cognitive deficits in schizophrenia, Parkinson's disease, neuropathic pain, bipolar disorder, and Alzheimer's disease.

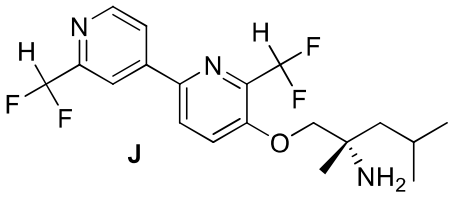
In addition, studies using Huh-7.5 cells indicate a potential utility for AAK1 kinase inhibitors in the treatment of hepatitis C (HCV) infection. Reduction of AAK1 protein using RNA interference mediated gene silencing, treatment with the kinase inhibitor sunitinib (a potent AAK1 inhibitor), and overexpression 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

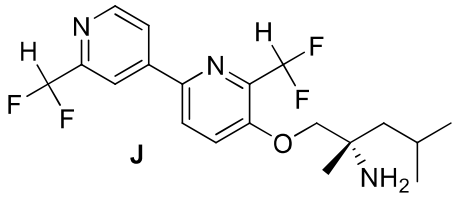
This application is directed to methods of making the compound (*S*)-1-((2',6-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (Compound J):



J

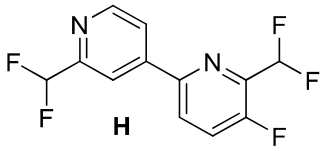
and salts thereof. Compound J is an inhibitor of adaptor associated kinase 1 (AAK1) and is believed to be useful in the treatment of diseases and disorders including pain.

In an aspect, there is provided a method of preparing (S)-1-((2',6-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (Compound J):



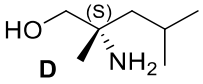
J

which comprises contacting Compound H:



H

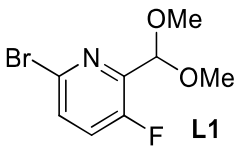
with Compound D:



D

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

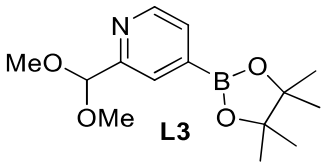
In another aspect, there is provided a compound, which is 6-bromo-2-(dimethoxymethyl)-3-fluoropyridine (Compound L1):



L1

.

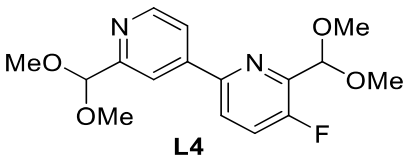
In another aspect, there is provided a compound, which is 2-(dimethoxymethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (Compound L3):



L3

.

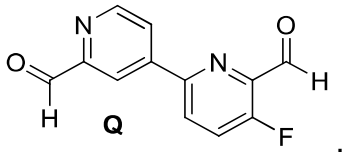
In another aspect, there is provided a compound, which is 2',6-bis(dimethoxymethyl)-5-fluoro-2,4'-bipyridine (Compound L4):



L4

or a salt thereof.

In another aspect, there is provided a compound, which is 5-fluoro-[2,4'-bipyridine]-2',6-dicarbaldehyde (Compound Q):

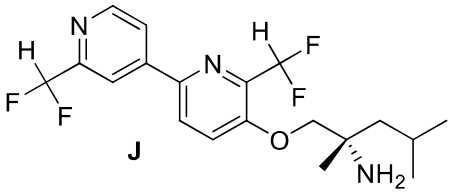


Q

.

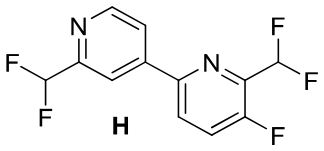
In another aspect, there is provided a crystalline form of the compound as defined above, which has a melting point of about 150°C.

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



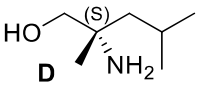
J

which comprises contacting Compound H:



H

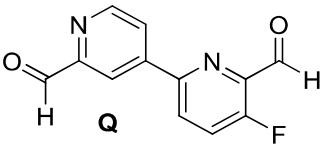
with Compound D:



D

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

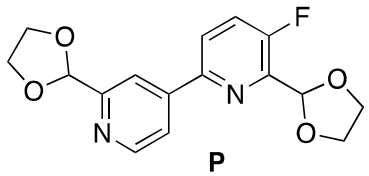
In one example, Compound H is prepared by contacting Compound Q:



Q

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

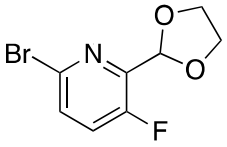
In one example, Compound Q is prepared by contacting Compound P:



P

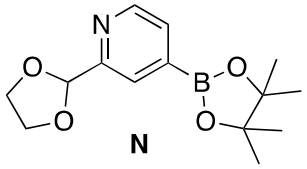
with an acid under conditions sufficient to form Compound Q.

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



L

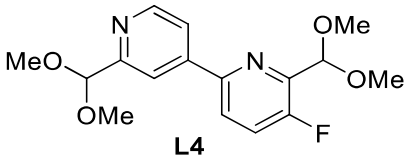
with Compound N:



N

under conditions sufficient to form Compound P.

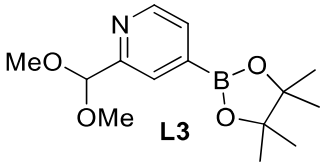
In one example, Compound Q is prepared by contacting Compound L4:



L4

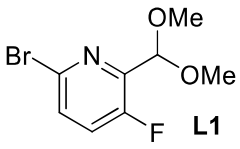
with an acid under conditions sufficient to form Compound Q.

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



L3

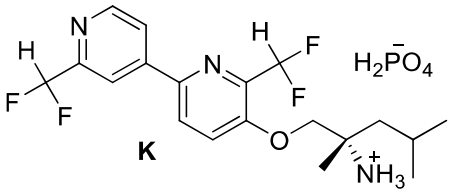
with Compound L1:



L1

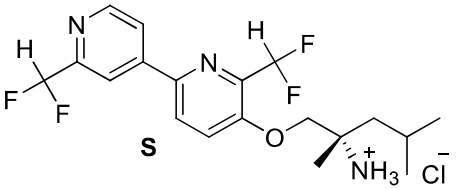
in the presence of a catalyst and a base under conditions sufficient to form Compound L4.

This disclosure also encompasses a method of preparing Compound K:



K

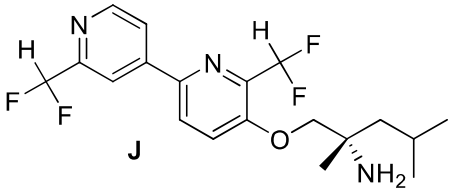
which comprises contacting Compound S:



S

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

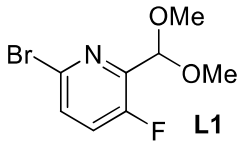
In one example, Compound S is prepared by contacting Compound J:



J

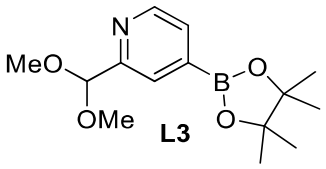
with hydrochloric acid in a solvent under conditions sufficient to form Compound S.

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



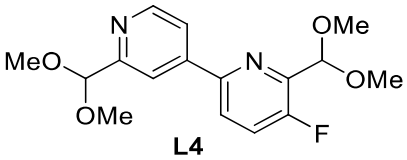
L1 .

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



L3 .

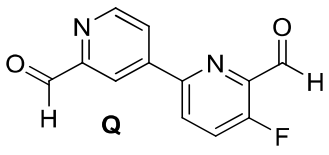
This disclosure also encompasses 2',6-bis(dimethoxymethyl)-5-fluoro-2,4'-bipyridine (Compound L4):



L4

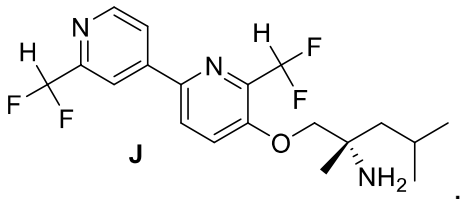
and salts thereof.

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



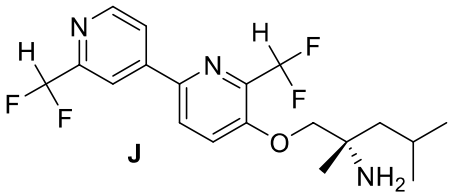
Q .

This disclosure 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):



J

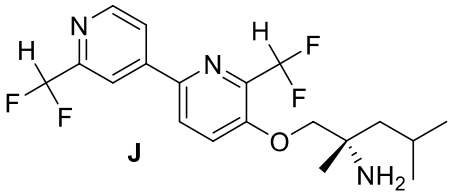
This disclosure also encompasses a method of determining the purity of a sample of (*S*)-1-((2',6-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (Compound J):



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 disclosure also encompasses 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, below.

4 BRIEF DESCRIPTION OF THE DRAWINGS

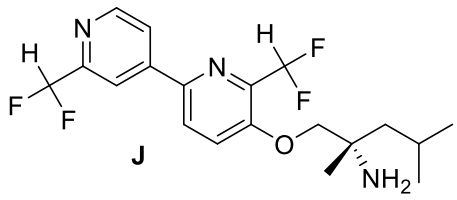
FIG. 1 provides a representative X-ray powder diffraction (XRPD) pattern of crystalline solid form I of ((*S*)-1-((2',6-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-aminium dihydrogen phosphate (Compound K). The spectrum was obtained using a Bruker X-ray diffractometer with a LYNXEYE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

CLAIMS

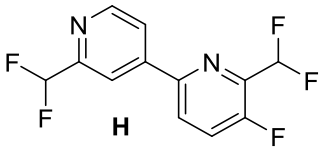
What is claimed is:

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



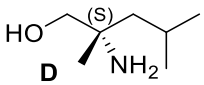
J

which comprises contacting Compound H:



H

with Compound D:



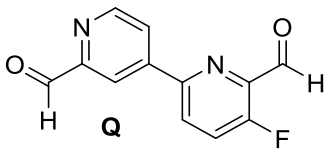
D

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:

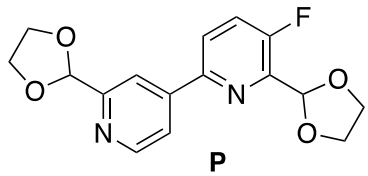


Q

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:

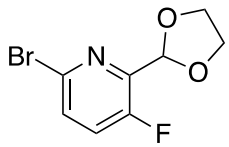


P

with an acid under conditions sufficient to form Compound Q.

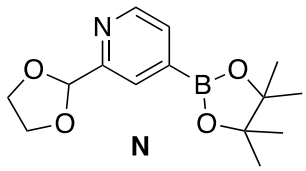
7. The method of claim 6, wherein the acid is hydrochloric acid.

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



L

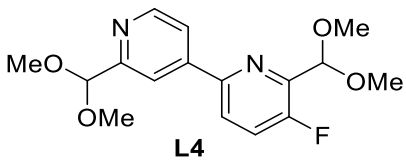
with Compound N:



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:

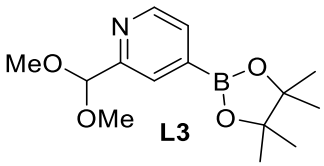


L4

with an acid under conditions sufficient to form Compound Q.

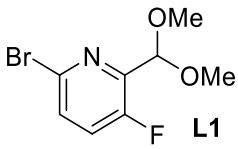
10. The method of claim 9, wherein the acid is hydrochloric acid.

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.

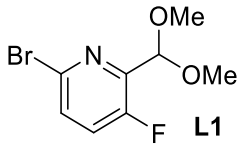
13. The method of claim 11 or 12, wherein the ligand is Xphos.

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.

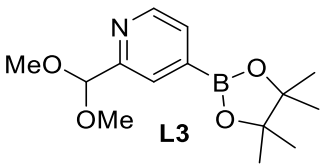
16. The method of claim 13, wherein the solvent is isopropyl alcohol.

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



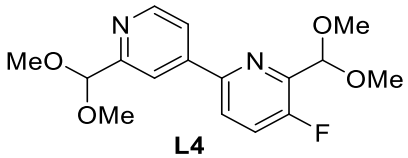
L1.

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



L3.

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



L4

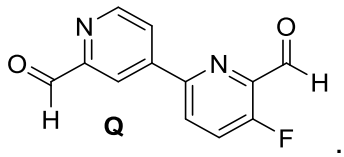
or a salt thereof.

20. The compound of claim 19, which is a hydrochloride, phosphate, or maleate salt.

21. The compound of claim 20, which is crystalline 2',6-bis(dimethoxymethyl)-5-fluoro-2,4'-bipyridine phosphate salt having a melting point of about 125°C.

22. The compound of claim 21, 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.

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



Q

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24. A crystalline form of the compound of claim 23, which has a melting point of about 150°C.