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(54) Title: METHODS AND COMPOUNDS USEFUL IN THE SYTHESIS OF AN AAK1 INHIBITOR

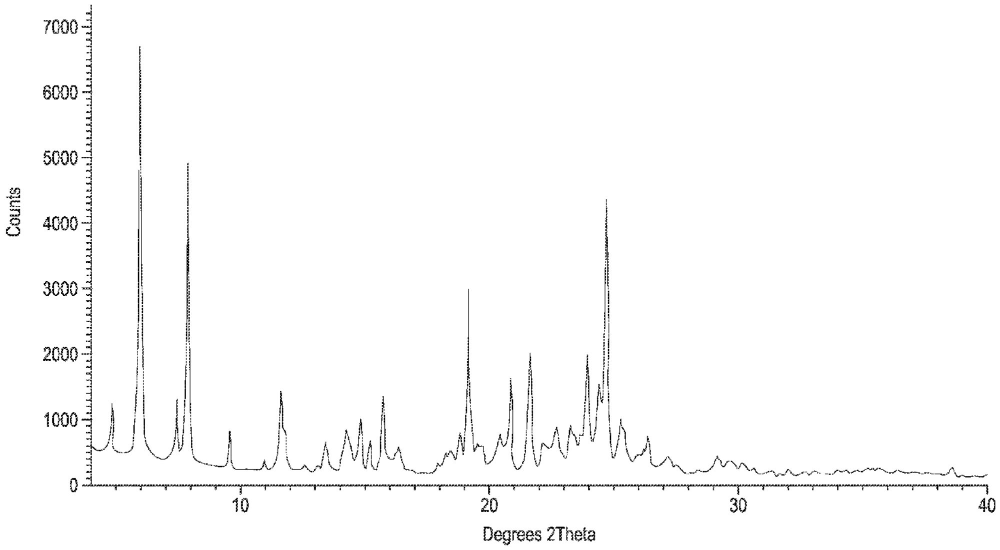

FIG. 1

(57) **Abstract:** Methods for the synthesis of (*S*)-1-((2',6-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine and salts thereof are disclosed, as well as compounds useful therein.

[Continued on next page]

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METHODS AND COMPOUNDS USEFUL IN THE SYTHESIS OF AN AAK1 INHIBITOR

1 FIELD OF THE INVENTION

This application relates to methods of making (S)-1-((2',6-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine and salt forms thereof, and to synthetic intermediates useful therein.

2 BACKGROUND OF THE INVENTION

Adaptor associated kinase 1 (AAK1) is a member of the Ark1/Prk1 family of serine/threonine kinases. AAK1 mRNA exists in two splice forms termed short and long. The long form predominates and is highly expressed in brain and heart (Henderson and Conner, Mol. Biol. Cell. 2007, 18, 2698-2706). AAK1 is enriched in synaptosomal preparations and is co-localized with endocytic structures in cultured cells. AAK1 modulates clathrin coated endocytosis, a process that is important in synaptic vesicle recycling and receptor-mediated endocytosis. AAK1 associates with the AP2 complex, which links receptor cargo to the clathrin coat. The binding of clathrin to AAK1 stimulates AAK1 kinase activity (Conner *et al.*, *Traffic* 2003, 4, 885-890; Jackson *et al.*, J. Cell. Biol. 2003, 163, 231-236). AAK1 phosphorylates the mu-2 subunit of AP-2, which promotes the binding of mu-2 to tyrosine containing sorting motifs on cargo receptors (Ricotta *et al.*, J. Cell Bio. 2002, 156, 791-795; Conner and Schmid, J. Cell Bio. 2002, 156, 921-929). Mu2 phosphorylation is not required for receptor uptake, but phosphorylation enhances the efficiency of internalization (Motely *et al.*, Mol. Biol. Cell. 2006, 17, 5298-5308).

AAK1 has been identified as an inhibitor of Neuregulin-1/ErbB4 signaling in PC12 cells. Loss of AAK1 expression through RNA interference mediated gene silencing or treatment with the kinase inhibitor K252a (which inhibits AAK1 kinase activity) results in the potentiation of Neuregulin-1 induced neurite outgrowth. These treatments result in increased expression of ErbB4 and accumulation of ErbB4 in or near the plasma membrane (Kuai *et al.*, *Chemistry and Biology* 2011, 18, 891-906). NRG1 and ErbB4 are putative schizophrenia susceptibility genes (Buonanno, Brain Res. Bull. 2010, 83, 122-131). SNPs in both genes have been associated with multiple schizophrenia endophenotypes (Greenwood *et al.*, Am. J. Psychiatry 2011, 168, 930-946). Neuregulin 1 and ErbB4 KO mouse models have shown schizophrenia relevant morphological changes and behavioral phenotypes (Jaaro-Peled *et al.*, Schizophrenia Bulletin 2010, 36, 301-313; Wen et al., Proc. Natl. Acad. Sci. USA. 2010, 107, 1211-1216). In addition, a single nucleotide polymorphism in an intron of the AAK1 gene has been associated with the age of onset of Parkinson's disease (Latourelle *et al.*, BMC Med. Genet. 2009, 10, 98). These results suggest that inhibition of AAK1 activity may have utility in the treatment of schizophrenia, cognitive deficits in schizophrenia, Parkinson's disease, neuropathic pain, bipolar disorder, and Alzheimer's disease.

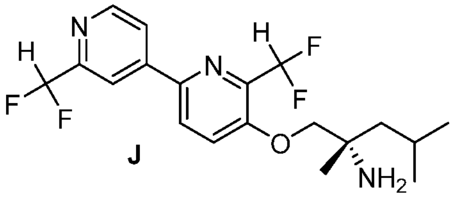
In addition, studies using Huh-7.5 cells indicate a potential utility for AAK1 kinase inhibitors in the treatment of hepatitis C (HCV) infection. Reduction of AAK1 protein using RNA interference mediated gene silencing, treatment with the kinase inhibitor sunitinib (a potent AAK1 inhibitor), and overexpression of Mu2 (AAK1 substrate) phosphorylation site mutant all result in reduced HCV virion assembly. Furthermore, the same treatments were shown to inhibit HCV entry, suggesting AAK1 inhibitors can disrupt two host dependent stages of the virus life cycle (Neveu *et al.*, PLoS Pathog. 2012, 8, 1-16; Neveu *et al.*, J. Virol. 2015, posted online 4 February). AAK1 inhibitors may also be useful against HIV and HBV (*See, e.g.*, Boge *et al.*, J. Biol. Chem. 1998, 273, 15773-15778).

A number of AAK1 inhibitors have disclosed in the literature, and it has been suggested that some may be useful in the treatment of neuropathic pain. *See, e.g.*, Hartz, R.A., *et al.*, J. Med. Chem., 2021 Aug 12;64(15):11090-11128. However, human clinical trials are necessary to evaluation the full potential of any drug.

The specific AAK1 inhibitor (S)-1-((2',6-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine has been prepared on a small, laboratory scale. *See, e.g.*, U.S. patent no. 9,902,722. Unfortunately, synthetic approaches useful in the laboratory setting are rarely suitable for large-scale manufacture of pharmaceutically acceptable material. For example, the creation of potentially harmful reaction byproducts needs to be minimized, and the use of toxic solvents and reagents are preferably avoided. Moreover, reaction conditions that may work on a gram scale are often inefficient or even dangerous when scaled up. Consequently, a need exists for synthetic methods that can be used to prepare pharmaceutically acceptable (S)-1-((2',6-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine in commercially useful quantities.

3 SUMMARY OF THE INVENTION

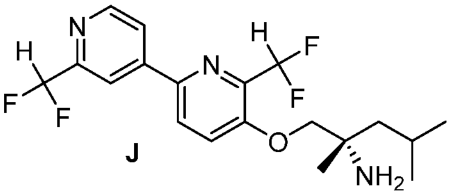
This application is directed to methods of making the compound (S)-1-((2',6-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (Compound J):



J

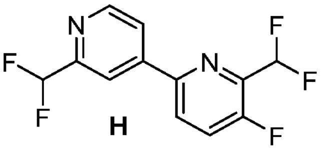
and salts thereof. Compound J is an inhibitor of adaptor associated kinase 1 (AAK1) and is believed to be useful in the treatment of diseases and disorders including pain.

In one embodiment, this invention encompasses a method of preparing (S)-1-((2',6-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (Compound J):



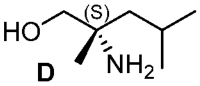
J

which comprises contacting Compound H:



H

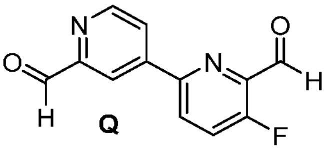
with Compound D:



D

or a salt thereof in the presence of a base under conditions sufficient to form Compound J.

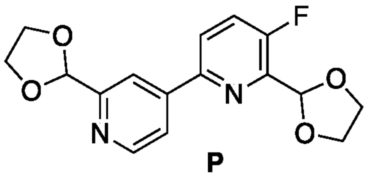
In one embodiment, Compound H is prepared by contacting Compound Q:



Q

with a fluorinating agent under conditions sufficient to form Compound H. (This invention encompasses crystalline forms of Compound Q. A particular crystalline form has a melting point of about 150 °C.)

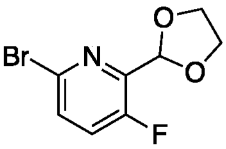
In one embodiment, Compound Q is prepared by contacting Compound P:



P

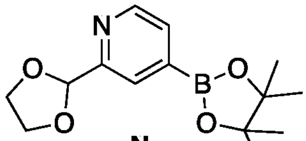
with an acid under conditions sufficient to form Compound Q.

In one embodiment, Compound P is prepared by contacting Compound L:



L

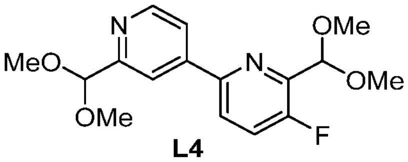
with Compound N:



N

under conditions sufficient to form Compound P.

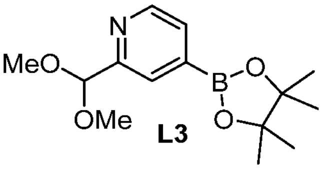
In one embodiment, Compound Q is prepared by contacting Compound L4:



L4

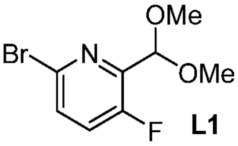
with an acid under conditions sufficient to form Compound Q.

In one embodiment, Compound L4 is prepared by contacting Compound L3:



L3

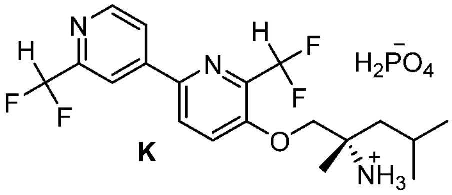
with Compound L1:



L1

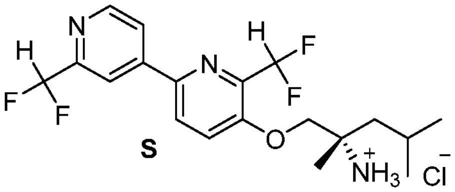
in the presence of a catalyst and a base under conditions sufficient to form Compound L4.

This invention also encompasses a method of preparing Compound K:



K

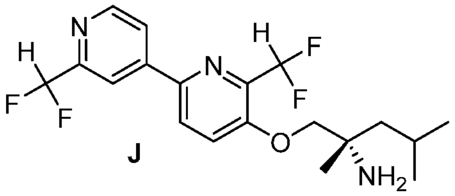
which comprises contacting Compound S:



S

with phosphoric acid in a solvent under conditions sufficient to form Compound K.

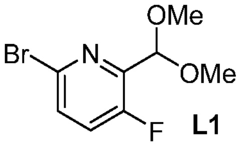
In one embodiment, Compound S is prepared by contacting Compound J:



J

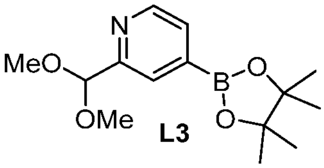
with hydrochloric acid in a solvent under conditions sufficient to form Compound S.

This invention also encompasses the synthetic intermediate 6-bromo-2-(dimethoxymethyl)-3-fluoropyridine (Compound L1):



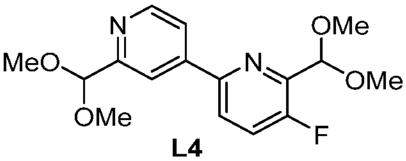
L1 .

This invention also encompasses 2-(dimethoxymethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (Compound L3):



L3 .

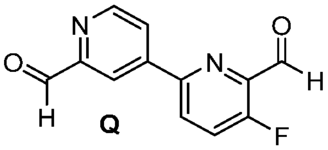
This invention also encompasses 2',6-bis(dimethoxymethyl)-5-fluoro-2,4'-bipyridine (Compound L4):



L4

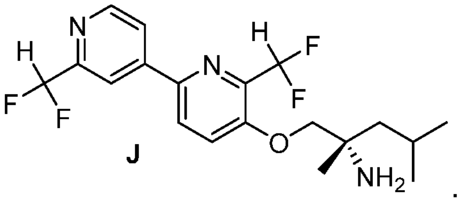
and salts thereof.

This invention also encompasses the compound 5-fluoro-[2,4'-bipyridine]-2',6-dicarbaldehyde (Compound Q):

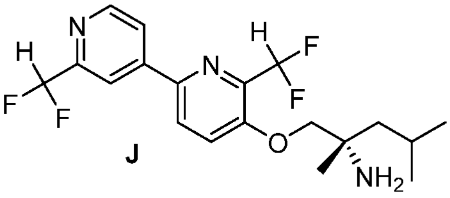


Q .

This invention also encompasses a crystalline pharmaceutically acceptable salt of (*S*)-1-((2',6-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (Compound J):

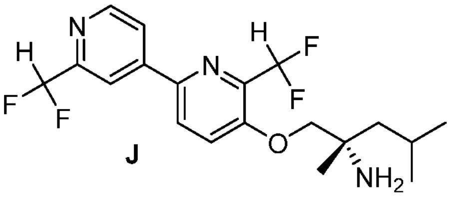


This invention also encompasses a method of determining the purity of a sample of (S)-1-((2',6-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (Compound J):



or a pharmaceutically acceptable salt thereof, which comprises testing the sample for the presence of one or more of the compounds listed in Table 1.

This invention also encompasses a composition comprising (S)-1-((2',6-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (Compound J):



or a pharmaceutically acceptable salt thereof, which composition comprises less than 0.01 percent by weight of one or more of the compounds listed in Table 1, below.

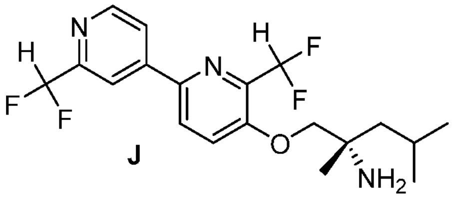
4 BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 provides a representative X-ray powder diffraction (XRPD) pattern of crystalline solid form I of ((S)-1-((2',6-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-aminium dihydrogen phosphate (Compound K). The spectrum was obtained using a Bruker X-ray diffractometer with a LYNXEYE detector (copper Kα radiation).

FIG. 2 provides a representative differential scanning calorimetry (DSC) thermogram of a crystalline solid form of Compound K. The thermogram was obtained using a TA Instruments DSC Q2000 instrument and a hermetically sealed gold crucible filled under ambient conditions. Two scans were performed. After the melting was completed in the first scan, the sample was rapidly cooled at approximately -40 K per minute to -50° C, and a second scan was recorded. The heating rate was 10 K per minute in both scans.

5 DETAILED DESCRIPTION

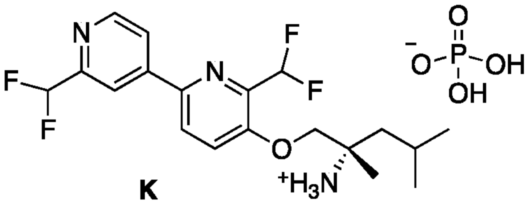
This invention is directed to synthetic intermediates and synthetic methods for the preparation of (S)-1-((2',6-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (Compound J):



J

and pharmaceutically acceptable salts thereof in quantities (*e.g.*, greater than 1kg, 5kg, or 10kg) sufficient for the manufacture of dosage forms suitable for use in human clinical trials and subsequent commercialization. Methods of this invention minimize the formation of harmful impurities while maximizing synthetic yields.

Particular methods of this invention are used to prepare ((S)-1-((2',6-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4- dimethylpentan-2-aminium dihydrogen phosphate (Compound K):



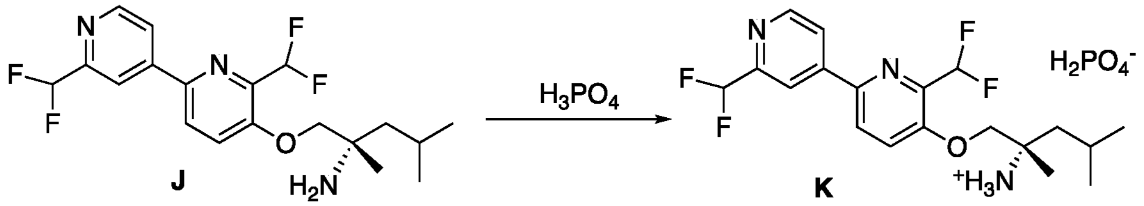
K

and crystalline solid forms thereof. A particular crystalline form of this salt, referred to herein as Form I, has an XRPD spectrum substantially the same as that shown in Figure 1, with diffraction peaks at one or more of about 4.81, 5.99, 7.44, 7.89, 11.66, 14.85, 15.77, 19.19, 20.86, 21.65, 23.96, 24.48, or 24.73 degrees 2-theta. When used herein to refer to XPRD peaks, the term “about” means ± 0.2 degrees 2-theta.

Crystalline Form I of Compound K has a melting point of about 184°C (see Figure 2) as determined by differential scanning calorimetry (DSC) (melting endotherm). When referring to a temperature, the terms “substantially” and “about” mean ±2°C.

Crystalline Form I of Compound K is the most stable of the forms discovered for this salt: neither the form itself, its morphology, nor its purity changed after having been stored at 40°C and 75% relative humidity for up to four weeks. Moreover, while Form I has a lower melting point than a hydrochloride salt of Compound J (a form of which was found to have a melting point of about 247°C), the phosphate salt does not show evidence of concomitant degradation. Instead, the melting of Form I is observed to recrystallize to another, metastable form having a melting point of about 172.5°C. The large-scale manufacture and purification of Form I are further aided by its water solubility, which is 26.8 mg/mL at 25°C. By comparison, a hydrochloride salt of Compound J had a measured aqueous solubility of 2.9 mg/mL at 25°C.

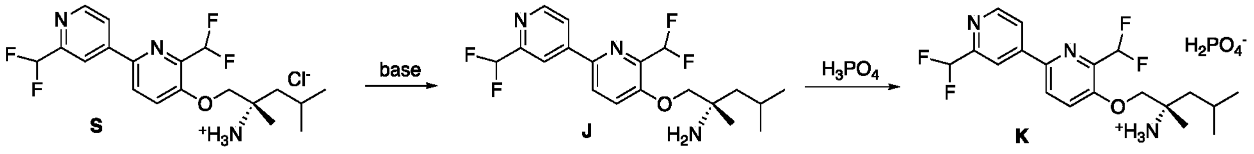
One embodiment of the invention, which can be used to prepare Form I, is shown below:



Here, Compound K is prepared by contacting Compound J with phosphoric acid in a solvent under conditions sufficient to form Compound K. Examples of solvents include water, methanol, ethanol, n-butanol, isopropanol, isobutanol, t-butanol, methyl t-butyl ether, ethyl acetate, isopropyl acetate, THF and 2-methyl THF, and mixtures thereof. A particular solvent is isopropanol.

In some embodiments, Compound J is contacted with phosphoric acid at a temperature of from about 0°C to about 100°C or from about 50°C to about 60°C. (When referring to reaction conditions, the term "about" when used to refer to temperature may be construed as ± 10°C unless otherwise indicated.) In some embodiments, Compound J is contacted with phosphoric acid for about 0.5 hours to about 24 hours or for about 2 hours to about 16 hours. (When referring to reaction conditions, the term "about" when referring to time may be construed as ± 5 percent unless otherwise indicated. For example, "about 2 hours" is the same as 2 hours ± 6 minutes.) In some embodiments, from about 0.8 to about 1.2 molar equivalents (*e.g.*, about 1 molar equivalent) of the phosphoric acid is utilized relative to Compound J. (Unless otherwise indicated, the term "about" when referring to molar equivalents or concentration may be construed as ± 5 percent.) In some embodiments, the concentration of Compound J in the solvent is from about 2% to about 25%.

In one embodiment of the invention, Compound K is prepared from Compound S as shown below:



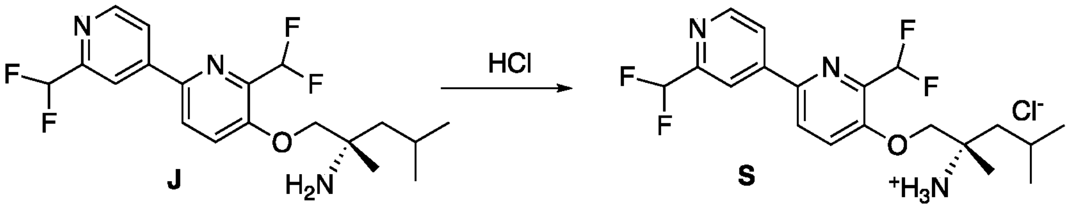
In this approach, Compound S is neutralized with a base under conditions sufficient to form Compound J, which is contacted with phosphoric acid under conditions sufficient to form Compound K. Suitable bases for the neutralization include NaOH, KOH, Na_2CO_3, and K_2CO_3. A preferred base is sodium hydroxide.

The neutralization of Compound S with a base is typically carried out in a solvent such as water, water/MTBE, water/THF and water/2-MeTHF (a preferred solvent is water/MTBE), and at a temperature of from about 0°C to about 60°C (*e.g.*, from about 20°C to about 40°C). In some embodiments, the neutralization is carried out for about 0.5 hours to about 24 hours (*e.g.*, for about 1 hour to about 2 hours.) In some embodiments, from about 0.8 to about 5 molar equivalents of the base is utilized relative to Compound S. In some embodiments, the concentration of Compound S in the solvent is from about 2% to about 25%.

The exposure of Compound J to phosphoric acid in the second step shown above is typically carried out in a solvent such as water, methanol, ethanol, n-butanol, isopropanol, isobutanol, t-butanol, methyl t-butyl ether, ethyl acetate, isopropyl acetate, THF and 2-methyl THF, or mixtures thereof. A preferred solvent is isopropanol.

In some embodiments, the exposure of Compound J to phosphoric acid is carried out at a temperature of from about 0 °C to about 100 °C (*e.g.*, from about 50 °C to about 60 °C.) In some embodiments, the exposure of Compound J to phosphoric acid is carried out for about 0.5 hours to about 24 hours (*e.g.*, about seven hours to about 14 hours.) In some embodiments, from about 0.8 to about 1.2 molar equivalents of the phosphoric acid is utilized relative to Compound J in step 2. In some embodiments, the concentration of Compound J in the solvent is from about 2% to about 25%.

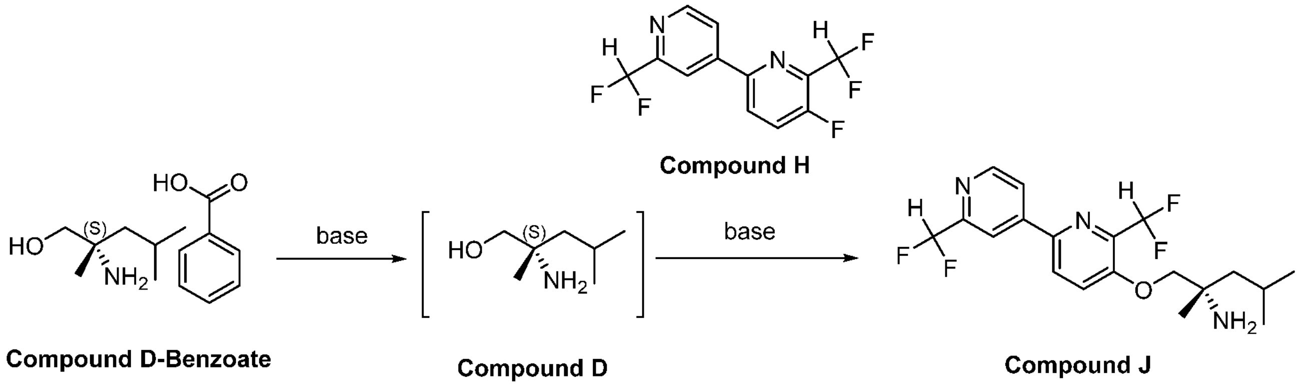
Compound S can be prepared as shown below:



In one embodiment, Compound S is prepared by exposing Compound J to hydrochloric acid in a solvent under conditions sufficient to form Compound S. In some embodiments, the solvent is water, IPA, water/IPA mixture, MeOH, MeOH/water, EtOH, EtOH/water, n-BuOH or n-BuOH/water. A preferred solvent is isopropanol.

The exposure of Compound J to hydrochloric acid is carried out at a temperature of from about 0 °C to about 60 °C (*e.g.*, from about 50 °C to about 60 °C) for about 0.5 hours to about 24 hours (*e.g.*, about 4 hours to about 8 hours.) From about 0.8 to about 1.2 molar equivalents of the hydrochloric acid is typically used relative to Compound J. In some embodiments, the concentration of Compound J in the solvent is from about 2% to about 25%.

One embodiment of the invention encompasses the method of preparing Compound J shown below:



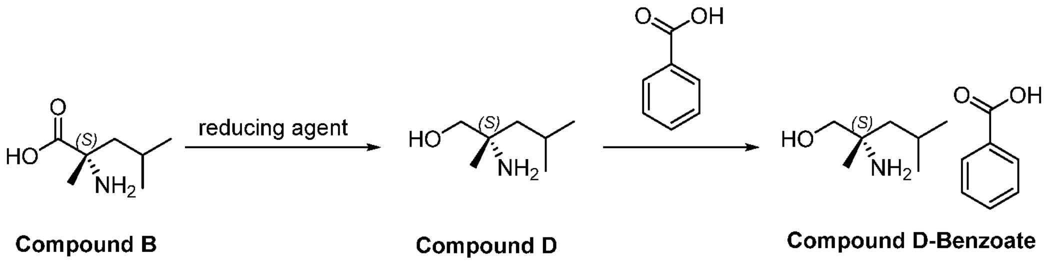
Here, Compound J is prepared by neutralizing Compound D-benzoate with a base under conditions sufficient to form Compound D, which is contacted with Compound H in the presence of a base under conditions sufficient to form Compound J. Compound D need not be isolated.

Solvents suitable for use in these reactions include THF, 2-methyl THF, 1,4-dioxane, MTBE, DME, diglyme, t-butanol, and t-amyl alcohol. A particular solvent is THF. The base utilized in both steps may be added at the start of the first. Examples of suitable bases include potassium t-butoxide, sodium t-butoxide, potassium t-amylate, sodium t-amylate, sodium hexamethydisilazide, potassium hexamethyldisilazide, lithium diisopropylamide, n-butyl lithium, sec-butyl lithium, and t-butyl lithium. A particular base is potassium t-butoxide.

In some embodiments of the invention, the neutralization of Compound D-benzoate is carried out at a temperature of from about -50 °C to about 50 °C (*e.g.*, from about 15 °C to about 25 °C) for about 0.5 hours to about 24 hours (*e.g.*, for about 3 hours to about 5 hours.) In some embodiments, Compound H is contacted with Compound D in the presence of a base at a temperature of from about -50 °C to about 50 °C (*e.g.*, from about 0 °C to about 25 °C) for about 2 hours to about 5 hours.

From about 1.8 to about 3 molar equivalents (*e.g.*, from about 2.5 to 3 molar equivalents) of the base is used relative to Compound H and from about 1 to about 1.5 molar equivalents (*e.g.*, about 1.2 molar equivalents) of Compound D-benzoate is used relative to Compound H.

Compound D-benzoate can be prepared as shown below:



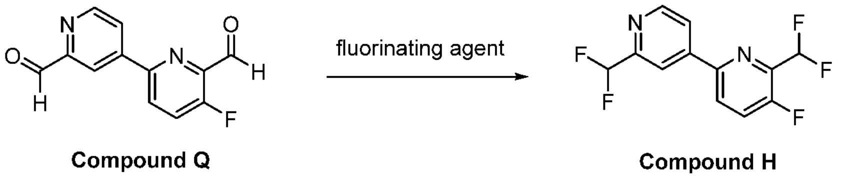
wherein Compound B is contacted with a reducing agent under conditions sufficient to form Compound D, which is contacted with benzoic acid under conditions sufficient to form Compound D-benzoate.

Examples of reducing agents include $NaBH_4/BF_3{\cdot}Et_2O$, $NaBH_4/I_2$, $NaBH_4$/TMSCl, $NaBH_4/H_2SO_4$, $NaBH_4$/MsOH, $NaBH_4$/TsOH, $NaBH_4$/HCl, $NaBH_4/AlCl_3$, CDI/$NaBH_4$, BH_3 THF complex, BH_3 dimethyl sulfide complex, diborane, $LiAlH_4$ and Li/$AlCl_3$/t-BuOH. In some embodiments of the invention, the reducing agent is $NaBH_4/BF_3{\cdot}Et_2O$. The amount of the reducing agent can be from about 0.5 to about 4 molar equivalents (*e.g.*, about 2 molar equivalents) relative to Compound B.

The reduction of Compound B is typically carried out in a solvent such as THF, 2-Me-THF, THF, 2-methyl THF, 1,4-dioxane, MTBE, DME and diglyme, or mixtures thereof. A preferred solvent is THF. In some embodiments, the concentration of Compound B in the solvent is from about 2% to about 25%. The reduction may be carried out at a temperature of from about -50 °C to about 50 °C (*e.g.*, from about 0 °C to about 25 °C) for about 0.5 hours to about 24 hours (*e.g.*, about 5 hours to about 8 hours.)

According to the approach shown above, Compound D is contacted with benzoic acid in a solvent such as MTBE, MTBE/heptane, THF, THF/heptane, EtOAc, EtOAc/heptane, IPAc, IPAc/heptane, EtOH, EtOH/heptane, IPA, IPA/heptane, toluene, and acetonitrile. A preferred solvent is MTBE. In some embodiments of this invention, this reaction is carried out at a temperature of from about 0 °C to about 60 °C (*e.g.*, from about 45 °C to about 50 °C) for about 1 to 2 hours. In some embodiments, from about 0.8 to about 1.5 molar equivalents of benzoic acid is utilized relative to Compound D (*e.g.*, about 1.1 molar equivalents). In some embodiments, the concentration of Compound D in the solvent is from about 2% to about 25%.

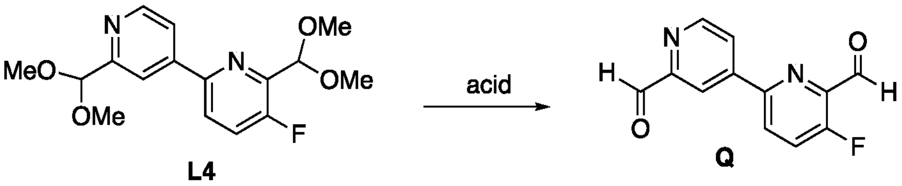
Another intermediate useful in the large-scale synthesis of Compound J and pharmaceutically acceptable salts thereof is Compound H, which can be prepared as shown below:



In this approach, Compound H is prepared by contacting Compound Q with a fluorinating agent under conditions sufficient to form Compound H. Examples of fluorinating agents include SF_4, $PhSF_3$, R_2NSF_3 (DAST, Morph-DAST), dialkylamidodifluorosulfinium tetrafluoroborate ($[R_2N{=}SF_2]$ (XtalFluor-E, XtalFluor-M)BF_4), Deoxo-Fluor (BAST), Selectfluor, and 4-tert-butyl-2,6-dimethylphenylsulfur trifluoride. A preferred fluorinating agent is DAST. Depending on the particular agent used, from about 1 to about 5 molar equivalents (*e.g.*, about 3.5) of the fluorinating agent is used relative to Compound Q.

Compound Q is preferably contacted with the fluorinating agent in a solvent such as methylene chloride, chloroform, CCl_4 and toluene. A preferred solvent is methylene chloride. The concentration of Compound Q in the solvent may vary from about 2% to about 25%. The reaction typically occurs at a temperature of from about -20° C to about 60° C (*e.g.,* from about 0° C to about 25° C) for about 1 hour to about 100 hours (*e.g.*, from about 24 hours to about 30 hours.)

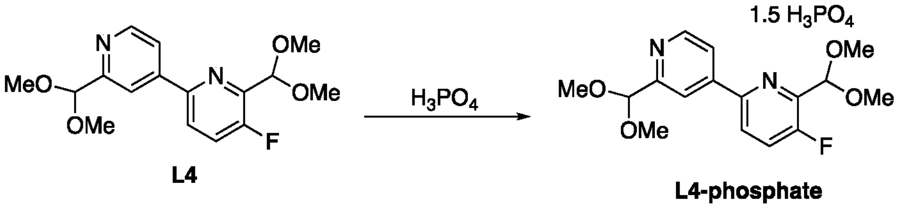
Compound Q can be prepared from Compound L4 as shown below:



In this approach, Compound Q is prepared by contacting Compound L4 or a salt thereof (*e.g.*, the phosphoric acid salt L4-phosphate) with an acid under conditions sufficient to form Compound Q. Examples of suitable acids include HCl, HBr, HI, H_2SO_4, H_3PO_4, HNO_3, MsOH, TsOH and HBF_4. A preferred acid is hydrochloric acid.

Reaction with the acid is preferably carried out in a solvent such as water or DMSO/water (a preferred solvent is water) and at a temperature of from about 0° C to about 100° C (*e.g.*, from about 55° C to about 60° C). The reaction is typically carried out for about 1 hour to about 24 hours (*e.g.*, two hours). The concentration of Compound L4 can be varied to optimize yield, and may be, for example, from about 2 to about 25%. In some embodiments of the invention, from about 1 to about 10 molar equivalents (*e.g.*, 5 molar equivalents) of the acid is utilized relative to Compound L4.

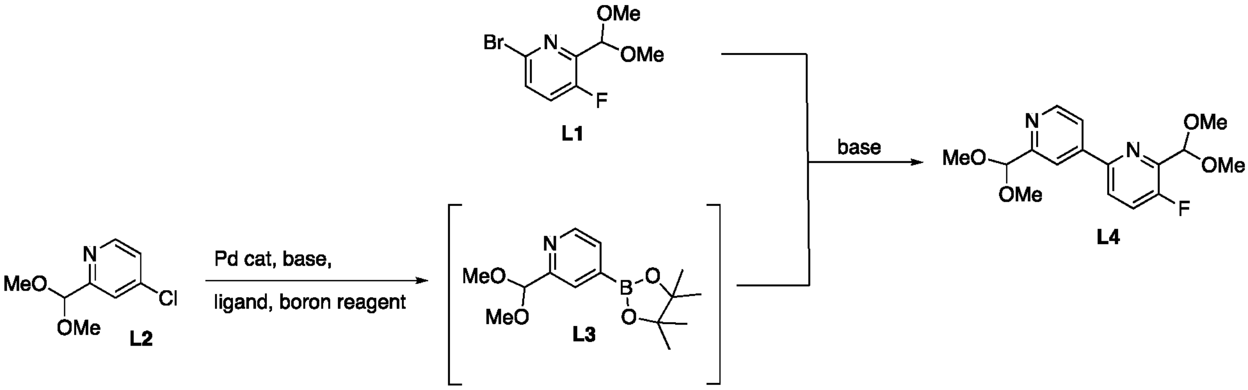
A particularly useful salt of Compound L4 is L4-phosphate, which can be prepared as shown below:



In this approach, Compound L4 is contacted with phosphoric acid under conditions sufficient to prepare Compound L4-phosphate. The reaction can be carried out in solvents such as MeOH, EtOH, IPA, EtOAc, IPAc, MTBE, THF, 2-Me-THF, toluene, heptane, or mixtures thereof. A preferred solvent system is toluene/methanol/heptane.

The reaction is typically run at a temperature of from about 0° C to about 60° C (*e.g.*, about 15° C to about 45° C) for about 1 hour to about 24 hours (*e.g.*, about 10 hours to about 12 hours). In some embodiments of the invention, from about 1 to about 2 (*e.g.*, about 1.6) molar equivalents of the phosphoric acid is utilized relative to Compound L4. The concentration of Compound L4 in the solvent can range from about 2% to about 25%.

Compound L4 can be prepared using the approach shown below:



Here, Compound L2 is contacted with a palladium catalyst, base, ligand, and boron reagent under conditions sufficient to form Compound L3, which is contacted with Compound L1 in the presence of a catalyst and a base under conditions sufficient to form Compound L4.

The preparation of Compound L3 is typically done in a solvent such as THF, 2-MeTHF, 1,4-dioxane, DME, MTBE, Et_2O, or ACN. In some embodiments, the solvent is 2-MeTHF. Examples of palladium catalysts that may be used to prepare Compound L3 include $Pd(OAc)_2$, $PdCl_2(dppf)$, $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, and $Pd_2(dba)_3$. A preferred catalyst is $Pd_2(dba)_3$. Bases useful in the formation of Compound L3 include NaOAc, KOAc, $NaHCO_3$, $KHCO_3$, Na_2CO_3, K_2CO_3, K_2HPO_4, and K_3PO_4. A preferred base is KOAc. Suitable ligands include PCy_3, SPhos and Xphos. A preferred ligand is Xphos. Boron reagents useful in the reaction include tetrahydrodiboron, PinBH and Pin_2B_2. A preferred boron reagent is Pin_2B_2.

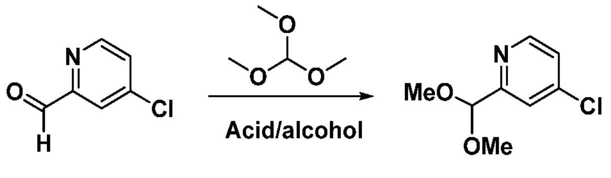
In some embodiments of the invention, Compound L2 is contacted with the palladium catalyst, base, ligand, and boron reagent at a temperature of from about 0°C to about 100°C (*e.g.*, from about 70°C to about 80°C) for about 0.5 hours to about 48 hours (*e.g.*, about 16 hours to about 24 hours.) In some embodiments, from about 0.8 to about 2 (*e.g.*, 1) molar equivalents of the boron reagent is utilized relative to Compound L2. In some embodiments, the concentration of Compound L2 in the solvent is from about 2% to about 25%.

The next step of the reaction shown above, wherein Compound L3 is reacted with Compound L1, is typically carried out in a solvent such as water, THF, 2-MeTHF, 1,4-dioxane, DME, MTBE, Et_2O, and mixtures thereof. A preferred solvent is water/2-MeTHF. The concentration of Compound L1 can range from about 2% to about 25%, but like the conditions for all of the reactions disclosed herein, these numbers can be varied using means well known to those skilled in the art to maximize product yield and minimize cost.

Examples of bases that can be used for the formation of Compound L4 include Na_2CO_3, K_2CO_3, Na_3PO_4, K_3PO_4, NaOH and KOH. A preferred base is sodium carbonate (Na_2CO_3).

Depending on the base, about 1 to 2 molar equivalents (*e.g.*, 2 molar equivalents) of base are used relative to Compound L2. This step is carried out at a temperature of from about 20°C to about 100°C (*e.g.*, from about 70°C to about 80°C) for about 1 hours to about 48 hours (*e.g.*, about 16 hours to about 24 hours). From about 1 to about 2 molar equivalents (*e.g.*, 1 equivalent) of Compound L1 is used relative to Compound L2.

The synthetic intermediate Compound L2 can be prepared as shown below:



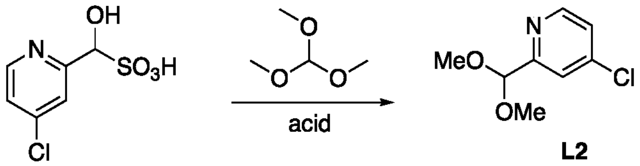
SM3 Compound L2

In this approach, the compound SM3 is contacted with trimethoxymethane in the presence of an acid under conditions sufficient to form the Compound L2. Examples of suitable acids include H_2SO_4, MsOH, TsOH, H_3PO_4, HNO_3, HCl, and HBr. A preferred acid is hydrochloric acid.

The reaction shown above is typically conducted in a solvent such as 1,4-dioxane, DME, Et_2O, THF, 2-Me-THF, toluene, DCM, MTBE, ACN, methanol. A preferred solvent is methanol. The temperature at which this reaction is conducted can range from about 0°C to about 80°C (*e.g.*, from about 60°C to about 65°C), and its duration can range from about 0.5 hours to about 48 hours (*e.g.*, about 6 to about 10 hours).

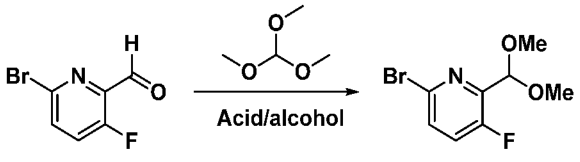
In some embodiments of the invention, from about 0.01 to about 1 molar equivalents (*e.g.*, about 0.2 molar equivalents) of the acid is utilized relative to SM3, and from about 1 to about 4 molar equivalents (*e.g.*, about 2 molar equivalents) of trimethoxymethane are used relative to SM3. The concentration of SM3 in the solvent can range from about 2% to about 30%.

Compound L2 may also be prepared as shown below using reaction conditions similar to those described above (albeit with more trimethoxymethane):



L2

The synthetic intermediate Compound L1 can be prepared as shown below:



SM2 Compound L1

In this approach, Compound L1 is prepared by contacting Compound SM2 with trimethoxymethane in the presence of an acid under conditions sufficient to form the acetal

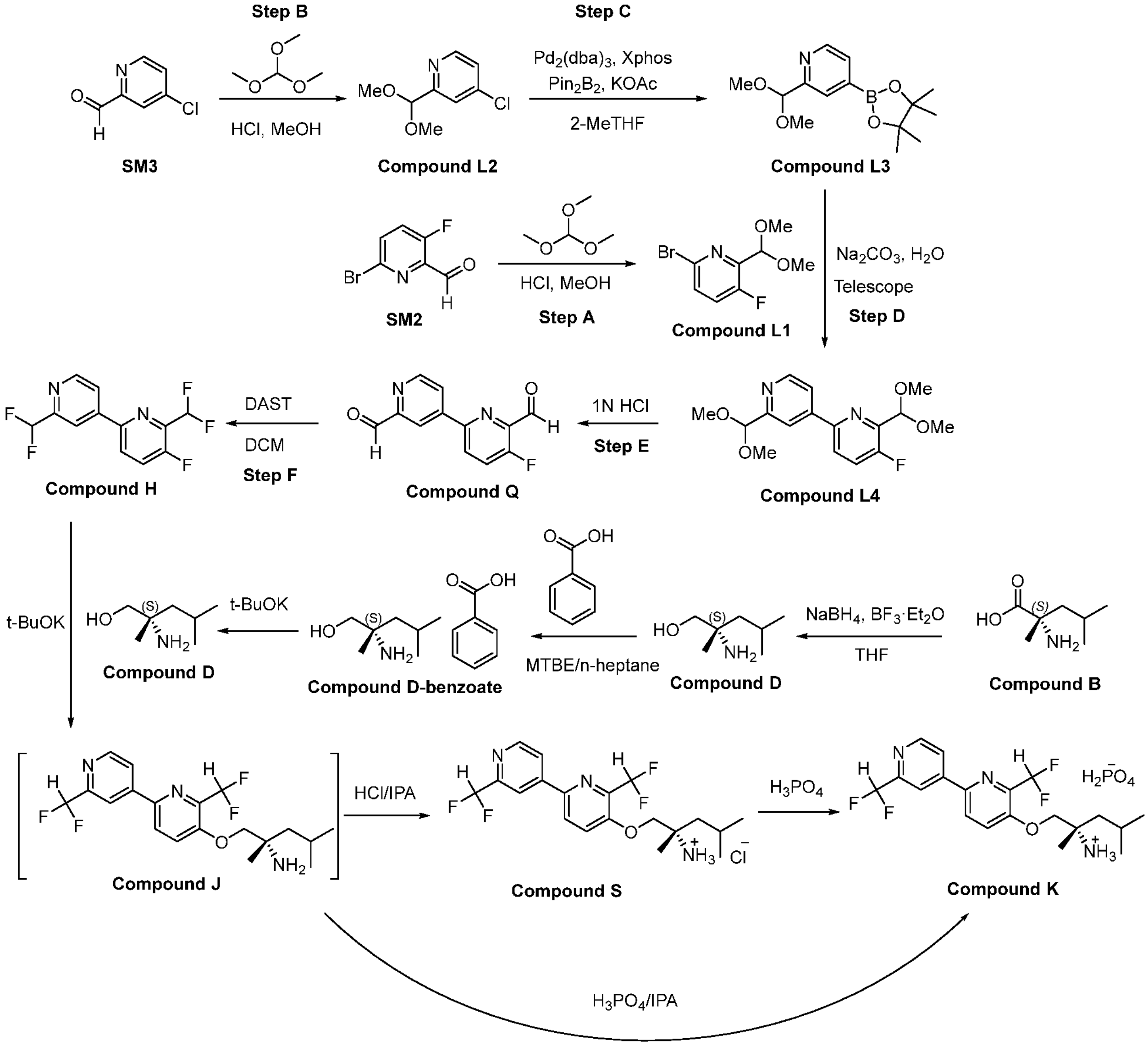
Compound L1. Examples of suitable acids include H_2SO_4, MsOH, TsOH, H_3PO_4, HNO_3, HCl, and HBr. A preferred acid is hydrochloric acid.

This reaction is preferably conducted in a solvent such as 1,4-dioxane, DME, Et_2O, THF, 2-Me-THF, toluene, DCM, MTBE, ACN and methanol. A preferred solvent is methanol.

In some embodiments of the invention, SM2 is contacted with trimethoxymethane in the presence of the acid at a temperature of from about 0 °C to about 80 °C (*e.g.*, from about 60 °C to about 65 °C) for about 0.5 hours to about 48 hours (*e.g.*, about 3 hours to about 6 hours). From about 0.01 to about 1 molar equivalents (*e.g.*, about 0.05 molar equivalents) of the acid is typically utilized relative to SM2. From about 1 to about 4 molar equivalents (*e.g.*, about 2 molar equivalents) of trimethoxymethane is typically used relative to SM2. In some embodiments, the concentration of SM2 in the solvent is from about 2% to about 30%.

In one embodiment of the invention, Compounds J, K, and S are prepared as shown in Scheme 1:

Scheme 1



In this approach, Compound J or a pharmaceutically acceptable salt thereof is prepared by a process comprising: a) contacting Compound L3 with Compound L1 in the presence of a catalyst and base under conditions sufficient to form Compound L4; b) contacting Compound L4, or a salt thereof, with an acid under conditions sufficient to form Compound Q; c) contacting Compound Q with a fluorinating agent under conditions sufficient to form Compound H; and d) contacting compound H with Compound D in the presence of a base under conditions sufficient to form said Compound J.

Compound S is prepared by a process comprising exposing Compound J to hydrochloric acid in a solvent.

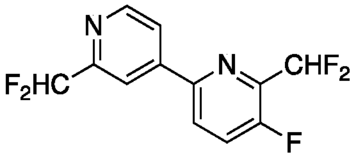
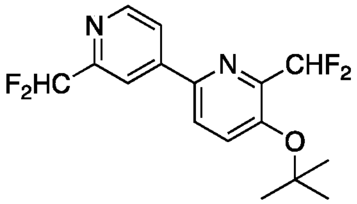
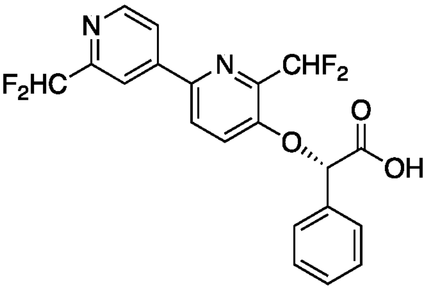
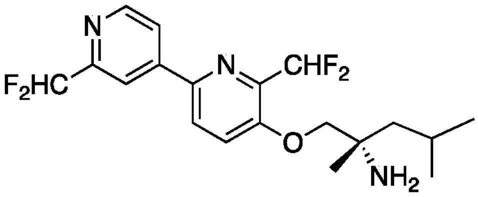
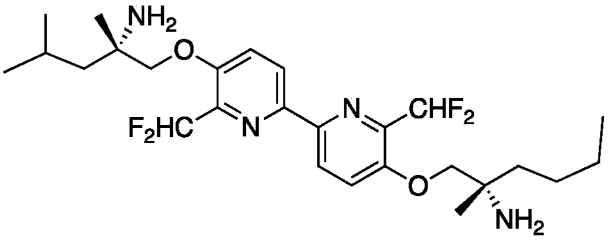
Compound K is prepared by a process comprising: a) neutralizing Compound S with a base under conditions sufficient to form Compound J; and b) exposing the resulting Compound J to phosphoric acid in a solvent under conditions sufficient to form Compound K.

In a specific embodiment of the invention, Compound K is prepared by a process comprising: a) contacting Compound L3 with Compound L1 in the presence of a catalyst and a base under conditions sufficient to form Compound L4; b) contacting Compound L4 with an acid under conditions sufficient to form Compound Q; c) contacting Compound Q with a fluorinating agent under conditions sufficient to form Compound H; d) contacting Compound H with Compound D in the presence of a base under conditions sufficient to form Compound J; e) contacting Compound J to hydrochloric acid in a solvent under conditions sufficient to form Compound S; f) neutralizing Compound S with a base under conditions sufficient to form Compound J; and g) exposing the resulting Compound J to phosphoric acid in a solvent under conditions sufficient to form Compound K.

In another embodiment, Compound K is prepared by a process comprising: a) contacting Compound L3 with Compound L1 in the presence of a catalyst and base under conditions sufficient to form Compound L4; b) contacting L4 with an acid under conditions sufficient to form Compound Q; c) contacting Compound Q with a fluorinating agent under conditions sufficient to form Compound H; d) contacting compound H with Compound D in the presence of a base under conditions sufficient to form Compound J; e) exposing the resulting Compound J to phosphoric acid in a solvent under conditions sufficient to form said Compound K.

This invention encompasses methods of ensuring that the final active pharmaceutical ingredient has a purity suitable for administration to human patients. To this end, potential impurities including those shown below in Table 1 were synthesized and characterized by ^{1}H NMR and mass spectroscopy.

Table 1

Impurity No.	Compound
1	 2',6-bis(difluoromethyl)-5-fluoro-2,4'-bipyridine
2	 5-(*tert*-butoxy)-2',6-bis(difluoromethyl)-2,4'-bipyridine
3	 (*S*)-2-((2',6-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2-phenylacetic acid
4	 (*S*)-1-((2',6-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine
5	 (*S*)-1-((5'-(((*S*)-2-amino-2,4-dimethylpentyl)oxy)-6,6'-bis(difluoromethyl)-[2,2'-bipyridin]-5-yl)oxy)-2-methylhexan-2-amine

The compounds in Table 1 were observed at various stages of the lab-scale development work that led to methods of the invention.

This invention comprises a method of testing the purity of Compound J or a pharmaceutically acceptable salt thereof by testing for the presence of one or more of the compounds listed in Table 1. A preferred method comprises testing for the presence of the one or more compounds using mass spectroscopy and/or HPLC.

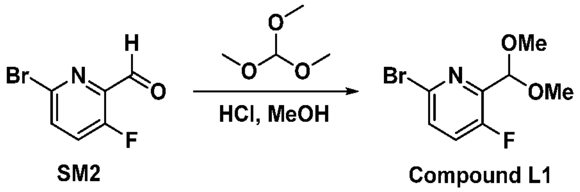
5.1 EXAMPLES

Various embodiments of the invention may be understood by considering the examples provided below. In these examples, unless otherwise indicated, all temperatures are set forth in degrees Celsius and all parts and percentages are by weight. Reagents may be purchased from commercial suppliers and were used without further purification unless otherwise indicated. (Reagents may also be prepared following standard literature procedures known to those skilled in the art.)

Unless otherwise specified, reactions were run at ambient temperature (or room temperature.) Reactions were typically assayed by HPLC and terminated as judged by the consumption of starting material.

Compound structures and purities were confirmed by one or more of the following methods: proton nuclear magnetic resonance (^{1}H NMR) spectroscopy, ^{13}C NMR spectroscopy, mass spectroscopy, infrared spectroscopy, melting point, X-ray crystallography, LC-MS and/or HPLC. Chemical shifts are reported in parts per million (ppm, δ) downfield from a standard, *e.g.,* an internal standard, such as TMS. Alternatively, ^{1}H NMR chemical shifts were referenced to signals from residual protons in deuterated solvents as known in the art. Peak multiplicities are designated as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; dt, doublet of triplets; q, quartet; br, broadened; and m, multiplet. Coupling constants are given in Hertz (Hz). Mass spectra (MS) data were obtained using a mass spectrometer with APCI or ESI ionization.

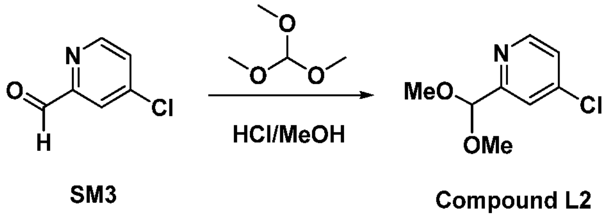
5.1.1 Synthesis of 6-bromo-2-(dimethoxymethyl)-3-fluoropyridine (Compound L1)



A solution of HCl/MeOH (10 mL of 3.9 M solution, 0.05 eq.) was charged into a mixture of SM2 (158.5 g, 777 mmol, 1 eq.), MeOH (1585 mL, 10V) and trimethoxymethane (166 g, 15.6 mol, 2.0 eq.). The resulting mixture was aged at 60-65°C (reflux) until reaction completions (3-6 h) and then cooled to 10-20°C. After being concentrated to 2-3V below 50°C and diluted with 2-Me-THF (10V), the reaction was quenched with 10% K_2CO_3 (3V). The organic layer was separated and concentrated to 1-2V below 50°C. It was flushed with 2-Me-THF (5V) and then diluted with more 2-Me-THF (5V) to give a solution of Compound L1 in 2-Me-THF (845.2 g, 99% purity, 21.7%

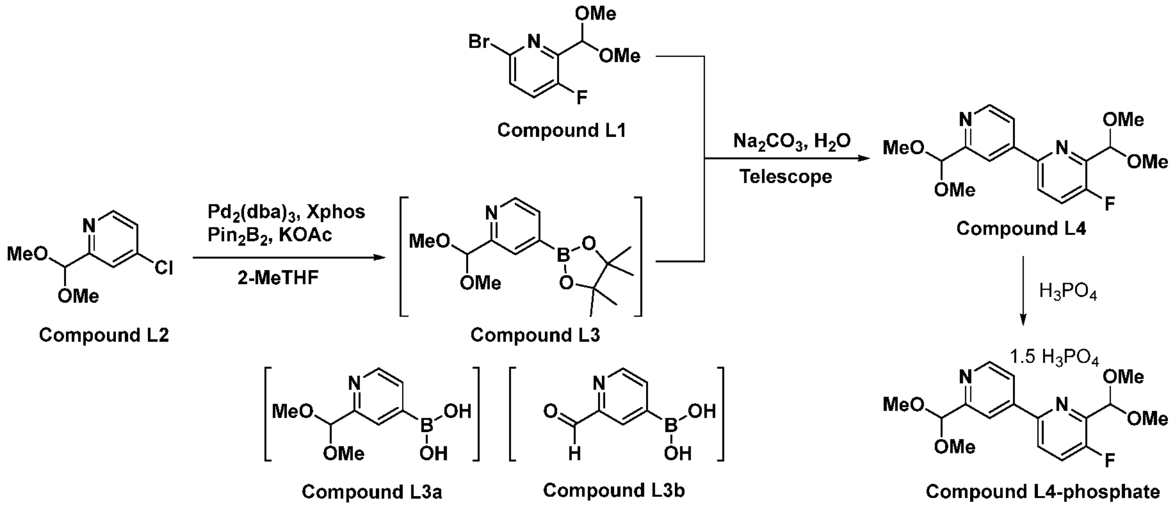
assay, 94.4% solution yield). LC-MS: m/z 250, 252, 220, 218 (M-OMe) ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.38 (dd, *J* = 3.5, 8.6 Hz, 1H), 7.17-7.30 (m, 1H), 5.37-5.48 (m, 1H), 3.39 (s, 6H).

5.1.2 Synthesis of 4-chloro-2-(dimethoxymethyl)pyridine (Compound L2)



HCl/MeOH (42.3 mL 3.9 M solution, 0.20 eq.) was charged into a mixture of SM3 (117.3 g, 819.5 mmol, 1 eq.), MeOH (1160 mL, 10V) and trimethoxymethane (174 g, 1.64 mol, 2.0 eq.). The mixture was heated to 60-65°C (reflux) until reaction completion (6-10 h) and then cooled to 10-20°C. After being concentrated to 3-5V and diluted with 2-Me-THF (10V), the reaction was quenched with 10% K_2CO_3 (3V, pH 8-9). The organic layer was separated and concentrated to 1-2V, flushed with 2-Me-THF (5V x 2), and then diluted with 2-Me-THF (5V) to give a solution of Compound L2 in 2-Me-THF (588.5 g, 99.18% purity by HPLC, 22.3% assay, 85.3% solution yield). ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.42-8.57 (m, 1H), 7.56 (d, *J* = 2.0 Hz, 1H), 7.25 (dd, *J* = 2.1, 5.3 Hz, 1H), 5.28-5.39 (m, 1H), 3.38 (s, 6H). LC-MS m/z 187, 156 (M-OMe).

5.1.3 Synthesis of 2',6-bis(dimethoxymethyl)-5-fluoro-2,4'-bipyridine phosphate (Compound L4-phosphate)

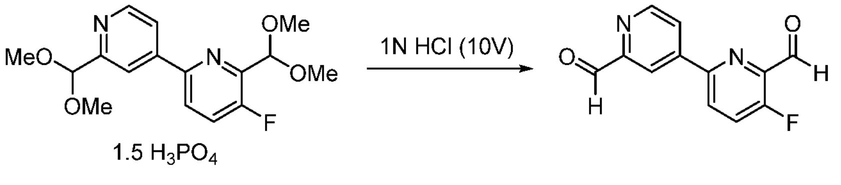


Preparation of L3: A mixture of compound L2 in 2-Me-THF (95.5 g, 1.00 eq., 5-6V), 2-Me-THF (10V), Pin_2B_2 (1.05 eq.), KOAc (3.0 eq.) and Xphos (0.02 eq.) was degassed by sparging with N_2. $Pd_2(dba)_3$ (0.01 eq.) was added, and the mixture degassed by sparging with N_2 again. The reaction mixture was heated to 70-80°C and stirred until the borylation of L2 was complete (16-24 h) to give L3, which was used directly for the next Suzuki coupling step.

Preparation of L4 via Suzuki coupling of L3 and L1: After cooling to 15-25°C, a solution of compound L1 in 2-Me-THF (0.96 eq., 5-6V), Na_2CO_3 (2.0 eq. solid) and H_2O (5V) were added sequentially. After degassing by sparging with N_2, the reaction mixture was aged at 70-80°C until the Suzuki coupling was complete (16-24 h). After cooling to 15-25°C, the reaction mixture was filtered through a pad of diatomite (0.5X) and the filter-cake was rinsed with 2-Me-THF (1-2V). The organic layer in the filtrate was separated, concentrated to 1-2V, diluted with toluene (10V) and washed with L-cysteine/NaOH (pH > 10)(5X, ratio of L-cysteine/NaOH/H_2O: 1/0.5/9) twice. The organic layer was then washed with H_2O (5X) and concentrated to 5V to give a toluene solution of Compound L4 free base in toluene. An analytical sample of L4 free base was obtained by crystallization in heptane/MTBE. ^1H NMR (400 MHz, chloroform-d) δ 8.66-8.77 (m, 1H), 8.06 (d, *J* =1.22 Hz, 1H), 7.94 (dd, *J* = 1.77, 5.20 Hz, 1H), 7.86 (dd, *J* = 3.55, 8.56 Hz, 1H), 7.51-7.60 (m, 1H), 5.63 (s, 1H), 5.44-5.48 (m, 1H), 3.54-3.60 (m, 6H), 3.43-3.49 (m, 6H); mp 41.8°C (DSC peak); XRPD 2θ: 6.70, 7.61, 9.67, 13.56, 13.77, 13.99, 15.36, 19.36, 20.71, 21.81, 23.10, 26.96, 27.72, 28.02, 29.36, 31.88, 32.04, 39.09.

Preparation of L4 phosphate: A solution of 85% H_3PO_4 (1.6 eq. based on Compound L4 free base) in MeOH (1-2V) was added over 2 h to the above L4 solution in toluene to afford a suspension. The suspension was concentrated to 3V below 45°C and *n*-heptane (10V) was added over 2 h. The mixture was concentrated to 10V below 45°C and the batch temperature was adjusted to 15-25°C. After stirring for 6-8 h, the mixture was filtered, and the filter-cake rinsed with *n*-heptane (1-2V). The wet cake was dried with a slight N_2 sweep under reduced pressure at 40°C to give 190.5 g of L4-Phosphate (93.2% yield). ^1H NMR (400 MHz, DMSO-d_6) δ 8.63-8.72 (m, 1H), 8.24 (dd, *J* = 3.6, 8.7 Hz, 1H), 8.11 (d, *J* = 1.1 Hz, 1H), 8.01 (dd, *J* = 1.8, 5.2 Hz, 1H), 7.92 (dd, *J* = 8.7, 9.9 Hz, 1H), 5.58 (s, 1H), 5.36 (s, 1H), 3.43 (s, 6H), 3.35 (s, 6H). LC-MS: $[M+H]^+$ 323.2; mp. 124.2°C (DSC peak); XRPD 2θ: 4.87, 7.35, 9.20, 12.76, 14.66, 15.06, 15.92, 16.99, 19.56, 19.81, 20.26, 21.55, 22.12, 23.09, 23.39, 23.73, 25.61, 26.25, 27.48, 27.73, 28.26, 29.55, 30.35, 31.10, 31.82, 34.13, 34.68, 36.04, 39.48.

5.1.4 Synthesis of 5-fluoro-[2,4'-bipyridine]-2',6-dicarbaldehyde (Compound Q)

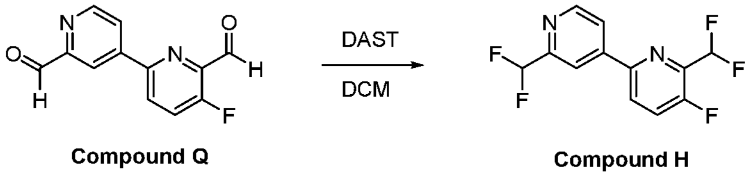


Compound L4-phosphate **Compound Q**

A mixture of compound L4-Phosphate (177 g, 111g L4 free base = 1.0X), 1N HCl (1110 mL, 10V) and toluene (555 mL, 5V) was stirred at 15-25°C for 0.5-1.0 h. The organic phase was separated off and the aqueous layer was stirred at 55-60°C for 2 h. The mixture was slowly (3 h) concentrated to remove generated MeOH under reduced pressure (-0.08 to -0.085 Mpa) at 55-

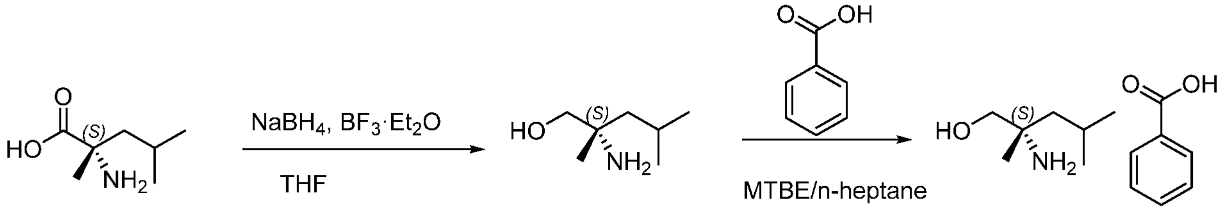
60 °C and then cooled to 30-40 °C. DCM (777V) was charged and the pH of the mixture was adjusted to 5-7 with 15% Na_2CO_3 (3.5-4.5X). The layers were separated, and the aqueous layer was extracted with DCM (2V). The combined organic layer was washed with H_2O (5V) and filtered through a pad of Na_2SO_4 (1X). The filter-pad was rinsed with DCM (2V) and the combined filtrate concentrated to 8-10V. The reactor wall was spray washed with 2V DCM and then *n*-heptane (8-10V) was charged over 2.0-5.0 h. The mixture was concentrated to 10-12V below 60 °C under normal atmospheric pressure (residual DCM in supernatant ≤ 40%). The suspension was aged at 30-40 °C for 1.0-2.0 h, 5-10 °C for 6-8 h and filtered. The filter-cake was washed with 1:4 DCM/*n*-heptane (1-2V) and dried under reduced pressure at 40-50 °C to give 80.19 g Compound Q (98% yield). LC-MS: $[M+H]^+$ 231; $[M+H+H_2O]^+$ 249; ^1H NMR (400 MHz, CHLOROFORM-d) δ 10.27 (s, 1H), 10.18 (s, 1H), 8.91-9.00 (m, 1H), 8.51-8.59 (m, 1H), 8.24-8.31 (m, 1H), 8.17(dd, *J* = 3.5, 8.7 Hz, 1H), 7.77 (t, *J* = 9.0 Hz, 1H); mp. 150 °C (DSC peak).

5.1.5 Synthesis of 2',6-bis(difluoromethyl)-5-fluoro-2,4'-bipyridine (Compound H)



A solution of compound Q (30.0 g, 1.00X) and Et_3N (0.044X) in dry DCM (KF ≤ 0.02%, 20X) was cooled to 0-5 °C. DAST (3.50X) was slowly added at 0-10 °C and the mixture was then aged at 20-25 °C until reaction completion (~ 24 h). The reaction mixture was quenched into 15% K_2CO_3 (28X) at 0-20 °C for two hours and aged at 20-25 °C for 0.5 h. The organic layer was separated, cooled to 10-20 °C and treated with 1 M HCl (9.9-11.1X) at 10-25 °C for 0.5-1 h. After settling for 0.5h, the mixture was filtered through a pad of Diatomite earth (~0.5X) followed by a small rinse DCM (2.0-3.0X). The filtrate was settled, and the organic layer was separated, washed with H_2O (10X) and filtered through a pad of silica gel (~1.5X). The silica pad was washed with DCM (5.0X – 6.0X three times) until the purity of Compound H in the filtrate fraction decreased <90%. The combined filtrate was concentrated to ~2-3V below 30 °C and then co-distilled with isopropanol 50 °C until residual DCM < 5.0% (6-7X total IPA used) with a final volume of 3-4V. The distillation residue was aged at 55-60 °C for 0.5 h, cooled to 35-40 °C, aged for 0.5 h. Water (9.0-10.0X) was slowly added at 33-40 °C (1-3 h) and the mixture stirred for 0.5 h. After aging at 15-20 °C, the suspension was filtered and the filter-cake washed sequentially with IPA/H_2O (1:4, w/w, 1X), H_2O (2X). The wet-cake was dried under reduced pressure at 40-45 °C until KF < 0.3% and residual IPA < 0.1% (18-24 h) to give 30.15 g compound H (82% yield). Melting point (mp) 75 °C (DSC peak). LC-MS: $[M+H]^+$ 275.2; ^1H NMR (400 MHz, CHLOROFORM-d) δ 8.71-8.89 (m, 1H), 8.22 (s, 1H), 7.91-8.12 (m, 2H), 7.71 (t, *J* = 8.9 Hz, 1H), 7.00 (s, 1H), 6.87 (s, 1H), 6.82-7.05 (m, 1H), 6.59 (s, 1H), 6.73 (s, 1H).

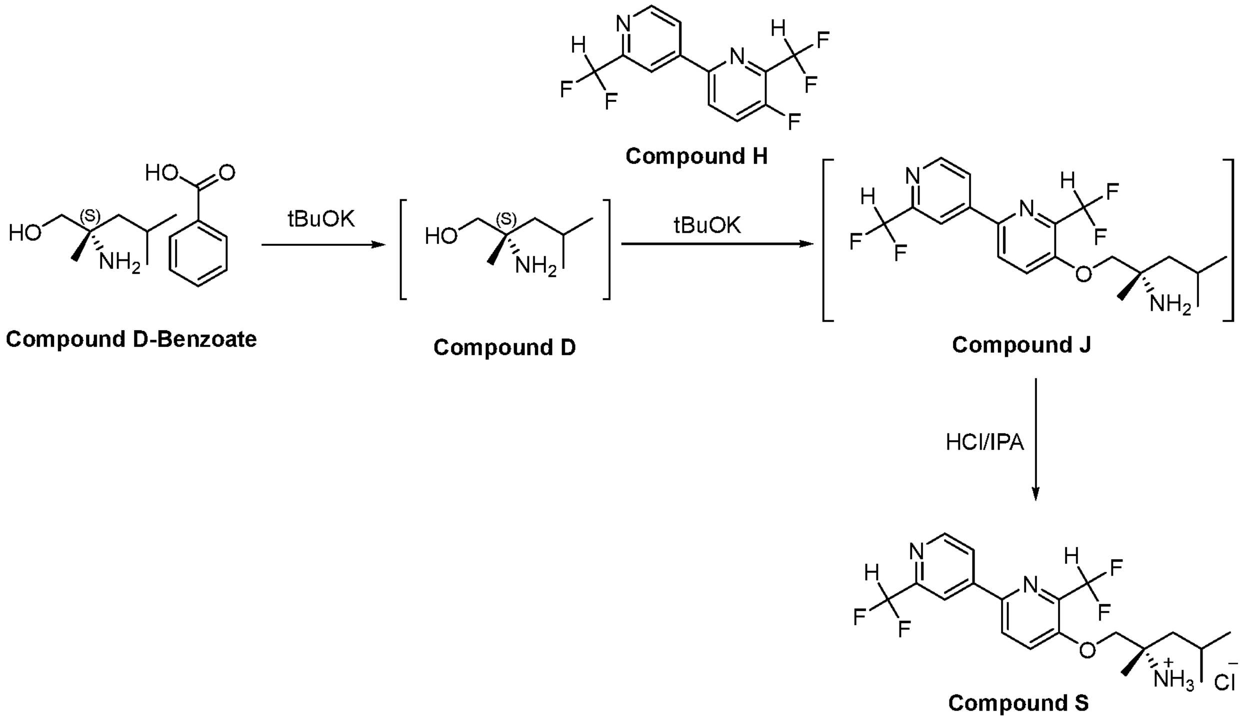
5.1.6 Synthesis of (S)-2-amino-2,4-dimethylpentan-1-ol benzoate (Compound D-Benzoate)



Compound B **Compound D** **Compound D-Benzoate**

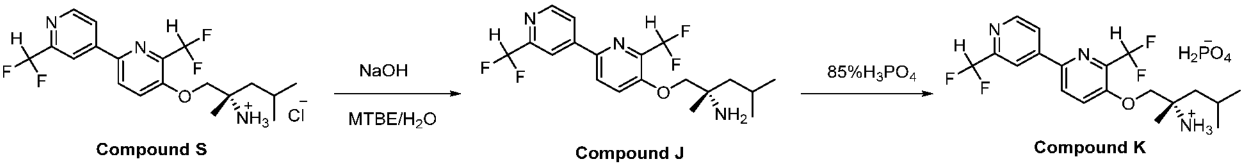
$BF_3.Et_2O$ (200 g, 2.0 equiv) was slowly added to a mixture of $NaBH_4$ (53 g, 2.0 equiv) in THF (1.0 L) at 0-10°C. The reaction mixture was warmed to 15 C and then (S)-(α)-methylleucine (100 g, 1.0 equiv) was added over 1 h at < 25°C. The mixture was aged at 20-25°C for 5-8 hours and slowly quenched into 10% aq. NaOH (750 mL) at 25-30°C. The organic layer was separated, washed with 15% aq. NaCl (200 mL) and then diluted with n-heptane (300 mL). 2N HCl (~300 mL) was added to the mixture until the pH reached 1-2. The organic layer was separated and extracted with 1 N HCl (300 mL). The combined aqueous layer was basified with 30% NaOH (~500 mL) until pH >13 and then extracted with MTBE (500 mL x 3). The combined organic extract was dried over anhydrous Na_2SO_4 (100-200 g), filtered, concentrated to ~200 mL, and then flushed with MTBE (200-500 mL) until moisture content in the concentrate was <0.5%. The solution of the amino alcohol D was then slowly (5 h) added to a solution of benzoic acid (93 g, 1.1 equiv) in MTBE (500 mL) at 45-50°C. After stirring for 1 h, the mixture was slowly (5-8 h) cooled to 20-25°C and aged for 5-8 h to give a suspension. The suspension was filtered, the filter-cake washed with 1/1 MTBE/n-heptane (150 mL) and dried at 40-50°C under reduced pressure to give Compound D-benzoate in 92% yield. mp. 125.4°C (DSC peak); ^1H NMR (400 MHz, METHANOL-d_4) δ 7.88-7.99 (m, 2H), 7.27-7.46 (m, 3H), 3.45-3.62 (m, 2H), 1.69-1.87 (m, 1H), 1.56-1.66 (m, 1H), 1.44-1.54 (m, 1H), 1.29 (s, 3H), 1.00 (d, *J* = 6.60 Hz, 6H); XRPD 2θ: 6.67, 6.83, 12.84, 13.37, 15.16, 16.95, 17.83, 19.90, 20.32, 21.23, 22.28, 23.70, 24.09, 24.42, 26.24, 26.91, 27.49, 30.60, 32.64, 33.98, 34.98, 35.13.

5.1.7 Synthesis of (S)-1-((2',6-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine hydrochloride (Compound S)



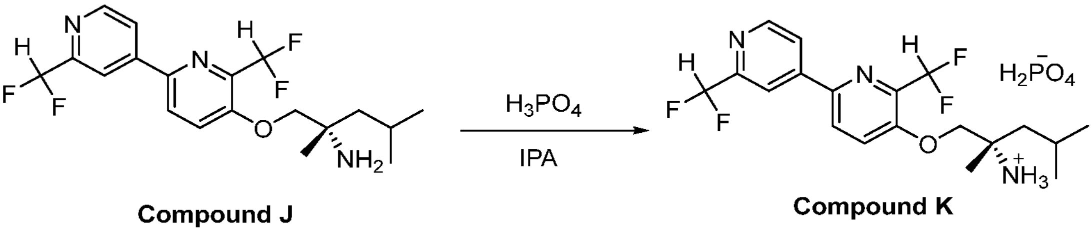
Solid t-BuOK (2.5-3.0 eq. based on Compound H) was charged in portions to a mixture of Compound D-benzoate (1.2 eq. based on Compound H) and THF (10.5-11.6X) at 15-20°C. The mixture was warmed to 20-25°C, stirred for 3-5 h and then cooled to 0-5°C. A solution of compound H (1.00X) in THF (3.6-4.5X) was slowly (~1 h) added while maintaining the batch temperature below 20°C. The reaction mixture was aged at 20-25°C until reaction completion (1-3 h). MTBE (6X) was added, and the mixture cooled to 10-15°C. H_2O (9.0-11.0X) was added slowly (1-3 h) while keeping the batch temperature below 25°C. The layers were separated, and the aqueous layer was extracted with MTBE (2.2X). The combined organic layer was concentrated to 2-3V under reduced at below 30°C. Free base compound J: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70-8.84 (m, 1H), 8.40 (d, *J* = 8.8 Hz, 1H), 8.33 (s, 1H), 8.22 (br d, *J* = 5.0 Hz, 1H), 7.81 (d, *J* =8.8 Hz, 1H), 7.17-7.41 (m, 1H), 6.89-7.13 (m, 1H), 3.82-3.95 (m, 2H), 1.74-1.88 (m, 1H), 1.55 (br s, 2H), 1.33-1.46 (m, 2H), 1.12 (s, 3H), 0.93 (t, J = 7.1 Hz, 6H). After solvent swap to IPA by co-distillation (6.0-6.5X) to 2-3V, more IPA (3.8-4.2X) was added and the mixture was heated to 50-60°C. A solution of 35% HCl (0.44-0.47X) in IPA (1.3-1.5X) was added slowly (~1 h) while keeping the batch at 50-60°C. The resulting suspension was aged at 50-60°C for 1.0-2.0 h, cooled to 20-30°C in 2.0-4.0 h, stirred at 20-30°C for 1.0-2.0 h and then filtered. The filter-cake was washed with MTBE (3.5-4.0X) and dried under reduced pressure at 40-50°C for 16-24 h to give Compound S. LC-MS m/z 386.1; mp. 246.4°C (DSC peak), ^{1}H NMR (400 MHz, DMSO-d6) δ 8.81 (d, *J* = 5.3 Hz, 1H), 8.51 (br s, 2H), 8.45 (d, *J* = 8.9 Hz, 1H), 8.34 (s, 1H), 8.24 (d, *J* = 5.1 Hz, 1H), 7.91 (d, *J* = 8.9 Hz, 1H), 7.56-7.87 (m, 1H), 6.90-7.23 (m, 1H), 4.29 (s, 2H), 1.72-1.91 (m, 2H), 1.54-1.72 (m, 1H), 1.42 (s, 3H), 0.86-1.00 (m, 6H).

5.1.8 Synthesis of (S)-1-((2',6-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine phosphate (Compound K)



A mixture of compound S (9.5 kg, 1.0X), MTBE (76.0 kg, 8.0X), water (50.0 kg, 5.3X) was treated with 20% aqueous NaOH (0.95 kg NaOH solid in 4.0 kg water) at 35-40°C until all solid dissolved (2.0-5.0 h). The reaction mixture was cooled to 20-25°C and stirred for 1.0-2.0 h. The organic layer was separated, washed with water (46.5 kg, 4.9X) and concentrated to ~25 L (2-3X) at ≤ 30°C under reduced pressure. After solvent swap to IPA by co-distillation under reduced pressure ≤ 50°C (79.0 kg IPA, 8.3X) with a final volume of 29-38 L (3-4X), the distillation residue was diluted with IPA (60 kg) and heated to 50-60°C. A solution of H_3PO_4 (2.8 kg, 0.29X) in IPA (5.0 kg, 0.53X) was added over 2.0-4.0 h. More IPA (22.0 kg, 2.3X) was added and the batch was stirred for 2.0-4.0 h at 50-60°C. The batch was cooled to 15-20°C over 2.0-4.0 h and then stirred for 1.0-2.0 h at 15-20°C. The resulting suspension was filtered, and the filter cake washed sequentially with IPA (27.0 kg, 2.84X) and MTBE (31 kg, 3.3X). The wet-cake was dried at 45-55°C for 17-24 h under reduced pressure to give compound K. The salt ratio between Compound J and phosphoric acid in Compound K was determined to be 1:1 (two separate HPLC methods using a UV and an IC detector, respectively). The purity of Compound K was 98.7-99.9 area % by HPLC. The crystallinity of Compound K was confirmed by XRPD and further supported by DSC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.78 (d, *J* = 5.1 Hz, 1H), 8.41 (d, *J* = 8.8 Hz, 1H), 8.31 (s, 1H), 8.21 (d, *J* = 5.1 Hz, 1H), 7.88 (brd, H), 7.47 (t, $J_{H\text{-}C\text{-}F}$ = 54 Hz, 1H), 7.04 (t, $J_{H\text{-}C\text{-}F}$ = 54 Hz, 1H), 4.03-4.29 (m, 2H), 1.72-1.87 (m, 1H), 1.60-1.69 (m, 1H), 1.49-1.59 (m, 1H), 1.33 (s, 3H), 0.92 (d, *J* = 6.6, 3H), 0.87 (d, *J* = 6.6, 3H); ^{13}C NMR (100 MHz, DMSO-d6) δ 21.62, 22.74, 24.61, 24.82, 44.69 54.57, 72.80, 110.53 (t, $J_{C\text{-}F}$ = 237 Hz), 113.84 (t, $J_{C\text{-}F}$ = 238 Hz), 116.68, 122.19, 125.03, 140.07 (t, $J_{C\text{-}F}$ = 22 Hz), 144.13, 145.98, 150.52, 152.80 (t, $J_{C\text{-}F}$ = 25 Hz), 153.51. XRPD: 4.80, 5.99, 7.43, 7.88, 9.57, 11.58, 14.84, 15.21, 15.75, 17.91, 18.83, 19.17, 20.41, 20.84, 21.67, 23.23, 23.95, 24.41, 24.72, 25.27, 26.37, 30.14.

5.1.9 Synthesis of (S)-1-((2',6-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine phosphate (Compound K)



To a solution of Compound J (9.14 g) in IPA (100 mL) was added Compound K seed (0.18 g) at 50-60°C. A solution of 85% phosphoric acid (2.87 g, 1.05 equiv) in IPA (7 mL) was added over a period of 2-4 h. The suspension was aged for 2-4 h, cooled to 15-20°C over 2-4 h and aged for 1-2 h. The suspension was filtered, and the filter cake washed with IPA (20 mL) followed by MTBE (44 mL). The wet cake was dried under reduced pressure at 45-55°C for 17-24 h to give 11.3 g of Compound K, 98% yield.

Compound K seed formation: IPA (1.0 mL) was added to Compound J (50.08 mg, 0134 mmol, 1.0 eq.) to form a clear solution at ambient temperature and then phosphoric acid (0.156 mL, 1M in IPA, 0.156 mmol, 1.20 eq.) was added. The mixture was stirred for 6 h to give a suspension and then aged at 60°C for 30 min. After cooling to room temperature, heptane (0.5 mL) was added, and the resulting mixture stirred for 1 h. The resulting suspension was filtered, and the filter-cake was washed with MTBE (0.5 mL), dried at 45-48°C under reduced pressure overnight to afford Compound K seed (59.28 mg, 94.4% yield).

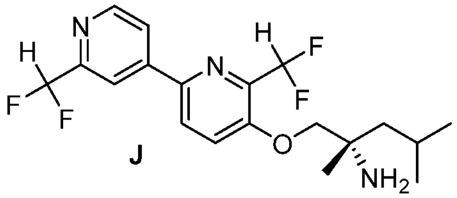
The salt ratio, purity, XRPD, DSC and TGA data are substantially identical to the data obtained for Compound K in Example 2.

Each reference (e.g., patents, patent applications, and publications) cited herein is incorporated herein by reference in its entirety.

CLAIMS

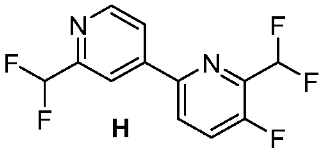
What is claimed is:

1. A method of preparing (S)-1-((2',6-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (Compound J):



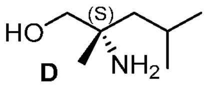
J

which comprises contacting Compound H:



H

with Compound D:



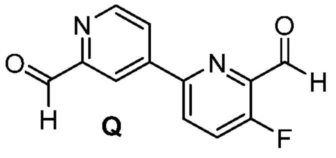
D

or a salt thereof in the presence of a base under conditions sufficient to form Compound J.

2. The method of claim 1, wherein the base is an alkoxide.

3. The method of claim 2, wherein the alkoxide is potassium tert-butoxide.

4. The method of any one of claims 1-3, wherein Compound H is prepared by contacting Compound Q:

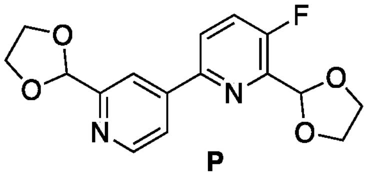


Q

with a fluorinating agent under conditions sufficient to form Compound H.

5. The method of claim 4, wherein the fluorinating agent is DAST.

6. The method of claim 4 or 5, wherein Compound Q is prepared by contacting Compound P:

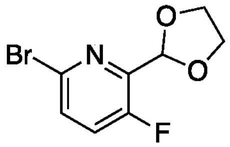


P

with an acid under conditions sufficient to form Compound Q.

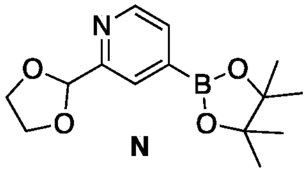
7. The method of claim 6, wherein the acid is hydrochloric acid.

8. The method of claim 6 or 7, wherein Compound P is prepared by contacting Compound L:



L

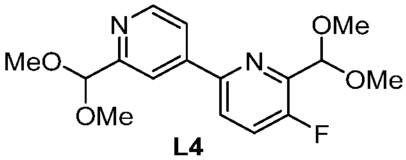
with Compound N:



N

under conditions sufficient to form Compound P.

9. The method of claim 4 or 5, wherein Compound Q is prepared by contacting Compound L4:

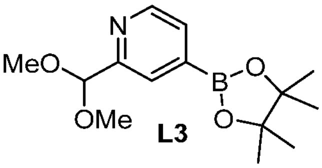


L4

with an acid under conditions sufficient to form Compound Q.

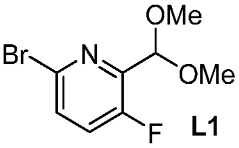
10. The method of claim 9, wherein the acid is hydrochloric acid.

11. The method of claim 9 or 10, wherein Compound L4 is prepared by contacting Compound L3:



L3

with Compound L1:



L1

in the presence of a catalyst, ligand and base under conditions sufficient to form Compound L4.

12. The method of claim 11, wherein the catalyst is Pd2(dba)2.

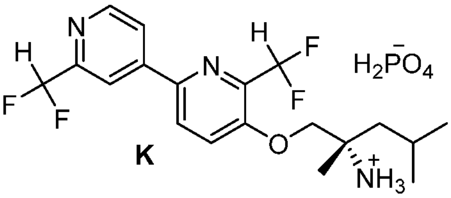
13. The method of claim 11 or 12, wherein the ligand is Xphos.

14. The method of any one of claims 11 - 13, wherein the base is sodium carbonate.

15. The method of any one of claims 1 - 14, wherein the salt of Compound D is a benzoate salt.

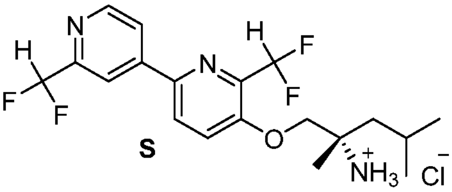
16. The method of claim 13, wherein the solvent is isopropyl alcohol.

17. A method of preparing Compound K:



K

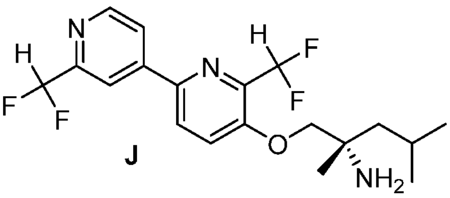
which comprises contacting Compound S (*e.g.*, in MTBE):



S

with aqueous NaOH to afford Compound J; and contacting Compound J with an acid (*e.g.*, phosphoric acid or hydrochloric acid) in a solvent under conditions sufficient to form Compound K.

18. The method of claim 17, wherein Compound S is prepared by contacting Compound J:



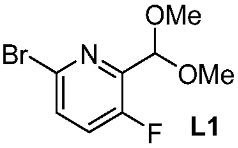
J

with hydrochloric acid in a solvent under conditions sufficient to form Compound S.

19. The method of claim 18, wherein the solvent is isopropyl alcohol.

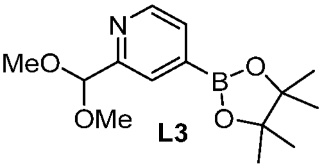
20. The method of claim 18, wherein Compound J is prepared according to any of claims 1 – 16.

21. A compound, which is 6-bromo-2-(dimethoxymethyl)-3-fluoropyridine (Compound L1):



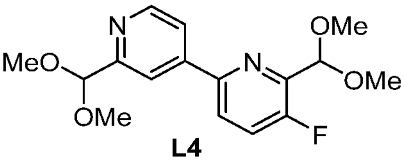
L1 .

22. A compound, which is 2-(dimethoxymethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (Compound L3):



L3 .

23. A compound, which is 2',6-bis(dimethoxymethyl)-5-fluoro-2,4'-bipyridine (Compound L4):



L4

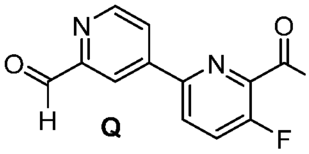
or a salt thereof.

24. The compound of 23, which is a hydrochloride, phosphate, or maleate salt.

25. The compound of claim 24, which is crystalline 2',6-bis(dimethoxymethyl)-5-fluoro-2,4'-bipyridine phosphate salt having a melting point of about 125 °C.

26. The compound of claim 25, which has an XRPD spectrum comprising a peak at one or more of about 6.70, 7.61, 9.67, 13.56, 13.77, 13.99, 15.36, 19.36, 20.71, 21.81, 23.10, 26.96, 27.72, 28.02, 29.36, 31.88, 32.04, 39.09 degrees 2 theta.

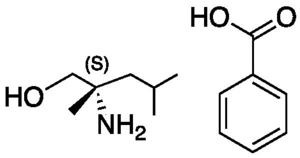
27. A compound, which is 5-fluoro-[2,4'-bipyridine]-2',6-dicarbaldehyde (Compound Q):



Q .

28. A crystalline form of the compound of claim 27, which has a melting point of about 150°C.

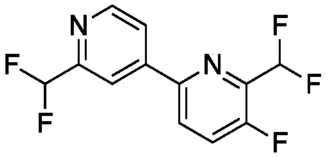
29. A compound, which is (S)-2-amino-2,4-dimethylpentan-1-ol benzoate (Compound D-Benzoate):



D-Benzoate .

30. A crystalline form of the compound of claim 29.

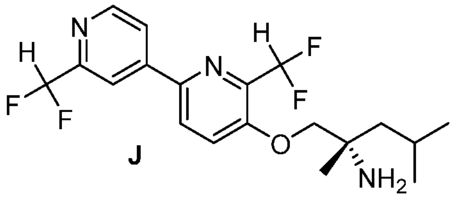
31. A compound, which is 2',6-bis(difluoromethyl)-5-fluoro-2,4'-bipyridine (Compound H):



H .

32. A crystalline form of the compound of claim 31.

33. A crystalline pharmaceutically acceptable salt of (S)-1-((2',6-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (Compound J):



J .

34. The crystalline pharmaceutically acceptable salt of claim 33, which is a hydrochloride salt.

35. The hydrochloride salt of claim 34, which has a melting point of 247 °C (decomposition).

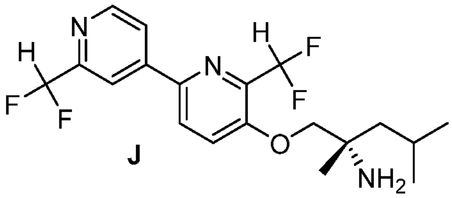
36. The hydrochloride salt of claim 34 which has an XRPD spectrum comprising a peak at one or more of about 9.2, 11.7, 13.9, 18.7, 22.2, 25.0, or 26.8 degrees 2 theta.

37. The crystalline pharmaceutically acceptable salt of claim 33, which is a phosphate salt.

38. The phosphate salt of claim 37, which has a melting point of about 184°C.

39. The phosphate salt of claim 38, which has an XRPD spectrum comprising a peak at one or more of about 4.81, 5.99, 7.44, 7.89, 11.66, 14.85, 15.77, 19.19, 20.86, 21.65, 23.96, 24.48, or 24.73 degrees 2-theta.

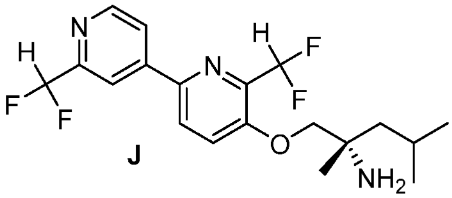
40. A method determining the purity of a sample of (S)-1-((2',6-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (Compound J):



J

or a pharmaceutically acceptable salt thereof, which comprises testing the sample for the presence of one or more of the compounds listed in Table 1.

41. A composition comprising (S)-1-((2',6-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (Compound J):



J

or a pharmaceutically acceptable salt thereof, which composition comprises less than 0.01 percent by weight of one or more of the compounds listed in Table 1.

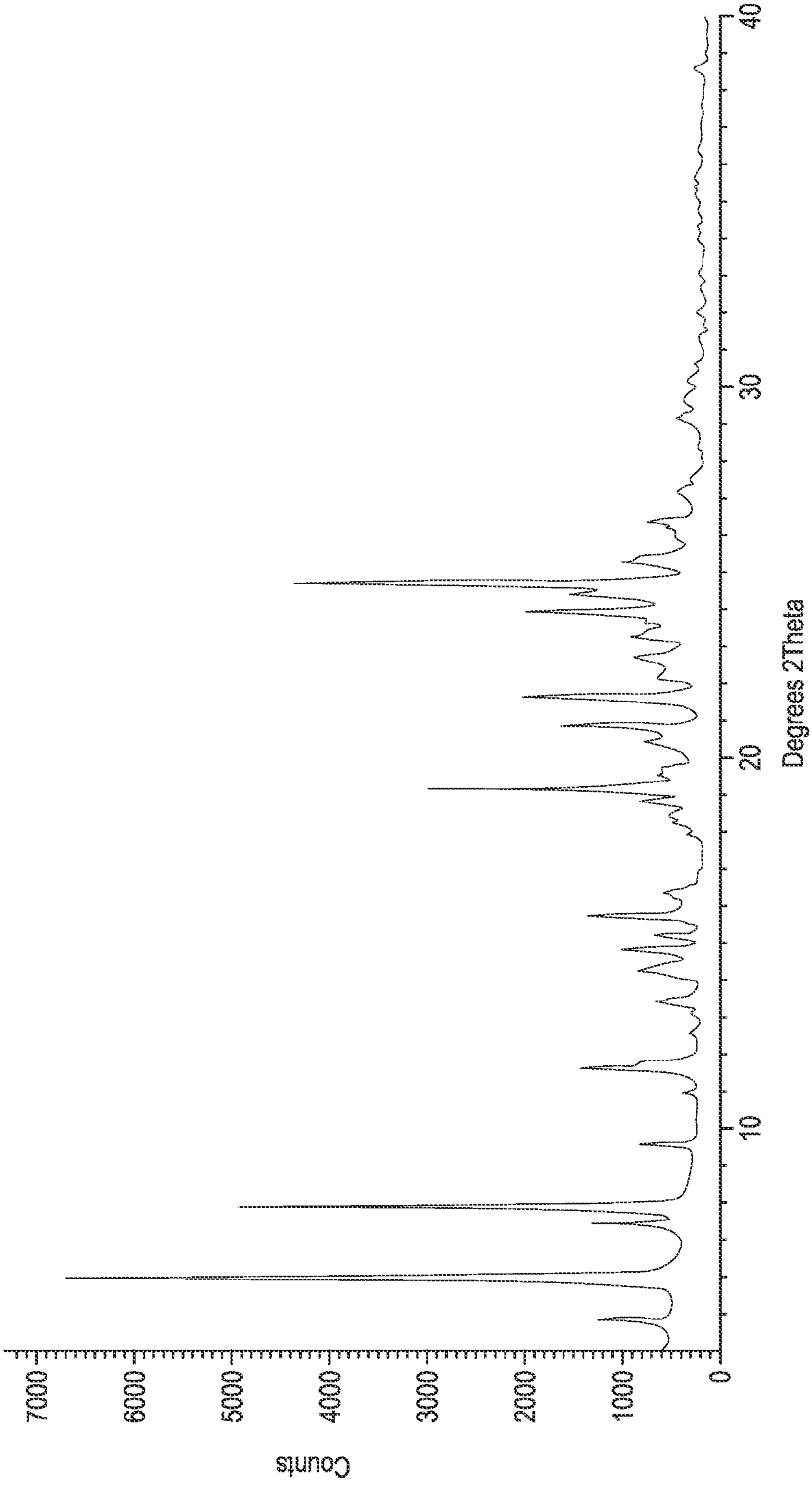

Counts
7000
6000
5000
4000
3000
2000
1000
0
10
20
30
40
Degrees 2Theta

FIG. 1

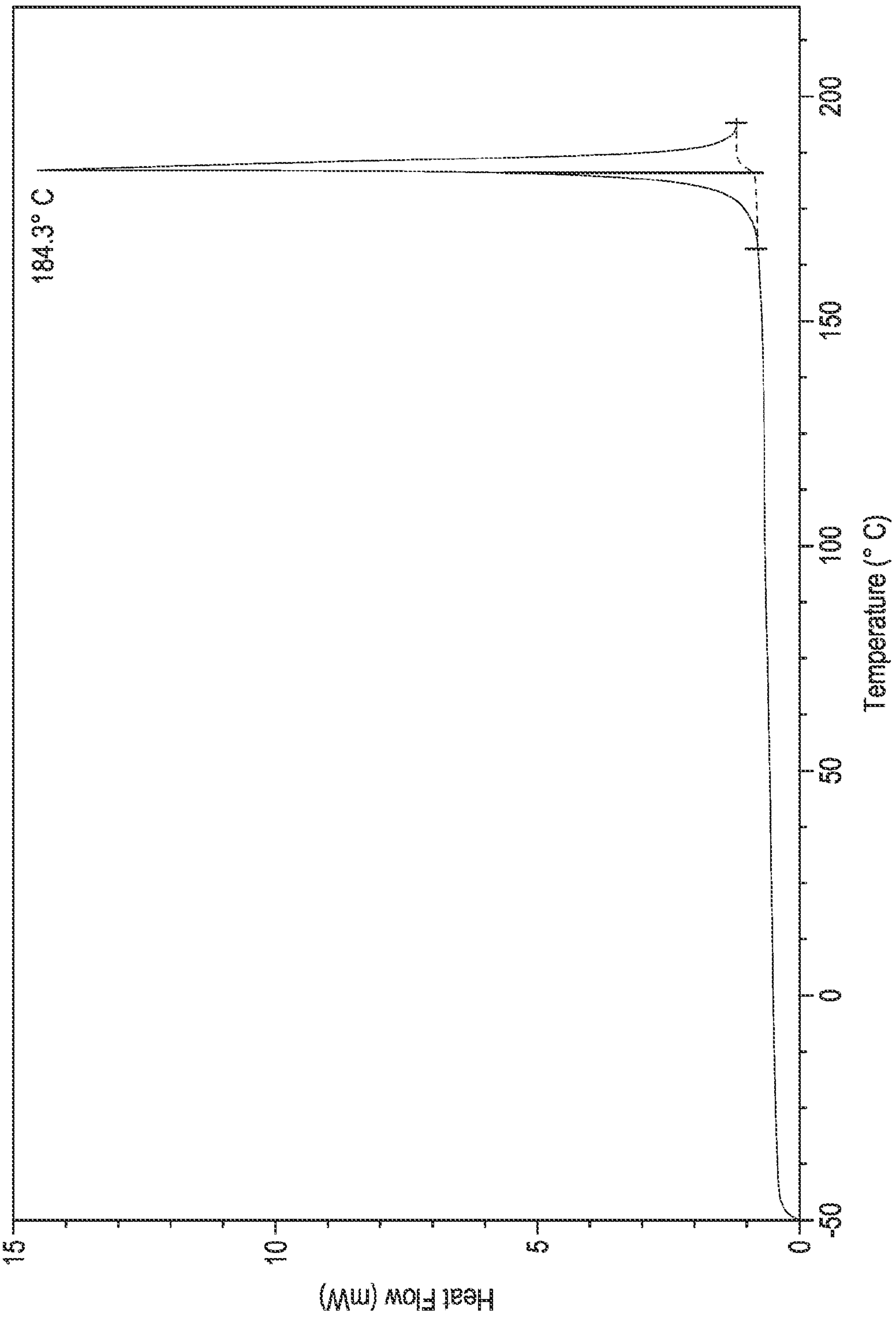


FIG. 2

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2023/013840

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D213/65 A61K31/444
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BIOSIS, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X A	WO 2017/059085 A1 (BRISTOL MYERS SQUIBB CO [US]) 6 April 2017 (2017-04-06) examples 123 and 326, parts E (title of product wrong, structure correct) and F -----	1-16,20 21-28
A	WO 2021/216441 A1 (LEXICON PHARMACEUTICALS INC [US]) 28 October 2021 (2021-10-28) "Compound 1"; page 5, line 18 - line 19; figure 1 -----	1-16,20

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search 18 July 2023	Date of mailing of the international search report 28/07/2023
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Stroeter, Thomas

International application No.
PCT/US2023/013840

INTERNATIONAL SEARCH REPORT

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
1-16, 21-28(completely); 20(partially)

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims;; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☒ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2023/013840

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2017059085 A1	06-04-2017	CN 108368084 A	03-08-2018
		CN 112142655 A	29-12-2020
		EP 3356340 A1	08-08-2018
		ES 2765730 T3	10-06-2020
		JP 6785302 B2	18-11-2020
		JP 2018537408 A	20-12-2018
		KR 20180056765 A	29-05-2018
		US 2018346440 A1	06-12-2018
		WO 2017059085 A1	06-04-2017
WO 2021216441 A1	28-10-2021	AU 2021259419 A1	10-11-2022
		CA 3175970 A1	28-10-2021
		CN 115484951 A	16-12-2022
		EP 4138829 A1	01-03-2023
		JP 2023522688 A	31-05-2023
		US 2022054464 A1	24-02-2022
		WO 2021216441 A1	28-10-2021

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-3(completely); 4-16, 20(partially)

   A method of preparing compound J

   ---

2. claims: 21-28(completely); 4-16, 20(partially)

   A method of preparing compound H via compound Q and further intermediates L1, L3 and L4 applied in this method

   ---

3. claims: 17-19, 33-39(completely); 20, 40, 41(partially)

   A salt of compound J and any related subject-matter such as a method of preparing the dihydrogenphosphate salt (compound K) from the hydrochloride salt (compound S).

   ---

4. claims: 29, 30

   Compound D as benzoate salt

   ---

5. claims: 31, 32

   Compound H, optionally in crystalline form

   ---

6. claims: 40, 41(partially)

   Subject-matter directed to compound J in its free-base form

   ---

(19)国家知识产权局

(12)发明专利申请

(10)申请公布号 CN 119095826 A

(43)申请公布日 2024.12.06

(21)申请号 202380021527.X

(22)申请日 2023.02.24

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(85)PCT国际申请进入国家阶段日
2024.08.13

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PCT/US2023/013840 2023.02.24

(87)PCT国际申请的公布数据
WO2023/167806 EN 2023.09.07

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专利代理师 刘慧 金海霞

(51)Int.Cl.
C07D 213/65(2006.01)
A61K 31/444(2006.01)

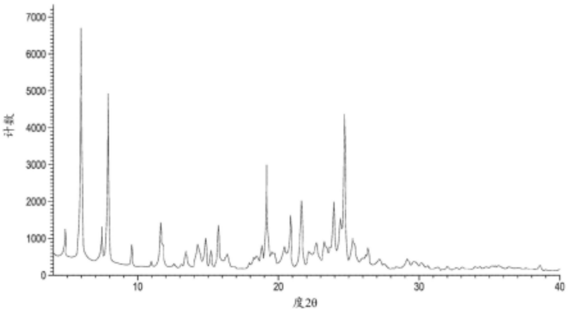
权利要求书5页 说明书20页 附图2页

(54)发明名称

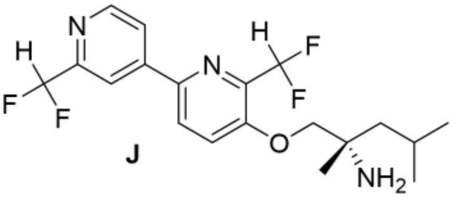
用于合成AAK1抑制剂的方法和化合物

(57)摘要

本文公开了合成(S)-1-((2',6-双(二氟甲基)-[2,4'-联吡啶]-5-基)氧基)-2,4-二甲基戊-2-胺及其盐的方法,以及其中有用的化合物。

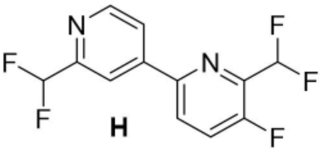


1.一种制备(S)-1-((2’,6-双(二氟甲基)-[2,4’-联吡啶]-5-基)氧基)-2,4-二甲基戊-2-胺(化合物J)：



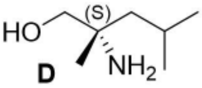
J

的方法,其包括在足以形成化合物J的条件下使化合物H：



H

与化合物D：



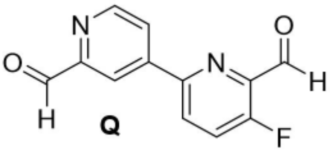
D

或其盐在碱的存在下接触。

2.如权利要求1所述的方法,其中所述碱是醇盐。

3.如权利要求2所述的方法,其中所述醇盐是叔丁醇钾。

4.如权利要求1至3中任一项所述的方法,其中化合物H是通过在足以形成化合物H的条件下使化合物Q：

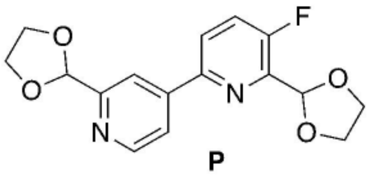


Q

与氟化剂接触来制备的。

5.如权利要求4所述的方法,其中所述氟化剂是DAST。

6.如权利要求4或5所述的方法,其中化合物Q是通过在足以形成化合物Q的条件下使化合物P：

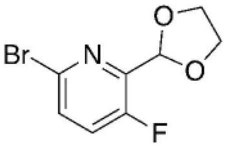


P

与酸接触来制备的。

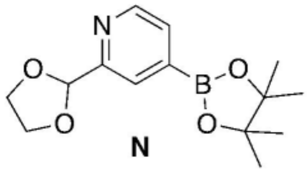
7.如权利要求6所述的方法,其中所述酸为盐酸。

8.如权利要求6或7所述的方法,其中化合物P是通过在足以形成化合物P的条件下使化合物L：



L

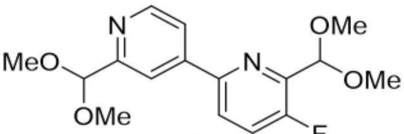
与化合物N：



N

接触来制备的。

9.如权利要求4或5所述的方法,其中化合物Q是通过在足以形成化合物Q的条件下使化合物L4：

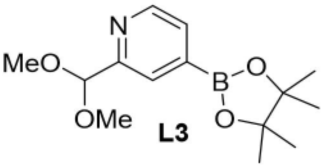


L4

与酸接触来制备的。

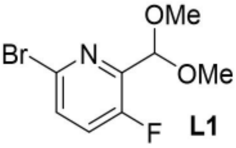
10.如权利要求9所述的方法,其中所述酸为盐酸。

11.如权利要求9或10所述的方法,其中化合物L4是通过在足以形成化合物L4的条件下使化合物L3：



L3

与化合物L1：



L1

在催化剂、配体和碱的存在下接触来制备的。

12.如权利要求11所述的方法,其中所述催化剂是Pd2(dba)2。

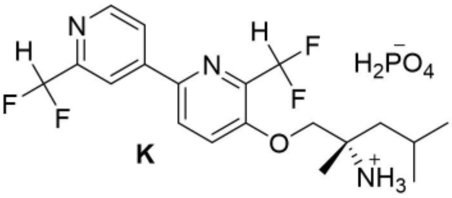
13.如权利要求11或12所述的方法,其中所述配体是Xphos。

14.如权利要求11至13中任一项所述的方法,其中所述碱是碳酸钠。

15.如权利要求1至14中任一项所述的方法,其中所述化合物D的盐是苯甲酸盐。

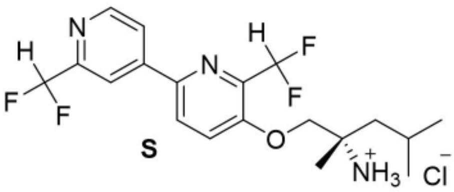
16.如权利要求13所述的方法,其中所述溶剂是异丙醇。

17.一种制备化合物K：



K

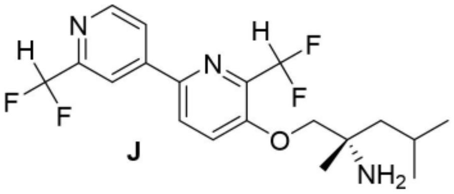
的方法,其包括使化合物S (例如,在MTBE中)：



S

与NaOH水溶液接触来获得化合物J；以及在足以形成化合物K的条件下使化合物J与酸(例如，磷酸或盐酸)在溶剂中接触。

18.如权利要求17所述的方法，其中化合物S是通过在足以形成化合物S的条件下使化合物J：



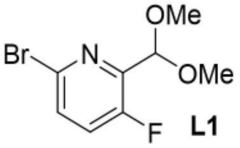
J

与盐酸在溶剂中接触来制备的。

19.如权利要求18所述的方法，其中所述溶剂是异丙醇。

20.如权利要求18所述的方法，其中化合物J是根据权利要求1至16中任一项制备的。

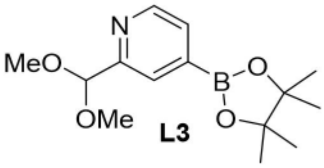
21.一种化合物，其为6-溴-2-(二甲氧基甲基)-3-氟吡啶(化合物L1)：



L1

。

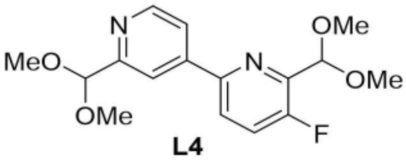
22.一种化合物，其为2-(二甲氧基甲基)-4-(4,4,5,5-四甲基-1,3,2-二氧杂环戊硼烷-2-基)吡啶(化合物L3)：



L3

。

23.一种化合物，其为2',6-双(二甲氧基甲基)-5-氟-2,4'-联吡啶(化合物L4)：



L4

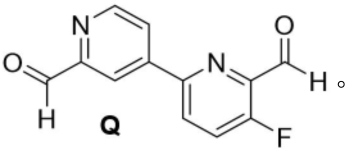
或其盐。

24.如权利要求23所述的化合物，其为盐酸盐、磷酸盐或马来酸盐。

25.如权利要求24所述的化合物，其为熔点为约125℃的结晶2',6-双(二甲氧基甲基)-5-氟-2,4'-联吡啶磷酸盐。

26.如权利要求25所述的化合物，其具有包含在约6.70、7.61、9.67、13.56、13.77、13.99、15.36、19.36、20.71、21.81、23.10、26.96、27.72、28.02、29.36、31.88、32.04、39.09度2θ中的一个或多个处的峰的XRPD光谱。

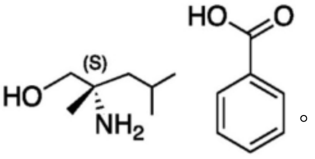
27.一种化合物，其为5-氟-[2,4'-联吡啶]-2',6-二甲醛(化合物Q)：



Q

28.一种如权利要求27所述的化合物的结晶形式，其熔点为约150℃。

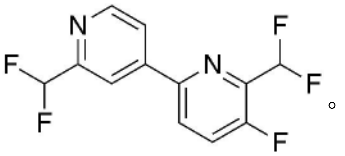
29.一种化合物，其为(S)-2-氨基-2,4-二甲基戊-1-醇苯甲酸盐(化合物D-苯甲酸盐)：



D-苯甲酸盐

30.一种如权利要求29所述的化合物的结晶形式。

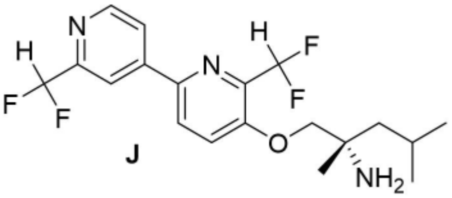
31.一种化合物，其为2’,6-双(二氟甲基)-5-氟-2,4’-联吡啶(化合物H)：



H

32.一种如权利要求31所述的化合物的结晶形式。

33.一种(S)-1-((2’,6-双(二氟甲基)-[2,4’-联吡啶]-5-基)氧基)-2,4-二甲基戊-2-胺(化合物J)：



J

的结晶药学上可接受的盐。

34.如权利要求33所述的结晶药学上可接受的盐，其为盐酸盐。

35.如权利要求34所述的盐酸盐，其熔点为247℃(分解)。

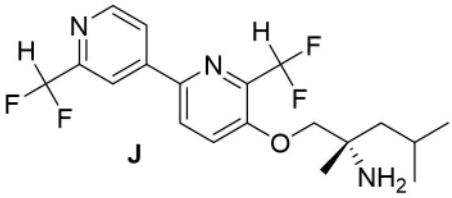
36.如权利要求34所述的盐酸盐，其具有包含在约9.2、11.7、13.9、18.7、22.2、25.0或26.8度2θ中的一个或多个处的峰的XRPD光谱。

37.如权利要求33所述的结晶药学上可接受的盐，其为磷酸盐。

38.如权利要求37所述的磷酸盐，其熔点为约184℃。

39.如权利要求38所述的磷酸盐，其具有包含在约4.81、5.99、7.44、7.89、11.66、14.85、15.77、19.19、20.86、21.65、23.96、24.48或24.73度2-θ中的一个或多个处的峰的XPRD光谱。

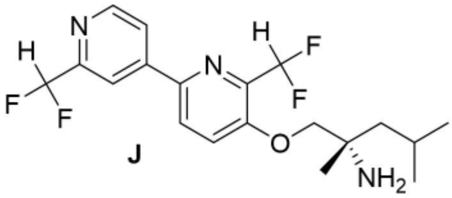
40.一种确定(S)-1-((2’,6-双(二氟甲基)-[2,4’-联吡啶]-5-基)氧基)-2,4-二甲基戊-2-胺(化合物J)：



J

或其药学上可接受的盐的样品的纯度的方法,其包括测试所述样品中表1所列的一种或多种化合物的存在。

41.一种包含(S)-1-((2’,6-双(二氟甲基)-[2,4’-联吡啶]-5-基)氧基)-2,4-二甲基戊-2-胺(化合物J):



J

或其药学上可接受的盐的组合物,所述组合物包含小于0.01重量%的表1所列的一种或多种化合物。

用于合成AAK1抑制剂的方法和化合物

技术领域

[0001] 本申请涉及制备(S)-1-((2',6-双(二氟甲基)-[2,4'-联吡啶]-5-基)氧基)-2,4-二甲基戊-2-胺及其盐形式的方法,以及其中有用的合成中间体。

背景技术

[0002] 衔接子相关激酶1 (AAK1)是丝氨酸/苏氨酸激酶Ark1/Prk1家族的成员。AAK1 mRNA以两种剪接形式存在,称为短剪接形式和长剪接形式。长形式占主导地位,并且在脑和心脏中高度表达(Henderson和Conner, Mol. Biol. Cell. 2007, 18, 2698-2706)。AAK1在突触体制剂中富集,并且与培养细胞中的内吞结构共定位。AAK1调节网格蛋白包被的内吞作用,该过程在突触囊泡循环和受体介导的内吞作用中非常重要。AAK1与AP2复合物相关,后者将受体货物与网格蛋白外壳连接起来。网格蛋白与AAK1结合可刺激AAK1激酶活性(Conner等人, Traffic 2003, 4, 885-890;Jackson等人, J. Cell. Biol. 2003,163, 231-236)。AAK1磷酸化AP-2的mu-2亚基,促进mu-2与货物受体上含有酪氨酸的分选基序结合(Ricotta等人, J. Cell Bio. 2002, 156, 791-795;Conner和Schmid, J. Cell Bio. 2002, 156, 921-929)。Mu2磷酸化不是受体摄取所需要的,但磷酸化可增强内化的效率(Motely等人, Mol. Biol. Cell. 2006, 17, 5298-5308)。

[0003] AAK1已被确定为PC12细胞中Neuregulin-1/ErbB4信号传导的抑制剂。通过RNA干扰介导的基因沉默或用激酶抑制剂K252a (抑制AAK1激酶活性)治疗导致AAK1表达丧失,会导致神经调节蛋白-1诱导的神经突生长增强。这些治疗导致ErbB4表达增加以及ErbB4在质膜内或附近的积累(Kuai等人, Chemistry and Biology 2011, 18, 891-906)。NRG1和ErbB4是推定的精神分裂症易感基因(Buonanno, Brain Res. Bull. 2010, 83, 122-131)。这两个基因中的SNP与多种精神分裂症内表型相关(Greenwood等人, Am. J. Psychiatry 2011, 168, 930-946)。神经调节蛋白1和ErbB4 KO小鼠模型已表现出精神分裂症相关形态变化和行为表型(Jaaro-Peled等人, Schizophrenia Bulletin 2010, 36, 301-313;Wen等, Proc. Natl. Acad. Sci. USA. 2010, 107, 1211-1216)。此外,AAK1基因内含子的单核苷酸多态性与帕金森病(Parkinson's disease)的发病年龄有关(Latourelle等人, BMC Med. Genet. 2009, 10, 98)。这些结果表明,抑制AAK1活性可能有助于治疗精神分裂症、精神分裂症的认知缺陷、帕金森病、神经性疼痛、躁郁症和阿尔茨海默病(Alzheimer's disease)。

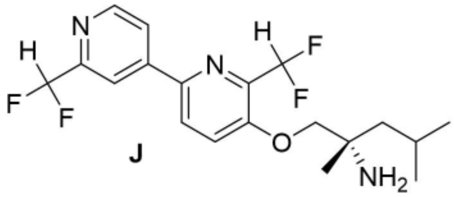
[0004] 此外,使用Huh-7.5细胞的研究表明AAK1激酶抑制剂在治疗丙型肝炎(HCV)感染方面的潜在用途。使用RNA干扰介导的基因沉默减少AAK1蛋白、用激酶抑制剂舒尼替尼(一种有效的AAK1抑制剂)治疗以及Mu2 (AAK1底物)磷酸化位点突变体的过度表达全部导致HCV病毒体组装减少。此外,相同的治疗被证明会抑制HCV进入,这表明AAK1抑制剂可以破坏病毒生命周期的两个宿主依赖性阶段(Neveu等人, PLoS Pathog. 2012, 8, 1-16;Neveu等人, J. Virol. 2015年2月4日在线发表)。AAK1抑制剂也可用于对抗HIV和HBV (参见,例如,Boge等人, J. Biol. Chem. 1998, 273, 15773-15778)。

[0005]　文献中已公开了许多AAK1抑制剂,并且有人提出一些可用于治疗神经性疼痛。参见,例如,Hartz, R.A.等人, J. Med. Chem., 2021年8月12日;64(15):11090-11128。然而,要评估任何药物的全部潜力,人体临床试验是必须的。

[0006]　特定的AAK1抑制剂(S)-1-((2',6-双(二氟甲基)-[2,4'-联吡啶]-5-基)氧基)-2,4-二甲基戊-2-胺已经在小的实验室规模中制备。参见,例如,美国专利号9,902,722。不幸的是,实验室环境下可用的合成方法很少适合大规模制造药学上可接受的材料。例如,需要最大限度减少潜在有害反应副产物的产生,并且最好避免使用有毒溶剂和试剂。此外,在克级规模上可行的反应条件在扩大规模时通常效率低下,甚至是危险的。因此,需要可用于制备商业上有用数量的药学上可接受的(S)-1-((2',6-双(二氟甲基)-[2,4'-联吡啶]-5-基)氧基)-2,4-二甲基戊-2-胺的合成方法。

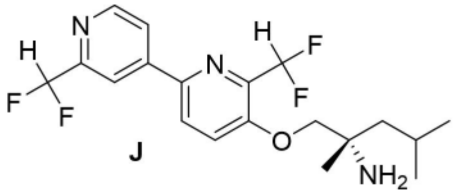
发明内容

[0007]　本申请涉及制备化合物(S)-1-((2',6-双(二氟甲基)-[2,4'-联吡啶]-5-基)氧基)-2,4-二甲基戊-2-胺(化合物J):

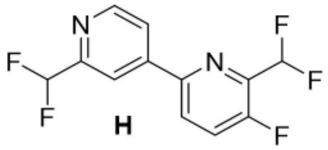
[0008]

J

[0009]　及其盐的方法。化合物J是衔接子相关激酶1 (AAK1)的抑制剂,并且据信可用于治疗包括疼痛在内的疾病和病症。

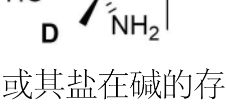
[0010]　在一个实施方案中,本发明涵盖一种制备(S)-1-((2',6-双(二氟甲基)-[2,4'-联吡啶]-5-基)氧基)-2,4-二甲基戊-2-胺(化合物J):

[0011]

J

[0012]　的方法,其包括在足以形成化合物J的条件下使化合物H:

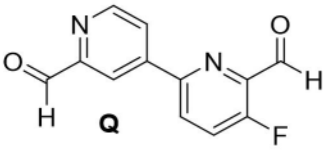
[0013]

H

[0014]　与化合物D:

[0015]

D

[0016]　或其盐在碱的存在下接触。

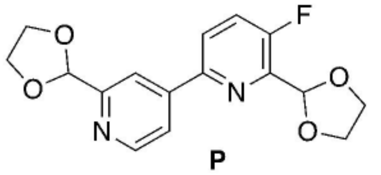
[0017]　在一个实施方案中,化合物H是通过在足以形成化合物H的条件下使化合物Q:

[0018] 

Q

[0019] 与氟化剂接触来制备的。(本发明涵盖化合物Q的结晶形式。具体的结晶形式的熔点为约150℃。)

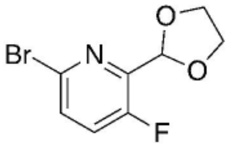
[0020] 在一个实施方案中,化合物Q是通过在足以形成化合物Q的条件下使化合物P:

[0021] 

P

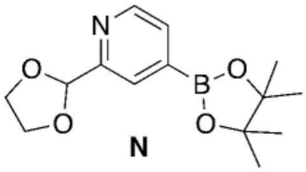
[0022] 与酸接触来制备的。

[0023] 在一个实施方案中,化合物P是通过在足以形成化合物P的条件下使化合物L:

[0024] 

L

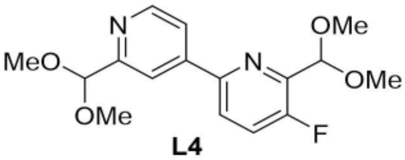
[0025] 与化合物N:

[0026] 

N

[0027] 接触来制备的。

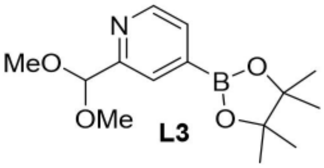
[0028] 在一个实施方案中,化合物Q是通过在足以形成化合物Q的条件下使化合物L4:

[0029] 

L4

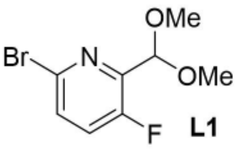
[0030] 与酸接触来制备的。

[0031] 在一个实施方案中,化合物L4是通过在足以形成化合物L4的条件下使化合物L3:

[0032] 

L3

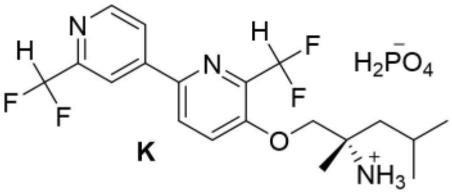
[0033] 与化合物L1:

[0034] 

L1

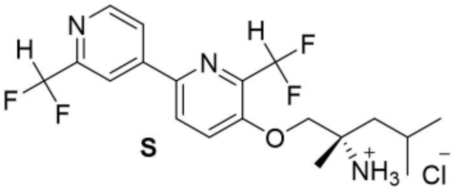
[0035] 在催化剂和碱的存在下接触来制备的。

[0036] 本发明还涵盖一种制备化合物K：

[0037] 

K

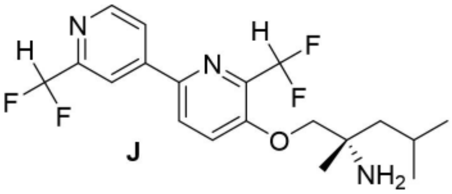
[0038] 的方法,其包括在足以形成化合物K的条件下使化合物S：

[0039] 

S

[0040] 与磷酸在溶剂中接触。

[0041] 在一个实施方案中,化合物S是通过在足以形成化合物S的条件下使化合物J：

[0042] 

J

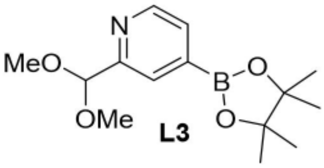
[0043] 与盐酸在溶剂中接触来制备的。

[0044] 本发明还涵盖合成中间体6-溴-2-(二甲氧基甲基)-3-氟吡啶(化合物L1)：

[0045] 。

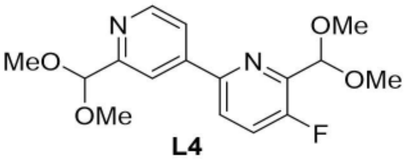
L1

[0046] 本发明还涵盖2-(二甲氧基甲基)-4-(4,4,5,5-四甲基-1,3,2-二氧杂环戊硼烷-2-基)吡啶(化合物L3)：

[0047] 。

L3

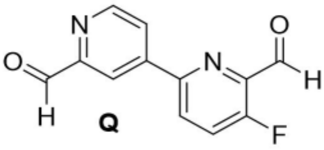
[0048] 本发明还涵盖2’,6-双(二甲氧基甲基)-5-氟-2,4’-联吡啶(化合物L4)：

[0049] 

L4

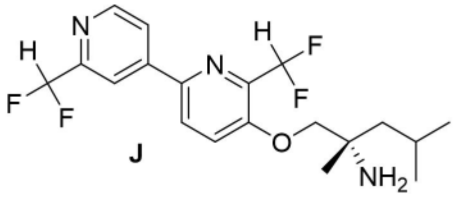
[0050] 及其盐。

[0051] 本发明还涵盖化合物5-氟-[2,4’-联吡啶]-2’,6-二甲醛(化合物Q)：

[0052] 。

Q

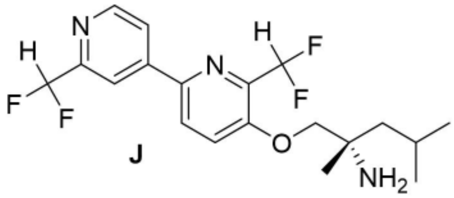
[0053] 本发明还涵盖(S)-1-((2',6-双(二氟甲基)-[2,4'-联吡啶]-5-基)氧基)-2,4-二甲基戊-2-胺(化合物J)：

[0054] 

J

[0055] 的结晶药学上可接受的盐。

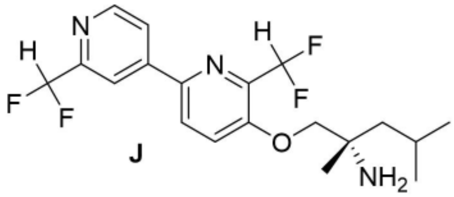
[0056] 本发明还涵盖一种确定(S)-1-((2',6-双(二氟甲基)-[2,4'-联吡啶]-5-基)氧基)-2,4-二甲基戊-2-胺(化合物J)：

[0057] 

J

[0058] 或其药学上可接受的盐的样品的纯度的方法,其包括测试样品中表1所列的一种或多种化合物的存在。

[0059] 本发明还涵盖一种包含(S)-1-((2',6-双(二氟甲基)-[2,4'-联吡啶]-5-基)氧基)-2,4-二甲基戊-2-胺(化合物J)：

[0060] 

J

[0061] 或其药学上可接受的盐的组合物,所述组合物包含小于0.01重量%的下表1所列的一种或多种化合物。

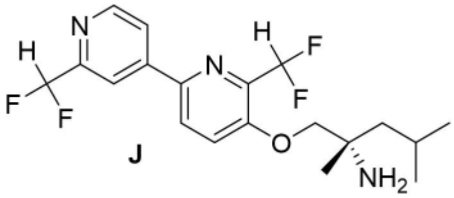
附图说明

[0062] 图1提供了((S)-1-((2',6-双(二氟甲基)-[2,4'-联吡啶]-5-基)氧基)-2,4-二甲基戊-2-铵二氢磷酸盐(化合物K)的结晶固体形式I的代表性X射线粉末衍射(XRPD)图案。光谱是使用带有LYNXEYE检测器(铜Kα辐射)的Bruker X射线衍射仪获得的。

[0063] 图2提供了化合物K的结晶固体形式的代表性差示扫描量热法(DSC)热分析图。所述热分析图是使用TA Instruments DSC Q2000仪器和在环境条件下填充的密封金坩埚获得的。进行了两次扫描。第一次扫描中熔融完成后,样品以大约-40 K/分钟的速度快速冷却至-50℃,然后记录第二次扫描。两次扫描中,加热速率均为10 K/分钟。

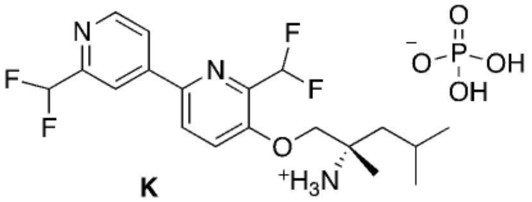
具体实施方式

[0064] 本发明涉及合成中间体以及用于制备(S)-1-((2',6-双(二氟甲基)-[2,4'-联吡啶]-5-基)氧基)-2,4-二甲基戊-2-胺(化合物J)：

[0065] 
J

[0066] 及其药学上可接受的盐的合成方法,其在数量(例如,大于1kg、5kg或10kg)上足以制造适用于人体临床试验和后续商业化的剂型。本发明的方法最大限度地减少了有害杂质的形成,同时最大限度地提高了合成产率。

[0067] 本发明的具体方法用于制备((S)-1-((2',6-双(二氟甲基)-[2,4'-联吡啶]-5-基)氧基)-2,4-二甲基戊-2-铵二氢磷酸盐(化合物K):

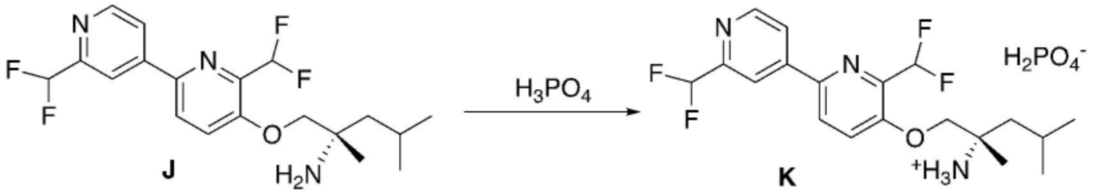
[0068] 
K

[0069] 及其结晶固体形式。此盐的具体结晶形式在本文中被称为形式I,其XRPD光谱与图1中所示的光谱基本上相同,衍射峰在约4.81、5.99、7.44、7.89、11.66、14.85、15.77、19.19、20.86、21.65、23.96、24.48或24.73度2-θ中的一个或多个处。当在本文用于指代XPRD峰时,术语“约”意指±0.2度2-θ。

[0070] 化合物K的结晶形式I的熔点为约184℃(参见图2),如通过差示扫描量热法(DSC)(熔融吸热)测定。当提及温度时,术语“基本上”和“约”意指±2℃。

[0071] 化合物K的结晶形式I是这种盐所发现的最稳定的形式:在40℃和75%相对湿度下储存长达四周后,其形式本身、形态和纯度都没有发生变化。此外,虽然形式I的熔点低于化合物J的盐酸盐(这是它的一种熔点为约247℃的形式),但磷酸盐并未显示出伴随降解的迹象。相反,观察到形式I熔融,重结晶为另一种亚稳形式,所述亚稳形式的熔点为约172.5℃。形式I的水溶性(25℃时为26.8 mg/mL)进一步有利于其大规模制造和纯化。相比之下,化合物J的盐酸盐在25℃时测量的水性溶解度为2.9 mg/mL。

[0072] 可用于制备形式I的本发明的一个实施方案如下所示:

[0073] 

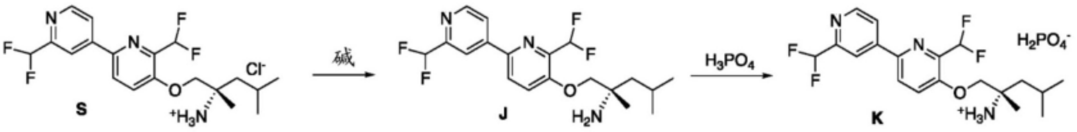
[0074] 在这里,化合物K是通过在足以形成化合物K的条件下使化合物J与磷酸在溶剂中接触来制备的。溶剂的实例包括水、甲醇、乙醇、正丁醇、异丙醇、异丁醇、叔丁醇、甲基叔丁基醚、乙酸乙酯、乙酸异丙酯、THF和2-甲基THF及其混合物。具体的溶剂是异丙醇。

[0075] 在一些实施方案中,使化合物J与磷酸在约0℃至约100℃或约50℃至约60℃的温度下接触。(当提及反应条件时,除非另有说明,否则术语“约”在用于指代温度时可解释为±10℃。)在一些实施方案中,化合物J与磷酸接触约0.5小时至约24小时或约2小时至约16小时。(当提及反应条件时,除非另有说明,否则术语“约”在指代时间时可解释为±5%。例

如，“约2小时”与2小时±6分钟相同。）在一些实施方案中，相对于化合物J，使用约0.8至约1.2摩尔当量（例如，约1摩尔当量）的磷酸。（除非另有说明，否则，当提及摩尔当量或浓度时，术语“约”可解释为±5%。）在一些实施方案中，溶剂中化合物J的浓度为约2%至约25%。

[0076] 在本发明的一个实施方案中，化合物K由化合物S制备，如下所示：

[0077]



[0078] 在此方法中，化合物S在足以形成化合物J的条件下用碱中和，使化合物J在足以形成化合物K的条件下与磷酸接触。适用于中和的碱包括NaOH、KOH、Na_2CO_3和K_2CO_3。优选的碱是氢氧化钠。

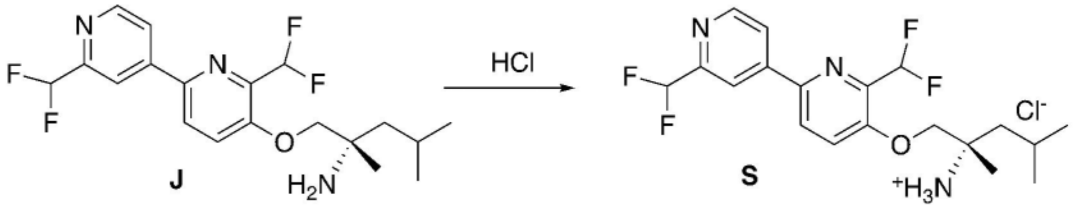
[0079] 化合物S与碱的中和通常可以在溶剂诸如水、水/MTBE、水/THF和水/2-MeTHF（优选的溶剂为水/MTBE）中，并且在约0℃至约60℃（例如，约20℃至约40℃）的温度下进行。在一些实施方案中，中和进行约0.5小时至约24小时（例如，约1小时至约2小时）。在一些实施方案中，相对于化合物S，使用约0.8至约5摩尔当量的碱。在一些实施方案中，溶剂中化合物S的浓度为约2%至约25%。

[0080] 以上所示第二步中化合物J暴露于磷酸通常在溶剂中进行，所述溶剂诸如水、甲醇、乙醇、正丁醇、异丙醇、异丁醇、叔丁醇、甲基叔丁基醚、乙酸乙酯、乙酸异丙酯、THF和2-甲基THF，或其混合物。优选的溶剂是异丙醇。

[0081] 在一些实施方案中，化合物J暴露于磷酸在约0℃至约100℃（例如，约50℃至约60℃）的温度下进行。在一些实施方案中，化合物J暴露于磷酸进行约0.5小时至约24小时（例如，约7小时至约14小时）。在一些实施方案中，在步骤2中，相对于化合物J，使用约0.8至约1.2摩尔当量的磷酸。在一些实施方案中，溶剂中化合物J的浓度为约2%至约25%。

[0082] 化合物S可以如下所示制备：

[0083]

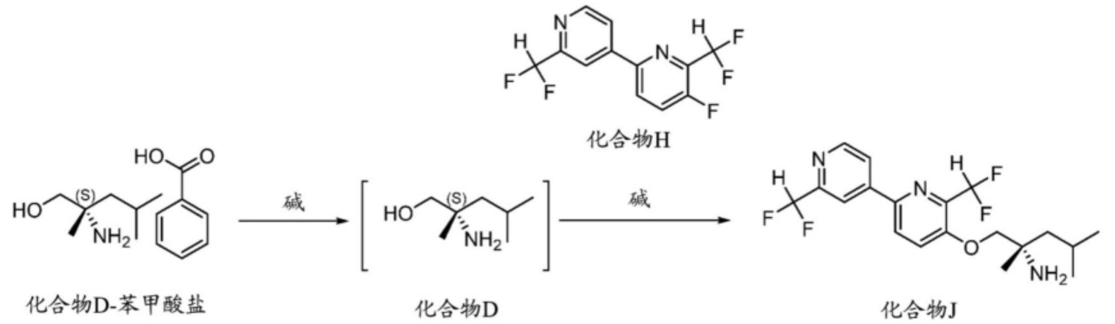


[0084] 在一个实施方案中，化合物S是通过将化合物J在足以形成化合物S的条件下暴露于溶剂中的盐酸来制备的。在一些实施方案中，溶剂是水、IPA、水/IPA混合物、MeOH、MeOH/水、EtOH、EtOH/水、n-BuOH或n-BuOH/水。优选的溶剂是异丙醇。

[0085] 将化合物J暴露于盐酸在约0℃至约60℃（例如，约50℃至约60℃）的温度下进行，持续约0.5小时至约24小时（例如，约4小时至约8小时）。相对于化合物J，通常使用约0.8至约1.2摩尔当量的盐酸。在一些实施方案中，溶剂中化合物J的浓度为约2%至约25%。

[0086] 本发明的一个实施方案涵盖制备如下所示的化合物J的方法：

[0087]



[0088] 在这里,化合物J是通过在足以形成化合物D的条件下用碱中和化合物D-苯甲酸盐来制备的,使所述化合物D在足以形成化合物J的条件下与化合物H在碱的存在下接触。化合物D不需要分离。

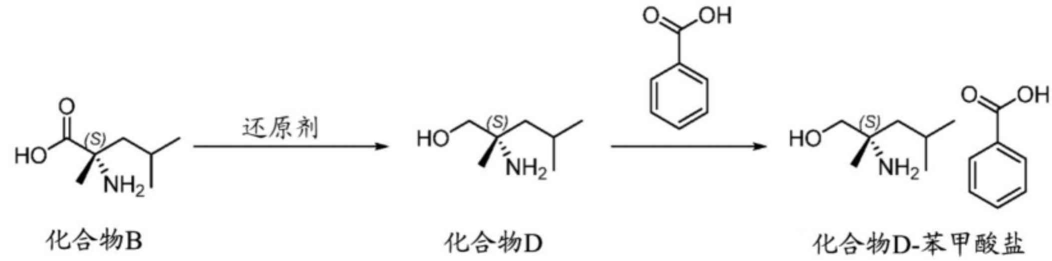
[0089] 适用于这些反应的溶剂包括THF、2-甲基THF、1,4-二氧六环、MTBE、DME、二甘醇二甲醚、叔丁醇和叔戊醇。具体的溶剂是THF。两个步骤中使用的碱可以在第一步开始时添加。合适的碱的实例包括叔丁醇钾、叔丁醇钠、叔戊醇钾、叔戊醇钠、六甲基二硅基胺基钠、六甲基二硅基胺基钾、二异丙基酰胺锂、正丁基锂、仲丁基锂和叔丁基锂。具体的碱是叔丁醇钾。

[0090] 在本发明的一些实施方案中,化合物D-苯甲酸盐的中和在约-50℃至约50℃ (例如,约15℃至约25℃)的温度下进行约0.5小时至约24小时(例如,约3小时至约5小时)。在一些实施方案中,使化合物H与化合物D在碱的存在下在约-50℃至约50℃ (例如,约0℃至约25℃)的温度下接触约2小时至约5小时。

[0091] 相对于化合物H,使用约1.8至约3摩尔当量(例如,约2.5至3摩尔当量)的碱,并且相对于化合物H,使用约1至约1.5摩尔当量(例如,约1.2摩尔当量)的化合物D-苯甲酸盐。

[0092] 化合物D-苯甲酸盐可以如下所示制备:

[0093]



[0094] 其中使化合物B在足以形成化合物D的条件下与还原剂接触,使所述化合物D在足以形成化合物D-苯甲酸盐的条件下与苯甲酸接触。

[0095] 还原剂的实例包括NaBH$_4$/BF$_3$·Et$_2$O、NaBH$_4$/I$_2$、NaBH$_4$/TMSCl、NaBH$_4$/H$_2$SO$_4$、NaBH$_4$/MsOH、NaBH$_4$/TsOH、NaBH$_4$/HCl、NaBH$_4$/AlCl$_3$、CDI/NaBH$_4$、BH$_3$ THF复合物、BH$_3$二甲基硫醚复合物、乙硼烷、LiAlH$_4$和Li/AlCl$_3$/t-BuOH。在本发明的一些实施方案中,还原剂是NaBH$_4$/BF$_3$·Et$_2$O。还原剂的量相对于化合物B可以为约0.5至约4摩尔当量(例如,约2摩尔当量)。

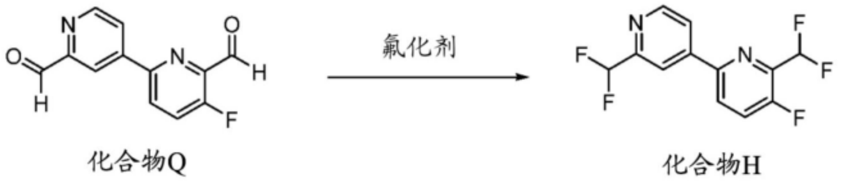
[0096] 化合物B的还原通常在溶剂诸如THF、2-Me-THF、THF、2-甲基THF、1,4-二氧六环、MTBE、DME和二甘醇二甲醚或其混合物中进行。优选的溶剂是THF。在一些实施方案中,溶剂中化合物B的浓度为约2%至约25%。还原可以在约-50℃至约50℃(例如,约0℃至约25℃)的温度下进行约0.5小时至约24小时(例如,约5小时至约8小时)。

[0097] 根据以上所示方法,使化合物D与苯甲酸在溶剂诸如MTBE、MTBE/庚烷、THF、THF/庚烷、EtOAc、EtOAc/庚烷、IPAc、IPAc/庚烷、EtOH、EtOH/庚烷、IPA、IPA/庚烷、甲苯和乙腈中接

触。优选的溶剂是MTBE。在本发明的一些实施方案中,此反应在约0℃至约60℃ (例如,约45℃至约50℃)的温度下进行约1至2小时。在一些实施方案中,相对于化合物D,使用约0.8至约1.5摩尔当量(例如,约1.1摩尔当量)的苯甲酸。在一些实施方案中,溶剂中化合物D的浓度为约2%至约25%。

[0098] 另一种用于大规模合成化合物J及其药学上可接受的盐的中间体是化合物H,其可以如下所示制备:

[0099]

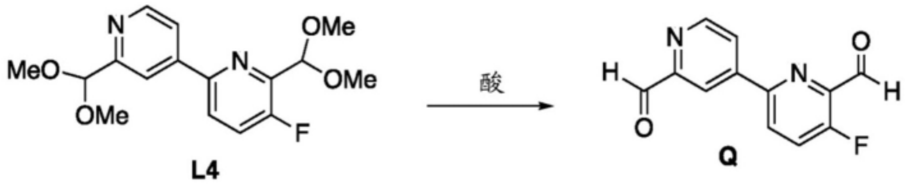


[0100] 在这种方法中,化合物H是通过在足以形成化合物H的条件下使化合物Q与氟化剂接触来制备的。氟化剂的实例包括SF_4、$PhSF_3$、R_2NSF_3 (DAST、Morph-DAST)、二烷基酰胺基二氟锍鎓四氟硼酸盐([$R_2N=SF_2$] (XtalFluor-E、XtalFluor-M)BF_4)、Deoxo-Fluor (BAST)、Selectfluor和4-叔丁基-2,6-二甲基苯基三氟化硫。优选的氟化剂是DAST。根据所使用的具体剂,相对于化合物Q,使用约1至约5摩尔当量(例如,约3.5)的氟化剂。

[0101] 优选地使化合物Q与氟化剂在溶剂诸如二氯甲烷、氯仿、CCl_4和甲苯中接触。优选的溶剂是二氯甲烷。溶剂中化合物Q的浓度可以在约2%至约25%之间变化。反应通常在约-20℃至约60℃(例如,约0℃至约25℃)的温度下发生,持续约1小时至约100小时(例如,约24小时至约30小时)。

[0102] 化合物Q可以由化合物L4制备,如下所示:

[0103]

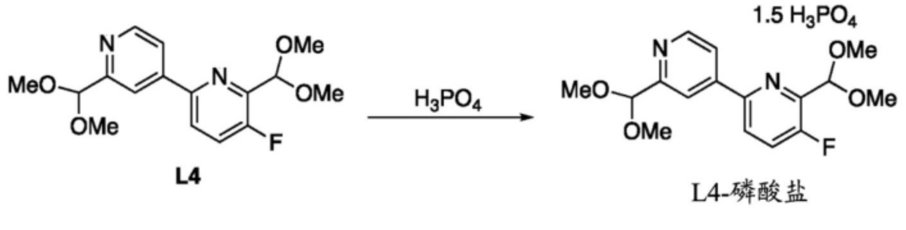


[0104] 在此方法中,化合物Q是通过在足以形成化合物Q的条件下使化合物L4或其盐(例如,磷酸盐L4-磷酸盐)与酸接触来制备的。合适的酸的实例包括HCl、HBr、HI、H_2SO_4、H_3PO_4、HNO_3、MsOH、TsOH和HBF_4。优选的酸是盐酸。

[0105] 与酸的反应优选地在溶剂诸如水或DMSO/水(优选的溶剂是水)中并且在约0℃至约100℃(例如,约55℃至约60℃)的温度下进行。此反应通常进行约1小时至约24小时(例如,两小时)。可以改变化合物L4的浓度来优化产率,并且可以为例如约2%至约25%。在本发明的一些实施方案中,相对于化合物L4,使用约1至约10摩尔当量(例如,5摩尔当量)的酸。

[0106] 具体可用的化合物L4的盐是L4-磷酸盐,其可以如下所示制备:

[0107]



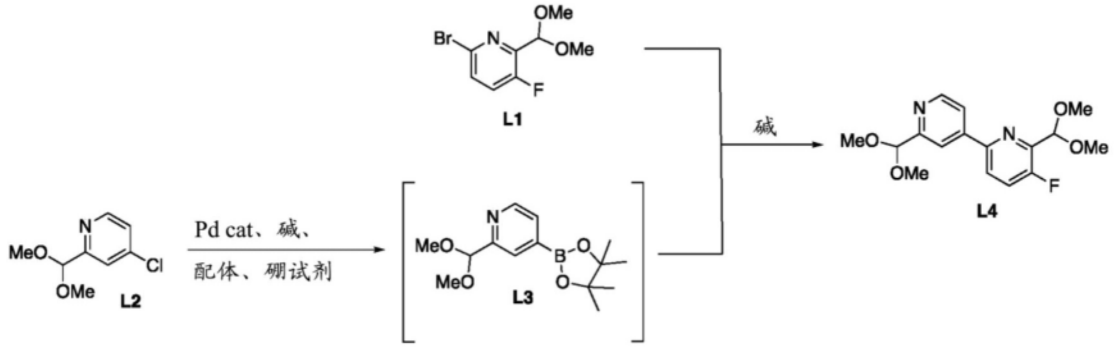
[0108] 在这种方法中,使化合物L4在足以制备化合物L4-磷酸盐的条件下与磷酸接触。反

应可以在溶剂诸如MeOH、EtOH、IPA、EtOAc、IPAc、MTBE、THF、2-Me-THF、甲苯、庚烷或其混合物中进行。优选的溶剂体系是甲苯/甲醇/庚烷。

[0109] 反应通常在约0℃至约60℃（例如，约15℃至约45℃）的温度下进行约1小时至约24小时（例如，约10小时至约12小时）。在本发明的一些实施方案中，相对于化合物L4，使用约1至约2（例如，约1.6）摩尔当量的磷酸。溶剂中化合物L4的浓度范围可为约2%至约25%。

[0110] 化合物L4可以使用如下所示方法制备：

[0111]



[0112] 在这里，使化合物L2在足以形成化合物L3的条件下与钯催化剂、碱、配体和硼试剂接触，使所述化合物L3在足以形成化合物L4的条件下与化合物L1在催化剂和碱的存在下接触。

[0113] 化合物L3的制备通常在溶剂诸如THF、2-MeTHF、1，4-二氧六环、DME、MTBE、Et_2O或ACN中进行。在一些实施方案中，溶剂是2-MeTHF。可用于制备化合物L3的钯催化剂的实例包括$Pd(OAc)_2$、$PdCl_2(dppf)$、$Pd(PPh_3)_4$、$PdCl_2(PPh_3)_2$和$Pd_2(dba)_3$。优选的催化剂是$Pd_2(dba)_3$。用于形成化合物L3的碱包括NaOAc、KOAc、$NaHCO_3$、$KHCO_3$、Na_2CO_3、K_2CO_3、K_2HPO_4和K_3PO_4。优选的碱是KOAc。合适的配体包括PCy_3、SPhos和Xphos。优选的配体是Xphos。反应中可用的硼试剂包括四氢二硼(tetrahydrodiboron)、PinBH和Pin_2B_2。优选的硼试剂是Pin_2B_2。

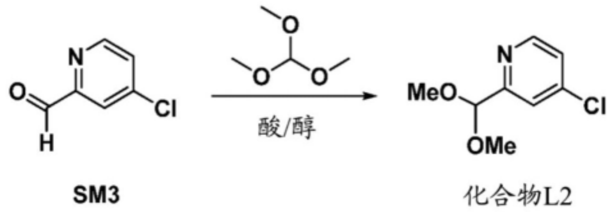
[0114] 在本发明的一些实施方案中，使化合物L2与钯催化剂、碱、配体和硼试剂在约0℃至约100℃（例如，约70℃至约80℃）的温度下接触约0.5小时至约48小时（例如，约16小时至约24小时）。在一些实施方案中，相对于化合物L2，使用约0.8至约2（例如，1）摩尔当量的硼试剂。在一些实施方案中，溶剂中化合物L2浓度为约2%至约25%。

[0115] 以上所示反应的下一步（其中使化合物L3与化合物L1反应）通常在溶剂诸如水、THF、2-MeTHF、1，4-二氧六环、DME、MTBE、Et_2O及其混合物中进行。优选的溶剂是水/2-MeTHF。化合物L1的浓度范围可为约2%至约25%，但与本文公开的所有反应的条件一样，可以使用本领域技术人员熟知的方法改变这些数字，来最大限度提高产品产率并且最大限度降低成本。

[0116] 可用于形成化合物L4的碱的实例包括Na_2CO_3、K_2CO_3、Na_3PO_4、K_3PO_4、NaOH和KOH。优选的碱是碳酸钠（Na_2CO_3）。根据碱，相对于化合物L2，使用约1至2摩尔当量（例如，2摩尔当量）的碱。此步骤在约20℃至约100℃（例如，约70℃至约80℃）的温度下进行约1小时至约48小时（例如，约16小时至约24小时）。相对于化合物L2，使用约1至约2摩尔当量（例如，1当量）的化合物L1。

[0117] 合成中间体化合物L2可以如下所示制备：

[0118]



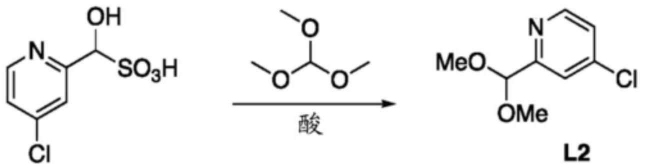
[0119] 在此方法中，化合物SM3在足以形成化合物L2的条件下与三甲氧基甲烷在酸的存在下接触。合适的酸的实例包括H_2SO_4、MsOH、TsOH、H_3PO_4、HNO_3、HCl和HBr。优选的酸是盐酸。

[0120] 以上所示反应通常在溶剂诸如1,4-二氧六环、DME、Et_2O、THF、2-Me-THF、甲苯、DCM、MTBE、ACN、甲醇中进行。优选的溶剂是甲醇。进行此反应的温度范围可为约0℃至约80℃(例如，约60℃至约65℃)，并且其持续时间范围可为约0.5小时至约48小时(例如，约6至约10小时)。

[0121] 在本发明的一些实施方案中，相对于SM3，使用约0.01至约1摩尔当量(例如，约0.2摩尔当量)的酸，并且相对于SM3，使用约1至约4摩尔当量(例如，约2摩尔当量)的三甲氧基甲烷。溶剂中SM3的浓度范围可为约2%至约30%。

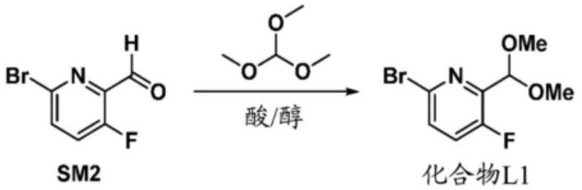
[0122] 化合物L2也可以如下所示使用与上述那些相似的反应条件(尽管使用更多的三甲氧基甲烷)制备：

[0123]



[0124] 合成中间体化合物L1可以如下所示制备：

[0125]



[0126] 在此方法中，化合物L1是通过在足以形成缩醛化合物L1的条件下，使化合物SM2与三甲氧基甲烷在酸的存在下接触来制备的。合适的酸的实例包括H_2SO_4、MsOH、TsOH、H_3PO_4、HNO_3、HCl和HBr。优选的酸是盐酸。

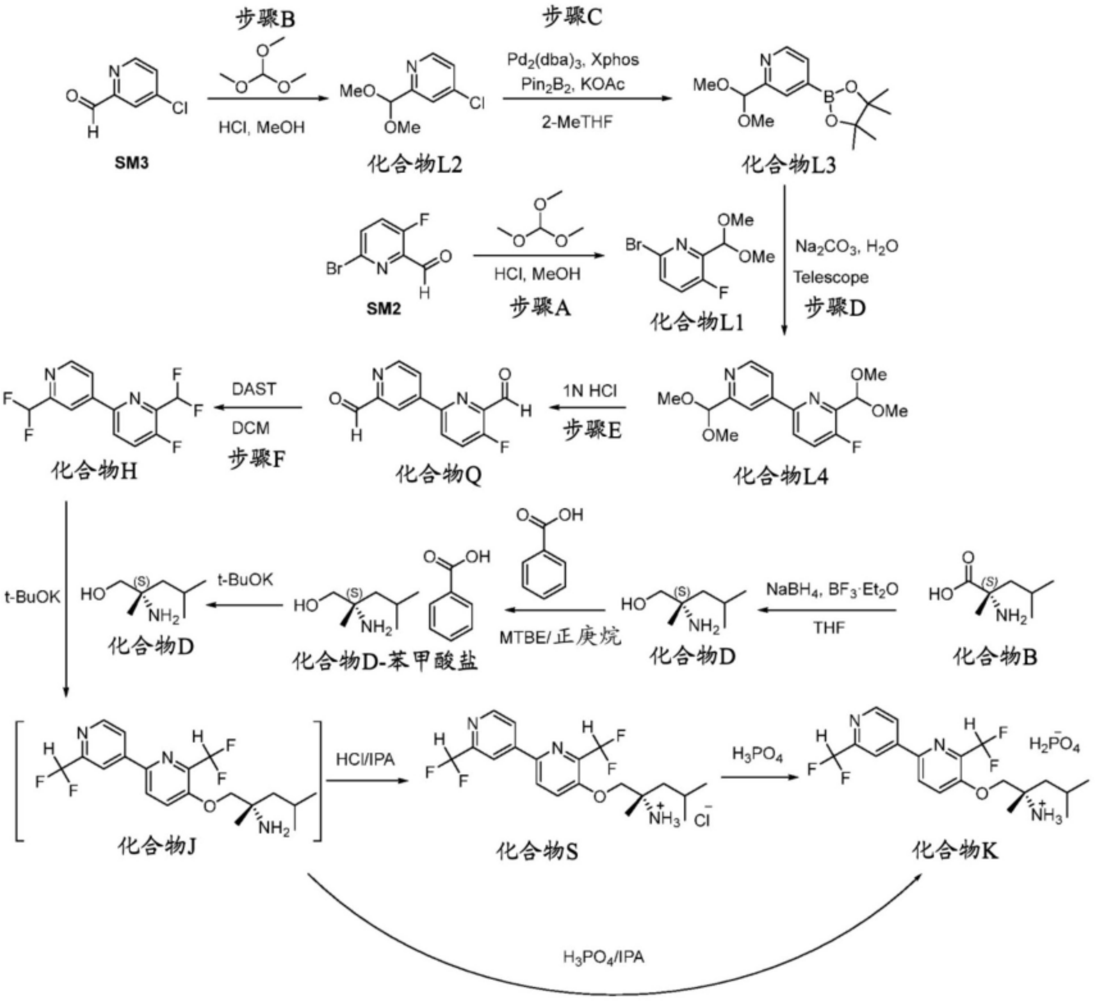
[0127] 此反应优选地在溶剂诸如1,4-二氧六环、DME、Et_2O、THF、2-Me-THF、甲苯、DCM、MTBE、ACN和甲醇中进行。优选的溶剂是甲醇。

[0128] 在本发明的一些实施方案中，使SM2与三甲氧基甲烷在酸的存在下在约0℃至约80℃(例如，约60℃至约65℃)的温度下接触约0.5小时至约48小时(例如，约3小时至约6小时)。相对于SM2，通常使用约0.01至约1摩尔当量(例如，约0.05摩尔当量)的酸。相对于SM2，通常使用约1至约4摩尔当量(例如，约2摩尔当量)的三甲氧基甲烷。在一些实施方案中，溶剂中SM2的浓度为约2%至约30%。

[0129] 在本发明的一个实施方案中，化合物J、K和S如方案1所示制备：

[0130] 方案1

[0131]



[0132] 在此方法中,化合物J或其药学上可接受的盐通过以下工艺制备:a)在足以形成化合物L4的条件下,使化合物L3与化合物L1在催化剂和碱的存在下接触;b)在足以形成化合物Q的条件下,使化合物L4或其盐与酸接触;c)在足以形成化合物H的条件下,使化合物Q与氟化剂接触;以及d)在足以形成所述化合物J的条件下,使化合物H与化合物D在碱的存在下接触。

[0133] 化合物S通过包括使化合物J在溶剂中暴露于盐酸的工艺来制备。

[0134] 化合物K通过包括以下的工艺来制备:a)在足以形成化合物J的条件下,用碱中和化合物S;以及b)在足以形成化合物K的条件下,使所得化合物J在溶剂中暴露于磷酸。

[0135] 在本发明的一个具体实施方案中,化合物K通过包括以下的工艺来制备:a)在足以形成化合物L4的条件下,使化合物L3与化合物L1在催化剂和碱的存在下接触;b)在足以形成化合物Q的条件下,使化合物L4与酸接触;c)在足以形成化合物H的条件下,使化合物Q与氟化剂接触;d)在足以形成化合物J的条件下,使化合物H与化合物D在碱的存在下接触;e)在足以形成化合物S的条件下,使化合物J与盐酸在溶剂中接触;f)在足以形成化合物J的条件下,用碱中和化合物S;以及g)在足以形成化合物K的条件下,使所得化合物J在溶剂中暴露于磷酸。

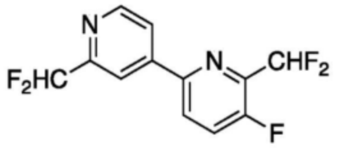
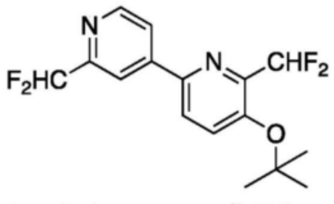
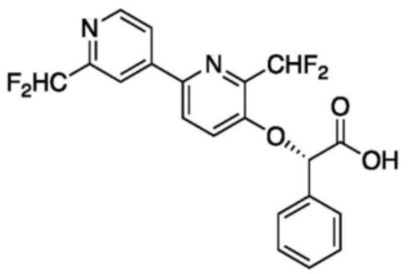
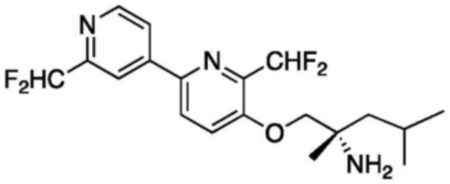
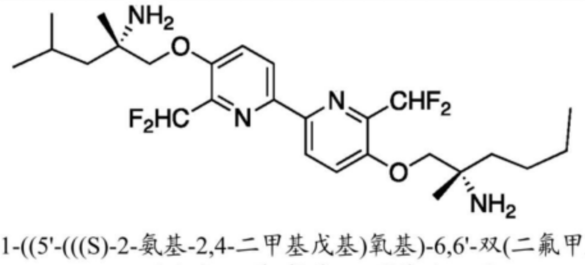
[0136] 在另一实施方案中,化合物K通过包括以下的工艺来制备:a)在足以形成化合物L4的条件下,使化合物L3与化合物L1在催化剂和碱的存在下接触;b)在足以形成化合物Q的条

件下,使L4与酸接触;c)在足以形成化合物H的条件下,使化合物Q与氟化剂接触;d)在足以形成化合物J的条件下,使化合物H与化合物D在碱的存在下接触;e)在足以形成所述化合物K的条件下,使所得化合物J在溶剂中暴露于磷酸。

[0137] 本发明涵盖确保最终活性药物成分具有适用于向人类患者施用的纯度的方法。为此,合成了包括下表1中所示的那些杂质的潜在杂质,并且通过^{1}H NMR和质谱进行了表征。

[0138] 表1

[0139]

杂质编号	化合物
1	 2',6-双(二氟甲基)-5-氟-2,4'-联吡啶
2	 5-(叔丁氧基)-2',6-双(二氟甲基)-2,4'-联吡啶
3	 (S)-2((2',6-双(二氟甲基)-[2,4'联吡啶]-5-基)氧基)-2-苯乙酸
4	 (S)-1-((2',6-双(二氟甲基)-[2,4'联吡啶]-5-基)氧基)-2,4-二甲基戊-2-胺
5	 (S)-1-((5'-(((S)-2-氨基-2,4-二甲基戊基)氧基)-6,6'-双(二氟甲基)-[2,2'-联吡啶]-5-基)氧基)-2-甲基己-2-胺

[0140] 表1中的化合物是在导致本发明方法的实验室规模开发工作的各个阶段观察到的。

[0141] 本发明包括一种通过测试表1所列的一种或多种化合物的存在来测试化合物J或其药学上可接受的盐的纯度的方法。优选的方法包括使用质谱和/或HPLC测试一种或多种化合物的存在。

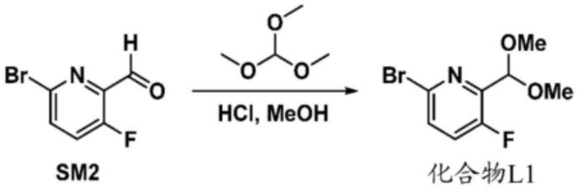
[0142] 5.1 实施例

[0143] 通过考虑下面提供的实施例可以理解本发明的各种实施方案。在这些实施例中，除非另有说明，否则所有温度均以摄氏度阐述并且所有份数和百分比均按重量计。试剂可从商业供应商处购买，并且无需进一步纯化即可使用，除非另有说明。(也可按照本领域技术人员已知的标准文献程序来制备试剂。)

[0144] 除非另有说明，否则反应均在环境温度(或室温)下进行。反应通常通过HPLC进行测定，并且根据起始材料的消耗来判断终止。

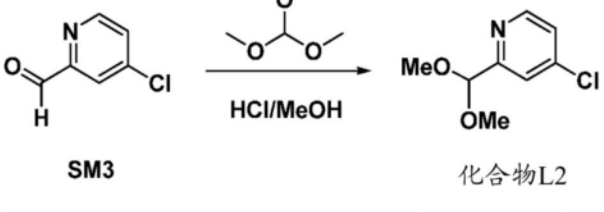
[0145] 化合物结构和纯度通过以下方法中的一种或多种来确认：质子核磁共振(^{1}H NMR)光谱、^{13}C NMR光谱、质谱、红外光谱、熔点、X射线晶体学、LC-MS和/或HPLC。化学位移以距离标准(例如，内部标准，诸如TMS)低场的百万分率(ppm，δ)为单位进行报告。或者，^{1}H NMR化学位移参考本领域已知的氘代溶剂中残留质子的信号。峰多重性指定如下：s，单峰；d，二重峰；dd，双二重峰；t，三重峰；dt，双三重峰；q，四重峰；br，加宽；以及m，多重峰。耦合常数以赫兹(Hz)为单位。使用具有APCI或ESI电离的质谱仪获取质谱(MS)数据。

[0146] 5.1.1 6-溴-2-(二甲氧基甲基)-3-氟吡啶(化合物L1)的合成

[0147] 

[0148] 将HCl/MeOH溶液(10 mL 3.9 M溶液，0.05当量)装入SM2 (158.5 g，777 mmol，1当量)、MeOH (1585 mL，10V)和三甲氧基甲烷(166 g，15.6 mol，2.0当量)的混合物中。将所得混合物在60-65℃(回流)下陈化直至反应完成(3-6小时)，然后冷却至10-20℃。在50℃以下浓缩至2-3V并且用2-Me-THF (10V)稀释后，用10% K_2CO_3 (3V)淬灭反应。分离有机层并且在50℃以下浓缩至1-2V。将其用2-Me-THF (5V)冲涮，然后用更多的2-Me-THF (5V)稀释，得到化合物L1在 2-Me-THF中的溶液(845.2 g，99%纯度，21.7%测定，94.4%溶液产率)。LC-MS：m/z 250, 252, 220, 218 (M-OMe) ^{1}H NMR (400 MHz, 氯仿-d) δ 7.38 (dd, J = 3.5, 8.6 Hz, 1H), 7.17-7.30 (m, 1H), 5.37-5.48 (m, 1H), 3.39 (s, 6H)。

[0149] 5.1.2 4-氯-2-(二甲氧基甲基)吡啶(化合物L2)的合成

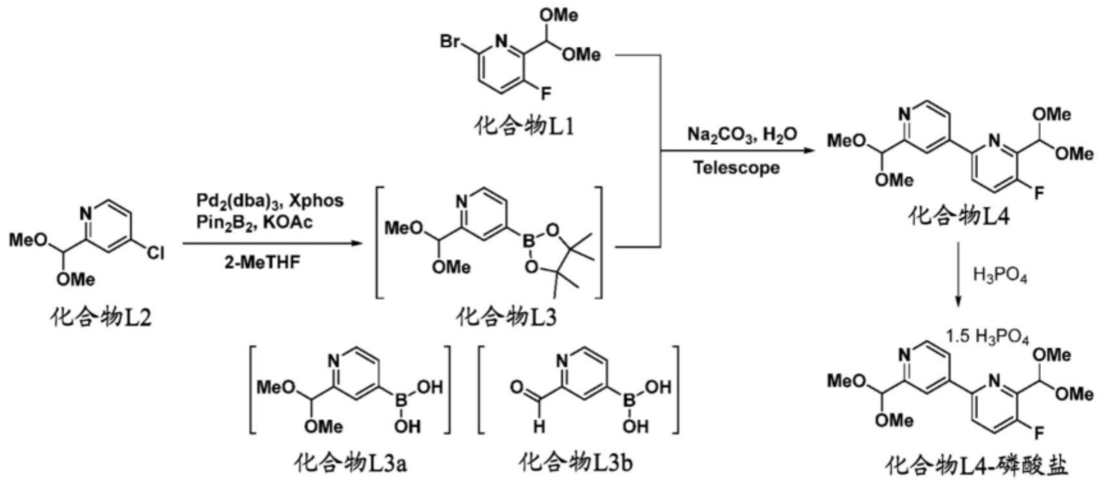
[0150] 

[0151] 将HCl/MeOH (42.3 mL 3.9 M溶液，0.20当量)装入SM3 (117.3 g，819.5 mmol，1

当量)、MeOH (1160 mL,10V)和三甲氧基甲烷(174 g,1.64 mol,2.0当量)的混合物中。将混合物加热至60-65℃(回流)直至反应完成(6-10小时),然后冷却至10-20℃。在浓缩至3-5V并且用2-Me-THF (10V)稀释后,用10% K_2CO_3 (3V,pH 8-9)淬灭反应。分离有机层并且浓缩至1-2V,用2-Me-THF (5V x 2)冲涮,然后用2-Me-THF (5V)稀释,得到化合物L2在2-Me-THF中的溶液(588.5 g,99.18% HPLC纯度,22.3%测定,85.3%溶液产率)。^{1}H NMR (400 MHz，氯仿-d) δ 8.42-8.57 (m，1H)，7.56 (d，J = 2.0 Hz，1H)，7.25 (dd，J = 2.1，5.3 Hz，1H)，5.28-5.39 (m，1H)，3.38 (s，6H)。LC-MS m/z 187，156 (M-OMe)。

[0152] 5.1.3 2',6-双(二甲氧基甲基)-5-氟-2,4'-联吡啶磷酸盐(化合物L4-磷酸盐)的合成

[0153]



[0154] L3的制备:将化合物L2在2-Me-THF (95.5 g,1.00当量,5-6V)、2-Me-THF (10V)、Pin_2B_2 (1.05当量)、KOAc (3.0当量)和Xphos (0.02当量)中的混合物通过用N_2喷射脱气。添加$Pd_2(dba)_3$ (0.01当量),并且将混合物再次通过用N_2喷射脱气。将反应混合物加热至70-80℃并且搅拌直至L2的硼化完成(16-24小时)以产生L3,其直接用于下一步Suzuki偶联步骤。

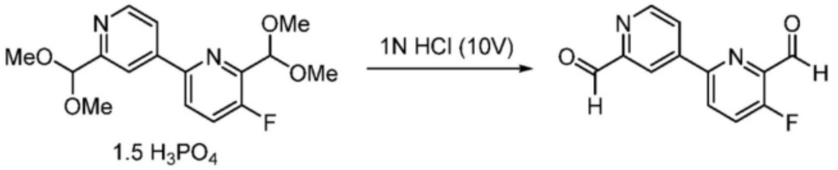
[0155] 经由L3和L1的Suzuki偶联制备L4:冷却至15-25℃后,依次添加化合物L1在2-Me-THF中的溶液(0.96当量,5-6V)、Na_2CO_3 (2.0当量 固体)和H_2O (5V)。通过用N_2喷射脱气后,将反应混合物在70-80℃下陈化直至Suzuki偶联完成(16-24小时)。冷却至15-25℃后,将反应混合物通过硅藻土垫(0.5X)过滤,并且用2-Me-THF (1-2V)冲洗滤饼。分离滤液中的有机层,浓缩至1-2V,用甲苯(10V)稀释并且用L-半胱氨酸/NaOH (pH>10) (5X,L-半胱氨酸/NaOH/H_2O的比率:1/0.5/9)洗涤两次。然后将有机层用H_2O (5X)洗涤并且浓缩至5V以得到化合物L4游离碱在甲苯中的甲苯溶液。通过在庚烷/MTBE中结晶获得L4游离碱的分析样品。^{1}H NMR (400 MHz，氯仿-d) δ 8.66-8.77 (m，1H)，8.06 (d，J =1.22 Hz，1H)，7.94 (dd，J = 1.77，5.20 Hz，1H)，7.86 (dd，J = 3.55，8.56 Hz，1H)，7.51-7.60 (m，1H)，5.63 (s，1H)，5.44-5.48 (m，1H)，3.54-3.60 (m，6H)，3.43-3.49 (m，6H)；mp 41.8℃ (DSC峰)；XRPD 2θ：6.70，7.61，9.67，13.56，13.77，13.99，15.36，19.36，20.71，21.81，23.10，26.96，27.72，28.02，29.36，31.88，32.04，39.09。

[0156] L4磷酸盐的制备:将85% H_3PO_4 (基于化合物L4游离碱1.6当量)在MeOH (1-2V)中的溶液在2小时内添加到以上L4的甲苯溶液中,得到悬浮液。将悬浮液在45℃以下浓缩至

3V,并且在2小时内添加正庚烷(10V)。将混合物在45℃以下浓缩至10V,并且将批次温度调节至15-25℃。搅拌6-8小时后,过滤混合物,并且用正庚烷(1-2V)冲洗滤饼。将湿饼在40℃下在减压下用轻微N_2吹扫干燥,得到190.5 g L4-磷酸盐(93.2%产率)。^{1}H NMR (400 MHz, DMSO-d_6) δ 8.63-8.72 (m, 1H), 8.24 (dd, J = 3.6, 8.7 Hz, 1H), 8.11 (d, J = 1.1 Hz, 1H), 8.01 (dd, J = 1.8, 5.2 Hz, 1H), 7.92 (dd, J = 8.7, 9.9 Hz, 1H), 5.58 (s, 1H), 5.36 (s, 1H), 3.43 (s, 6H), 3.35 (s, 6H)。LC-MS: $[M+H]^+$ 323.2; mp. 124.2℃ (DSC峰); XRPD 2θ: 4.87, 7.35, 9.20, 12.76, 14.66, 15.06, 15.92, 16.99, 19.56, 19.81, 20.26, 21.55, 22.12, 23.09, 23.39, 23.73, 25.61, 26.25, 27.48, 27.73, 28.26, 29.55, 30.35, 31.10, 31.82, 34.13, 34.68, 36.04, 39.48。

[0157] 5.1.4 5-氟-[2,4'-联吡啶]-2',6-二甲醛(化合物Q)的合成

[0158]



化合物L4-磷酸盐 化合物Q

[0159] 将化合物L4-磷酸盐(177 g,111g L4游离碱 = 1.0X)、1N HCl (1110 mL,10V)和甲苯(555 mL,5V)的混合物在15-25℃下搅拌0.5-1.0小时。分离出有机相并且将水层在55-60℃下搅拌2小时。将混合物在55-60℃下在减压(-0.08至-0.085 Mpa)下缓慢(3小时)浓缩以去除产生的MeOH,然后冷却至30-40℃。装入DCM (777V)并且用15% Na_2CO_3 (3.5-4.5X)将混合物的pH调节至5-7。分离各层并且用DCM (2V)萃取水层。将合并的有机层用H_2O (5V)洗涤并且通过Na_2SO_4垫(1X)过滤。用DCM (2V)冲洗滤垫并且将合并的滤液浓缩至8-10V。用2V DCM喷雾洗涤反应器壁,然后在2.0-5.0小时内装入正庚烷(8-10V)。将混合物在正常大气压下在60℃以下浓缩至10-12V(上清液中残留的DCM≤40%)。将悬浮液在30-40℃下陈化1.0-2.0小时,在5-10℃下陈化6-8小时,并且过滤。将滤饼用1:4 DCM/正庚烷(1-2V)洗涤并且在40-50℃下在减压下干燥以得到80.19 g化合物Q (98%产率)。LC-MS: $[M+H]^+$ 231; $[M+H+H_2O]^+$ 249; ^{1}H NMR (400 MHz, 氯仿-d) δ 10.27 (s, 1H), 10.18 (s, 1H), 8.91-9.00 (m, 1H), 8.51-8.59 (m, 1H), 8.24-8.31 (m, 1H), 8.17(dd, J = 3.5, 8.7 Hz, 1H), 7.77 (t, J = 9.0 Hz, 1H); mp. 150℃ (DSC峰)。

[0160] 5.1.5 2',6-双(二氟甲基)-5-氟-2,4'-联吡啶(化合物H)的合成

[0161]

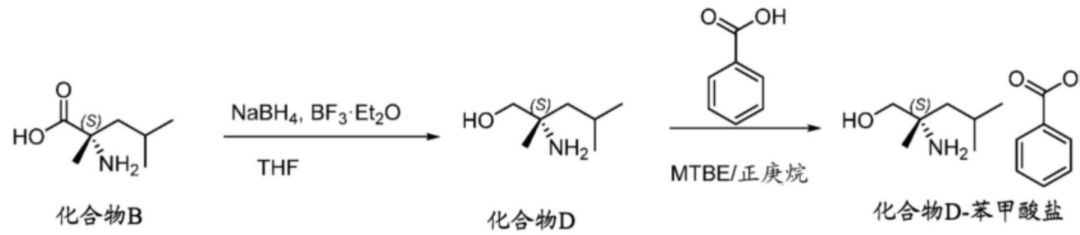
化合物Q 化合物H

[0162] 将化合物Q (30.0 g,1.00X)和Et_3N (0.044X)在无水DCM (KF ≤ 0.02%,20X)中的溶液冷却至0-5℃。在0-10℃下缓慢添加DAST (3.50X),然后将混合物在20-25℃下陈化直至反应完成(约24小时)。将反应混合物在0-20℃下放入15% K_2CO_3 (28X)中淬灭两小时,并且在20-25℃下陈化0.5小时。分离有机层,冷却至10-20℃并且用1 M HCl (9.9-11.1X)在10-25℃下处理0.5-1小时。静置0.5小时后,将混合物通过硅藻土垫(约0.5X)过滤,随后是少量冲洗DCM (2.0-3.0X)。静置滤液,并且分离有机层,用H_2O (10X)洗涤,并且通过硅胶

垫过滤(约1.5X)。用DCM (5.0X - 6.0X,三次)洗涤二氧化硅垫,直到滤液级分中化合物H的纯度降低到<90%。将合并的滤液在30℃以下浓缩至约2-3V,然后与异丙醇在50℃下共蒸馏,直到残留DCM < 5.0% (所用IPA总共为6-7X),最终体积为3-4V。将蒸馏残留物在55-60℃下陈化0.5小时,冷却至35-40℃,陈化0.5小时。在33-40℃(1-3小时)下缓慢添加水(9.0-10.0X),并且将混合物搅拌0.5小时。在15-20℃下陈化后,将悬浮液过滤,并且依次用IPA/H_2O (1:4,重量/重量,1X)、H_2O (2X)洗涤滤饼。将湿饼在40-45℃下在减压下干燥直至KF < 0.3%并且残留IPA < 0.1% (18-24小时),得到30.15 g化合物H (82%产率)。熔点(mp) 75℃ (DSC峰)。LC-MS: [M+H]$^+$ 275.2; ^{1}H NMR (400 MHz, 氯仿-d) δ 8.71-8.89 (m, 1H), 8.22 (s, 1H), 7.91-8.12 (m, 2H), 7.71 (t, J = 8.9 Hz, 1H), 7.00 (s, 1H), 6.87 (s, 1H), 6.82-7.05 (m, 1H), 6.59 (s, 1H), 6.73 (s, 1H)。

[0163] 5.1.6 (S)-2-氨基-2,4-二甲基戊-1-醇苯甲酸盐(化合物D-苯甲酸盐)的合成

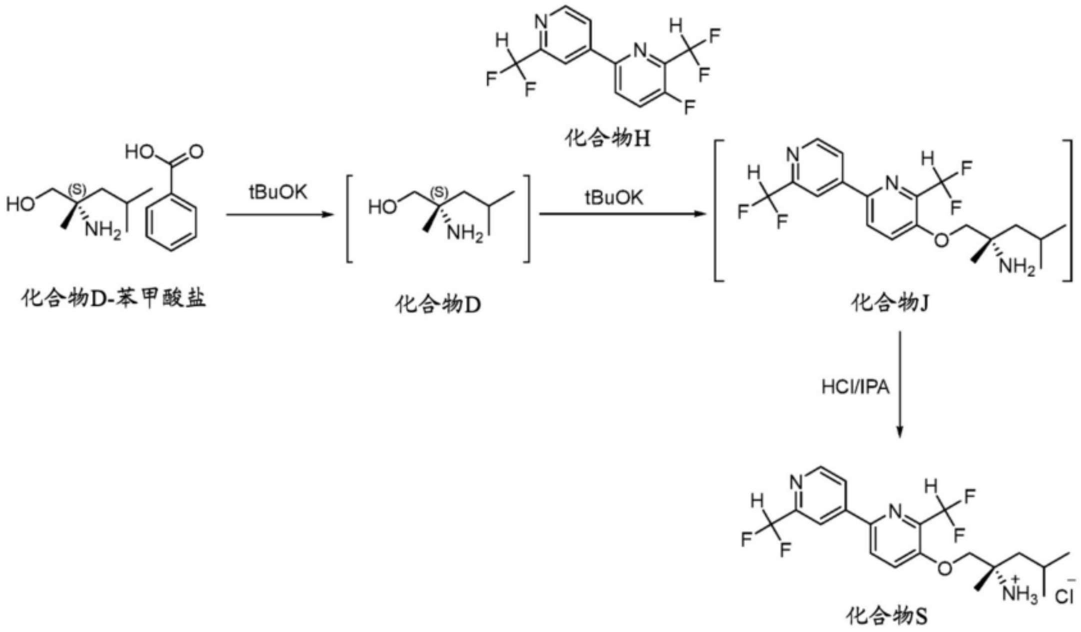
[0164]



[0165] 在0-10℃下将$BF_3.Et_2O$ (200 g,2.0当量)缓慢添加到$NaBH_4$ (53 g,2.0当量)在THF (1.0 L)中的混合物中。将反应混合物加热至15℃,然后在< 25℃下在1小时内添加(S)-(α)-甲基亮氨酸(100 g,1.0当量)。将混合物在20-25℃下陈化5-8小时,然后在25-30℃下放入10% NaOH水溶液(750 mL)中缓慢淬灭。将有机层分离,用15% NaCl水溶液(200 mL)洗涤,然后用正庚烷(300 mL)稀释。将2N HCl (约300 mL)添加到混合物中,直至pH达到1-2。将有机层分离并且用1 N HCl (300 mL)萃取。将合并的水层用30% NaOH (约500 mL)碱化直至pH >13,然后用MTBE (500 mL x 3)萃取。将合并的有机萃取物经无水Na_2SO_4 (100-200 g)干燥,过滤,浓缩至约200 mL,然后用MTBE (200-500 mL)冲涮,直至浓缩物中的水分含量<0.5%。然后在45-50℃下将氨基醇D的溶液缓慢(5小时)添加到苯甲酸(93 g,1.1当量)在MTBE (500 mL)中的溶液中。搅拌1小时后,将混合物缓慢(5-8小时)冷却至20-25℃并且陈化5-8小时以得到悬浮液。将悬浮液过滤,滤饼用1/1 MTBE/正庚烷(150 mL)洗涤,并且在40-50℃下在减压下干燥,得到化合物D-苯甲酸盐,产率为92%。mp. 125.4℃ (DSC峰); ^{1}H NMR (400 MHz, 甲醇-d_4) δ 7.88-7.99 (m, 2H), 7.27-7.46 (m, 3H), 3.45-3.62 (m, 2H), 1.69-1.87 (m, 1H), 1.56-1.66 (m, 1H), 1.44-1.54 (m, 1H), 1.29 (s, 3H), 1.00 (d, J = 6.60 Hz, 6H); XRPD 2θ: 6.67, 6.83, 12.84, 13.37, 15.16, 16.95, 17.83, 19.90, 20.32, 21.23, 22.28, 23.70, 24.09, 24.42, 26.24, 26.91, 27.49, 30.60, 32.64, 33.98, 34.98, 35.13。

[0166] 5.1.7 (S)-1-((2',6-双(二氟甲基)-[2,4'-联吡啶]-5-基)氧基)-2,4-二甲基戊-2-胺盐酸盐(化合物S)的合成

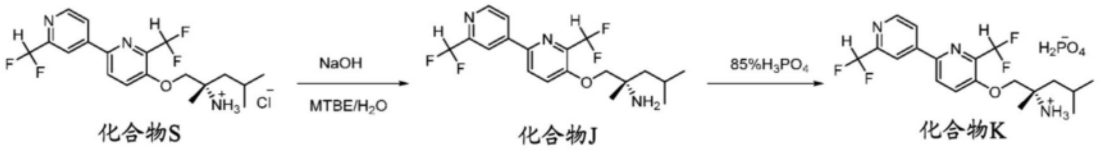
[0167]



[0168] 将固体t-BuOK (基于化合物H,2.5-3.0当量)在15-20℃下分批装入化合物D-苯甲酸盐(基于化合物H,1.2当量)和THF (10.5-11.6X)的混合物中。将混合物升温至20-25℃,搅拌3-5小时,然后冷却至0-5℃。缓慢(约1小时)添加化合物H (1.00X)在THF (3.6-4.5X)中的溶液,同时保持批料温度低于20℃。将反应混合物在20-25℃下陈化直至反应完成(1-3小时)。添加MTBE (6X),并且将混合物冷却至10-15℃。缓慢(1-3小时)添加H_2O (9.0-11.0X),同时保持批料温度低于25℃。分离各层并且用MTBE (2.2X)萃取水层。将合并的有机层在30℃以下在减压下浓缩至2-3V。游离碱化合物J:^{1}H NMR (400 MHz，DMSO-d_6) δ 8.70-8.84 (m，1H)，8.40 (d，J = 8.8 Hz，1H)，8.33 (s，1H)，8.22 (br d，J = 5.0 Hz，1H)，7.81 (d，J =8.8 Hz，1H)，7.17-7.41 (m，1H)，6.89-7.13 (m，1H)，3.82-3.95 (m，2H)，1.74-1.88 (m，1H)，1.55 (br s，2H)，1.33-1.46 (m，2H)，1.12 (s，3H)，0.93 (t，J = 7.1 Hz，6H)。通过共蒸馏(6.0-6.5X)将溶剂交换为IPA至2-3V后,添加更多IPA (3.8-4.2X),并且将混合物加热至50-60℃。缓慢(约1小时)添加35% HCl (0.44-0.47X)在IPA (1.3-1.5X)中的溶液,同时保持批料在50-60℃。将所得悬浮液在50-60℃下陈化1.0-2.0小时,在2.0-4.0小时内冷却至20-30℃,在20-30℃下搅拌1.0-2.0小时,然后过滤。滤饼用MTBE (3.5-4.0X)洗涤并且在40-50℃下在减压下干燥16-24小时以得到化合物S。LC-MS m/z 386.1; mp. 246.4℃ (DSC峰)，^{1}H NMR (400 MHz，DMSO-d6) δ 8.81 (d，J = 5.3 Hz，1H)，8.51 (br s，2H)，8.45 (d，J = 8.9 Hz，1H)，8.34 (s，1H)，8.24 (d，J = 5.1 Hz，1H)，7.91 (d，J = 8.9 Hz，1H)，7.56-7.87 (m，1H)，6.90-7.23 (m，1H)，4.29 (s，2H)，1.72-1.91 (m，2H)，1.54-1.72 (m，1H)，1.42 (s，3H)，0.86-1.00 (m，6H)。

[0169] 5.1.8 (S)-1-((2’,6-双(二氟甲基)-[2,4’-联吡啶]-5-基)氧基)-2,4-二甲基戊-2-胺磷酸盐(化合物K)的合成

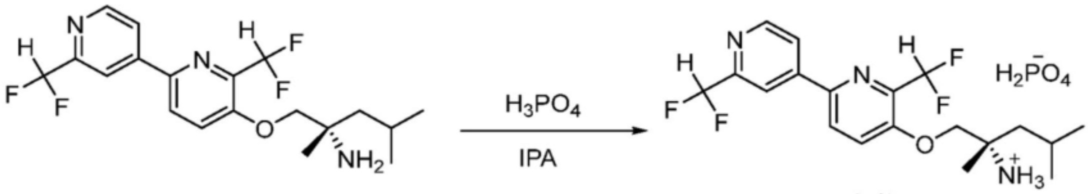
[0170]



[0171] 将化合物S (9.5 kg,1.0X)、MTBE (76.0 kg,8.0X)、水(50.0 kg,5.3X)的混合物用20% NaOH水溶液(0.95 kg NaOH固体在4.0 kg水中)在35-40℃下处理直至所有固体溶解(2.0-5.0小时)。将反应混合物冷却至20-25℃并且搅拌1.0-2.0小时。分离有机层，用水(46.5 kg,4.9X)洗涤，并且在≤30℃下在减压下浓缩至约25 L (2-3X)。在≤ 50℃下在减压下通过共蒸馏将溶剂交换为IPA (79.0 kg IPA,8.3X)，最终体积为29-38 L (3-4X)，然后用IPA (60 kg)稀释蒸馏残留物并且加热至50-60℃。在2.0-4.0小时内添加H_3PO_4 (2.8 kg,0.29X)在IPA (5.0 kg,0.53X)中的溶液。添加更多IPA (22.0 kg,2.3X)并且将批料在50-60℃下搅拌2.0-4.0小时。在2.0-4.0小时内将批料冷却至15-20℃，然后在15-20℃下搅拌1.0-2.0小时。将所得悬浮液过滤，并且依次用IPA (27.0 kg,2.84X)和MTBE (31 kg,3.3X)洗涤滤饼。将湿饼在45-55℃下在减压下干燥17-24小时，得到化合物K。化合物K中化合物J与磷酸之间的盐比率确定为1:1 (分别使用UV和IC检测器的两种单独的HPLC方法)。化合物K的纯度通过HPLC为98.7-99.9面积%。化合物K的结晶性通过XRPD得到确认，并且通过DSC得到进一步支持。^{1}H NMR (400 MHz，DMSO-d_6) δ 8.78 (d，J = 5.1 Hz，1H)，8.41 (d，J = 8.8 Hz，1H)，8.31 (s，1H)，8.21 (d，J = 5.1 Hz，1H)，7.88 (brd，H)，7.47 (t，$J_{H\text{-}C\text{-}F}$ = 54 Hz，1H)，7.04 (t，$J_{H\text{-}C\text{-}F}$ = 54 Hz，1H)，4.03-4.29 (m，2H)，1.72-1.87 (m，1H)，1.60-1.69 (m，1H)，1.49-1.59 (m，1H)，1.33 (s，3H)，0.92 (d，J = 6.6，3H)，0.87 (d，J = 6.6，3H)；^{13}C NMR (100 MHz，DMSO-d6) δ 21.62，22.74，24.61，24.82，44.69 54.57，72.80，110.53 (t，$J_{C\text{-}F}$ = 237 Hz)，113.84 (t，$J_{C\text{-}F}$ = 238 Hz)，116.68，122.19，125.03，140.07 (t，$J_{C\text{-}F}$ = 22 Hz)，144.13，145.98，150.52，152.80 (t，$J_{C\text{-}F}$ = 25 Hz)，153.51. XRPD: 4.80，5.99，7.43，7.88，9.57，11.58，14.84，15.21，15.75，17.91，18.83，19.17，20.41，20.84，21.67，23.23，23.95，24.41，24.72，25.27，26.37，30.14。

[0172] 5.1.9 (S)-1-((2',6-双(二氟甲基)-[2,4'-联吡啶]-5-基)氧基)-2,4-二甲基戊-2-胺磷酸盐(化合物K)的合成

[0173]



化合物J 化合物K

[0174] 在50-60℃下向化合物J (9.14 g)在IPA (100 mL)中的溶液中添加化合物K种子(0.18 g)。在2-4小时内添加85%磷酸(2.87 g,1.05当量)在IPA (7 mL)中的溶液。将悬浮液陈化2-4小时，在2-4小时内冷却至15-20℃并且陈化1-2小时。将悬浮液过滤，并且用IPA (20 mL)洗涤滤饼，随后用MTBE (44 mL)洗涤。将湿饼在45-55℃下在减压下干燥17-24小时，得到11.3 g化合物K,98%产率。

[0175] 化合物K种子形成:将IPA (1.0 mL)添加到化合物J (50.08 mg,0134 mmol,1.0当量)中，在环境温度下形成澄清溶液，然后添加磷酸(0.156 mL,1M在IPA中,0.156 mmol,1.20当量)。将混合物搅拌6小时以得到悬浮液，然后在60℃下陈化30 min。冷却至室温后，添加庚烷(0.5 mL)，并且将所得混合物搅拌1小时。将所得悬浮液过滤，并且用MTBE (0.5 mL)洗涤滤饼，在45-48℃下在减压下干燥过夜，得到化合物K种子(59.28 mg,94.4%产率)。

[0176] 盐比率、纯度、XRPD、DSC和TGA数据与实施例2中化合物K获得的数据基本相同。

[0177] 本文引用的每篇参考文献(例如,专利、专利申请和出版物)均以引用的方式整体并入本文。

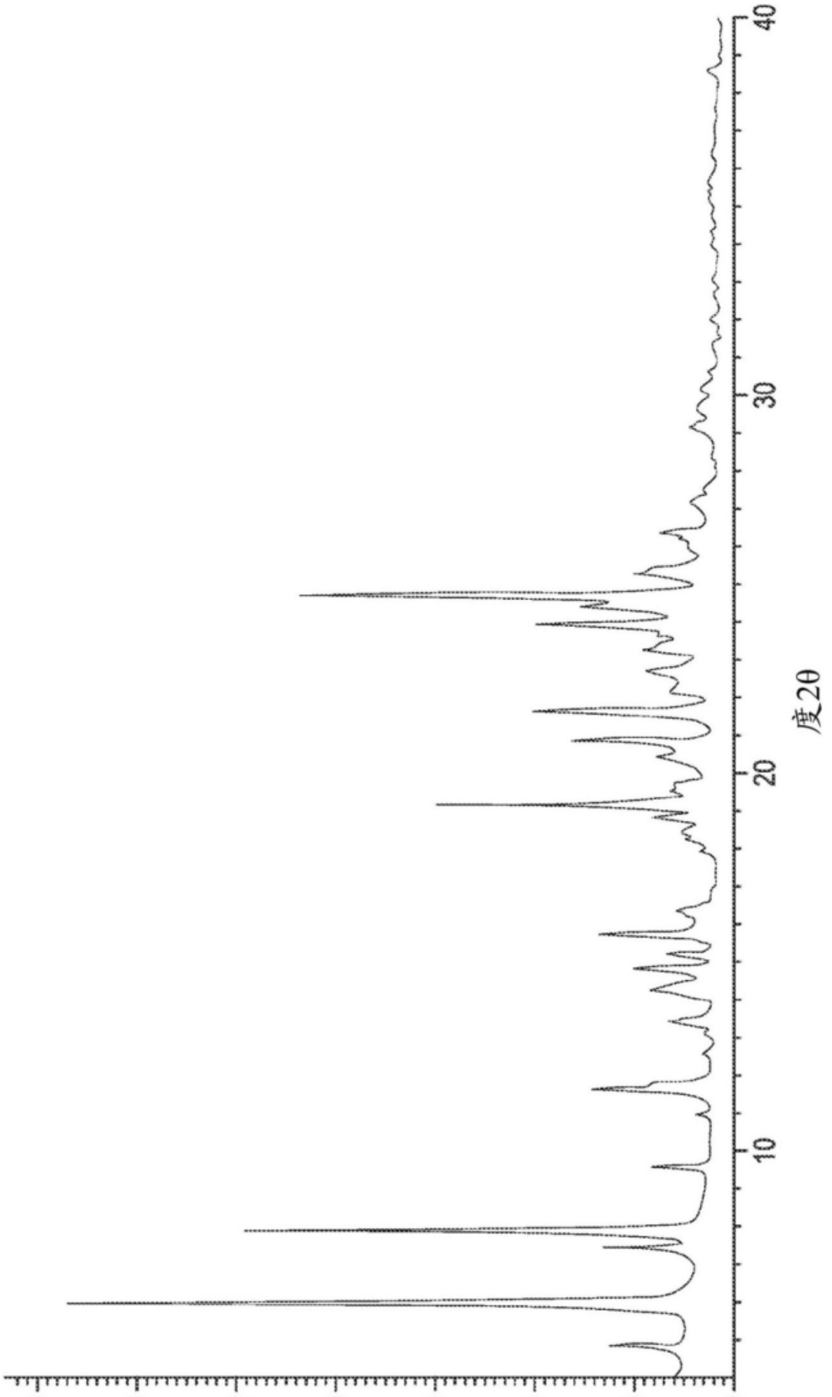


图1

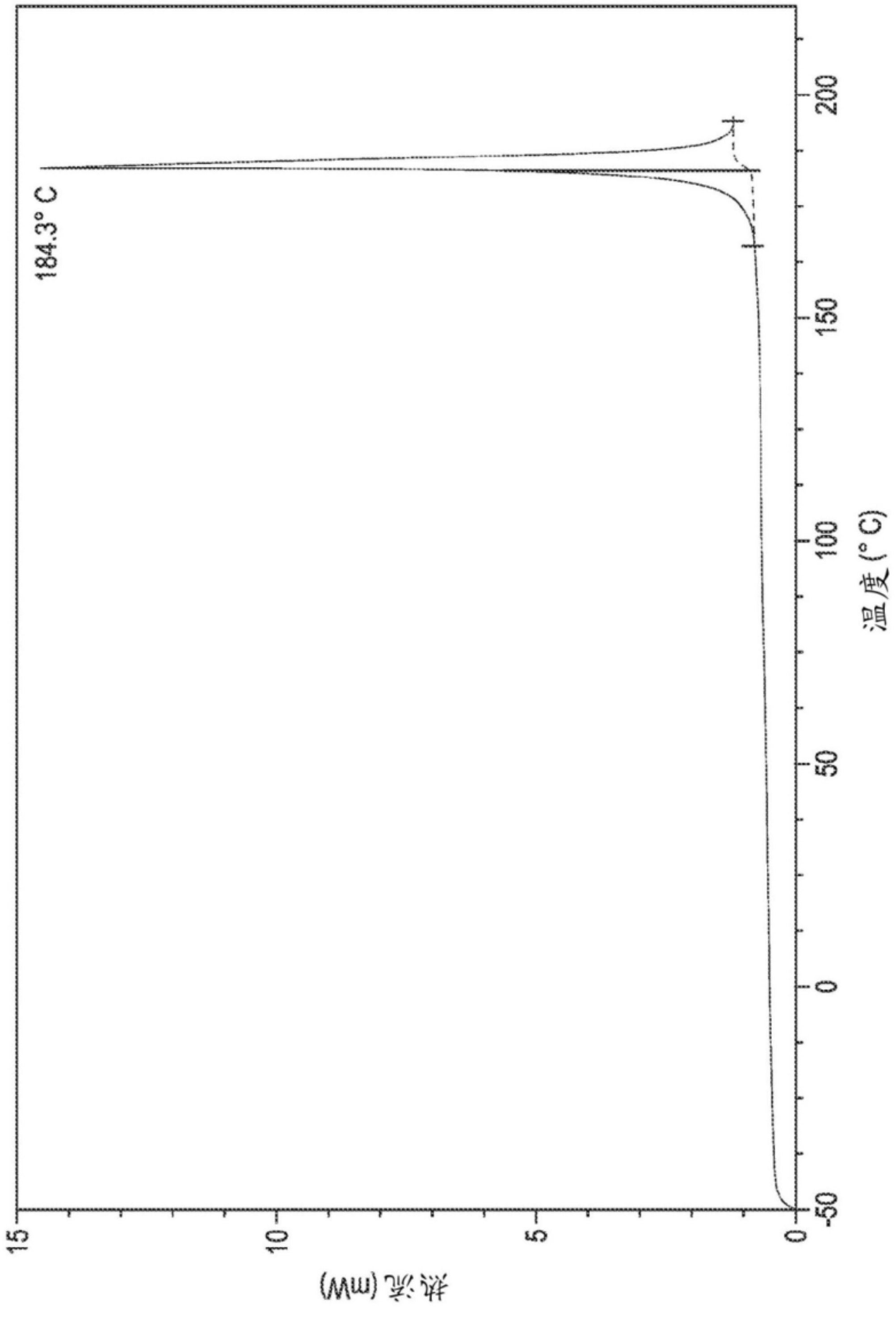


图2