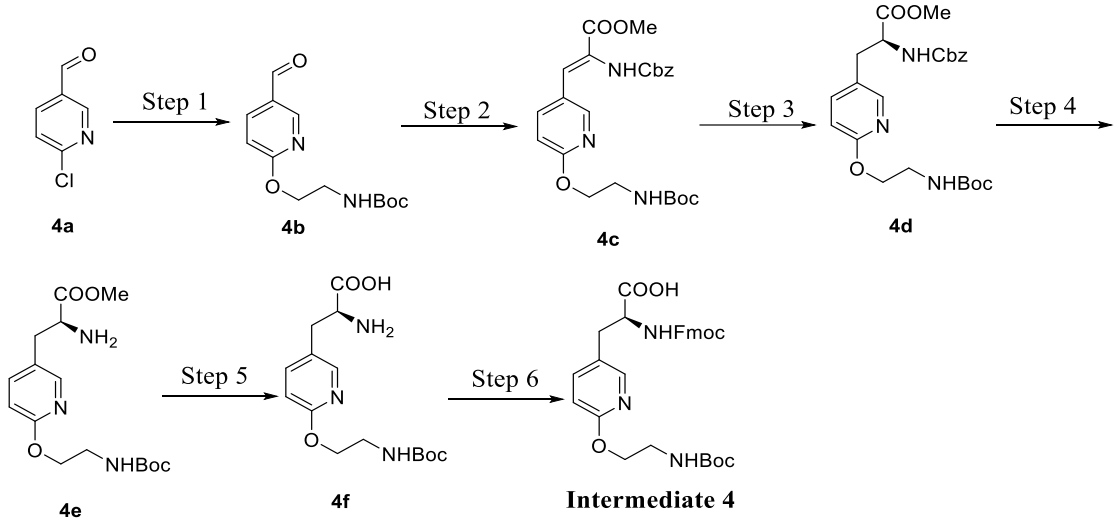
crude product, which was separated and purified by a silica gel chromatography column (DCM : MeOH = 10 : 1) to give **Intermediate 3** (2.7 g, 62.1%).

[0118] LC-MS (ESI): m/z= 587.2 $[M+H]^+$.

[0119] ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.65 (s, 1H), 7.88 (d, 2H), 7.67 (s, 2H), 7.41 (d, 2H), 7.36 – 7.24 (m, 2H), 7.03 – 6.88 (m, 2H), 6.65 (d, 1H), 4.26 – 4.09 (m, 4H), 3.91 (s, 2H), 3.28 (s, 2H), 2.99 (d, 1H), 2.90 – 2.68(m, 5H), 2.51 (s, 1H), 1.98 (s, 2H), 1.39 (s, 9H).

Intermediate 4:



[0120] Step 1: **Compound 4a** (2.0 g, 14.09 mmol) and N-(tert-butoxycarbonyl)ethanolamine (4.5 g, 28.18 mmol) were dissolved in N,N-dimethylacetamide (20 mL), and potassium carbonate (3.9 g, 28.18 mmol) was added. The mixture was stirred at 80°C under microwave irradiation for 2 h. After the reaction was completed, 20 mL of water was added to the reaction system. The resulting solution was extracted with ethyl acetate three times (40 mL × 3), dried over anhydrous sodium sulfate, concentrated under reduced pressure, and subjected to column chromatography (PE : PE = 4 : 1) to give **Compound 4b** (0.9 g, 24.0%).

[0121] LC-MS (ESI): m/z= 267.2 $[M+H]^+$.

[0122] Step 2: (±)-benzyloxycarbonyl-a-phosphonoglycine trimethyl ester (6.1 g, 18.47 mmol) was dissolved in dichloromethane (100 mL), DBU (3.1 g, 20.02 mmol) was added after nitrogen replacement, and the mixture was stirred for 30 min. Then, **Compound 4b** (4.1 g, 15.40 mmol) was dissolved in dichloromethane (100 mL), and the mixture was added dropwise to the reaction. The reaction was stirred overnight. The reaction mixture was diluted with dichloromethane (100 mL), washed with 5% aqueous citric acid solution (100 mL) and saturated brine (100 mL), then dried over anhydrous sodium sulfate, filtered, and spin-dried. Separation and purification by a silica gel chromatography column (EA : PE = 3 : 1) afforded **Compound 4c** (4.5 g, 62.0%).

for 2 h, and extracted with dichloromethane (100 mL × 3). The organic phases were combined, spin-dried, concentrated, and then separated and purified by a silica gel chromatography column (EA : PE = 5 : 1) to give **Compound 6d** (6.0 g, 86.9%).

[0147] LC-MS (ESI): m/z= 230.2 $[M-56+H]^+$.

[0148] Step 4: (±)-benzyloxycarbonyl-a-phosphonoglycine trimethyl ester (7.0 g, 21.05 mmol) was dissolved in dichloromethane (100 mL), DBU (6.43 g, 42.3 mmol) was added after nitrogen replacement, and the mixture was stirred for 30 min. Then, **Compound 6d** (6.0 g, 21.05 mmol) was dissolved in dichloromethane (100 mL), and the mixture was added dropwise to the reaction. The reaction was continued to be stirred overnight. The reaction mixture was diluted with dichloromethane (100 mL), washed with 5% aqueous citric acid solution (100 mL) and saturated brine (100 mL), then dried over anhydrous sodium sulfate, filtered, and spin-dried. Separation and purification by a silica gel chromatography column (EA : PE = 3 : 1) afforded **Compound 6e** (5.7 g, 55.3%).

[0149] LC-MS (ESI): m/z= 491.3 $[M+H]^+$.

[0150] Step 5: **Compound 6e** (5.7 g, 11.6 mmol) was dissolved in methanol (50 mL), and (+)-1,2-bis(2S,5S)-2,5-diethylphospholanobenzene(cyclooctadiene)rhodium trifluoromethanesulfonate (420 mg, 0.58 mmol) was added. The pressure was increased to about 2.5 MPa by filling with hydrogen using an autoclave, and the mixture was stirred overnight at room temperature. The solid was filtered off, and the reaction solution was concentrated to give **Compound 6f** (5.7 g, 99.9%).

[0151] LC-MS (ESI): m/z= 493.2 $[M+H]^+$.

[0152] Step 6: **Compound 6f** (3.0 g, 6.1 mmol) was dissolved in dichloromethane (50 mL), and in an ice bath, triethylamine (3.1 g, 30.5 mmol) was added, followed by iodotrimethylsilane (6.1 g, 30.5 mmol). The mixture was stirred at room temperature for 16 h, and concentrated at room temperature. Then, methanol (5 mL) was added to quench the reaction. Separation and purification by a C18 reverse phase column (water with 0.5% TFA : acetonitrile = 3 : 10) afforded **Compound 6g** (1.5 g, 95.5%).

[0153] LC-MS (ESI): m/z= 259.1 $[M+H]^+$.

[0154] Step 7: **Compound 6g** (1.5 g, 5.8 mmol) was dissolved in tetrahydrofuran (20 mL), and lithium hydroxide monohydrate (1.58 g, 37.7 mmol) and water (20 mL) were added. The reaction was stirred at room temperature for 2 h. Then, the pH of the aqueous phase was adjusted to neutral with dilute hydrochloric acid (1N). The next step was carried out directly.

[0155] LC-MS (ESI): m/z= 245.1 $[M+H]^+$.

stirred at this temperature for 3 h, quenched with water, and extracted with dichloromethane. The organic phases were combined, concentrated, and separated and purified by a silica gel chromatography column (EA : PE = 1 : 5) to give Compound **9f** (3.5 g, two-step yield: 66%).

[0192] LC-MS (ESI): m/z= 147.1 $[M+H]^+$

[0193] Step 6: **Compound 9f** (3.0 g, 20.55 mmol) was dissolved in acetonitrile (50 mL), and sodium bicarbonate (17.26 g, 205.5 mmol) was added, followed by thioacetamide (1.54 g, 20.55 mmol). The mixture was stirred at 80°C for 5 h, filtered, concentrated, and separated and purified by a silica gel chromatography column (EA : PE = 1 : 1) to give Compound 9g (3 g, 79%).

[0194] LC-MS (ESI): m/z= 186.2 $[M+H]^+$.

[0195] Step 7: **Compound 9g** (1 g, 5.38 mmol) was placed in a 50 ml round-bottom flask, 3M hydrochloric acid solution (10 mL) was added, and the mixture was stirred at 100°C for 5 h. The reaction was completed, and extracted with methyl tert-butyl ether. The aqueous phase was concentrated directly to give **Compound 9h** hydrochloride.

[0196] LC-MS (ESI): m/z= 148.2 $[M+H]^+$.

[0197] Step 8: **Compound 9h** (1 g, 6.8 mmol) was placed in a 50 ml round-bottom flask, trifluoroacetic acid (5 ml) and triphenylmethanol (2.12 g, 8.16 mmol) were added, and the mixture was stirred at room temperature for 10 min. The resultant was spin-dried to give the target **Compound 9i**. The next step was carried out directly.

[0198] LC-MS (ESI): m/z= 388.5 $[M-H]^+$.

[0199] Step 9: The crude **Compound 9i** from the previous step was dissolved in acetonitrile and water (50 ml/10 ml), and sodium bicarbonate (5.7 g, 68 mmol) and 9-fluorenylmethyl N-succinimidyl carbonate (3.44 g, 10.2 mmol) were added. The mixture was stirred at room temperature for 3 h, filtered, added with saturated brine (30 ml), and extracted with ethyl acetate. The organic phases were combined, concentrated, and separated and purified by a silica gel chromatography column (DCM : MeOH = 10 : 1) to give 2.2 g of racemate (two-step yield: 43%). The racemate was subjected to chiral resolution (instrument: SFC Prep 150 AP; and chromatographic column: Daicel AD-H (19 mm × 250 mm). The sample was dissolved in methanol, and filtered with a 0.45 μm filter head to prepare a sample solution. Preparative chromatography conditions: composition of mobile phases A and B: mobile phase A: CO2; and mobile phase B: methanol; isocratic elution: mobile phase B = 25%; and flow rate: 40 ml/min) to give **Intermediate 9** (P1) (890 mg) at 3.8 min and **Intermediate 10** (P2) (910 mg) at 4.2 min.

Serial No.	Starting material	Coupling reagent
1	Fmoc-Sar-OH (3.0 eq.)	DIC (3 eq.) and HOBT (3 eq.)
2	Fmoc-3Pal-OH (3.0 eq.)	DIC (3 eq.) and HOBT (3 eq.)
3	Fmoc-Asn(Trt)-OH (3.0 eq.)	DIC (3 eq.) and HOBT (3 eq.)
4	Fmoc-Glu(OtBu)-OH (3.0 eq.)	DIC (3 eq.) and HOBT (3 eq.)
5	Fmoc-ThpGly-OH (2.0 eq.)	DIC (2 eq.) and HOBT (2 eq.)
6	Fmoc-2-Nal-OH (3.0 eq.)	DIC (3 eq.) and HOBT (3 eq.)
7	Fmoc-4-[2-(Boc-amino-ethoxy)]-L-phenylalanine (3.0 eq.)	DIC (3 eq.) and HOBT (3 eq.)
8	Fmoc-Dap(Dde) -OH (2.0 eq.)	DIC (2 eq.) and HOBT (2 eq.)
9	Fmoc-Lys(Ac)-OH (3.0 eq.)	DIC (3 eq.) and HOBT (3 eq.)
10	Fmoc-7MeTrp-OH (2.0 eq.)	DIC (2 eq.) and HOBT (2 eq.)
11	Fmoc-Thr(tBu)-OH (3.0 eq.)	DIC (3 eq.) and HOBT (3 eq.)
12	Fmoc-Asn(Trt)-OH (3.0 eq.)	DIC (3 eq.) and HOBT (3 eq.)
13	Fmoc-Asp(OAll)-OH (2.0 eq.)	DIC (2 eq.) and HOBT (2 eq.)
14	Acetic anhydride	DIEA

[0246] Step 1: **Compound 10B** was obtained by using the materials in the above table as starting materials and adopting a method for **Compound 1**.

[0247] Step 2: 30 ml of dichloromethane was added to a solid-phase synthesis reactor, followed by phenylsilane (1 g) and tetrakis(triphenylphosphine)palladium (462 mg) successively. The mixture was bubbled with nitrogen, and reacted for 8 hours. The resin was washed with dichloromethane 5 times, N,N-dimethylformamide 5 times, 0.5% solution of sodium diethyldithiocarbamate in N,N-dimethylformamide for 15 min + 15 min, and then N,N-dimethylformamide three times to give the peptide resin **10C**.

[0248] Step 3: 2% solution of hydrazine hydrate in N,N-dimethylformamide was added to the reactor, and the mixture was reacted for 30 min. The resultant was washed with N,N-dimethylformamide solution 5 times to give the peptide resin **10D**.

[0249] Step 4: N-methylpyrrolidone (20 ml), benzotriazole-N,N,N',N'-tetramethylurea hexafluorophosphate (417.2 mg, 1.1 mmol), and DIEA (0.19 ml, 1.1 mmol) were added to the solid-phase synthesis reactor, and the mixture was reacted at room temperature for 16 h. The reaction was monitored with ninhydrin until it was colorless. The solvent was pumped off, and the resin was washed with N,N-dimethylformamide three times, methanol twice,

[0334] Step 5: 40 ml of cleavage solution (91% trifluoroacetic acid + 4% triisopropylsilane + 3% 1,2-ethanedithiol + 2% water) was added to a 100 ml reaction flask, and stirred evenly. Then, the peptide resin **44E/F** (5 g) was added, and the mixture was stirred at room temperature for 2 hours. The resin was filtered to obtain the filtrate, which was added to 300 ml of methyl tert-butyl ether (which was cooled to 0°C in advance). White floccules were precipitated, and centrifuged (3 min at 3000 rpm). The white precipitate was washed with methyl tert-butyl ether three times, and dried in vacuo to give the crude peptide **Compound 44E/F** as an off-white solid (1.5 g), which was purified by preparative HPLC. Separation method: 1. Instrument: Waters 2767 (preparative liquid chromatographic instrument); and chromatography column: SunFire@PrepC18 (19 mm × 250 mm). 2. The sample was filtered with a 0.45 μm filter head to prepare a sample solution. 3. Preparative chromatography conditions: a. composition of mobile phases A and B: A: 5 mmol/L ammonium acetate/H_2O, and B: CH_3CN; b. gradient elution: mobile phase = 5%-45%; c. flow rate: 12 ml/min; d. elution time: 30 min. Lyophilization was carried out to afford **Compound 44-1** (77 mg, purity: 94%, retention time: 13.198 min) and **Compound 44-2** (44 mg, purity: 98%, retention time: 14.509 min) as white solids.

[0335] **44-1.** LCMS m/z =903.8$[M/2+H]^+$.603.0$[M/3+H]^+$.

[0336] **44-2.** LCMS m/z =904.1$[M/2+H]^+$,

Example 45: