[0206]

The amount of amine compound (X) used is 0.5 to 10 moles, and preferably 0.8 to 5 moles, per mole of the compound represented by Formula (VII).

[0207]

Examples of condensation agents include benzotriazol-1-yloxy-trisdimethylaminophosphonium salts, 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride, a combination of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide and 1-hydroxybenzotriazole, O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethylhexauronium fluorophosphate, and the like. The amount added is usually 1 to 100 moles, and preferably 1 to 5 moles, per mole of the compound represented by Formula (VII).

[0208]

A base is optionally added during the above reaction. Examples of bases include organic bases, such as triethylamine, diisopropylethylamine, and pyridine; and inorganic bases, such as potassium carbonate. The amount added is usually 1 to 100 moles, preferably 1 to 10 moles, per mole of the compound represented by Formula (VII).

[0209]

The solvent is not particularly limited, and any solvent that does not adversely affect the reaction can be used. Examples of the solvent include toluene, chloroform, tetrahydrofuran, N,N-dimethylformamide, dimethylacetamide, N-methylpyrrolidin-2-one, mixtures thereof, and the like.

[0210]

The reaction temperature is usually -78 to 200°C, and preferably 0 to 50°C. The reaction time is usually 5 minutes to 3 days, preferably 5 minutes to 10 hours.

[0211]

The thus-obtained compound represented by Formula (XI) can be subjected to the subsequent step after or without isolation or purification by known isolation and purification means, such as concentration, vacuum concentration,

mm), produced by Waters Corporation

UV detection: 254 nm

Column flow rate: 18 mL/min

Mobile phase: Water/acetonitrile (0.1% formic acid)

Injection volume: 0.1 to 0.5 mL

[0250]

The symbols stand for the following.

[0251]

s: Singlet

d: Doublet

t: Triplet

q: Quartet

dd: Double doublet

dt: Double triplet

td: Triple doublet

tt: Triple triplet

ddd: Double double doublet

ddt: Double double triplet

dtd: Double triple doublet

tdd: Triple double doublet

m: Multiplet

br: Broad

brs: Broad singlet

THF: Tetrahydrofuran

DMF: N,N-dimethylformamide

DME: 1,2-Dimethoxyethane

DMSO: Dimethylsulfoxide

HATU: O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethylhexauronium fluorophosphate

TEA: Triethylamine

WSC HCl: 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride

t-BuOH: Tertiary butanol

DMAP: N,N-dimethylaminopyridine

$Pd(PPh_3)_4$: Tetrakis(triphenylphosphine)palladium(0)

tert-butyl N-[(3-exo)-8-[3-(4-cyano-3-fluoro-phenyl)-4-[2-fluoro-4-(2-methoxyethyl)phenyl]benzoyl]-8-azabicyclo[3.2.1]octan-3-yl]carbamate.

[0311]

Step 2

The tert-butyl N-[(3-exo)-8-[3-(4-cyano-3-fluoro-phenyl)-4-[2-fluoro-4-(2-methoxyethyl)phenyl]benzoyl]-8-azabicyclo[3.2.1]octan-3-yl]carbamate (15 mg) obtained in step 1 above was dissolved in TFA (0.3 mL), and the progress of the reaction was confirmed with LCMS, followed by vacuum concentration. The residue was purified by reversed-phase HPLC (mobile phase: water/acetonitrile) to give the title compound.

[0312]

Example 27: Synthesis of 4-[5-(3,8-diazabicyclo[3.2.1]octane-8-carbonyl)-2-[2-fluoro-4-(2-methoxyethyl)phenyl]phenyl]-2-fluoro-benzonitrile

The procedure of steps 1 to 4 in Example 22 was repeated using tert-butyl 3,8-diazabicyclo[3.2.1]octane-3-carboxylic acid instead of tert-butyl N-[(3-endo)-8-azabicyclo[3.2.1]octan-3-yl]carbamate to give the title compound.

[0313]

Example 28: Synthesis of 4-[5-[(3-exo)-3-amino-8-azabicyclo[3.2.1]octane-8-carbonyl]-2-[2-fluoro-4-(2-hydroxy-2-methyl-propyl)phenyl]phenyl]-2-fluoro-benzonitrile

Step 1

Methyl 2-(4-bromo-3-fluoro-phenyl)acetate (500 mg) was dissolved in THF (2.2 mL). At -30°C, a solution of 3 M MeMgBr in ether (5.40 mL) was added thereto dropwise, followed by stirring at room temperature overnight. The reaction solution was introduced into an aqueous ammonium chloride solution, ethyl acetate was added thereto, and the mixture was washed sequentially with water and saturated brine. After the organic layer was dried over anhydrous sodium sulfate, the solvent was distilled off. The residue was purified by silica gel column chromatography (mobile phase: ethyl acetate/hexane = 10% → 50%)

sodium sulfate, the solvent was distilled off. The residue was purified by silica gel column chromatography (mobile phase: hexane/ethyl acetate) to give [4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methyl acetate.

[0317]

Step 2

The tert-butyl N-[(3S)-1-[4-chloro-3-(4-cyanophenyl)benzoyl]pyrrolidin-3-yl]carbamate (100 mg) obtained in Example 9 (step 2) and the [4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methyl acetate (130 mg) obtained in step 1 above were dissolved in 1,4-dioxane (1.2 mL). At room temperature, $Pd(dba)_2$ (6.8 mg), tripotassium phosphate (100 mg), and a solution of 1 M PCy_3 in THF (0.02 mL) were added thereto, and the mixture was stirred in a microwave reactor at 160°C for 1 hour. The reaction solution was filtered through NH-silica gel, and the solvent of the filtrate was distilled off. The residue was purified by silica gel column chromatography (mobile phase: ethyl acetate/hexane = 30% → 100%) to give [4-[4-[(3S)-3-(tert-butoxycarbonylamino)pyrrolidine-1-carbonyl]-2-(4-cyanophenyl)phenyl]phenyl]methyl acetate.

[0318]

Step 3

The [4-[4-[(3S)-3-(tert-butoxycarbonylamino)pyrrolidine-1-carbonyl]-2-(4-cyanophenyl)phenyl]phenyl]methyl acetate (100 mg) obtained in step 2 above was dissolved in MeOH (2 mL). At room temperature, K_2CO_3 (65 mg) was added thereto, followed by stirring at room temperature for 30 minutes. Chloroform was added thereto, the mixture was washed sequentially with a saturated aqueous ammonium chloride solution and saturated brine, and dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (mobile phase: ethyl acetate/hexane = 40% → 100%) to give tert-butyl N-[(3S)-1-[3-(4-cyanophenyl)-4-[4-(hydroxymethyl)phenyl]benzoyl]pyrrolidin-3-yl]carbamate.

[0319]

Step 4

The tert-butyl N-[(3S)-1-[3-(4-cyanophenyl)-4-[4-(hydroxymethyl)phenyl]benzoyl]pyrrolidin-3-yl]carbamate (15 mg) obtained in step 3 above was dissolved in TFA (0.3 mL), and the progress of the reaction was confirmed with LCMS, followed by vacuum concentration. The residue was purified by reversed-phase HPLC (mobile phase: water/acetonitrile) to give the title compound.

[0320]

Example 30: Synthesis of 4-[5-[(3S)-3-aminopyrrolidine-1-carbonyl]-2-[4-(2-methoxyethyl)phenyl]phenyl]benzonitrile

Step 1

1-Bromo-4-(2-methoxyethyl)benzene (450 mg) was dissolved in 1,4-dioxane (5.2 mL). Then, bis(pinacolato)diboron (797 mg), KOAc (411 mg), and $PdCl_2$(dppf) (77 mg) were added thereto, followed by stirring at 90°C overnight. Ethyl acetate was added thereto, the mixture was passed through Celite, and the filtrate was washed sequentially with water and saturated brine. After the organic layer was dried over anhydrous sodium sulfate, the solvent was distilled off. The residue was purified by silica gel column chromatography (mobile phase: ethyl acetate/hexane = 2% → 20%) to give 2-[4-(2-methoxyethyl)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane.

[0321]

Step 2

The tert-butyl N-[(3S)-1-[4-chloro-3-(4-cyanophenyl)benzoyl]pyrrolidin-3-yl]carbamate (300 mg) obtained in Example 9 (step 2) and the 2-[4-(2-methoxyethyl)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (369 mg) obtained in step 1 above were dissolved in 1,4-dioxane (2 mL). At room temperature, $Pd(dba)_2$ (32 mg), tripotassium phosphate (300 mg), and a solution of 1 M PCy_3 in THF (0.07 mL) were added thereto, and the mixture was stirred in a microwave reactor at 160°C for 45 minutes. The reaction solution was passed through Celite, and the solvent of

The procedure of steps 1 to 4 in Example 22 was repeated using tert-butyl N-[(3-exo)-9-azabicyclo[3.3.1]nonan-3-yl]carbamate instead of tert-butyl N-[(3-endo)-8-azabicyclo[3.2.1]octan-3-yl]carbamate to give the title compound.

[0436]

Example 128: Synthesis of 4-[5-[(3-endo)-3-amino-8-azabicyclo[3.2.1]octane-8-carbonyl]-2-(4-methyl-2,3-dihydro-1,4-benzoxazin-7-yl)phenyl]-2-fluoro-benzonitrile

The procedure of steps 1 to 5 in Example 41 was repeated using 7-bromo-4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazine instead of 1-(4-bromo-3-fluoro-phenyl)-2-methyl-propan-2-ol to give the title compound.

[0437]

Example 129: Synthesis of 4-[5-[(3-endo)-3-amino-9-azabicyclo[3.3.1]nonane-9-carbonyl]-2-[2-fluoro-4-(2-methoxyethyl)phenyl]phenyl]-2-fluoro-benzonitrile

The procedure of steps 1 to 4 in Example 22 was repeated using tert-butyl N-[(3-endo)-9-azabicyclo[3.3.1]nonan-3-yl]carbamate instead of tert-butyl N-[(3-endo)-8-azabicyclo[3.2.1]octan-3-yl]carbamate to give the title compound.

[0438]

Example 130: Synthesis of 4-[5-[(3-endo)-3-amino-8-azabicyclo[3.2.1]octane-8-carbonyl]-2-(6-fluoro-1-methyl-benzimidazol-5-yl)phenyl]-2-fluoro-benzonitrile

The procedure of steps 1 to 5 in Example 41 was repeated using 5-bromo-6-fluoro-1-methyl-benzimidazole instead of 1-(4-bromo-3-fluoro-phenyl)-2-methyl-propan-2-ol to give the title compound.

[0439]

Example 131: Synthesis of 4-[5-[(3-endo)-3-amino-8-azabicyclo[3.2.1]octane-8-carbonyl]-2-[6-(dimethylamino)-3-pyridyl]phenyl]-2-fluoro-benzonitrile

The procedure of steps 1 to 5 in Example 41 was repeated using 5-bromo-N,N-dimethylpyridin-2-amine instead of 1-(4-bromo-3-fluoro-phenyl)-2-methyl-propan-2-ol to give the title

azabicyclo[2.2.1]heptan-2-yl)-2,4-dinitrobenzenesulfonamide-isomer-B hydrochloride to give the title compound.

[0541]

Example 185: Synthesis of 5'-((1S,2S,4R)-rel-2-amino-7-azabicyclo[2.2.1]heptane-7-carbonyl)-2'-(6,7-difluoro-1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)-3-fluoro-[1,1'-biphenyl]-4-carbonitrile

The procedure of steps 3 to 4 in Example 172 was repeated using the 3-(4-cyano-3-fluoro-phenyl)-4-(6,7-difluoro-1-methyl-benzotriazol-5-yl)benzoic acid obtained in step 1 of Example 175 instead of 3-(4-cyano-3-fluoro-phenyl)-4-[6,7-difluoro-1-(2-hydroxy-2-methyl-propyl)indol-5-yl]benzoic acid, and using tert-butyl ((1S,2S,4R)-rel-7-azabicyclo[2.2.1]heptan-2-yl)carbamate hydrochloride instead of tert-butyl N-[(3S)-pyrrolidin-3-yl]carbamate to give the title compound.

[0542]

Example 186: Synthesis of 5'-((3-endo)-3-amino-8-azabicyclo[3.2.1]octane-8-carbonyl)-3-fluoro-2'-(6-fluoro-1-(2-hydroxy-2-methylpropyl)-7-methoxy-1H-indazol-5-yl)-[1,1'-biphenyl]-4-carbonitrile

Step 1

5-Bromo-2,3,4-trifluoro-benzaldehyde (480 mg) was dissolved in 1,2-dimethoxyethane (4.8 mL). At room temperature, hydrazine monohydrate (7.68 mL) was added thereto, followed by stirring at 80°C for 5 hours. Ethyl acetate was added thereto, the mixture was washed sequentially with water and saturated brine, and dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (mobile phase: hexane/ethyl acetate) to give 5-bromo-6,7-difluoro-1H-indazole.

[0543]

Step 2

The 5-bromo-6,7-difluoro-1H-indazole (97 mg) obtained in step 1 above was dissolved in DMF (1.38 mL). At room temperature, methanol (0.1 mL), cesium carbonate (271 mg), 2,2-