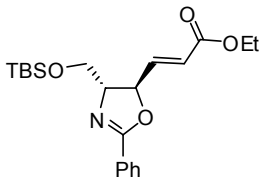
Supplementary Material for Organic & Biomolecular Chemistry

Electronic Supplementary Information

Stereoselective Synthesis of (+)-Polyoxamic Acid based on the Synthesis of Chiral Oxazine

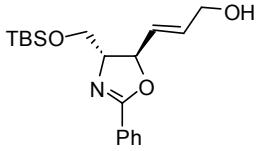
Jae-Eun Joo,[a] Van-Thoai Pham,[a] Yong-Shou Tian,[a] Yun-Sung Chung,[a] Chang-Young Oh,[b] Kee-Young Lee[b] and Won-Hun Ham*[a]

(*E*)-Ethyl 3-((4*R*,5*R*)-4-((*tert*-butyldimethylsilyloxy)methyl)-2-phenyl-4,5-dihydrooxazol-5-yl)acrylate (7)



Oxazoline **6** (5.0 g, 15.75 mmol) was dissolved in dry methanol (200 mL) and cooled to -78 °C. Ozone was passed through the solution until starting material had been consumed (TLC analysis). The reaction mixture was quenched with $(CH_3)_2S$ (5.0 mL) and allowed to warm to rt. The solvents were evaporated under reduced pressure. The crude aldehyde was immediately employed in the next step without further purification. To a stirred solution of LiCl (0.80 g, 18.90 mmol) in CH_3CN (100 mL) were added triethylphosphonoacetate (3.7 mL, 18.90 mmol), *N*,*N*-diisopropylethylamine (3.3 mL, 18.90 mmol) and stirring was allowed to continue for 1 h. The crude aldehyde in CH_3CN (50 mL) was added and the reaction mixture was stirred for 2 h. The reaction mixture was poured into H_2O (150 mL) and extracted with EtOAc(100 mL X 3). The organic layer was washed with brine, dried with $MgSO_4$ and evaporated *in vacuo*. Purification by silica gel chromatography (ethyl acetate:hexane = 1:6) gave (*E*)-α,β-unsaturated ester **7** (5.09 g**,** 83% yield, 2 steps) as a colorless oil; $[\alpha]_D^{25}$ -53.7 (c 1.0, $CHCl_3$); IR(neat) 3027, 2948, 1725, 1651, 1322 1274 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.11 (s, 3H), 0.12 (s, 3H), 0.84 (s, 9H), 1.23 (t, *J*=7Hz, 3H), 3.65 (dd, *J*=10, 7 Hz, 1H), 3.93 (dd, *J*=10, 4Hz, 1H), 4.10 (ddd, *J*=7, 7, 4Hz, 1H), 4.17 (q, *J*=7 Hz, 2H), 5.14 (ddd, *J*=7, 5, 1.5 Hz, 1H), 6.06 (dd, *J*=15.5, 5 hz, 1H), 6.96 (m, 1H), 7.35-7.38 (m, 2H), 7.42-7.46 (m, 1H), 7.93-7.95 (m, 2H); ^{13}C NMR (125MHz, $CDCl_3$) δ -5.13, -5.11, 14.42, 18.42, 26.02, 60.84, 64.88, 74.39, 81.03, 121.35, 127.55, 128.57, 128.62, 131.85, 145.51, 164.02, 166.18; HRMS (FAB^+) (M^+ +H) m/z calcd for $C_{20}H_{30}O_4NSi$ 390.2101 found 390.2096.

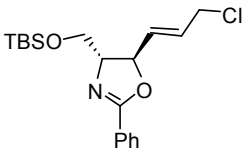
(*E*)-3-((4*R*,5*R*)-4-((*tert*-Butyldimethylsilyloxy)methyl)-2-phenyl-4,5-dihydrooxazol-5-yl)prop-2-en-1-ol (8)



i-Bu_2AlH (1.0 M solution in hexane, 39.7 mL, 39.7 mmol) was added to a solution of the α,β-unsaturated ester **7** (5.16 g, 13.25 mmol) in dry THF (130 mL) at -78 °C. The reaction mixture was stirred at -78 °C for 2 h and diluted with ether (130 mL) and sat. aqueous NH_4Cl (65 mL). After being stirred for 2 h at rt, the resulting suspension was filtered through celite pad. The filtrate was concentrated *in vacuo* to give the crude product, which upon purification by column chromatography on silica gel (ethyl acetate:hexane = 1:2) gave the allyl alcohol **8 (**4.55 g, 99%) as a colorless oil; $[\alpha]_D^{25}$ +6.6 (c 1.0, $CHCl_3$); IR(neat) 3271, 1644, 1495, 1450, 1331 cm^{-1}; ^1H NMR (500MHz, $CDCl_3$) δ 0.08 (d, 6H), 0.87 (s, 9H), 3.69 (dd, *J*=10.5, 6.5Hz, 1H), 3.90

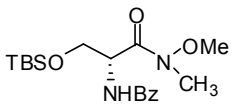
(dd, *J*=10.5, 4 Hz, 1H), 4.06 (ddd, *J*=6.5, 6.5, 4 Hz, 1H), 4.20 (d, *J*=5 Hz, 2H), 5.07 (dd, *J*=6.5, 6.5 Hz, 1H), 5.86 (dd, 15.5, 6.5 Hz, 1H), 5.98 (m, 1H), 7.41 (m, 2H), 7.48 (m, 1H), 7.96 (m, 1H) ^{13}C NMR (500MHz , $CDCl_3$) δ -5.10, -5.09, 18.43, 26.03, 62.77, 64.84, 74.26, 82.45, 127.90, 128.55, 129.57, 131.65, 132.02, 132.05, 164.21; HRMS (FAB$^+$) (M^++H) m/z calcd for $C_{19}H_{29}O_3NSi$ 348.1995 found 348.2000.

(4*R*,5*R*)-4-((*tert*-Butyldimethylsilyloxy)methyl)-5-((*E*)-3-chloroprop-1-enyl)-2-phenyl-4,5-dihydrooxazole (9)



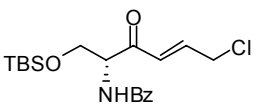
p-Toluenesulfonyl chloride (6.38 g, 33.45 mmol) and *N*,*N*-dimethylamino-pyridine (2.04 g, 16.73 mmol) were added to a stirred solution of above allyl alcohol (1.16 g, 3.35 mmol) in dry CH_2Cl_2 (35 mL) at rt and stirring was allowed to continue for 24 h. The reaction mixture was quenched with H_2O (50 mL) and extracted with CH_2Cl_2 (30 mL X 3). The organic layer was washed with brine, dried with $MgSO_4$ and evaporated *in vacuo*. Purification by silica gel chromatography (ethyl acetate : hexane = 1:6) gave allyl chloride **9** (1.05 g, 86% yield) as a colorless oil; $[\alpha]_D^{25}$ +6.3 (c 1.0, $CHCl_3$); IR(neat) 1649, 1494, 1450, 1328, 1061 cm^{-1}; ^{1}H NMR (500MHz, $CDCl_3$) δ 0.0 4 (d, 6H), 0.87 (s, 9H), 3.67 (dd, *J*=11, 7, 1H), 3.94 (dd, *J*=11, 4, 1H), 4.06-4.09 (m, 3H), 5.05 (dd, *J*=6, 6, 1H), 5.88 (m, 2H), 7.38 (m, 2H), 7.45 (m, 1H), 7.95 (m, 2H); ^{13}C NMR (125MHz, $CDCl_3$) δ -5.10, -5.90, 18.44, 26.04, 44.14, 64.93, 74.40, 81.97, 127.84, 128.01, 128.54, 128.57, 131.69, 133.18, 164.03; HRMS (FAB$^+$) (M^++H) m/z calcd for $C_{19}H_{29}O_2NSiCl$ 366.1656 found 366.1658.

(*R*)-*N*-(3,8,8,9,9-Pentamethyl-4-oxo-2,7-dioxa-3-aza-8-siladecan-5-yl)benzamide (11)



To a solution of *N*,*O*-dimethylhydroxylamine hydrochloride (867 mg, 8.89 mmol) in CH_2Cl_2 (10 mL) was added trimethylaluminum (4.45 mL of a 2 M solution in hexane, 8.89mmol) at 0 ^{o}C (Caution: CH_4-evolution). The mixture was stirred for 30 min at room temperature. Subsequently, a solution of *N*-benzoyl-*O*-TBS-L-serine methyl ester (1.00 g, 2.96 mmol) in CH_2Cl_2 (5 mL) was added dropwise. The mixture was stirred at room temperature for 1 hour, after which time TLC analysis indicated complete reaction. The reaction mixture was cooled to 0^{o}C and carefully quenched with 10% sodium potassium tartrate (2.20 mL). After being stirred for 1 h at room temperature, the resulting suspension was filtered through celite pad, washed with CH_2Cl_2. The filtrate was concentrated *in vacuo* to give the crude product, which upon purification by column chromatography on silica gel (ethyl acetate : hexane = 1:2) gave the Weinreb amide **11** (987 mg, 91% yield) as a colorless oil; $[\alpha]_D^{25}$ -4.28 (c 1.0, $CHCl_3$); IR (neat) 3326, 2931, 2857, 1644, 1111, 838 cm^{-1}; ^{1}H NMR (500MHz, $CDCl_3$) δ 0.02-0.05 (m, 6H), 0.92 (s, 9H), 3.29 (s, 3H), 3.83 (s, 3H), 3.96 (dd, *J*=4.5, 10.0 Hz, 1H), 4.06 (dd, *J*=4.5, 10.0 Hz, 1H), 5.25 (m, 1H), 7.09 (d, *J*=7.5 Hz, 1H), 7.44-7.52 (m, 3H), 7.83-7.85 (m, 2H); ^{13}C NMR (125MHz, $CDCl_3$) δ 0.02, 0.05, 23.76, 31.31, 57.48, 67.06, 68.73, 132.62, 134.07, 137.13, 139.26, 172.43; HRMS (FAB$^+$) (M^++H) m/z calcd for $C_{18}H_{31}N_2O_4Si$ 367.2053 found 367.2050.

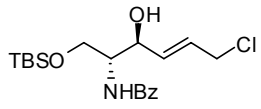
(*R*,*E*)-*N*-(1-(*tert*-Butyldimethylsilyloxy)-6-chloro-3-oxohex-4-en-2-yl)benzamide (13)



Vinyltin **12** (1.50 g, 4.09 mmol) was dissolved in dry THF (10 mL) and cooled to -78 ^{o}C. MeLi (1.6M solution in hexane, 2.60 mL, 4.09 mmol) was added dropwise. The mixture was stirred for 30 min at same temperature. Subsequently, a solution of Weinreb amide **11** (0.50 g, 1.36 mmol) in dry THF (5 mL) was added dropwise and stirring was allowed to continue for 30 min, after which time TLC

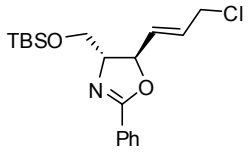
analysis indicated complete reaction. The reaction was quenched by sat. aqueous NH_4Cl (10 mL) then warmed to room temperature. The layers were separated and the aqueous layer was extracted with ethyl acetate (20 mL x 2). The combined organic layer washed with sat. $NaHCO_3$ solution (20 mL), brine (20 mL), dried with $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo*. The resulting substance was purified by silica gel column chromatography (ethyl acetate : hexane = 1:2) gave the amino ketone **13** (447 mg, 86% yield) as a colorless oil; $[\alpha]_D^{25}$ -6.11 (c 1.3, $CHCl_3$); IR (neat) ν_{max}: 3422, 2929, 2857, 1703, 1657, 1515, 1109, 837 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.03-0.09 (m, 6H), 0.87-0.91 (m, 9H), 4.02 (dd, *J*=4.5, 10.2 Hz, 1H), 4.26 (dd, *J*=3.0, 4.5 Hz, 1H), 4.27 (dd, *J*=1.8, 5.7 Hz, 2H), 5.06-5.11 (m, 1H), 6.67 (ddd, *J*= 1.5, 1.8, 15.3 Hz, 1H), 7.03-7.08 (m, 1H), 7.11 (d, *J*=3.0 Hz, 1H), 7.47-7.60 (m, 3H), 7.86-7.89 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -5.34, -5.32, 18.28, 25.95, 42.97, 59.67, 63.28, 127.29, 127.46, 128.36, 128.88, 132.02, 134.16, 141.50, 167.13, 195.89; HRMS (FAB^+) (M^++H) m/z calcd for $C_{19}H_{29}NO_3SiCl$ 382.1605 found 382.1606.

***N*-((*2R,3S,E*)-1-(*tert*-Butyldimethylsilyloxy)-6-chloro-3-hydroxyhex-4-en-2-yl)benzamide (14)**



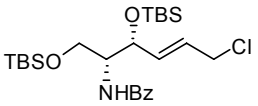
To a solution of amino ketone **13** (365 mg, 0.96 mmol) in ethanol (10 mL) was added lithium tri-*tert*-butoxyaluminohydride (1N solution in THF, 1.92 mL, 1.92 mmol) at –78 °C. After the reaction mixture was stirred at the same temperature for 2 h, 10% aq. solution of citric acid (10 mL) was added. The resulting mixture was warmed to room temperature and extracted with ethyl acetate (10 mL X 3). The organic layers were combined, washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give the crude products. The column chromatography on silica gel (ethyl acetate : hexane = 1:1) gave amino alcohol **14** (323 mg, 87% yield, ratio *anti:syn* = 10:1 by ^1H-NMR) as a colorless oil; $[\alpha]_D^{25}$ -4.22 (c 1.0, $CHCl_3$); IR (neat) ν_{max}: 3425, 3064, 2953, 2856, 1644, 1521, 1255, 1112, 837 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.08-0.13 (m, 6H), 0.92-0.95 (m 9H), 3.91 (dd, *J* = 3.0, 10.5 Hz, 1H), 3.99-4.03 (m, 1H), 4.05 (d, *J*=3.0, 5.4 Hz, 1H), 4.12 (d, *J*=6.0 Hz, 2H), 4.15-4.25 (m, 1H), 4.47-4.44 (m, 2H), 5.87-6.10 (m, 2H), 6.97 (d, *J*=8.1 Hz, 1H), 7.42-7.59 (m, 3H), 7.78-7.85 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -5.38, -5.35, 18.30, 54.03, 63.38, 73.74, 127.17, 127.99, 128.80, 128.91, 131.98, 134.32, 134.41, 167.86; HRMS (FAB^+) (M^++H) m/z calcd for $C_{19}H_{30}NO_3SiCl$ 384.1762 found 384.1764.

(4*R*,5*R*)-4-((*tert*-Butyldimethylsilyloxy)-methyl)-5-((*E*)-3-chloroprop-1-enyl)-2-phenyl-4,5-dihydrooxazole (9)



To a stirred solution of amino alcohol **14** (100 mg, 0.26 mmol), 4-nitrobenzoic acid (9 mg, 0.052 mmol) and triphenyl phosphine (103 mg, 0.39 mmol) in dry THF (4.00 mL) was added diethyl azodicarboxylate (40% in Toluene, 0.17 mL, 0.39 mmol) dropwise at room temperature and stirring was allowed to continue for 15 min, after which time TLC analysis indicated complete reaction. The reaction mixture was added the aqueous saturated sodium bicarbonate (3 mL) and the mixture was extracted with diethyl ether (5 mL x 2). The extracts were washed with brine (10 mL), dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (ethyl acetate : hexane = 1:8) gave the oxazoline **9** (85 mg, 89% yield) as colorless oil. The spectroscopic data of the resulting oxazoline **9** was completely identical to those formed from oxazoline **6**.

***N*-((5*R*,6*R*)-5-((*E*)-3-Chloroprop-1-enyl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecan-6-yl)benzamide (5)**



Aqueous 1N-HCl (14 mL, 14 mmol) was added to a stirred solution of allyl chloride **9** (1.03 g, 2.81 mmol) in THF (28 mL) and MeOH (28 mL) at rt and the reaction mixture was stirred for 12 h. Sat. aqueous $NaHCO_3$ (70 mL) was added, and stirring was allowed to continue for 3 h. The reaction mixture was extracted with EtOAc (50 mL X 4), washed with brine (50 mL), dried with $MgSO_4$ and evaporated *in vacuo*. Purification by silica gel chromatography (ethyl acetate : hexane = 1:1) gave alcohol (728 mg, 96% yield) as a white solid.

Imidazole (0.92 g, 13.46 mmol) and *tert*-butyldimethyl chlorosilane (2.03 g, 13.46 mmol) were added to a stirred solution of alcohol (605 mg, 2.24 mmol) in DMF (25 mL) at rt and stirring was allowed to continue for 2 h. The reaction mixture was quenched with H_2O (100 mL) and extracted with EtOAc (20 mL X 5). The organic layer was washed with brine, dried with $MgSO_4$ and evaporated *in vacuo*. Purification by silica gel chromatography (ethyl acetate : hexane = 1:8) gave silyl ether **5 (**1.04 g, 93% yield) as a colorless oil; $[\alpha]_D^{25}$ -0.7 (c 1.0, $CHCl_3$); IR (neat) ν_{max} : 2953, 2929, 2857, 1651, 1508, 1472, 1254, 1123, 965, 837, 777, 694 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.07-0.15 (m, 12H), 0.92 (s, 9H), 0.95 (s, 9H), 3.57 (dd, *J*=10, 9, 1H), 3.82 (dd, *J*=10, 4.5, 1H), 3.99 (m, 2H), 4.09 (m, 1H), 4.66 (dd, *J*=3.5, 3.5, 1H), 5.81 (m, 2H), 6.53 (d, *J*=9, 1H), 7.41 (m, 2H), 7.47 (m, 1H), 7.74 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: -5.20, -5.07, -4.79, -3.91, 18.37, 18.84, 26.03, 26.05, 26.09, 26.10, 26.15, 28.27, 44.52, 55.17, 60.76, 69.88, 127.01, 127.39, 128.12, 128.86, 130.01, 131.73, 134.75, 135.53, 167.13; HRMS (FAB^+) (M^++H) m/z calcd for $C_{25}H_{45}O_3NClSi_2$ 498.2627 found 498.2625.