Supplementary Material

The synthesis of CCL113

Conditions: (a) $SOCl_2$, MeOH, 0 ˚C→ rt, 2.5 h, 93%; (b) (i) PMBCl, KI, NaH, THF, 0˚C→ 50˚C, 2 h; (ii) $NaBH_4$, EtOH/THF=2/1, rt, 1.5 h, 73% (two steps); (c) (i) MeI, NaH, THF, rt, 1 h; (ii) CAN, MeCN/H_2O=100/1, rt, 2 h, 93% (two steps); (d) BsCl, NaH, KI, THF, 0˚C→ rt, 1 h, 74%; (e) PhSSPh, LHMDS, THF, -78˚C. 40 min, 30%; (f) (i) *m*CPBA, CH_2Cl_2, 0˚C, 15 min; (ii) PPh_3, toluene, 100˚C, 1.5 h, 53% (two steps). $SOCl_2$: Thionyl chloride; PMBCl: 4-methoxybenzyl chloride; CAN: Ceric ammonium nitrate; BsCl: Benzenesulfonyl chloride; PhSSPh: Diphenyl disulfide; LHMDS: Lithium bis(trimethylsilyl)amide; *m*CPBA: 3-chloroperoxybenzoic acid; PPh_3: Triphenylphosphine.

methyl (R)-5-oxopyrrolidine-2-carboxylate (2). To a solution of D-Pyroglutamic acid 1 (25 g, 193 mmol) in MeOH (200 ml) was added thionyl chloride (0.7 ml, 9.68 mmol) dropwise at 0˚C. After stirring for 30 min, the reaction mixture was warmed to room temperature and was stirred for 2 h. The solvent was removed under reduced pressure, and the residue was dissolved in CH_2Cl_2 and washed with water. The organic layer was dried over Na_2SO_4, filtered and concentrated to give 2 (26 g, 93%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): 2.19-2.28 (m, 1H), 2.30-2.53 (m, 3H), 3.78 (s, 3H), 4.27 (dd, *J*=5.2, 8.8 Hz, 1H), 6.54 (brs, 1H).

(R)-5-(hydroxymethyl)-1-(4-methoxybenzyl)pyrrolidin-2-one (3). To a solution of 2 (26 g, 181 mmol) in THF (360 ml) was added sodium hydride (60% dispersion in paraffin liquid, 8.0 g, 200 mmol) at 0˚C. After stirring for 30 min, 4-methoxybenzyl chloride (29 ml, 218 mmol) and potassium iodide (3.0 g, 18.1 mmol) were added, and the reaction mixture was warmed to 50˚C. After stirring for 1.5 h, the reaction mixture was cooled to 0˚C and was quenched with saturated aqueous NH_4Cl. The water layer was extracted three times with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated. To a solution of the residue in EtOH/THF (2/1, 360 ml) was added sodium borohydride (6.9 g, 181 mmol) at room temperature. After stirring for 1.5 h, the reaction mixture was cooled to 0˚C, and 1M aqueous HCl was added to quench the reaction. The solvent was removed under reduced pressure, and the residue was dissolved in ethyl acetate and washed with brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate=1/2 to 1/4) to give 3 (31 g, 73%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): 1.55 (brs, 1H), 1.92-2.10 (m, 2H), 2.35-2.44 (m, 1H), 2.52-2.60 (m, 1H), 3.49-3.59 (m, 2H), 3.74 (d, *J*=11.6 Hz, 1H), 3.80 (s, 3H), 4.27 (d, *J*=14.8 Hz, 1H), 4.67 (d, *J*=14.8 Hz, 1H), 6.86 (d, *J*=8.8 Hz, 2H), 7.21 (d, *J*=8.8 Hz, 2H).

(R)-5-(methoxymethyl)pyrrolidin-2-one (4). To a solution of 3 (22 g, 94 mmol) and methyl iodide (7.0 ml, 112 mmol) in THF (300 ml) was added sodium hydride (60% dispersion in paraffin liquid, 4.5 g, 112 mmol) at room temperature. After stirring for 1 h, the reaction mixture was cooled to 0˚C. Saturated aqueous NH_4Cl was added to quench the reaction. The water layer was extracted three times with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. To a solution of the residue in acetonitrile (100.0 ml) was added ceric ammonium nitrate (153 g, 282 mmol) in a mixture of acetonitrile and water (100/2, v/v, 102 ml) at room temperature. After stirring for 2 h, the reaction mixture was diluted with CH_2Cl_2 followed by filtration through Celite. The filtrate was added $NaHCO_3$ (153 g) and stirred for 5 min. The resulting slurry was filtered through Celite. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography ($CHCl_3$/MeOH=50/1 to 20/1) to give 4 (11 g, 93%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): 1.72-1.81 (m, 1H), 2.18-2.27 (m, 1H), 2.37-2.42 (m, 2H), 3.25 (dd, *J*=8.4, 9.2 Hz, 1H), 3.37 (s, 3H), 3.42 (dd, *J*=4.0, 9.2 Hz, 1H), 3.84-3.91 (m, 1H), 6.26 (brs, 1H).

(R)-5-(methoxymethyl)-1-(phenylsulfonyl)pyrrolidin-2-one (5). To a suspension of sodium hydride (60% dispersion in paraffin liquid, 408 mg, 10.2 mmol) and potassium iodide (1.8 g, 11.0 mmol) in THF (10 ml) was added a solution of 4 (1.1 g, 8.5 mmol) in THF (10 ml) at 0˚C, then the reaction mixture was warmed to room temperature. After stirring for 30 min, a solution of benzenesulfonyl chloride (1.5 ml, 11.9 mmol) in THF (10 ml) was added. After stirring for 30 min, the reaction mixture was cooled at 0˚C and was quenched with saturated aqueous NH_4Cl. The water layer was extracted three times with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate=4/1 to 3/1) to give 5 (1.7 g, 74%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): 2.05 (dd, *J*=9.6, 11.2 Hz, 1H), 2.16-2.35 (m, 2H), 2.67 (ddd, *J*=11.2, 11.2, 17.2 Hz, 1H), 3.21 (s, 3H), 3.54 (dd, *J*=2.0, 10.0 Hz, 1H), 3.75 (dd, *J*=4.0, 10.0 Hz, 1H), 4.47-4.51 (m, 1H), 7.54 (dd, *J*=7.6, 8.0 Hz, 2H), 7.64 (ddd, *J*=1.6, 7.6, 7.6 Hz, 1H), 8.08 (dd, *J*=1.6, 8.0 Hz, 2H).

(5R)-5-(methoxymethyl)-1-(phenylsulfonyl)-3-(phenylthio) pyrrolidin-2-one (6). To a solution of 5 (808 mg, 3.0 mmol) and diphenyl disulfide (786 mg, 3.6 mmol) in THF (15 ml) was added lithium bis(trimethylsilyl)amide (1.0 M solution in THF, 3.3 ml, 3.3 mmol) at -78˚C. The reaction mixture was allowed to warm to room temperature, and the stirring continued for 40 min. Saturated aqueous NH_4Cl was added to quench the reaction. The water layer was extracted three times with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate=4/1 to 1/1) to give 6 (343 mg, 30%) as a colorless oil and 5 (534 mg, 66%). ^{1}H NMR (400 MHz, $CDCl_3$): 2.13 (ddd, *J*=9.2, 11.2, 13.2 Hz, 1H), 2.42 (dd, *J*=8.8, 13.2 Hz, 1H), 3.22 (s, 3H), 3.52 (dd, *J*=2.4, 10.4 Hz, 1H), 3.79 (dd, *J*=3.2, 10.0 Hz, 1H), 4.06 (dd, *J*=8.8, 11.2 Hz, 1H), 4.29-4.32 (m, 1H), 7.18-7.26 (m, 3H), 7.35 (dd, *J*=1.2, 8.0 Hz, 2H), 7.53-7.57 (m, 2H), 7.65-7.69 (m, 1H), 8.05-8.08 (m, 2H).

(R)-5-(methoxymethyl)-1-(phenylsulfonyl)-1,5-dihydro-2H-pyrrol-2-one (CCL113). To a solution of 6 (343 mg, 0.91 mmol) in CH_2Cl_2 (10 ml) was added 3-chloroperoxybenzoic acid (contains 30% water, 223 mg, 0.91 mmol) at 0˚C. After stirring for 15 min, saturated aqueous $Na_2S_2O_3$ was added to quench the reaction. After the addition of saturated aqueous $NaHCO_3$, the water layer was extracted three times with CH_2Cl_2. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. To a solution of the residue in toluene (10 ml) was added triphenylphosphine (238 mg, 0.91 mmol) at room temperature, and the reaction mixture was warmed to 100˚C. After stirring for 1.5 h, the reaction

mixture was cooled to room temperature. The solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate=3/1 to 2/1) to give CCL113 (128 mg, 53%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): 3.30 (s, 3H), 3.66 (dd, *J*=6.4, 9.2 Hz, 1H), 4.03 (dd, *J*=3.6, 9.2 Hz, 1H), 4.88-4.92 (m, 1H), 6.06 (dd, *J*=1.2, 6.0 Hz, 1H), 7.31 (dd, *J*=1.6, 6.0 Hz, 1H), 7.55 (dd, *J*=7.6, 7.6 Hz, 2H), 7.64 (dd, *J*=7.6, 7.6 Hz, 1H), 8.08 (d, *J*=7.6 Hz, 2H).

Figure S1. CCL113 chemical synthesis.