1621, 1455, 1390, 1096, 1058 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) _ 7.38_7.24 (m, 5H), 5.78 (ddt, *J* = 17.2, 10.4, 6.0 Hz, 1H), 5.24_5.11 (m, 2H), 4.89 (d, *J* = 5.2 Hz, 1H), 4.00_3.90 (m, 2H), 3.73_3.63 (m, 2H), 3.51_3.48 (m, 1H), 3.08 (bs, 1H), 2.43 (bs, 1H); ¹³C NMR (CDCl₃, 100 MHz) _ 140.8, 134.4, 128.3, 127.7, 126.2, 117.6, 82.16, 74.02, 71.24, 61.38, 51.36.

(2S, 3R)-2-benzyloxyoctan-1,3-diol: Diol of 8a

$[\alpha]_D^{26}$ +13.8° (c = 0.85, CH₂Cl₂); IR (CH₂Cl₂) 3690, 3601, 3053, 2988, 2934, 2308, 1606, 1424, 1266 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) _ 7.37_7.28 (m, 5H), 4.62 (s, 2H), 3.86_3.75 (m, 3H), 3.35 (dt *J* = 4.4, 4.0 Hz, 1H), 2.46_2.34 (m, 2H), 1.50_1.44 (m, 3H), 1.34_1.24 (m, 6H), 0.87 (t, *J* = 6.8 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz) _ 138.0, 128.5, 128.0, 127.9, 81.45, 71.90, 61.06, 32.90, 31.78, 25.57, 22.55, 13.99.

(2S, 3R)-2-benzyloxy-pent-4-ene-1,3-diol: Diol of 8b

$[\alpha]_D^{26}$ +14.1° (c = 0.75, CH₂Cl₂); IR (CH₂Cl₂) 3682, 3601, 2930, 2880, 1606, 1355, 1208, 1096 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) _ 7.36_7.24 (m, 5H), 5.95_5.86 (m, 1H), 5.39_5.34 (m, 1H), 5.25_5.21 (m, 1H), 4.69_4.61 (m, 1H), 4.40_4.37 (m, 1H), 3.80_3.73 (m, 2H), 3.44 (dt, *J* = 4.8, 4.4 Hz, 1H), 2.63 (bs, 1H), 2.30 (bs, 1H); ¹³C NMR (CDCl₃, 100 MHz) _ 136.8, 128.6, 128.5, 128.0, 127.9, 116.5, 81.25, 72.82, 72.22, 61.38.

[3(2_R, 3_R), 4S]-3-(2_-methoxy-3_-hydroxybutanoyl)-4-benzyl-1,3-oxazolidine-2-thione (9a):

$[\alpha]^{27}_D +276^\circ$ ($c = 0.70$, CH_2Cl_2); IR (CH_2Cl_2) 3053, 2984, 2937, 2308, 1718, 1366, 1328, 1197 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 7.33_7.20 (m, 5H), 5.90 (d, $J = 5.6$ Hz, 1H), 5.08_5.02 (m, 1H), 4.39_4.36 (m, 2H), 4.17_4.14 (m, 1H), 3.40 (s, 3H), 3.26 (dd, $J = 13.6, 3.6$ Hz, 1H), 2.75 (dd, $J = 13.2, 10.0$ Hz, 1H), 2.66 (bd, $J = 8.4$ Hz, 1H) 1.34 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 186.0, 172.5, 134.8, 129.4, 129.0, 127.5, 82.70, 71.13, 69.44, 60.12, 58.52, 37.59, 19.33.

[3(2_R, 3_R), 4S]-3-(2_-methoxy-3_-hydroxyoctanoyl)-4-benzyl-1,3-oxazolidine-2-thione (9b):

$[\alpha]^{23}_D +222^\circ$ ($c = 0.70$, CH_2Cl_2); IR (CH_2Cl_2) 3049, 2988, 2934, 2308, 1710, 1424, 1370, 1316, 1189 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 7.34_7.21 (m, 5H), 5.93 (d, $J = 6.8$ Hz, 1H), 5.08_5.02 (m, 1H), 4.40_4.34 (m, 2H), 3.94_3.88 (m, 1H), 3.38 (s, 3H), 3.28 (dd, $J = 13.6, 3.6$ Hz, 1H), 2.75 (dd, $J = 13.6, 10.0$ Hz, 1H), 2.55 (d, $J = 10.4$ Hz, 1H), 2.02_1.55 (m, 2H), 1.41_1.23 (m, 6H), 0.89_0.85 (m, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 186.2, 172.9, 134.9, 129.4, 129.0, 127.5, 81.96, 73.58, 71.07, 60.19, 58.41, 37.45, 33.67, 31.62, 25.15, 22.54, 13.97.

3(2_R, 3_R), 4S]-3-(2_-methoxy-3_-hydroxypent-4-enoyl)-4-benzyl-1,3-oxazolidine-2-thione (9c):

$[\alpha]^{23}_D +220^\circ$ ($c = 0.69$, CH_2Cl_2); IR (CH_2Cl_2) 3065, 2988, 2687, 2308, 1710, 1424, 1370, 1328, 1266, 1200 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 7.34_7.21 (m, 5H), 6.11_6.03 (m, 2H), 5.41_5.36 (m, 1H), 5.29_5.27 (m, 1H), 5.06_5.00 (m, 1H), 4.59_4.53 (m, 1H), 4.41_4.33 (m, 2H), 3.42 (s, 3H), 3.26 (dd, $J = 13.2, 3.2$ Hz, 1H), 2.89 (d, $J = 9.6$ Hz, 1H), 2.71 (dd, $J = 13.6, 10.4$ Hz, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 185.9, 171.7, 136.0, 134.9, 129.4, 129.1, 127.5, 117.2, 81.43, 73.55, 71.16, 60.19, 58.63, 37.66.

Syn adducts:

3(2_S, 3_R), 4S]-3-(2_-allyloxy-3_-hydroxyhexanoyl)-4-benzyl-1,3-oxazolidine-2-thione: Syn w/ butyraldehyde

$[\alpha]^{21}_D +13.5^\circ$ ($c = 1.1$, CH_2Cl_2); IR (CH_2Cl_2) 3056, 2989, 2308, 2254, 1702, 1366, 1328, 1198 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 7.34_7.21 (m, 5H), 6.04 (d, $J = 1.6$ Hz, 1H), 5.94 (ddt, $J = 17.2, 10.4, 6.0$ Hz, 1H), 5.36_5.30 (m 1H), 5.26_5.23 (m, 1H), 4.91_4.86 (m, 1H), 4.35_4.21 (m, 3H), 4.03_3.98 (m, 2H), 3.36 (dd, $J = 13.2, 3.2$ Hz, 1H), 2.80 (dd, $J = 13.2, 10.0$ Hz, 1H), 2.05 (bs, 1H), 1.69_1.47 (m, 4H), 1.42_1.33 (m, 1H), 0.92 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 185.2, 172.2, 135.1, 133.9, 129.4, 129.0, 127.5, 118.6, 79.37, 72.24, 72.05, 70.93, 60.97, 37.49, 36.39, 18.87, 13.97.

3(2_S, 3_R), 4S]-3-(2_-allyloxy-3_-hydroxyhex-4-enoyl)-4-benzyl-1,3-oxazolidine-2-thione: Syn w/ crotonaldehyde

$[\alpha]^{22}_D +39.0^\circ$ ($c = 0.85$, CH_2Cl_2); IR (CH_2Cl_2) 3056, 2927, 2308, 1710, 1605, 1366, 1328, 1196 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 7.34_7.20 (m, 5H), 6.18 (d, $J = 3.2$ Hz, 1H), 5.97_5.88 (m, 1H), 5.80_5.73 (m, 1H), 5.65_5.59 (m, 1H), 5.36_5.31 (m, 1H),

5.25_5.22 (m, 1H), 4.87_4.81 (m, 1H), 4.45 (bs, 1H), 4.34_4.31 (m, 1H), 4.26_4.19 (m, 2H), 4.10_4.06 (m, 1H), 3.18 (dd, $J = 13.2, 3.2$ Hz, 1H), 2.79 (dd, $J = 13.2, 10.0$ Hz, 1H), 2.52 (bs, 1H), 1.69 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) _ 185.2, 171.9, 135.1, 133.9, 129.4, 129.1, 129.01, 128.98, 127.5, 118.6, 79.48, 73.61, 72.24, 70.83, 60.89, 37.47, 17.69.

Correlation Studies:

Interception of **7a** with structure (**9a**)