SUPPORTING INFORMATION

for

Efficient Synthesis of (S)-3-(4-Fluorophenyl)Morpholin-2-One, A Key Chiral Intermediate of Aprepitant

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1. **General Information** The reactions were conducted under nitrogen atmosphere in oven-dried glassware with a magnetic stirring bar. Isopropanol and ethyl acetate were purchased from China Reagents and used after standard purifications. *L*-DBTA were purchased from either China Reagents Inc. and used directly without further purifications. ^1H NMR spectra were recorded on a DRX400 or DRX 500 NMR Spectrometer with CDCl_3 as the solvent. ^1H shifts were referenced to CDCl_3 at 7.26 ppm as external standard and obtained with ^1H decoupling. ^{13}C chemical shifts were referenced to CDCl_3 at 77.14 ppm and obtained with ^1H decoupling. ^{31}P chemical shifts were referenced to 85% H_3PO_4 in D_2O at 0.0 ppm as external standard and obtained with ^1H decoupling. MS was measured on Agilent 1100 Series LC/MSD mass spectrometer. HPLC spectra were collected on Agilent 1200 Infinity Series.

2. Preparation of compound 8

To a 2-liter three-necked round flask was charged 2-aminoethanol (52 mL, 867 mmol, 1.5 equiv) and toluene (500 mL). To the mixture was charged acetic acid (~163 mL) and the pH of the mixture reached ~4.0. Chloroform (480 mL), toluene (150 mL) and ethyl 2-(4-fluorophenyl)-2-oxoacetate (**7**, 113.3 g, 678 mmol) were added sequentially and the resulting mixture was heated to reflux under nitrogen for 3 h and then distilled out most of solvent. The residue was purified by column chromatography to provide compound **8** (65.4 g, 339 mmol, 50%) as a white solid. **8**: ^1H NMR (CDCl_3 , 500 MHz): δ 8.00 (dd, $J = 9.0, 5.5$ Hz, 2H), 7.10 (t, $J = 8.7$ Hz, 2H), 4.50 (m, 2H), 4.02 (m, 2H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 165.6, 163.6, 156.5 (d, $J = 371$ Hz), 130.9 (d, $J = 8.7$ Hz), 130.2 (d, $J = 3.3$ Hz), 125.4 (d, $J = 21.6$ Hz), 66.3, 47.9; ^{19}F NMR (CDCl_3 , 376

MHz): δ 104.4; ESI MS m/z : 194 ($M^+ + 1$); HRMS (ESI) calculated for $[M+H, C_{10}H_9FNO_2]^+$: 194.0617; found: 194.0614.

3. Preparation of compound ($\pm$)-9

To a solution of 3-(4-fluorophenyl)-5,6-dihydro-2H-1,4-oxazin-2-one (**8**, 20 g, 104 mmol) in EtOAc (100 mL) was charged 5% Pd/C (2 g). The mixture was stirred under 1 atm hydrogen pressure for 2 h. TLC showed complete conversion. The mixture was filtered and concentrated under vacuum to provide the crude ($\pm$)-**9** as a solid (20 g, 103 mmol, 99%). ($\pm$)-**9**: 1H NMR ($CDCl_3$, 400 MHz): δ 7.36 (m, J = 8.4, 5.6 Hz, 2H), 6.98 (t, J = 8.6 Hz, 2H), 4.60 (s, 1H), 4.41 (m, 1H), 4.32 (m, 1H), 3.09 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.0, 162.5 (d, J = 246 Hz), 134.1 (d, J = 3.2 Hz), 129.8 (d, J = 8.1 Hz), 125.3 (d, J = 21.4 Hz), 70.2, 62.5, 41.8; ^{19}F NMR ($CDCl_3$, 376 MHz): δ 114.1; ESI MS m/z : 196 ($M^+ + 1$); HRMS (ESI) calculated for $[M+H, C_{10}H_{11}FNO_2]^+$: 196.0774; found: 196.0771.

4. Preparation of compound (S)-9

To a solution of ($\pm$)-**9** (10.00 g, 0.051 mol) in EtOAc (50 mL) at room temperature

was charged a solution of *L*-DBTA (9.17 g, 0.026 mol) in isopropanol (50 mL) over 10 min. The resulting mixture was stirred at rt for 1 h and then filtered. The crystalline solid was treated with saturated NaHCO₃ solution (50 mL) and extracted with EtOAc (50 mL X 3). The organic layer was washed with water and brine, dried over sodium sulfate, concentrated to provide (*S*)-**9** as a colorless crystalline solid (4.9 g, 49% yield, 97% ee). (*S*)-**9**: [α]_D²⁵ = +42.2 ° (c = 1, CHCl₃); ¹H NMR (CDCl₃, 400 MHz): δ 7.37 (m, *J* = 8.4, 5.6 Hz, 2H), 6.99 (t, *J* = 8.6 Hz, 2H), 4.61 (s, 1H), 4.42 (m, 1H), 4.33 (m, 1H), 3.10 (m, 2H); ¹³C NMR (CDCl₃, 125 MHz): δ 168.7, 162.2 (d, *J* = 246 Hz), 133.8 (d, *J* = 3.2 Hz), 129.5 (d, *J* = 8.1 Hz), 125.0 (d, *J* = 21.4 Hz), 79.9, 62.2, 41.5; ¹⁹F NMR (CDCl₃, 376 MHz): δ 114.1; ESI MS *m/z*: 196 (*M*⁺+1); HRMS (ESI) calculated for [*M*+H, C₁₀H₁₁FNO₂]⁺: 196.0774; found:196.0770. (Chiral HPLC conditions: Chiralcel OD-H column, hexanes/isopropanol 80/20, 1 mL/min, isocratic, 7.35 min (*S*), 7.62 min (*R*))

fig2-3

^{19}F NMR of Compound 9

Chiral HPLC conditions of (±)-**9** : Chiralcel AD-H column, hexanes/isopropanol 80/20, 1 mL/min, isocratic, 7.35 min (*R*), 7.62 min (*S*).

信号 1: DAD1 C, Sig=210,4 Ref=360,100

峰 #	保留时间 [min]	信号	类型	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	7.349	1	MF	6557.37451	590.78357	50.3586
2	7.617	1	FM	6463.99756	566.33789	49.6414

总量 : 1.30214e4 1157.12146

Figure 1: HPLC spectra of (±)-**9**

信号 1: DAD1 C, Sig=210,4 Ref=360,100

峰 #	保留时间 [min]	信号	类型	峰面积 [mAU*s]	峰高 [mAU]	峰面积 %
1	7.222	1	MF	39.18640	6.47423	1.2318
2	7.464	1	FM	3142.12915	274.26376	98.7682

总量 : 3181.31555 280.73800

Figure 2: HPLC spectra of (S)-9