Synthesis of a Chiral Aziridine Derivative as a Versatile Intermediate for HIV Protease Inhibitors

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Experimental procedure and physical properties of compounds

Preparation of dimethyl D-tartrate To a solution of D-tartaric acid (19.1 g, 127 mmol) in anhydrous methanol (60 mL) was slowly added thionyl chloride (48.3 mL, 665 mmol) at 0 ^{o}C. After an hour, the reaction mixture was heated to reflux for 3 hours, to give a pale yellow solution. Gaseous hydrogen and methanol were removed under reduced pressure. After extraction of the aqueous layer (40 mL) with ethyl acetate (40 mL X 8), combined ethyl acetate solution was dried over anhydrous $MgSO_4$, filtered, and concentrated to give a pale yellow oil (22.5 g, 126 mmol) : ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.40~3.42 (br s, 1H), 3.87 (s, 3H), 4.57 (s, 1H).

Preparation of compound 7 To a solution of dimethyl D-tartarate (22.5 g, 126 mmol) in anhydrous dichloromethane (300 mL) was added *p*-toluenesulfonic acid monohydrate (12.0 g, 63.0 mmol) and 2,2-dimethoxypropane (101 mL, 825 mmol) at room temperature. Then the reaction mixture was heated to reflux for 4 hours, and was concentrated under reduced pressure. After extraction of water solution (40 mL) with ethyl acetate (100 mL), ethyl acetate solution was dried over anhydrous $MgSO_4$, filtered, and concentrated to give a reddish oil **7** (24.1 g, 124 mmol) : ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50 (s, 6H), 3.83 (s, 6H), 4.82 (s, 2H)

※ A direct synthetic procedure of **7** from D-tartaric acid is also available in *Organic Synthesis*, vol VIII, Freeman, John Wiley & Sons. Inc., pp. 155-156, **1990**, in which the yield was reported to be 85-92%.

Preparation of compound 8 To a solution of **7** (24.0 g, 124 mmol) in anhydrous methanol (400 mL) was slowly added sodium borohydride (23.4 g, 618 mmol) at 0^{o}C. The reaction temperature

was allowed to rise to room temperature. After the reaction mixture was stirred for 4 hours, it was concentrated under reduced pressure. Then the mixture was transferred to a separatory funnel, and distilled water (400 mL) was added. After extraction with ethyl acetate (400 mL X 4), the organic solution was dried over anhydrous $MgSO_4$, filtered, and concentrated to give a pale yellow oil (17.2 g, 106 mmol) : ^{1}H NMR (300 MHz, $CDCl_3$) 1.44 (s, 6H), 2.52 (br s, 2H), 3.69~3.82 (m, 4H), 4.00~4.01 (m, 2 H)

Preparation of compound 9 To a solution of **8** (17.2 g, 106 mmol) in acetonitrile (300 mL) were added triethylamine (34.0 mL, 244 mmol), lithium chloride (40.0 g, 944 mmol), and methanesulfonyl chloride (17.3 mL, 224 mmol) in sequence at 0^{o}C. After stirring for 30 minutes, the reaction mixture was heated to reflux overnight. Then the mixture was concentrated under reduced pressure and extracted with ethyl acetate (500 mL X 2) from aqueous sodium bicarbonate solution. After being dried over anhydrous $MgSO_4$, the mixture was filtered and concentrated to give a dark brown liquid. The nonpolar dark brown impurity was separated by extraction of the liquid with water (200 mL) and n-hexane (200 mL). After extraction of the aquous solution with ethyl acetate (200x4 mL), the ethyl acetate solution was dried over anhydrous $MgSO_4$, filtered, and concentrated to give white crystalline **9** (8.35 g, 52.5 mmol, 50% from **8**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.58 (br s, 2H), 3.64~3.76 (m, 4H), 3.96~3.98 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 45.85, 71.02.

Preparation of 1,4-Dichlorobutan-2(*S*),3*(S)*-diol sulfate (10)

A three-necked round-bottomed flask equipped with a reflux condenser and topped with a $CaCl_2$ drying tube connected to an HCl trap, a stopper, and a rubber septum was charged with 1,4-dichlorobutane-2(*S*),3(*S*)-diol (159 mg, 1.0 mmol) and CCl_4 (1 mL). Thionyl chloride (88 □, 1.2 mmol) was added via a syringe to the flask, and the resulting solution was refluxed for 30 min. The reaction mixture was concentrated by rotary evaporation, the residue was pumped under reduced pressure for 1 h, and to this residue was added a cold solution of CCl_4 (3 mL) and CH_3CN (3 mL). The flask was cooled in an ice bath and cold water (4.5 mL) was added. $RuCl_3.H_2O$ (1.15 mg, 0.01 mmol) and $NaIO_4$ (0.428 g, 2.0 mmol) were added at once and the reaction mixture was stirred vigorously at 0^{o}C. After stirring for 1 h, ether (6 mL) was added and layers were separated. The aqueous layer was extracted with ether (2.5 mLx3). The combined organic layers were washed with brine (3 mL), dried over anhydrous $MgSO_4$ and concentrated to give **10** (206.4 mg, 93 %) as a white solid: Rf (silica gel; 33 % EtOAc in *n*-Hex) 0.65; $[\alpha]_{D^{25}}$ = +57.5 (*c* 1.02, MeOH); ^{1}H NMR (200 MHz, , $CDCl_3$) δ 5.02 (2H, m), 3.93 (4H, m); ^{13}C NMR (125 MHz, , $CDCl_3$) δ 81.15, 41.73; IR (KBr pallet) 2979,1384, 1209, 1021, 985, 896, 653 cm^{-1}.

Preparation of *N*-(1,4-Dichloro-2(*S*)-hydroxy-3(*R*)-butyl)phthalimide (11)

A mixture of 1,4-dichlorobutane-2(*S*),3*(S)*-diol sulfate (57.2 mg, 0.258 mmol) and phthalimide

potassium salt (51.4 mg, 0.272 mmol) in dry DMF (1.3 mL) was stirred under nitrogen atmosphere at rt for 1 h. Solvent was removed under reduced pressure. The residue was dissolved with dry THF (3 mL). To the resulting solution were added conc. H_2SO_4 (13 μL) and water (5 μL) were added. After 30 min excess sodium bicarbonate (~52 mg) was added and the reaction mixture was stirred for 30 min. Filtration through a Celite and silica gel bed and concentration of the filtrate under reduced pressure provided *N*-(1,4-Dichloro-2(*S*)-hydroxy-3(*R*)-butyl)phthalimide **11** (77.8 mg, quantitative) as a colorless oil: ^{1}H NMR (300 MHz, , $CDCl_3$) δ 8.02~7.72 (4H, m), 4.68~4.60 (1H, m), 4.56~4.47 (1H, m), 4.25 (1H, dd, *J* = 10.81, 11.55 Hz), 4.10 (1H, dd, *J* = 4.13, 11.64 Hz), 3.67 (1H, dd, *J* = 3.93, 11.65 Hz), 3.58 (1H, dd, *J* = 5.81, 11.64 Hz), 3.06 (1H, d, *J* = 5.21 Hz); ^{13}C NMR (75 MHz, , $CDCl_3$) 168.27, 134.65, 134.41, 131.42, 123.89, 123.69, 70.51, 55.25, 47.33, 41.80.

Preparation of 2(*R*)-(*t*-Butyloxycarbonyl)amino-1,4-dichloro-3(*S*)-hydroxybutane (12)

To a solution of *N*-(1,4-dichloro-2(*S*)-hydroxy-3(*R*)-butyl)phthalimide (48.6 mg, 0.169 mmol) in isopropanol (1 mL) was added 80 % hydrazine monohydrate (11.3 μL, 0.187 mmol) at 0^{o}C under N_2. After 16 h, solvent was removed under reduced pressure. The resulting solid was dissolved in MeOH (1 mL). To the reaction mixture was added 35 % HCl (21.0 μL, 0.240 mmol) at rt. After 16 h, solvent was removed under reduced pressure. To the residue were added THF (0.5 mL) and water (0.5 mL). To the mixture was added $(Boc)_2O$ (46.5 mg, 0.213 mmol) and NEt_3 (49.5 L, 0.355 mmol) at 0^{o}C. After 16 h, the reaction mixture was diluted with water (1 mL) and extracted with EtOAc (2 mLx3). The combined organic layers were washed with brine (1 mL), dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under reduced pressure and silica gel column chromatography (25% EtOAc in *n*-Hex) gave 2(*R*)-(*t*-butyloxycarbonyl)amino-1,4-dichloro-3(*S*)-hydroxybutane (32.7 mg, 75% yield) as a white solid: Rf (silica gel; 25 % EtOAc in *n*-Hex) 0.40; $[\alpha]_D^{23}$ = 29.8 (*c* 1.00, MeOH); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.78 (1H, br d), 3.96~3.82 (1H, m), 3.82~3.63 (1H, m), 3.60~3.50 (2H, m) 3.44 (1H, dd, *J* = 7.14, 11.27 Hz), 2.56 (1H, br s), 1.26 (9H, s); ^{13}C-NMR (75 MHz, , $CDCl_3$) δ 155.3, 80.5, 71.2, 53.0, 48.0, 45.8, 28.3; IR (KBr pellet) 3450, 3357, 2982, 1682, 1519, 1344, 1168, 1010, 597 cm^{-1}; mp 142~145 ^{o}C; HRMS (CI) *m/z* calcd 258.0664 for $[M+H]^+$ $C_9H_{18}NO_3Cl_2$ found 258.0669.

Preparation of 2(*S*)-*t*-Butyldimetylsilyloxy-3(*R*)-(t-butyloxycarbonyl)amino-1,4-dichlorobutane (13)

To a stirred solution of **12** (100.0 mg, 0.389 mmol) in dry DMF (2.5 mL) were added imidazole (79.4 mg, 1.67 mmol), DMAP (4.8 mg, 0.039 mmol) and *tert*-butyldimethylsilyl chloride (175.9 mg, 1.167 mmol) at room temperature under N_2. The resulting solution was stirred at 50^{o}C for 12 h. The reaction mixture was diluted with EtOAc (30 mL), washed with 0.1 N citric acid solution (5 mL), sat aq $NaHCO_3$ (5 mL), water (5 mL) and brine (5 mL), and dried over anhydrous magnesium sulfate, filtered, concentrated and column-chromatographed (10 % EtOAc in *n*-Hex) to provide 2(*S*)-*t*-butyldimetylsilyloxy-3(*R*)-(t-butyloxycarbonyl)amino-1,4-dichlorobutane as a colorless solid

(144.6mg, quantitative): Rf (silica gel; 10 % EtOAc in *n*-Hex) 0.52; ^{1}H-NMR (300 MHz, , $CDCl_3$) δ 4.84~4.81 (1H, br d), 4.12~4.04 (1H, m), 4.03~3.93 (1H, m), 3.87 (1H, dd, *J* = 4.7, 11.16 Hz), 3.68 (1H, dd, *J* = 3.46, 11.15 Hz), 3.60 (2H, d), 1.45 (9H, s), 0.90 (9H, s), 0.14 (3H, s), 0.13 (3H, s).

Preparation of *N*-*t*-Butyloxycarbonyl-2(*R*)-(1(*S*)-*t*-butyldimetylsilyloxy-2-chloroethyl)aziridine (1)

To a magnetically stirred solution of **13** (375.4 mg, 1.008 mmol) in THF (10 mL) was added NaH slowly at 0^{o}C under N_2. After 5 h, the reaction mixture was slowly added to sat aq ammonium chloride solution (40 mL) and ice (20 g). The resulting solution was extracted with EtOAc (60 mLx4). The combined organic layers were washed with brine (50 mL), dried over anhydrous magnesium sulfate, filtered, concentrated and purified on a silica gel column chromatography (10% EtOAc in *n*-Hex) to provide *N*-*t*-butyloxycarbonyl-2(*R*)-(1(*S*)-*t*-butyldimetylsilyloxy-2-chloroethyl)aziridine (339.5 mg, quantitative) as a colorless oil: Rf (silica gel; 10 % EtOAc in *n*-Hex) 0.60; ^{1}H-NMR (300 MHz, , $CDCl_3$) 3.69 (1H, dd, *J* = 3.92, 11.10 Hz), 3.68 (1H, dd, *J* = 6.08, 11.09 Hz), 3.53 (1H, ddd, *J* = 3.95, 6.20, 6.15 Hz), 2.51 (1H, m, *J* = 3.62, 6.21, 6.24 Hz), 2.33 (1H, d, *J* = 6.13 Hz), 2.07 (1H, d, *J* = 3.59 Hz), 1.44 (9H, s), 0.89 (9H, s), 0.09 (3H, s), 0.06 (3H, s); ^{13}C NMR(75 MHz, , $CDCl_3$) 161.92, 8.37, 73.38, 47.84, 39.34, 30.10, 27.85, 25.68, 18.12, -4.51, -4.84.

Preparation of 2(*S*)-*t*-Butyldimetylsilyloxy-3(*S*)-(t-butyloxycarbonyl)amino-1-chloro-4-phenylbutane (14)

To a magnetically stirred solution of **1** (36.0 mg, 0.107 mmol) in toluene was added copper bromide dimethyl sulfide complex (11.0 mg, 0.054 mmol) at room temperature under N_2. The reaction mixture was cooled to -78 ^{o}C, then treated with a 2 M solution of PhMgCl in THF (0.54 mL, 1.072 mmol). The resulting mixture was warmed to -20^{o}C and stirred overnight. The mixture was treated with sat aq NH_4Cl solution (4 mL) and extracted with EtOAc (5 mLx3). The combined organic layers were washed with brine (50 mL), dried over anhydrous magnesium sulfate, filtered, concentrated and column-chromatographed (3% EtOAc in *n*-Hex) to provide 2(*S*)-*t*-butyldimetylsilyloxy-3(*R*)-(*t*-butyloxycarbonyl)amino-1-chloro-4-phenylbutane (33.5 mg, 75 %) as a colorless oil: ^{1}H-NMR (300 MHz, , $CDCl_3$) 7.31~7.19 (H, m), 4.46 (1H, d, *J* = 7.44 Hz), 4.16~4.01 (2H, m), 3.52~3.41 (2H, m), 2.96 (1H, dd, *J* = 4.32, 14.19 Hz), 2.66 (1H, dd, *J* = 10.61, 13.55 Hz), 1.33 (9H, s), 0.94 (9H, s), 0.13 (3H, s), 0.12 (3H, s); ^{13}C-NMR (75 MHz, $CDCl_3$) 155.06, 138.16, 129.22, 128.39, 126.34, 79.32, 74.15, 53.83, 45.53, 34.23, 28.26, 25.84, 18.14, - 4.31, - 4.76.

Preparation of 3(*S*)-*t*-Butyldimetylsilyloxy-2(*S*)-(t-butyloxycarbonyl)amino-4-chloro-1-phenylthiobutane (15)

To a solution of aziridine **1** (100 mg, 0.29 mmol) in dry MeOH (0.9 mL) was added PhSH (44 □, 0.43 mmol) and TEA (80 □, 0.58 mmol) at room temperature. The reaction mixture was stirred for 18 h and solvent was removed under reduced pressure. The residue was dissolved in EtOAc and

washed with brine. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude product was purified on silica gel column chromatography to give 110 mg (82 %) of compound **15** as a colorless oil: $[\alpha]^{19}_D$ -42 (*c* 1.3, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) 0.14 (6H, d), 0.94 (9H, s), 1.44 (9H, s), 3.15~3.21 (2H, m), 3.50~3.56 (2H, m), 3.99~4.03 (1H, m), 4.13 (1H, br s), 4.79 (1H, br s), 7.19~7.23 (1H, m), 7.29~7.32 (2H, m), 7.39~7.40 (2H, m); ^{13}C NMR (150 MHz, $CDCl_3$) -4.82, -4.47, 18.03, 25.75, 28.27, 33.86, 45.54, 52.18, 73.38, 79.52, 126.39, 128.97, 129.75, 135.91, 155.03; IR (neat, cm^{-1}) 3354, 3148, 3060, 2952, 2874, 1700, 1495, 1470, 1367, 1254, 1171, 1078, 1043, 960, 916, 832, 778, 739, 690; HRMS (CI) *m/z* calcd for $C_{21}H_{37}NO_3ClSSi$ $[M + H]^+$ 446.1943, found 446.1942.

Preparation of 3(*S*)-(*t*-Butyloxycarbonyl)amino-1,2(*S*)-epoxy-4-phenylbutane (16)

To a magnetically stirred solution of **15** (30.0 mg, 0.073 mmol) in THF (0.5 mL) was added a 1 M solution of TBAF in THF (0.11 mL, 0.109 mmol) at 0°C. Stirring was continued at room temperature for 40 min. The reaction mixture was treated with sat aq NH_4Cl solution (0.5 mL), diluted with water (2 mL), and extracted with EtOAc (3 mLx3). The combined organic layers were washed with brine (3 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was dissolved in MeOH (0.5 mL) and treated with KOH at 0°C. Stirring was continued at room temperature for 2 h. Solvent was removed under reduced pressure, and the residue diluted with water (2 mL), and extracted with EtOAc (3 mLx3). The combined organic layers were washed with brine (3 mL), dried over anhydrous magnesium sulfate, filtered, concentrated and column-chromatographed (10 % EtOAc in *n*-Hex) to provide 3(*S*)-(*t*-butyloxycarbonyl)amino-1,2(*S*)-epoxy-4-phenylbutane (14.4 mg, 75 %) as a white solid: ^{1}H-NMR (300 MHz, , $CDCl_3$) 7.35~7.22 (5H, m), 4.46 (1H, br s), 3.70 (1H, bs), 2.98 (1H, dd, *J* = 5.16, 14.00 Hz), 2.90 (1H, m), 2.85~2.79 (1H, m), 2.78~2.73 (1H, m), 1.38 (9H, s); ^{13}C-NMR (75 MHz, $CDCl_3$) 155.20, 136.66, 129.44, 128.54, 126.67, 79.64, 53.18, 52.58, 46.91, 37.58, 28.25.

Preparation of compound 17 To a solution of compound **16** (200 mg, 0.76 mmol) in 2.0 mL of dry isopropanol was added isobutylamine (0.38 mL, 3.8 mmol) and the mixture was stirred for 5 h at 50℃. The mixture was concentrated under reduced pressure and dried *in vaccuo* to give 230 mg of compound **17** (90%). $[\alpha]_D^{26}$ +8.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300MHz, $CDCl_3$) δ0.91 (6H, d, *J*=6.6 Hz), 1.36 (9H, s), 1.68~1.78 (2H, m), 2.42 (2H, d, *J*=6.6 Hz), 2.83~3.03 (5H, m), 3.45~3.47 (1H, m), 3.82 (1H, br s), 4.68 (1H, br s), 7.22~7.32 (5H, m),

Preparation of compound 18 To a solution of compound **17** (64 mg, 0.19 mmol) in 1.0 mL of dry CH_2Cl_2 was added triethylamine (30 μL, 0.23 mmol) and 4-nitrobenzensulfonyl chloride (55 mg, 0.25 mmol) at 0℃. The mixture was stirred for 30 min at this temperature and the flask was

warmed to room temperature. The mixture was stirred for 12 h and poured into sat aq $NaHCO_3$ solution (2 mL) and extracted with Et_2O (10 mL). The organic extract was dried over anhyd $MgSO_4$ and concentrated to give crude product. Silica gel column chromatography provided 82 mg of analytically pure compound **18** (88%). ^{1}H NMR (300MHz, $CDCl_3$) δ0.86~0.89 (6H, m), 1.36 (9H, s), 1.83~1.93 (1H, m), 2.89~3.00 (4H, m), 3.19~3.21 (2H, m), 3.76~3.85 (3H, m), 4.64 (1H, br s), 7.22~7.34 (5H, m), 7.96 (2H, d, *J*=8.7 Hz), 8.34 (2H, d, *J*=8.7 Hz).

Preparation of compound 19 To a solution of (*S*)-(+)-3-hydroxytetrahydrofuran (200 mg, 2.27 mmol) in 7 mL dry CH_3CN was added triethylamine (0.9 mL, 6.81 mmol) and *N,N'*-disuccinimidyl carbonate (871 mg, 3.4 mmol) at room temperature. The mixture was stirred for 4 h and poured into EtOAc (50 mL). The mixture was washed with sat aq $NaHCO_3$ solution (15 mL) and dried over $MgSO_4$. Filtered solution was concentrated to give crude compound **19.** Column chromatography provided 426 mg of compound **19** (82%).

Preparation of compound 20 To a solution of compound **18** (93 mg, 0.19 mmol) in 1 mL of dry CH_2Cl_2 was passed anhyd HCl gas for 0.5 h. After removal of HCl gas bubbler, the mixture was stirred for 1 h. The solvent was removed *in vaccuo* and the residue was dissolved in 1 mL of dry CH_2Cl_2. To the mixture were added triethylamine (30 μL, 0.23 mmol) and compound **19** (44 mg, 0.19 mmol) at room temperature. The mixture was stirred for 4 h until no starting material remained by TLC and it was poured into brine (2 mL) and extracted with EtOAc (10 mL). The organic extract was dried over anhyd $MgSO_4$ and concentrated under reduced pressure to give crude compound **20**. The crude product was recrystallized in ethyl acetate to give 86 mg (85% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ0.86~0.91 (6H. m), 1.65~1.95 (2H, m), 2.08~2.21 (1H, m), 2.85~3.02 (4H, m), 3.05~3.24 (2H, m), 3.63~3.68 (2H, m), 3.76~3.87 (5H, m), 4.89 (1H, br s), 5.14 (1H, br s), 7.14~7.35 (5H, m), 7.96 (2H, d, *J*=8.7 Hz), 8.36 (2H, d, *J*=8.7 Hz).

Preparation of compound 5 A mixture of compound **20** (36 mg, 0.067 mmol) and $SnCl_2.2H_2O$ (77 mg, 0.34 mmol) in 1 mL of EtOAc was heated to 70℃. After 1 h the starting material disappeared and the solution was allowed to cool to room temperature. The mixture was poured into sat aq $NaHCO_3$ solution (3 mL) and extracted with EtOAc (10 mL). The organic extract was dried over anhyd $MgSO_4$ and concentrated under reduced pressure to give 30 mg of compound **5** (90%). ^{1}H NMR (300MHz, $CDCl_3$) δ0.85~0.92 (6H, m), 1.78~2.21 (3H, m), 2.72~3.11 (6H, m), 3.58~4.11(7H, m), 4.20 (2H, s) 4.93 (1H, br s), 5.11 (1H, br s), 6.67 (2H, d, *J*=8.6 Hz), 7.22~7.32 (5H, m), 7.54 (2H, d, *J*=8.6 Hz).