Regio- and Stereocontrolled Metal-Mediated Carbonyl Propargylation or Allenylation of Enantiomerically Pure Azetidine-2,3-diones. Synthesis of Highly Functionalized 3-Substituted 3-hydroxy-β-lactams

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Procedure for the Synthesis of (+)-4-[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-1-(4-pentynyl)-azetidine-2,3-dione, (+)-1d. Acetoxyacetyl chloride (5.93 g, 43 mmol), in anhydrous dichloromethane (35 mL), was added dropwise via syringe to a solution of the 2,3-*O*-(isopropylidene)-D-glyceraldehyde derived imine (5.65 g, 29 mmol) and Et_3N (12.1 mL, 87 mmol) in dichloromethane (140 mL), at 0 ºC under argon. The resulting mixture was allowed to warm to room temperature, and was stirred for 16 h. The crude mixture was diluted with CH_2Cl_2 (100 mL) and washed with saturated $NaHCO_3$ (2 x 20 mL) and brine (40 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue eluting with EtOAc/hexanes (1/2) gave 5.56 g (65%) of **(–)-(3*R*,4*S*)-3-acetoxy-4-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-1-pentynyl-2-azetidinone** as a colorless solid. Mp: 78-79 ºC (hexanes/ethyl acetate). $[\alpha]_D$ = - 4.5 (*c* 0.8, $CHCl_3$). ^{1}H-NMR: δ 1.34 and 1.43 (s, each 3H), 1.85 (m, 2H), 1.98 (t, 1H, *J* = 2.7 Hz), 2.11 (s, 3H), 2.24 (td, 2H, *J* = 7.0, 2.7 Hz), 3.37 (td, 1H, *J* = 13.7, 6.3 Hz), 3.55 (m, 1H), 3.56 (dd, 1H, *J* = 8.8, 5.8 Hz), 3.78 (dd, 1H, *J* = 9.0, 4.9 Hz), 3.94 (dd, 1H, *J* = 8.8, 6.6 Hz), 4.21 (dt, 1H, *J* = 9.0, 6.1 Hz), 5.77 (d, 1H, *J* = 4.9 Hz). ^{13}C-NMR: δ 169.2, 164.5, 109.9, 82.9, 76.3, 69.0, 66.3, 60.4, 60.3, 41.1, 26.7, 26.1, 25.0, 20.4, 16.2. IR (KBr): ν 1760, 1748. MS (EI), *m/z* : 296 (M^+ + 1, 15), 295 (M^+, 100). (Anal. Calcd for $C_{15}H_{21}NO_5$: C, 61.00; H, 7.17; N, 4.74. Found: C, 61.10; H, 7.05; N, 4.62). Sodium methoxide (341 mg, 6.30 mmol) was added in portions at room temperature to a solution of the above acetoxy-β-lactam (1.86 g, 6.30 mmol) in methanol (60 mL). The reaction was stirred for 20 min. and then water was added (10 mL). The methanol was removed under reduced pressure, the aqueous residue was extracted with ethyl acetate (4 x 20 mL) and the organic layer was dried ($MgSO_4$). The solvent was removed under reduced pressure, and 1.52 g (95%) of analytically

pure **(+)-(3*R*,4*S*)-4-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-hydroxy-1-(*p*-methoxyphenyl)-2-azetidinone** was obtained. Colorless solid. Mp: 133-135 ºC (hexanes/ethyl acetate). $[\alpha]_D$ = + 14.1 (*c* 0.7, $CHCl_3$). ^{1}H-NMR: δ 1.34 and 1.44 (s, each 3H), 1.85 (m, 2H), 1.98 (t, 1H, *J* = 2.4 Hz), 2.22 (tt, 2H, *J* = 7.3, 2.4 Hz), 3.33 (dt, 1H, *J* = 13.7, 6.3 Hz), 3.50 (dt, 1H, *J* = 13.7, 6.8 Hz), 3.69 (dd, 1H, *J* = 8.3, 4.9 Hz), 3.76 (dd, 1H, *J* = 8.8, 5.4 Hz), 4.21 (dd, 1H, *J* = 8.8, 6.8 Hz), 4.33 (dd, 1H, *J* = 12.7, 6.8 Hz), 4.81 (d, 1H, *J* = 4.9 Hz), 5.22 (brs, 1H). ^{13}C-NMR: δ 170.5, 109.6, 82.9, 76.5, 74.9, 68.9, 66.7, 61.6, 40.7, 26.7, 26.1, 25.0, 16.2. IR (KBr, cm^{-1}): ν 3338, 1740. MS (EI), *m/z* : 254 (M^+ + 1, 18), 253 (M^+, 100). (Anal. Calcd for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.58; H, 7.44; N, 5.63). A solution of dimethyl sulfoxide (430 mg, 5.5 mmol) in dichloromethane (1.8 mL) was added dropwise to a stirred solution of oxalyl chloride (350 mg, 2.76 mmol) in dichloromethane (3.0 mL) at -78 ºC. After 20 min, a solution of the above alcohol (580 mg, 2.3 mmol) in dichloromethane (2.0 mL) was added and the mixture was stirred for 2h at -78 ºC. Triethylamine (1.78 mL) was added at -78 ºC, and the mixture was allowed to warm to room temperature. Water (5 mL) was added and the mixture was partitioned between dichloromethane and water. The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexane (1:1) gave 412 mg (71%) of azetidine-2,3-dione **(+)-1d** as a pale yellow solid. Colorless oil. $[\alpha]_D$ = + 33.4 (*c* 0.9, $CHCl_3$). ^{1}H-NMR: δ 1.34 and 1.46 (s, each 3H), 1.98 (m, 2H), 2.01 (t, 1H, *J* = 2.4 Hz), 2.32 (td, 2H, *J* = 7.0, 2.7 Hz), 3.68 (dt, 1H, *J* = 14.2, 6.5 Hz), 3.95 (m, 2H), 4.14 (m, 1H), 4.19 (d, 1H, *J* = 6.6 Hz), 4.26 (dd, 1H, *J* = 8.8, 6.8 Hz). ^{13}C-NMR: δ 193.5, 163.4, 110.4, 82.4, 74.8, 73.6, 69.6, 65.8, 42.2, 26.6, 25.7, 24.9, 16.3. IR ($CHCl_3$, cm^{-1}): ν 1770, 1740. MS (EI), *m/z* : 252 (M^+ + 1, 24), 251 (M^+, 100). (Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 62.06; H, 6.94; N, 5.47).

Zinc Promoted Reaction between Propargyl Bromide and Azetidine-2,3-dione (+)-1a. Synthesis of Homopropargyl Alcohol (+)-(3*R*,4*S*)-4-[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3-hydroxy-1-(*p*-methoxyphenyl)-3-(2-propynyl)-2-azetidinone, (+)-2a. Propargyl bromide (53 mg, 0.444 mmol) was added to a well stirred solution of the azetidine-2,3-dione **(+)-1a** (43 mg, 0.148 mmol) and zinc dust (58 mg, 0.89 mmol) in THF/NH_4Cl (aq. sat.) (1:5, 2.0 mL) at 0 ºC. The mixture was stirred at 0 ºC for 4 h, before being extracted with ethyl acetate (3 x 5 mL). The organic extract was washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of

the residue using dichloromethane/ethyl acetate (9:1) as an eluent gave 34 mg (70%) of isomerically pure compound **(+)-4a**, as a colorless oil. $[\alpha]_D$ = + 57.4 (*c* 1.0, $CHCl_3$). ^{1}H-NMR: δ 1.37 and 1.48 (s, each 3H), 2.09 (t, 1H, *J* = 2.4 Hz), 2.80 (t, 2H, *J* = 2.4 Hz), 3.80 (s, 3H), 3.94 (dd, 1H, *J* = 9.3, 6.8 Hz), 4.26 (d, 1H, *J* = 6.8 Hz), 4.28 (dd, 1H, *J* = 8.8, 6.8 Hz), 4.47 (m, 2H), 6.87 and 7.56 (d, 2H, *J* = 9.0 Hz). ^{13}C-NMR: δ 166.9, 156.9, 130.3, 120.2, 114.1, 109.9, 82.7, 76.3, 72.1, 72.0, 66.7, 65.7, 55.4, 26.4, 25.7, 25.2. IR ($CHCl_3$, cm^{-1}): ν 3346, 1744. MS (CI), *m/z* : 332 (M^+ + 1, 100), 331 (M^+, 32). (Anal. Calcd for $C_{18}H_{21}NO_5$: C, 65.24; H, 6.39; N, 4.23. Found: C, 65.32; H, 6.31; N, 4.19).

Zinc Promoted Reaction between Propargyl Bromide and Azetidine-2,3-dione (–)-1b. Synthesis of Homopropargyl Alcohol (-)-(3*R*,4*S*)-4-[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3-hydroxy-1-(2-propenyl)-3-(2-propynyl)-2-azetidinone, (–)-2b. Propargyl bromide (119 mg, 0.853 mmol) was added to a well stirred solution of the azetidine-2,3-dione **(–)-1b** (64 mg, 0.284 mmol) and zinc dust (111 mg, 1.70 mmol) in THF/NH_4Cl (aq. sat.) (1:6, 3.5 mL) at 0 ºC. The mixture was stirred at 0 ºC for 30 h, before being extracted with ethyl acetate (3 x 5 mL). The organic extract was washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using dichloromethane/ethyl acetate (9:1) as an eluent gave 40 mg (53%) of isomerically pure compound **(–)-2b**, as a colorless oil. $[\alpha]_D$ = - 49.5 (*c* 1.5, $CHCl_3$). ^{1}H-NMR: δ 1.35 and 1.45 (s, each 3H), 2.09 (t, 1H, *J* = 2.7 Hz), 2.69 (dd, 2H, *J* = 2.7, 1.5 Hz), 3.69 (d, 1H, *J* = 16.1 Hz), 3.75 (d, 1H, *J* = 6.8 Hz), 3.87 (dd, 2H, *J* = 9.0, 5.0 Hz), 4.19 (dd, 1H, *J* = 9.0, 7.0 Hz), 4.24 (ddt, 1H, *J* = 15.1, 4.9, 1.5 Hz), 4.37 (ddd, 2H, *J* = 11.7, 6.6, 4.9 Hz), 4.79 (s, 1H), 5.26 (m, 2H), 5.78 (m, 1H). ^{13}C-NMR: δ 169.4, 131.4, 119.1, 109.9, 83.1, 78.1, 75.8, 71.6, 66.6, 64.5, 43.8, 26.6, 25.3, 24.9. IR (KBr, cm^{-1}): ν 3343, 1745. MS (CI), *m/z* : 266 (M^+ + 1, 100), 265 (M^+, 22). (Anal. Calcd for $C_{14}H_{19}NO_4$: C, 65.24; H, 6.39; N, 4.23. Found: C, 65.32; H, 6.31; N, 4.19).

Indium Promoted Reaction between 1-Bromo-2-butyne and Azetidine-2,3-dione 1a. Synthesis of Homoallenyl Alcohol (+)-(3*R*,4*S*)-4-[(*S*)-2,2-Dimethyl-1,3-dio-xolan-4-yl]-3-hydroxy-3-(1-methyl-1,2-propadienyl)-1-(*p*-methoxyphenyl)-2-azeti-dinone, (+)-4a. 1-Bromo-2-butyne (69 mg, 0.52 mmol) was added to a well stirred solution of the azetidine-2,3-dione **(+)-1a** (50.5 mg, 0.173 mmol) and indium powder (119.1 mg, 1.04 mmol) in THF/NH_4Cl (aq. sat.) (1:8, 2.25 mL) at 0 ºC. The mixture was stirred at 0 ºC for 45 min, before being extracted with ethyl acetate (3 x 5 mL). The organic extract was washed with brine, dried ($MgSO_4$) and concentrated under

reduced pressure. Chromatography of the residue using EtOAc/hexanes (1:3) as an eluent gave 44 mg (74%) of isomerically pure compound **(+)-4a**, as as colorless oil. $[\alpha]_D$ = + 75.4 (*c* 0.7, $CHCl_3$). ^{1}H-NMR: δ 1.36 and 1.51 (s, each 3H), 1.85 (t, 3H, *J* = 3.0 Hz), 3.79 (s, 3H), 3.80 (dd, 1H, *J* = 8.8, 6.4 Hz), 4.14 (brs, 1H), 4.24 (d, 1H, *J* = 7.7 Hz), 4.32 (dd, 1H, *J* = 8.8, 6.8 Hz), 4.49 (q, 1H, *J* = 7.0 Hz), 4.98 (dd, 2H, *J* = 6.4, 3.0 Hz), 6.86 and 7.63 (dd, each 2H, *J* = 7.0, 2.5 Hz). ^{13}C-NMR: δ 205.2, 166.6, 156.7, 130.7, 120.0, 114.0, 109.7, 98.6, 83.5, 79.4, 76.8, 66.8, 66.5, 55.4, 26.6, 25.0, 13.9. IR (KBr, cm^{-1}): ν 3340, 1742. MS (CI), *m/z* : 346 (M^+ + 1, 100), 345 (M^+, 20). (Anal. Calcd for $C_{19}H_{23}NO_5$: C, 66.07; H, 6.71; N, 4.06. Found: C, 66.13; H, 6.65; N, 4.00).

Tin Promoted Reaction between 1-Bromo-3-phenyl-2-propyne and Azetidine-2,3-dione (+)-1a. Synthesis of Homoallenyl Alcohol (+)-(3*R*,4*S*)-4-[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3-hydroxy-3-(1-phenyl-1,2-propadienyl)-1-(*p*-metho-xyphenyl)-2-azetidinone, (+)-4c. 1-Bromo-3-phenyl-2-butyne (99.5 mg, 0.51 mmol) was added to a well stirred solution of the azetidine-2,3-dione **(+)-1a** (49.7 mg, 0.17 mmol) and tin powder (121.1 mg, 1.02 mmol) in THF/NH_4Cl (aq. sat.) (1:7, 2.25 mL) at 0 ºC. The mixture was allowed to warm to room temperature and was stirred at room temperature for 30 h, before being extracted with ethyl acetate (3 x 5 mL). The organic extract was washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using EtOAc/hexanes (1:3 containing 1% of triethylamine) as an eluent gave 52 mg (75%) of isomerically pure compound **(+)-4c**, as as colorless oil. $[\alpha]_D$ = + 48.22 (*c* 0.9, $CHCl_3$). ^{1}H-NMR: δ 1.36 and 1.46 (s, each 3H), 3.77 (dd, 1H, *J* = 8.8, 6.8 Hz), 4.00 (s, 1H), 4.28 (dd, 1H, *J* = 8.7, 6.8 Hz), 4.37 (d, 1H, *J* = 6.8 Hz), 4.55 (q, 1H, *J* = 6.8 Hz), 5.29 (s, 2H), 6.84 (dd, 2H, *J* = 7.0, 2.5 Hz), 7.28 (m, 1H), 7.35 (m, 2H), 7.57 (dd, 2H, *J* = 7.0, 2.5 Hz), 7.64 (m, 2H). ^{13}C-NMR: δ 207.6, 166.1, 156.7, 132.5, 130.7, 128.6, 128.4, 127.8, 120.1, 113.9, 109.8, 105.9, 84.2, 80.9, 76.5, 66.7, 66.3, 55.4, 26.4, 25.2. IR (KBr, cm^{-1}): ν 3341, 1744. MS (CI), *m/z* : 408 (M^+ + 1, 100), 407 (M^+, 28). (Anal. Calcd for $C_{24}H_{25}NO_5$: C, 70.75; H, 6.18; N, 3.44. Found: C, 70.67; H, 6.28; N, 3.38).